

Minerva Access is the Institutional Repository of The University of Melbourne

Author/s:

Gourlay, Caitlyn Grace

Title:

The acute and habitual effects of alcohol consumption on sleep in late adolescents

Date:

2020

Persistent Link:

<https://hdl.handle.net/11343/260484>

Terms and Conditions:

Terms and Conditions: Copyright in works deposited in Minerva Access is retained by the copyright owner. The work may not be altered without permission from the copyright owner. Readers may only download, print and save electronic copies of whole works for their own personal non-commercial use. Any use that exceeds these limits requires permission from the copyright owner. Attribution is essential when quoting or paraphrasing from these works.

**The acute and habitual effects of alcohol consumption
on sleep in late adolescents**

Caitlyn Grace Gourlay

Submitted in total fulfilment of the requirements
of the degree of Doctor of Philosophy

July 2020

Melbourne School of Psychological Sciences
Faculty of Medicine, Dentistry and Health Sciences
The University of Melbourne
Australia

Abstract

Adolescence is a critical time period for human development. It is associated with major interrelated changes to the brain and sleep regulatory systems. These changes continue into young adulthood, and often coincide with the onset and acceleration of alcohol use. This is concerning as research suggests alcohol consumption may harm the developing brain and sleep systems. Indeed, sleep is an essential neurophysiological process that is necessary for optimal health, functioning, and development. Disturbances to sleep are associated with adverse physiological and psychological consequences. Alcohol is well-known for its sleep disturbing properties. Research has reliably shown that pre-sleep alcohol ingestion in light-drinking late adolescents leads to characteristic objective sleep disruption. These effects are bi-phasic, manifesting as sedation in the first half of the sleep period, followed by major sleep disruption in the second half. However, there is growing evidence that young people may be less sensitive to the initial sedative effects of alcohol. Critically, the effects of acute alcohol consumption on sleep have not yet been investigated in young people who habitually engage in heavy alcohol use.

It is well-established that chronic heavy alcohol use leads to enduring sleep disturbances, such as degradations in slow wave sleep (SWS), that persist into periods of long-term abstinence. This has been investigated exclusively in adults with long-term alcohol use disorders. It is currently unknown whether heavy-drinking young people also suffer disturbances to normal sleep. Due to their ongoing development, it is possible that young people experience unique alcohol-related sleep disturbances. These disturbances could negatively impact physical and mental health. The current study aimed to investigate the effects of acute and habitual alcohol use

on sleep quality, architecture, and electroencephalography (EEG) spectral power, in male and female late adolescents, aged 18 to 21 years.

Forty-six late adolescents were recruited (mean $\pm$ standard deviation): 9 light-drinking males (20.0 ± 0.9 years; 13.5 ± 10.3 standard drinks [10g of ethanol] in the previous 30 days), 13 light-drinking females (19.4 ± 1.2 years; 12.3 ± 8.0 standard drinks), 11 heavy-drinking males (20.1 ± 0.7 years; 133.4 ± 78.8 standard drinks), and 13 heavy-drinking females (19.2 ± 0.9 years; 81.9 ± 25.6 standard drinks).

Following an initial adaptation night, participants completed in-laboratory polysomnography under two conditions: pre-bedtime alcohol (peak breath alcohol concentration [BrAC] .10%) and placebo (BrAC .00%) consumption. Experimental nights were non-consecutive and counterbalanced over participants. Participants abstained from alcohol for 48 hours prior to testing. This single-blind, mixed-model study design included two repeated- (acute alcohol vs. placebo consumption, first vs. second half of the sleep period) and two between- (male vs. female, habitual heavy vs. light drinking) measures factors. Sleep quality (sleep onset latency, arousals, wake after sleep onset, sleep efficiency) and architecture (stage N1 sleep, stage N2 sleep, SWS, rapid eye movement [REM] sleep) variables were independently scored using standard American Academy of Sleep Medicine (2007) criteria by two experienced sleep researchers. Discrepancies between scorers were resolved by an independent adjudicator. All scorers were blinded to participant group and experimental condition. Power spectral analysis was conducted for five EEG frequency bands: beta (16 – 30 hertz; Hz), sigma (12 – <16 Hz), alpha (8 – <12 Hz), theta (4 – <8 Hz), and delta (0.5 – <4 Hz) for each sleep stage. Data were analysed using mixed-model analysis of variance and post-hoc t-tests. Correlations between

habitual alcohol consumption, and sleep quality and architecture variables, were also performed.

Mean BrAC at lights out was $.08 \pm .01$ percent following pre-sleep alcohol, and $.00 \pm .00$ percent following placebo consumption. Following acute alcohol consumption, in the first half of the sleep period, both heavy- and light-drinking late adolescents demonstrated fewer arousals ($p < .001$), less stage N1 sleep ($p < .001$), more SWS ($p = .007$), longer REM sleep onset latencies ($p < .001$), and less REM sleep ($p < .001$), compared to placebo. There were no differences observed in sleep onset latency ($p = .720$), wake after sleep onset ($p = .850$), or sleep efficiency ($p = .811$). In the first half of the sleep period, alpha EEG spectral power was higher following alcohol consumption in stage N2 sleep ($p < .001$), SWS ($p < .001$), and REM sleep ($p = .005$). Although delta spectral power was higher in SWS ($p = .008$) and REM sleep ($p < .001$) in the first half of the sleep period, delta power was lower in stage N2 sleep ($p = .006$). In the second half of the sleep period, there were more arousals ($p < .001$), more wake after sleep onset ($p < .001$), lower sleep efficiency ($p < .001$), more stage N1 sleep ($p < .001$), and less SWS ($p = .004$), following acute alcohol consumption compared to placebo, in both heavy- and light-drinking late adolescents. No differences in EEG spectral power were observed in the second half of the sleep period.

By design, heavy-drinking participants had consumed more alcohol in the previous 30 days, and across their lifetimes, than light drinkers ($p < .001$). There were no differences in objective sleep quality between heavy- and light-drinking late adolescents. However, a correlational analysis showed that, in the placebo condition, higher alcohol consumption in the previous 30 days was associated with higher wake after sleep onset ($\rho = .312$, $p = .035$), and lower sleep efficiency ($\rho = -.327$, $p = .027$).

Heavy drinkers had less all-night visually scored SWS ($p = .026$), and more stage N2 sleep ($p = .008$), than same-aged light drinkers, in the placebo condition.

Furthermore, higher previous 30-day alcohol consumption was related to lower SWS ($\rho = -.261$, $p = .040$) and higher stage N2 sleep ($\rho = .250$, $p = .027$) percentage, in the placebo condition. Irrespective of experimental condition, heavy drinkers had shorter REM sleep onset latencies, compared to same-aged light drinkers ($p = .038$).

Although there were no differences in all-night REM sleep percentage, heavy drinkers had less REM sleep in the second half of the sleep period compared to light drinkers, irrespective of condition ($p = .016$). There were no differences in delta spectral power between heavy- and light-drinking late adolescents in any sleep stage. However, heavy-drinking late adolescents had higher sigma spectral power in SWS ($p = .029$), and stage N2 sleep ($p = .021$), than same-aged light drinkers, regardless of experimental condition. There was an interaction between sex, acute alcohol use, and habitual alcohol use, for all-night SWS percentage ($p = .003$). This interaction suggested that heavy-drinking males had higher all-night SWS percentage following alcohol consumption compared to placebo, however, heavy-drinking females had lower all-night SWS. In light-drinking males and females, there were no differences in all-night SWS percentage following alcohol or placebo consumption.

The current study demonstrated that both heavy- and light-drinking late adolescents experience substantial sleep disruption following a high dose of alcohol prior to sleep. In contrast to the adult literature, the current investigation reported no differences in sleep onset latency, wake after sleep onset, or sleep efficiency, in the first half of the sleep period. This supports growing evidence that young people may experience less initial physiological sedation following alcohol consumption. However, a direct adult comparison is needed to verify this. This unique

physiological response could potentially contribute to higher levels of alcohol use in young people, as it permits them to consume higher doses of alcohol before experiencing sedation. The current study replicated previous findings of higher alpha and delta spectral power following pre-sleep alcohol in young people. This may represent alpha-delta sleep – a potential electrophysiological indicator of sleep disruption. It is possible that these objective sleep disturbances may compromise the restorative properties of sleep and contribute to the alcohol hangover. The current study reported more wake after sleep onset, and less sleep efficiency, following acute alcohol consumption, which may contribute to sleep restriction in young people. Critically, this investigation provided novel evidence that pre-sleep alcohol consumption disrupts sleep in heavy-drinking late adolescents. This indicates that this population may be repeatedly experiencing sleep disruption during the final stages of neural development. Furthermore, these effects may be amplified in heavy-drinking young women, however further research is needed to replicate these novel findings.

Finally, the present study uniquely demonstrated that heavy habitual alcohol use in young people is associated with disturbances to normal sleep, irrespective of pre-sleep alcohol consumption. Despite their relatively short drinking histories, the pattern of deficits was similar to those reported in adults with long-term alcohol use disorders, including lower all-night SWS percentage. Furthermore, some sleep abnormalities may be unique to this developing age group, such as elevated sigma spectral power during SWS and stage N2 sleep. Evidence suggests SWS plays a functional role in neurophysiological growth and repair, and learning and memory. Enduring degradations in SWS may be particularly detrimental in young people, as neural development is still ongoing, and academic pressure is high, during this time

period. Although longitudinal research is required, the sleep deficits observed in the current investigation may represent alcohol-related changes to the brain and sleep systems, and/or a predisposition to heavy alcohol use. In summary, the current study provided key objective evidence that both acute and habitual alcohol use in late adolescence disrupts sleep. This could have deleterious effects on the health, functioning, and development of young people. It is imperative that action is taken to prevent or reduce alcohol-related sleep disturbances during the final stages of human development. Interventions should aim to delay and reduce alcohol consumption, enhance cognitive function, and improve sleep quality to protect the health and wellbeing of young people.

Declaration

This is to certify that:

- i. this thesis comprises only my original work towards the PhD,*
- ii. due acknowledgement has been made in the text to all other material used,*
- iii. this thesis is less than 100,000 words in length, exclusive of tables, graphs, bibliographies and appendices.*

Caitlyn Grace Gourlay

July 2020

Publications

Refereed conference proceedings and publications contributed to by this thesis:

Gourlay, C. G., Colrain, I. M., Chan, J. K. M., Trinder, J., and Nicholas, C. L. (2019). The effects of acute and chronic alcohol consumption on sleep electroencephalogram power in young adults. (2019). *Journal of Sleep Research*, 28 (Suppl. 1), 17. 31st Annual Scientific Meeting of the Australian Sleep Association. *15-minute oral presentation.*

Gourlay, C. G., Colrain, I. M., Chan, J. K. M., Trinder, J., and Nicholas, C. L. (2018). The effects of acute and chronic alcohol use on sleep architecture in male and female young adults. *Journal of Sleep Research*, 27 (Suppl. 2), 2. 30th Annual Scientific Meeting of the Australian Sleep Association. *15-minute oral presentation. Nominated for the New Investigator Award.*

Gourlay, C. G., Colrain, I. M., Chan, J. K. M., Trinder, J. and Nicholas, C. L. (2016). RSA abstracts: The effects of acute and chronic alcohol use on sleep architecture in male and female college age students. *Alcoholism: Clinical and Experimental Research*, 40(S1), 162A.

Gourlay, C. G., Colrain, I. M., Ayton, H. C., Couchman, A., Chan, J. K. M., Trinder, J., and Nicholas, C. L. (2016). The effects of acute and chronic alcohol use on sleep architecture in male and female young adults. 7th Australian Society for Medical Research Victorian Student Symposium. *15-minute oral presentation.*

Gourlay, C. G., Colrain, I. M., Chan, J. K. M., Trinder, J., and Nicholas, C. L. (2016). Abstracts: The effects of acute and chronic alcohol use on sleep architecture in male and female young adults. *Journal of Sleep Research*, 25 (Suppl. 2), 34. 28th Annual Scientific Meeting of the Australian Sleep Association. *15-minute oral presentation.*

Gourlay, C. G., Ayton, H. C., Chan, J. K. M., Couchman, A., Colrain, I. M., Trinder, J., and Nicholas, C. L. (2015). Acute and chronic alcohol consumption disturbs sleep architecture in late adolescence. 6th Australian Society for Medical Research Victorian Student Symposium. *Poster presentation.*

Gourlay, C. G., Trinder, J., Ayton, H. C., Couchman, A., Chan, J. K. M., Colrain, I. M. and Nicholas, C. L. (2015). Sleep electroencephalogram delta power spectra in heavy and light drinking college age students. *Sleep*, 38 (Abstract Supplement), A84 –A85.

Gourlay, C. G., Ayton, H. C., Chan, J. K. M., Couchman, A., Colrain, I. M., Trinder, J., and Nicholas, C. L. (2015). Abstracts: Sleep electroencephalogram power spectra in heavy and light drinking youth. *Sleep and Biological Rhythms*, 13 (Suppl. 1), 42. 27th Annual Scientific Meeting of the Australian Sleep Association. *15-minute oral presentation*.

Gourlay, C. G., Trinder, J., Ayton, H. C., Couchman, A., Chan, J. K. M., Colrain, I. M. and Nicholas, C. L. (2014). Slow wave sleep is lower in heavy drinking college students. *Sleep*, 37 (Abstract Supplement), A39. 28th Annual Scientific Meeting of the American Academy of Sleep Medicine and Sleep Research Society. *Poster presentation*.

Gourlay, C. G., Colrain, I. M., Ayton, H. C., Couchman, A., Chan, J. K. M., Trinder, J. and Nicholas, C. L. (2014). RSA / ISBRA abstracts: The acute and chronic effects of alcohol consumption on sleep architecture in college aged students. *Alcoholism: Clinical and Experimental Research*, 38 (s1), 274A. 37th Annual Research Society of Alcoholism Scientific Meeting and 17th Congress of International Society for Biomedical Research on Alcoholism. *Poster presentation*.

Gourlay, C. G., Ayton, H. C., Chan, J. K. M., Couchman, A., Colrain, I. M., Trinder, J., and Nicholas, C. L. (2014). Abstracts: Acute and chronic alcohol consumption disturbs sleep architecture in late adolescence. *Sleep and Biological Rhythms*, 12 (Suppl. 1), 80-81. 26th Annual Scientific Meeting of the Australasian Sleep Association. *6-minute oral presentation and poster. Recipient of Poster Prize*.

Nicholas, C. L. **Gourlay, C. G.,** and Chan, J. K. M. (2018). Social drinking: Current findings on acute and chronic effects upon sleep disturbance and brain activity in adolescents and young adults. In P. N. Murphy (Ed.), *The Routledge International Handbook of Psychobiology 1st Edition* (pp. 367 – 388). Oxford: Routledge.

Acknowledgements

“To live is to change, and to be perfect is to have changed often.”

— John Henry Newman

I cannot believe how far I have come, and the amount I have grown, since commencing this PhD. This experience has taught me how to overcome challenges and embrace change. It has set me firmly on a path of lifelong growth and learning. Importantly, this is a journey I have cherished, and one that was only possible with the guidance, friendship, and support of others.

“If I have seen further than others, it is by standing upon the shoulders of giants.”

— Isaac Newton

Firstly, I would like to thank my supervisor, and PhD great grandfather, Professor John Trinder. I first encountered John as a lecturer in third-year undergraduate psychology. His passion and expertise immediately enamoured me with sleep science. Thank you for igniting my passion, welcoming me warmly to the sleep laboratory family, and your careful and expert editing.

I would like to thank my mentor, and PhD grandfather, Professor Ian Colrain. I met Ian at my first ever conference in Minneapolis. Ian immediately took me under his wing and made sure I had an incredible experience. Thank you for supporting me and making valuable contributions to my thesis.

I would like to thank my supervisor and mentor, Dr Julia Chan. Before you were my supervisor, you were my friend and inspiration. I have never met someone as loyal, intelligent, and hardworking as you. Thank you for developing my leadership, writing, and critical thinking skills. Your endless support, patience, and dedication, as both a friend and supervisor, is the reason I completed this PhD. Words cannot express how grateful I am to have you in my life. Thank you for always believing in me.

I would like to thank my primary supervisor, Dr Christian Nicholas. In my Honours year, Christian shared with me his long-held passion for sleep and alcohol research. I have never once become tired of reading, writing, or talking about the effects of alcohol on sleep. Thank you for sharing this passion with me, and teaching me the skills I needed to be an excellent and independent sleep researcher. Thank you for your incredible patience and expertise, and supporting me to undertake this PhD.

I would like to thank my Melbourne University Sleep Laboratory family. The endless laughs, support, and friendships have made this PhD an absolute joy. I have shared so many wonderful moments and made lifelong friends. Professor Amy Jordan – thank you for creating a relaxed and supportive laboratory environment. Dr Jenifer Cori – thank you for your close friendship and every adventure we shared, from Melbourne to New York City. Davey Munro – thank you for always making me laugh and lifting my spirits. Candice Wen – thank you for your bright smile and friendship. Dr Marina Cavuoto – thank you for all of your support and laughter. Thank you to everyone else who has been a part of the sleep laboratory, no matter how brief, and supported me on this journey.

I would like to thank every participant who volunteered to take part in this study. It was wonderful to meet so many vibrant and interesting young people. Thank you for tolerating all the glue, wires, and alcohol, and making it fun. You made all 144 sleepless nights worth it. This research would not have been possible without your enthusiasm, kindness, and generosity.

Thank you to my incredible friends and family for backing me on this journey.

Aleisha Citroen – thank you for your never-ending kindness and support. Lauren Galeotti – thank you for being my dance partner and confidant. Jill Feinberg – thank you for always looking after me. Natalie Coulson – thank you for your unwavering support and friendship. Aliey Cheah – thank you for your love and generosity. Cassandra Zara – thank you for your closeness and care. Susan Crase – thank you for your enduring friendship. Edele Harrison, Anthony, and Keira Slater – thank you for your endless generosity and beautiful approach to life. Liz and Paddy Dempsey – thank you for all the fun and adventures. Annie Blunden – thank you for being my friend and cheerleader.

Thank you to my wonderful extended family – the Gourlay’s, Hudspeth’s, Williams’, Bruce’s, Taylor’s, and Wheeler’s. Thank you for every smile, laugh, meal, and all the love, that you have generously given me over the years.

Thank you to Dr Therese Thornton and her beautiful family, Bas, Sophie, and Henry. I first met Therese as a third-year undergraduate student when she was my tutor. I had no idea then that you would become one of the most important people in my life. You are one the kindest and most inspiring people I know. Thank you for your endless support, mentoring, and friendship. You and your family bring so much joy to my life.

Thank you to my wonderful partner, Dr Michael Wheeler. I met Michael attending a student conference at the Royal Melbourne Hospital, so our PhDs quite literally brought us together. Meeting and getting to know you has been one of the best experiences of my life. I have never laughed so much or been so happy. I am so proud of everything you have achieved and the person that you are. Thank you for believing in me and supporting me throughout everything. A special thank you to your incredible family, Gerri, Matt and Alan Wheeler.

I would like to thank my brother, Justin Gourlay. Thank you for loving and supporting me unconditionally. I am so incredibly proud to be your sister. Finally, I would like to thank my parents, Catherine and Timothy Gourlay. Mum – thank you for loving me fiercely and whole-heartedly. Your incredible strength, selflessness, and belief in me has been unwavering. Thank you for every sacrifice you have made for me and teaching me your work ethic. Dad – thank you for supporting me through every moment. You have been with me every step of the way and never failed to make me laugh. Thank you for loving me and believing in me. I am so proud to be your daughter. Every word is for you both.

I dedicate this PhD thesis to the loving memory of my grandmothers –

June Hudspeth (1925 – 2018)

Gwen Gourlay (1930 – 2018)

Caitlyn Grace Gourlay

Table of Contents

Abstract	i
Declaration	vii
Publications	ix
Acknowledgements	xi
Table of Contents.....	xv
List of Tables.....	xix
List of Figures	xxv
List of Abbreviations	xxxiii
Preface	xxxv

CHAPTER 1- Sleep processes, function, and physiology.....	1
1.1 Functions of sleep	3
1.2 Normal sleep in humans	6
1.2.1 Sleep architecture, quality, and duration.....	8
1.2.1.1 Sleep architecture	8
1.2.1.2 Sleep quality and duration.....	13
1.2.2 Sleep across the lifespan	15
1.2.2.1 Sex differences in sleep across the lifespan	21
1.2.3 Slow wave and rapid eye movement sleep homeostasis.....	22
1.2.4 Neurophysiology of slow wave sleep	29
1.2.5 Adolescent maturation of sleep and neural processes.....	33
1.2.5.1 Sex differences in adolescent maturation of sleep and neural processes	38
1.3 Summary.....	40

CHAPTER 2- Prevalence and physiological impacts of alcohol use.....	41
2.1 Prevalence	43
2.2 Physiological effects	46
2.2.1 Metabolism, absorption, and excretion	46
2.2.2 Effects of acute use	49
2.2.3 Effects of chronic use.....	54
2.2.4 Alcohol use in adolescents and young adults.....	64

2.2.4.1 Effects of acute use.....	64
2.2.4.2 Effects of habitual use	68
2.3 Summary	81
CHAPTER 3- Impacts of alcohol use on sleep	83
3.1 Acute use.....	85
3.1.1 Withdrawal from acute use	92
3.2 Chronic use	94
3.2.1 Withdrawal from chronic use.....	97
3.2.2 Sustained recovery/extended abstinence.....	101
3.2.3 Acute alcohol consumption during early abstinence.....	106
3.3 Adolescents and young adults.....	108
3.3.1 Acute use.....	109
3.3.2 Habitual use.....	115
3.3.3 Acute and habitual alcohol use	124
3.4 Summary.....	126
CHAPTER 4- The present study	127
4.1 Rationale	129
4.2 Aims.....	131
4.3 Hypotheses.....	131
CHAPTER 5- Methodology	133
5.1 Participants.....	135
5.1.1 Recruitment.....	135
5.1.1.1 General health questionnaire	135
5.1.1.2 Screening interview	136
5.2 Design	139
5.3 General laboratory procedures.....	140
5.3.1 Recruitment, payment, and consent	140
5.3.2 Experimental procedures.....	141
5.3.3 Equipment and application.....	146
5.3.3.1 Electrophysiological measurements	147

5.3.3.2 Respiratory and body movement monitoring equipment	149
5.4 Data acquisition and analysis.....	150
5.4.1 Data acquisition.....	150
5.4.2 Data analysis	151
5.4.2.1 Sleep disordered breathing and body movement	151
5.4.2.2 Sleep quality and architecture	151
5.4.2.3 Electroencephalogram spectral analysis.....	153
5.4.2.4 Final statistical analyses	154
CHAPTER 6- Results	157
6.1 Participant demographics.....	159
6.1.1 Habitual alcohol use.....	161
6.1.2 Sex.....	162
6.1.3 Habitual alcohol use and sex interactions	162
6.1.4 Alcohol dosing	163
6.2 Acute and habitual effects of alcohol on sleep quality and architecture.....	164
6.2.1 Acute alcohol effects on sleep quality and architecture.....	166
6.2.1.1 Sleep quality	166
6.2.1.2 Sleep architecture	168
6.2.2 Habitual alcohol effects on sleep quality and architecture	173
6.2.3 Acute and habitual alcohol interactions on sleep quality and architecture.....	176
6.2.4 Sex and alcohol interaction effects on sleep quality and architecture.....	178
6.2.5 Correlations	181
6.2.5.1 Heavy-drinking late adolescents	183
6.2.5.2 Light-drinking late adolescents	184
6.3 Acute and habitual effects of alcohol on sleep EEG power spectra	185
6.3.1 Acute alcohol effects on sleep EEG power spectra	202
6.3.2 Habitual alcohol effects on sleep EEG power spectra	209

6.3.3 Sex and alcohol interaction effects on sleep EEG power spectra	209
6.3.3.1 Acute alcohol effects and sex interactions	209
6.3.3.2 Habitual alcohol effects and sex interactions	212
CHAPTER 7- Discussion.....	215
7.1 Acute effects of alcohol on sleep in young people	219
7.1.1 Sex differences	235
7.2 Habitual effects of alcohol on sleep in young people	239
7.2.1 Sex differences	267
7.3 Acute and habitual alcohol use interactions	270
7.3.1 Sex differences	271
7.4 Broader implications and integration of findings	276
7.5 Strengths, limitations, and future directions	290
7.6 Conclusions.....	295
References.....	297
Appendices	421
Appendix A: Advertisement, plain language statements, and consent forms	423
Appendix B: Participant screening tools	435
Appendix C: Power spectral plots	449
Appendix D: Complete spectral analysis: Sleep stage	467
Appendix E: Complete spectral analysis: Acute effects.....	469
Appendix F: Complete spectral analysis: Habitual effects.....	475
Appendix G: Complete spectral analysis: Sex × acute effects	481
Appendix H: Complete spectral analysis: Sex × habitual effects.....	487

List of Tables

Table 5.1	<i>Sleep quality and architecture dependent variables extracted from experimental participant sleep polysomnography data.</i>	152
Table 5.2	<i>Rules employed to determine sleep cycle length in young adults based on: Trinder and colleagues (1982).</i>	153
Table 6.1	<i>Final participant demographics broken down by sex and habitual alcohol use. Mean ($\pm$ standard deviation). NB, SD=standard drinks (10 g of alcohol). BMI= body mass index. BrAC=breath alcohol concentration.</i>	161
Table 6.2	<i>Means ($\pm$ standard deviations) for sleep onset latency, wake after sleep onset (WASO), arousal index, sleep efficiency, stage N1 sleep (N1), stage N2 sleep (N2), stage N3/slow wave sleep (N3/SWS), rapid eye movement (REM) sleep, and SWS and REM sleep latency, for heavy- and light-drinking females and males in the first and second halves of the sleep period.</i>	165
Table 6.3	<i>Means ($\pm$ standard deviations) for sleep onset latency, wake after sleep onset (WASO), arousal index, and sleep efficiency for acute condition (alcohol vs. placebo) by half night (first vs. second half of the sleep period).</i>	167
Table 6.4	<i>Means ($\pm$ standard deviations) for percentage of stage N1 sleep (N1), stage N2 sleep (N2), stage N3/slow wave sleep (N3/SWS), rapid eye movement (REM) sleep, and minutes of SWS and REM sleep latency, for acute condition (alcohol vs. placebo) by half night (first vs. second half of the sleep period).</i>	170
Table 6.5	<i>Means ($\pm$ standard deviations) for sleep onset latency, wake after sleep onset (WASO), arousal index, sleep efficiency, stage N1 sleep (N1), stage N2 sleep (N2), stage N3/slow wave sleep (N3/SWS), rapid eye movement (REM) sleep, and SWS and REM sleep latency for habitual alcohol use (heavy vs. light drinker) by half night (first vs. second half of the sleep period).</i>	173

Table 6.6	<i>Means ($\pm$ standard deviations) for sleep onset latency, wake after sleep onset (WASO), arousal index, sleep efficiency, stage N1 sleep (N1), stage N2 sleep (N2), stage N3/slow wave sleep (N3/SWS), rapid eye movement (REM) sleep, and SWS and REM sleep latency for habitual alcohol use (heavy vs. light drinker), acute condition (alcohol vs. placebo) and half night (first vs. second half of the sleep period).....</i>	177
Table 6.7	<i>Means ($\pm$ standard deviations) for beta spectral power (microvolts squared; μV^2) during stage N1 sleep (N1), stage N2 sleep (N2), stage N3/slow wave sleep (SWS), and rapid eye movement (REM) sleep, at frontal (F), central (C), and occipital (O) electrode sites, in heavy- and light-drinking females and males after alcohol or placebo in the first and second halves of the sleep period.....</i>	186
Table 6.8	<i>Means ($\pm$ standard deviations) for alpha spectral power (microvolts squared; μV^2) during stage N1 sleep (N1), stage N2 sleep (N2), stage N3/slow wave sleep (SWS), and rapid eye movement (REM) sleep, at frontal (F), central (C), and occipital (O) electrode sites, in heavy- and light-drinking females and males after alcohol or placebo in the first and second halves of the sleep period.....</i>	187
Table 6.9	<i>Means ($\pm$ standard deviations) for sigma spectral power (microvolts squared; μV^2) during stage N1 sleep (N1), stage N2 sleep (N2), stage N3/slow wave sleep (SWS), and rapid eye movement (REM) sleep, at frontal (F), central (C), and occipital (O) electrode sites, in heavy- and light-drinking females and males after alcohol or placebo in the first and second halves of the sleep period.....</i>	188
Table 6.10	<i>Means ($\pm$ standard deviations) for theta spectral power (microvolts squared; μV^2) during stage N1 sleep (N1), stage N2 sleep (N2), stage N3/slow wave sleep (SWS), and rapid eye movement (REM) sleep, at frontal (F), central (C), and occipital (O) electrode sites, in heavy- and light-drinking females and males after alcohol or placebo in the first and second halves of the sleep period.....</i>	189

Table 6.11	<i>Means ($\pm$ standard deviations) for delta spectral power (microvolts squared; μV^2) during stage N1 sleep (N1), stage N2 sleep (N2), stage N3/slow wave sleep (SWS), and rapid eye movement (REM) sleep, at frontal (F), central (C), and occipital (O) electrode sites, in heavy- and light-drinking females and males after alcohol or placebo in the first and second halves of the sleep period.....</i>	190
Table D.1	<i>Spectral power: F statistics, effect size (η^2), power, and significance levels (p) for each acute condition (alcohol and placebo) and electrode site; frontal, central, and occipital electrode sites across all sleep stages; stage N1, stage N2, slow wave sleep (N3), and rapid eye movement (REM) sleep, and the first and second half of the sleep period. *$p < .05$ **$p < .001$</i>	468
Table E.1	<i>Spectral power: F statistics, effect size (η^2), power, and significance levels (p) across frontal, central, and occipital electrode sites for the first and second half of the sleep period in stage N1 sleep. *$p < .05$ **$p < .001$</i>	470
Table E.2	<i>Spectral power: F statistics, effect size (η^2), power, and significance levels (p) across frontal, central, and occipital electrode sites for the first and second half of the sleep period in stage N2 sleep. *$p < .05$ **$p < .001$</i>	471
Table E.3	<i>Spectral power: F statistics, effect size (η^2), power, and significance levels (p) across frontal, central, and occipital electrode sites for the first and second half of the sleep period in stage slow wave sleep. *$p < .05$ **$p < .001$</i>	472
Table E.4	<i>Spectral power: F statistics, effect size (η^2), power, and significance levels (p) across frontal, central, and occipital electrode sites for the first and second half of the sleep period in stage REM sleep. *$p < .05$ **$p < .001$</i>	473

Table F.1	<i>Spectral power: F statistics, effect size (η^2), power, and significance levels (p) across frontal, central, and occipital electrode sites for the first and second half of the sleep period in stage N1 sleep.....</i>	476
Table F.2	<i>Spectral power: F statistics, effect size (η^2), power, and significance levels (p) across frontal, central, and occipital electrode sites for the first and second half of the sleep period in stage N2 sleep.....</i>	477
Table F.3	<i>Spectral power: F statistics, effect size (η^2), power, and significance levels (p) across frontal, central, and occipital electrode sites for the first and second half of the sleep period in slow wave sleep.</i>	478
Table F.4	<i>Spectral power: F statistics, effect size (η^2), power, and significance levels (p) across frontal, central, and occipital electrode sites for the first and second half of the sleep period in REM sleep.....</i>	479
Table G.1	<i>Spectral power: F statistics, effect size (η^2), power, and significance levels (p) across frontal, central, and occipital electrode sites for the first and second half of the sleep period in stage N1 sleep.....</i>	482
Table G.2	<i>Spectral power: F statistics, effect size (η^2), power, and significance levels (p) across frontal, central, and occipital electrode sites for the first and second half of the sleep period in stage N2 sleep.....</i>	483
Table G.3	<i>Spectral power: F statistics, effect size (η^2), power, and significance levels (p) across frontal, central, and occipital electrode sites for the first and second half of the sleep period in slow wave sleep.</i>	484
Table G.4	<i>Spectral power: F statistics, effect size (η^2), power, and significance levels (p) across frontal, central, and occipital electrode sites for the first and second half of the sleep period in REM sleep.....</i>	485
Table H.1	<i>Spectral power: F statistics, effect size (η^2), power, and significance levels (p) across frontal, central, and occipital electrode sites for the first and second half of the sleep period in stage N1 sleep.....</i>	488

Table H.2	<i>Spectral power: F statistics, effect size (η^2), power, and significance levels (p) across frontal, central, and occipital electrode sites for the first and second half of the sleep period in stage N2 sleep.....</i>	<i>489</i>
Table H.3	<i>Spectral power: F statistics, effect size (η^2), power, and significance levels (p) across frontal, central, and occipital electrode sites for the first and second half of the sleep period in slow wave sleep.</i>	<i>490</i>
Table H.4	<i>Spectral power: F statistics, effect size (η^2), power, and significance levels (p) across frontal, central, and occipital electrode sites for the first and second half of the sleep period in REM sleep.....</i>	<i>491</i>

List of Figures

- Figure 1.1.** Borbely's two-process theory of factors influencing sleep drive and timing. Process S: homeostatic sleep drive; Process C: circadian rhythm (24-hour time). Adapted from Borbely (1982a)..... 7
- Figure 1.2.** Approximate distribution of sleep cycles and stages across a normal night of sleep a healthy adult. REM: rapid eye movement sleep; N1: stage N1 sleep; N2: stage N2 sleep; N3: stage N3/slow wave sleep. Adapted from Carskadon and Dement (2017). 9
- Figure 1.3.** Electroencephalogram (EEG) frequency for each distinct state of sleep and wake (Carskadon & Dement, 2017; Groppe et al., 2013). REM: rapid eye movement sleep; N1: stage N1 sleep; N2: stage N2 sleep; N3/SWS: stage N3/slow wave sleep. 10
- Figure 1.4.** Mean minutes of sleep onset latency (sleep latency), wake after sleep onset (WASO), rapid eye movement sleep (REM), stage N3 sleep/slow wave sleep (SWS), stage N2 sleep (Stage 2), and stage N1 sleep (Stage N1) across the lifespan. Adapted from Ohayon et al. (2004). 15
- Figure 1.5.** Synaptic density, cerebral metabolic rate, and delta wave amplitude; combined gamma distribution models for each measure standardised at 30 years old. Adapted from Feinberg et al. (1990). 34
- Figure 1.6.** Cortical surface grey matter volumes between approximately 5 to 25 years of age (right lateral and top views). Adapted from Gogtay et al. (2004). 37
- Figure 2.1.** Percent of Australians who exceeded single occasion risk guidelines for alcohol consumption (≥ 5 standard drinks) once or more per month by age group in 2016. Adapted from AIHW (2017). 46

Figure 2.2. Average blood alcohol concentration (g/kg) as a function of time (minutes) following the ingestion of 0.75 g of pure alcohol per kilogram of body weight over 15 minutes at t=0 in 39 males (mean age=23.64 years, standard deviation=3.09 years). Adapted from Brunelle et al. (2007).	48
Figure 5.1. Three-step recruitment process participants underwent to determine suitability for inclusion in the sleep experiment.	135
Figure 5.2. Formula for calculating the number of standard drinks in an alcoholic beverage (AGDH, 2012).	137
Figure 5.3. The three nights of the sleep experiment were all completed within a two-week period. The second two experimental nights were non-consecutive and counterbalanced over participants. The 9-hour sleep recording consisted of standard polysomnography (PSG).	141
Figure 5.4. Detailed procedure timeline for all three nights of the sleep experiment. This consisted of an adaptation night (top pane), and two experimental nights: alcohol condition, and a placebo condition (bottom pane). Notes: TBW= total body water, PSG= polysomnography.	144
Figure 5.5. Formula for calculating the alcohol dose required to achieve target blood alcohol concentration (BAC) of .10 percent (Curtin & Fairchild, 2003).	145
Figure 5.6. Positioning of electroencephalogram (EEG) scalp electrodes according to the international 10/20 system (electrode positions used in the present study are circled in red; Jasper, 1958).	148
Figure 5.7. Positioning of face electrodes.	148
Figure 5.8. Location of body sensors for the detection of undiagnosed sleep disorders, and electrocardiogram (ECG). (EMG=electromyogram).	150
Figure 6.1. Participant recruitment and attrition for each recruitment phase. See Section 5.1.1 for inclusion and exclusion criteria.	159

- Figure 6.2.** Final participant sample size (n) broken down into groups by habitual alcohol use and sex of the participants who completed the sleep experiment..... 160
- Figure 6.3.** Means ($\pm$ standard errors) for percentage of total sleep time for stage N1 sleep (N1), stage N2 sleep (N2), stage N3/slow wave sleep (SWS), and rapid eye movement (REM) sleep by half night and acute condition, placebo: white bars, alcohol: black bars. Horizontal lines represent main half night comparisons and asterisks represent significant interaction effects. $*p < .05$. $**p < .001$ 171
- Figure 6.4.** Means ($\pm$ standard errors) for slow wave sleep (SWS) and rapid eye movement (REM) sleep latency (minutes) in alcohol (black bars) and placebo (white bars) conditions. The horizontal line represents the main effect of acute condition (alcohol vs. placebo). 172
- Figure 6.5.** Means ($\pm$ standard errors) for percentage of total sleep time for stage N1 sleep (N1), stage N2 sleep (N2), stage N3/slow wave sleep (SWS), and rapid eye movement (REM) sleep by half night and habitual alcohol use, light drinkers: white bars, heavy drinkers: black bars. Horizontal perforated lines represent the main effects of half night and solid horizontal line represents the interaction between habitual alcohol use and half night. 174
- Figure 6.6.** Means ($\pm$ standard errors) for slow wave sleep (SWS) and rapid eye movement (REM) sleep latency (minutes) in heavy drinkers (black bars) and light drinkers (white bars). The horizontal line represents the main effect of habitual alcohol use (heavy vs. light drinking)..... 175
- Figure 6.7.** Four-way interactions between sex (female vs. male), habitual alcohol use (heavy vs. light drinking), acute condition (alcohol vs. placebo), half night (first vs. second half of the sleep period) for wake after sleep onset (WASO) in minutes (top pane; four-way interaction, $p = .014$) and sleep efficiency (bottom pane; four-way interaction, $p = .013$). 179

Figure 6.8. Means ($\pm$ standard errors) for beta spectral power (microvolts squared; μV^2) in stage N1 sleep (N1), stage N2 sleep (N2), stage N3/slow wave sleep (SWS), rapid eye movement sleep (REM) for heavy-drinking (HD) and light-drinking (LD) females (F) and males (M), after alcohol (black bars) and placebo (white bars) in the first (left panes) and second (right panes) halves of the sleep period at frontal (top panes), central (middle panes), and occipital (bottom panes) electrode sites. 192

Figure 6.9. Means ($\pm$ standard errors) for alpha spectral power (microvolts squared; μV^2) in stage N1 sleep (N1), stage N2 sleep (N2), stage N3/slow wave sleep (SWS), rapid eye movement sleep (REM) for heavy-drinking (HD) and light-drinking (LD) females (F) and males (M), after alcohol (black bars) and placebo (white bars) in the first (left panes) and second (right panes) halves of the sleep period at frontal (top panes), central (middle panes), and occipital (bottom panes) electrode sites. 194

Figure 6.10. Means ($\pm$ standard errors) for sigma spectral power (microvolts squared; μV^2) in stage N1 sleep (N1), stage N2 sleep (N2), stage N3/slow wave sleep (SWS), rapid eye movement sleep (REM) for heavy-drinking (HD) and light-drinking (LD) females (F) and males (M), after alcohol (black bars) and placebo (white bars) in the first (left panes) and second (right panes) halves of the sleep period at frontal (top panes), central (middle panes), and occipital (bottom panes) electrode sites..... 196

Figure 6.11. Means ($\pm$ standard errors) for theta spectral power (microvolts squared; μV^2) in stage N1 sleep (N1), stage N2 sleep (N2), stage N3/slow wave sleep (SWS), rapid eye movement sleep (REM) for heavy-drinking (HD) and light-drinking (LD) females (F) and males (M), after alcohol (black bars) and placebo (white bars) in the first (left panes) and second (right panes) halves of the sleep period at frontal (top panes), central (middle panes), and occipital (bottom panes) electrode sites. 198

- Figure 6.12.** Means ($\pm$ standard errors) for delta spectral power (microvolts squared; μV^2) in stage N1 sleep (N1), stage N2 sleep (N2), stage N3/slow wave sleep (SWS), rapid eye movement sleep (REM) for heavy-drinking (HD) and light-drinking (LD) females (F) and males (M), after alcohol (black bars) and placebo (white bars) in the first (left panes) and second (right panes) halves of the sleep period at frontal (top panes), central (middle panes), and occipital (bottom panes) electrode sites 200
- Figure 7.1.** A visual representation of the theoretical vicious cycle, or bi-directional relationships, uniting alcohol consumption, sleep disturbances, and neural and/or cognitive deficits in young people. 283
- Figure 7.2.** Potential intervention pathways to delay and/or reduce alcohol consumption, improve sleep disturbances, and enhance neural and/or cognitive function in young people. 287
- Figure C.1.** Power (microvolts squared; μV^2) for 1 to 4 Hz frequency activity during stage N1 sleep following alcohol (dashed lines) and placebo (solid lines) at frontal (top panes), central (middle panes) and occipital (bottom panes) electrode sites in the first (1st and 3rd panes) and second (2nd and 4th panes) halves of the sleep period in heavy- (black lines) and light- (blue lines) drinking females (two left panes) and males (two right panes). 450
- Figure C.2.** Power (microvolts squared; μV^2) for 5 to 30 Hz frequency activity during stage N1 sleep following alcohol (dashed lines) and placebo (solid lines) at frontal (top panes), central (middle panes) and occipital (bottom panes) electrode sites in the first (1st and 3rd panes) and second (2nd and 4th panes) halves of the sleep period in heavy- (black lines) and light- (blue lines) drinking females (two left panes) and males (two right panes). 452

Figure C.3. Power (microvolts squared; μV^2) for 1 to 4 Hz frequency activity during stage N2 sleep following alcohol (dashed lines) and placebo (solid lines) at frontal (top panes), central (middle panes) and occipital (bottom panes) electrode sites in the first (1st and 3rd panes) and second (2nd and 4th panes) halves of the sleep period in heavy- (black lines) and light- (blue lines) drinking females (two left panes) and males (two right panes). 454

Figure C.4. Power (microvolts squared; μV^2) for 5 to 30 Hz frequency activity during stage N2 sleep following alcohol (dashed lines) and placebo (solid lines) at frontal (top panes), central (middle panes) and occipital (bottom panes) electrode sites in the first (1st and 3rd panes) and second (2nd and 4th panes) halves of the sleep period in heavy- (black lines) and light- (blue lines) drinking females (two left panes) and males (two right panes). 456

Figure C.5. Power (microvolts squared; μV^2) for 1 to 4 Hz frequency activity during slow wave sleep (SWS; N3) following alcohol (dashed lines) and placebo (solid lines) at frontal (top panes), central (middle panes) and occipital (bottom panes) electrode sites in the first (1st and 3rd panes) and second (2nd and 4th panes) halves of the sleep period in heavy- (black lines) and light- (blue lines) drinking females (two left panes) and males (two right panes). 458

Figure C.6. Power (microvolts squared; μV^2) for 5 to 30 Hz frequency activity during slow wave sleep (SWS; N3) following alcohol (dashed lines) and placebo (solid lines) at frontal (top panes), central (middle panes) and occipital (bottom panes) electrode sites in the first (1st and 3rd panes) and second (2nd and 4th panes) halves of the sleep period in heavy- (black lines) and light- (blue lines) drinking females (two left panes) and males (two right panes). 460

Figure C.7. Power (microvolts squared; μV^2) for 1 to 4 Hz frequency activity during rapid eye movement (REM) sleep following alcohol (dashed lines) and placebo (solid lines) at frontal (top panes), central (middle panes) and occipital (bottom panes) electrode sites in the first (1st and 3rd panes) and second (2nd and 4th panes) halves of the sleep period in heavy- (black lines) and light- (blue lines) drinking females (two left panes) and males (two right panes). 462

Figure C.8. Power (microvolts squared; μV^2) for 5 to 30 Hz frequency activity during rapid eye movement (REM) sleep following alcohol (dashed lines) and placebo (solid lines) at frontal (top panes), central (middle panes) and occipital (bottom panes) electrode sites in the first (1st and 3rd panes) and second (2nd and 4th panes) halves of the sleep period in heavy- (black lines) and light- (blue lines) drinking females (two left panes) and males (two right panes). 464

List of Abbreviations

AASM	American Academy of Sleep Medicine
ANOVA	Analysis of variance
BAC	Blood alcohol concentration
BrAC	Breath alcohol concentration
ECG	Electrocardiogram
EEG	Electroencephalogram
EMG	Electromyogram
EOG	Electrooculogram
GABA	Gama-aminobutyric acid
GABA _A	Gamma-aminobutyric acid type A receptor
Hz	Hertz
μV	micro Volts
μV ²	micro Volts squared
MRI	Magnetic resonance imaging
mRNA	Messenger ribonucleic acid
NMDA	N-methyl-D-aspartate
PSG	Polysomnogram/polysomnography/polysomnographic
REM	Rapid eye movement
SD	Standard deviation
SEM	Standard error of the mean
SWS	Slow wave sleep
WASO	Wake after sleep onset

General Introduction and Thesis Overview

Sleep is a fundamental human process that is essential for health and well-being (Krueger, Frank, Wisor, & Roy, 2016). Functionally, sleep can be used as a measure of brain health and neural connectivity (Colrain, Nicholas, & Baker, 2014). Disturbances to normal sleep are associated with negative physiological and psychological consequences (Carskadon, 2004; Medic, Wille, & Hemels, 2017). Adolescence is a critical time period for human development associated with major and related changes to the brain and sleep systems that continue into young adulthood (Baker, Turlington, & Colrain, 2012; Colrain & Baker, 2011; Feinberg & Campbell, 2010; Gogtay et al., 2004; Hagenauer, Perryman, Lee, & Carskadon, 2009; Sowell, Thompson, & Toga, 2004; Tarokh, Van Reen, LeBourgeois, Seifer, & Carskadon, 2011).

Concerningly, adolescents and young adults consume the highest amounts of alcohol per drinking occasion globally (AIHW, 2017; Merrill & Carey, 2016; Naimi, Nelson, & Brewer, 2010; Patrick et al., 2013; WHO, 2018; Windle, 2016). The impacts of alcohol use on the developing brain and sleep systems may be unique and long-lasting (Guerri & Pascual, 2010; Jacobus & Tapert, 2013; Lubman, Yucel, & Hall, 2007; Miller, 2006; Sadrian, Wilson, & Saito, 2013; Silveri, Dager, Cohen-Gilbert, & Sneider, 2016). It is well-established that both acute and habitual alcohol consumption adversely impacts normal sleep (Brower, 2003; Chan, Trinder, Andrewes, Colrain, & Nicholas, 2013; Chan, Trinder, Colrain, & Nicholas, 2015; Colrain, Turlington, & Baker, 2009b; Ebrahim, Shapiro, Williams, & Fenwick, 2013). Alcohol-related sleep disturbances in young people could have detrimental consequences for health and development, and may potentially reflect underlying changes to the brain and sleep systems.

The current thesis will commence by outlining the importance, characteristics, and physiology of normal sleep across the human lifespan, including the interdependent sleep and neural changes that commence in adolescence and continue into young adulthood. The following chapters will explore the physiological effects of acute and habitual alcohol consumption on the human nervous system and behaviour, including sleep. There will be a detailed focus on the unique impacts of alcohol use during the final stages of human development. This leads directly to the rationale and focus of the current investigation, which aims to examine the effects of acute and habitual alcohol use on objective measures of sleep in late adolescents aged 18 to 21 years.

CHAPTER 1

Sleep processes, function, and physiology

Sleep is a complex and necessary behaviour comprised of neurophysiologically distinct stages (Carskadon & Dement, 2017; Guilleminault, 1994; Krause et al., 2017; O'Mara, 2018; Rechtschaffen & Bergmann, 2002; Rechtschaffen, Bergmann, Everson, Kushida, & Gilliland, 2002). The gold standard of sleep measurement is polysomnography (PSG) which is used to identify sleep architecture (i.e., the distribution of sleep stages across the sleep period), quality, and duration (AASM, 2007). Further to this, aspects of sleep can also be used as functional, non-invasive measures of brain structure and function, and neurochemical state (Colrain et al., 2014). Deviations in the amount and quality of sleep are detrimental to both physical and mental health (Carskadon, 2004; Medic et al., 2017).

1.1 Functions of sleep

The existence of sleep or sleep-like behaviour across all species underlines the evolutionary importance and fundamental nature of sleep (Hartse, 2011; Siegel, 2003). This is further highlighted by the conservation of sleep at the expense of other essential behaviours, such as feeding and mating (Hartse, 2011; Siegel, 2003). Despite its natural selection as a behaviour necessary for life, the precise function of sleep is still unknown (Hartse, 2011; Siegel, 2003). There are currently several prominent theories, for example, immobility during sleep is protective from predation (Capellini, Nunn, McNamara, Preston, & Barton, 2008; McNamara, Barton, & Nunn, 2010; Svensson et al., 2018), and may promote both passive and active energy conservation (Collet et al., 2016; Rechtschaffen et al., 2002; White, Weil, & Zvillich, 1985).

The literature also suggests that sleep may be biologically essential for the restoration and enhancement of neuronal processes (Huber, Ghilardi, Massimini, & Tononi, 2004; Krueger et al., 2016; Mendelsohn & Larrick, 2013; Nobili et al., 2012; Siegel, 2001; Tononi & Cirelli, 2006; Van Cauter, 2000). This is consistent with the well-known, and potentially catastrophic, effects of both total and partial sleep deprivation (Carskadon, 2004; Medic et al., 2017). Total sleep deprivation grossly impacts physiological and psychological function in both humans and animals, and at its most extreme can result in death (Guilleminault, 1994; Krause et al., 2017; Rechtschaffen & Bergmann, 2002; Rechtschaffen et al., 2002). The physiological impacts of total sleep deprivation in humans include increased 24-hour blood pressure, immune changes, and hypothalamo-pituitary-adrenal axis alterations (Leproult, Copinschi, Buxton, & Van Cauter, 1997; Malhotra & Loscalzo, 2009; Matsumoto et al., 2001). The psychological impacts of total sleep deprivation including memory and cognitive impairments, and mood instability (Krause et al., 2017; Lim & Dinges, 2010; Lo et al., 2012; Van Dongen, Maislin, Mullington, & Dinges, 2003). As an example, Van Dongen and colleagues (2003) experimentally maintained three days (88 hours) of total sleep deprivation in 48 healthy men and women aged 21 to 31 years. This led to the accumulation of substantial neurobehavioural impairments as time awake increased, including reduced alertness, diminished working memory, and slowed cognitive processing. These findings indicate that sleep is necessary for optimal physiological and psychological well-being.

Partial sleep deprivation, or sleep restriction, has also been linked with short- and long-term physical and psychological consequences (Krause et al., 2017; Medic et al., 2017; Owens, 2014; Vogel, Braungardt, Meyer, & Schneider, 2012). In the

short term, sleep restriction in humans can lead to elevated stress responsivity, such as sympathoadrenal activation and somatic pain, and psychosocial consequences related to impaired cognitive performance and emotional dysregulation (Medic et al., 2017 and Banks, 2007 for reviews). In the long-term, consequence include an increased risk of developing disease and health problems such as cardiovascular disease (Malhotra & Loscalzo, 2009), metabolic disorders (e.g., obesity and type 2 diabetes; Tan, Chapman, Cedernaes, & Benedict, 2018), cancer (Haus & Smolensky, 2013), psychiatric disorders (Krystal, 2012), and death (Rod et al., 2011). The neurocognitive effects of prolonged sleep restriction include depressed mood, impaired working memory, poor attention, and reduced overall cognitive performance (Banks & Dinges, 2007). Critically, the negative consequences of partial sleep deprivation on health and performance accumulate and worsen over time (Banks & Dinges, 2007). The primary mechanism through which partial and total sleep restriction detrimentally impacts physical and mental health has been suggested to be increased allostatic load, or neurobiological and physiological stress (McEwen, 2006). Taken together, these findings further highlight that achieving adequate sleep is critical.

Sleep disorders, including obstructive sleep apnoea, periodic limb movement disorder, and insomnia, result in ongoing disturbances to normal sleep, and are associated with detrimental effects on both physical and psychological health. These include increased risk of morbidity and mortality (Choi, Song, Lee, & Jeong, 2017; Li et al., 2014; Marshall et al., 2008), cognitive impairments (Fortier-Brochu & Morin, 2014; Jackson, Howard, & Barnes, 2011; Leng et al., 2016), and increased risk of depression (Ejaz, Khawaja, Bhatia, & Hurwitz, 2011; Koo et al., 2016; Riemann & Voderholzer, 2003). Sleep disturbance is a symptom reported in most

physical and mental health conditions (Agargun, Kara, & Solmaz, 1997; Armitage, 1995; Liu & Ancoli-Israel, 2008; Malhotra & Loscalzo, 2009; Monti & Monti, 2005). There is also evidence that improving sleep may improve health (Buysse, Grunstein, Horne, & Lavie, 2010). Taken together, these findings provide evidence that sleep is necessary for physical and psychological well-being. Furthermore, the relationship between sleep and health is likely bi-directional (Krystal, 2012; Zee & Turek, 2006).

1.2 Normal sleep in humans

In humans, two distinct internal mechanisms are thought to regulate sleep timing and intensity (Borbely & Achermann, 1999). This is known as the two-process model of sleep. It includes a circadian factor (Process C) and a homeostatic factor (Process S). Process C, or the circadian system, is the endogenous biological clock which regulates behaviour and physiological processes across a 24-hour day. The circadian rhythm dictates times of activity and sleep, such that sleep is most likely to occur on the falling phase of the circadian oscillator, with wake occurring as it rises (Borbely, 1982a; Figure 1.1). As well as sleep and wake, Process C also dictates other internal physiological functions, such as body temperature, hormone release, and metabolism (Czeisler & Klerman, 1999; Eckel-Mahan & Sassone-Corsi, 2013; Refinetti & Menaker, 1992). This 24-hour rhythmicity is entrained by zeitgebers, the most notable of which is light (Czeisler et al., 1989; Duffy & Wright, 2005). Zeitgebers are detected by the suprachiasmatic nucleus, the neural area responsible for the control of circadian rhythms (Mohawk, Green, & Takahashi, 2012).

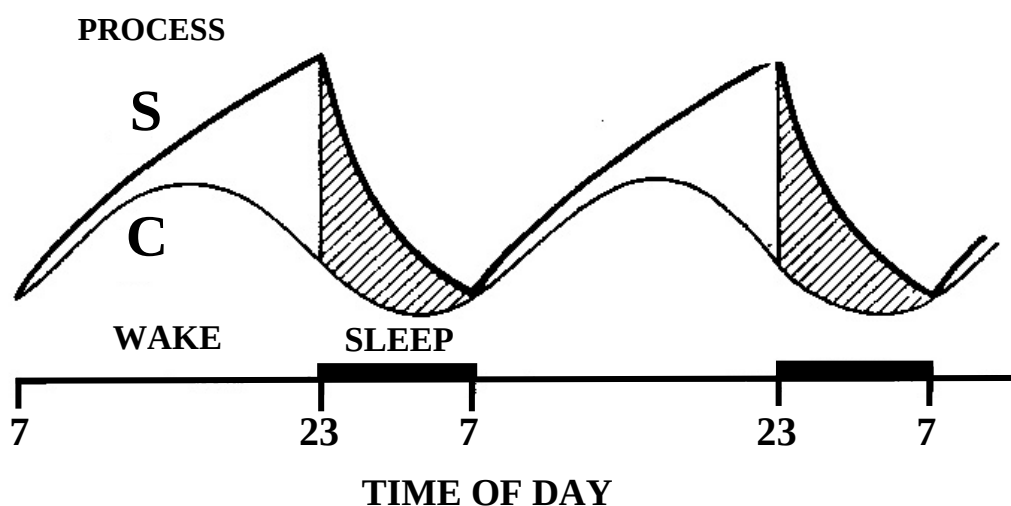


Figure 1.1. Borbely's two-process theory of factors influencing sleep drive and timing. Process S: homeostatic sleep drive; Process C: circadian rhythm (24-hour time). Adapted from Borbely (1982a).

Homeostatic sleep drive is the second internal process that dictates wake and sleep (Achermann & Borbely, 2017; Borbely, 1982; Borbely & Achermann, 1999). Homeostatic sleep pressure, or Process S, increases during periods of wake and dissipates during sleep. (See Figure 1.1.) Homeostatic sleep drive acts to ensure the appropriate amount of sleep is obtained, and deviations from this amount results in increased sleep pressure and 'rebound' sleep (i.e., increased sleep duration following sleep deprivation). Homeostatic sleep drive is a primary factor determining the amount and density of sleep. For example, after one night of total sleep deprivation, sleep duration increases by 10 to 20 percent in the following sleep period (Benoit et al., 1980; Webb & Agnew, 1975). Arousal threshold (i.e., the intensity at which a stimulus can wake an individual from sleep) is also higher during a recovery sleep, further indicating increased sleep depth and intensity (Williams, Hammack, Daly, Dement, & Lubin, 1964). This homeostatic regulation is thought to highlight sleep's functional importance.

1.2.1 Sleep architecture, quality, and duration

1.2.1.1 Sleep architecture

Despite its characteristic appearance of lifelessness, sleep is a dynamic behaviour comprised of complex physiological and neurological processes. Sleep can be separated into two distinct states: non-rapid eye movement and rapid eye movement (REM) sleep (Carskadon & Dement, 2017). Across an entire sleep period, approximately 75 to 80 percent of sleep time is dedicated to non-REM sleep, and 20 to 25 percent to REM sleep. These two discrete states alternate cyclically across the sleep period and are characterised by distinct patterns of neurotransmitter release and neurological activation.

Neural activity during sleep is typically measured using electroencephalography (EEG), a central component of PSG. EEG is a relatively non-invasive measure of electrical activity of the brain recorded via electrodes placed on the scalp. Different states of consciousness (wake and sleep) can be uniquely identified by visual or computerised analysis of the frequency and amplitude (i.e., voltage) of the electrical signals recorded via the EEG. Further classifications of each discrete sleep stage are made using the electrical signals generated by eye and muscle movements, measured via the electrooculogram and electromyogram, respectively (AASM, 2007). Each of these discrete stages alternate cyclically throughout the sleep period, advancing first through stages of non-REM sleep, followed by a period of REM sleep (Carskadon & Dement, 2017; Figure 1.2). This progression of sleep stages across the night is commonly referred to as sleep architecture. The average duration of a sleep cycle is 90 minutes; however, this varies between individuals. Typically, a person will complete four to six cycles across a nocturnal sleep period

(Carskadon & Dement, 2017). The proportion of time dedicated to each sleep stage within a sleep cycle changes across the night. (See Figure 1.2).

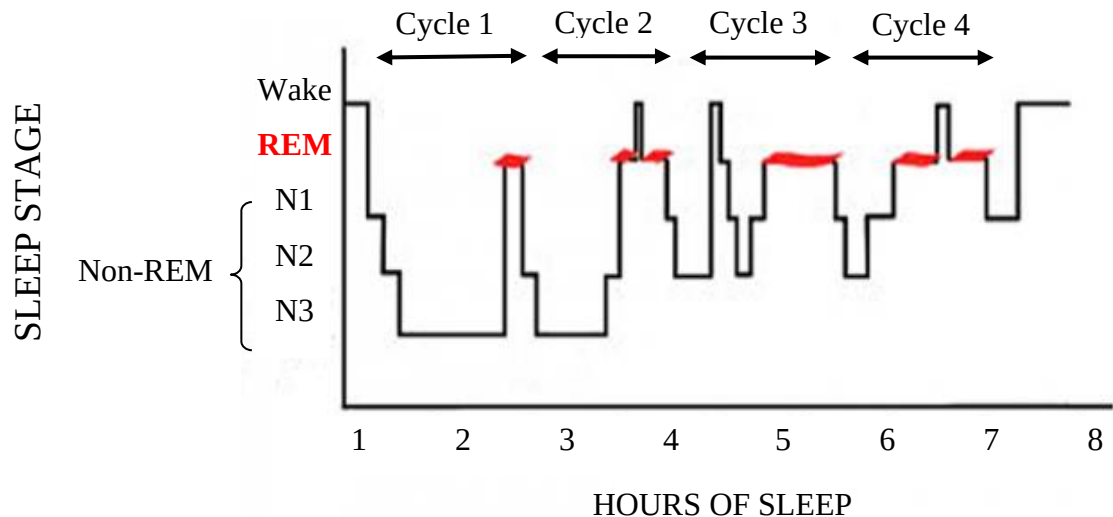


Figure 1.2. Approximate distribution of sleep cycles and stages across a normal night of sleep a healthy adult. REM: rapid eye movement sleep; N1: stage N1 sleep; N2: stage N2 sleep; N3: stage N3/slow wave sleep. Adapted from Carskadon and Dement (2017).

During periods of wake, neural electrical activity, as measured by the EEG, show characteristic patterns of high frequency and low amplitude waveforms (Groppe et al., 2013). (See Figure 1.3.) Specifically, when a person is awake and alert with their eyes open, fast frequency beta (13 – 30 Hertz; Hz) activity dominates the EEG. However, during periods of relaxed wakefulness with eyes closed, EEG activity slows, and alpha (8 – 13 Hz) frequency begins to predominate.

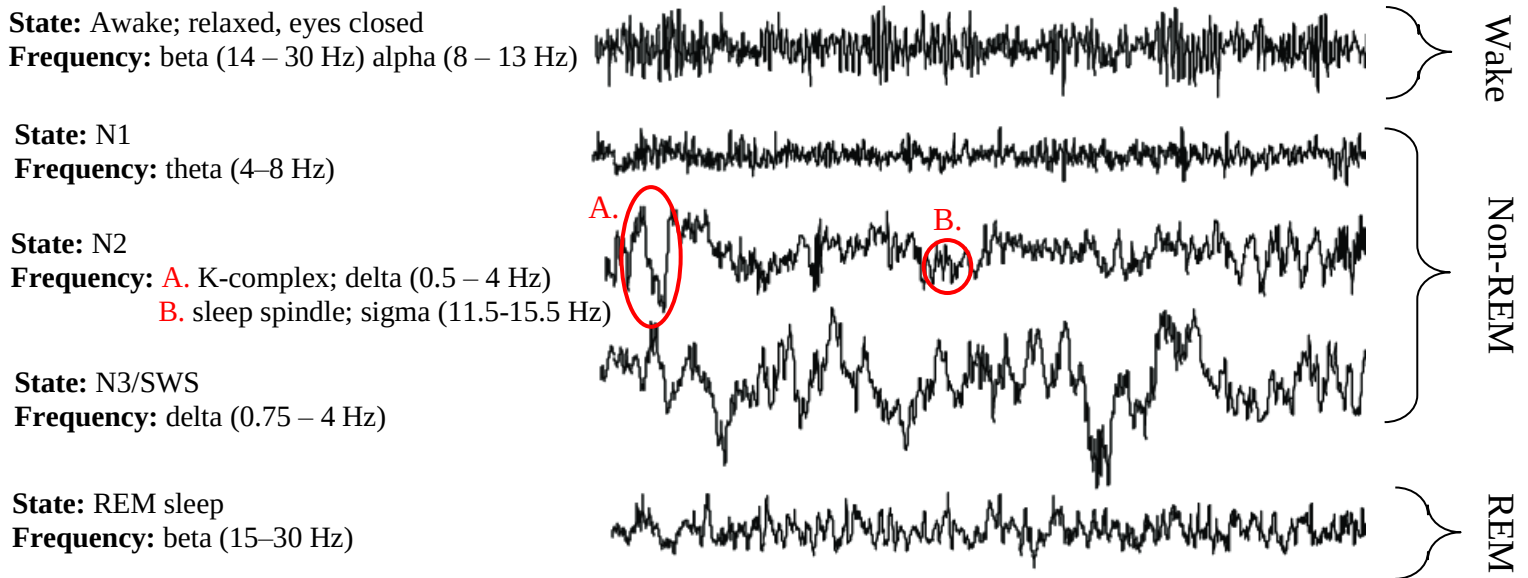


Figure 1.3. Electroencephalogram (EEG) frequency for each distinct state of sleep and wake (Carskadon & Dement, 2017; Groppe et al., 2013). REM: rapid eye movement sleep; N1: stage N1 sleep; N2: stage N2 sleep; N3/SWS: stage N3/slow wave sleep.

Non-REM sleep is divided into three distinct stages: stage N1 sleep, stage N2 sleep, and stage N3 or slow wave sleep (SWS). In healthy adults, sleep is normally entered from wake through stage N1 sleep. Typically, EEG frequencies become progressively slower and more synchronised with increasing depth of sleep stage, where stage N1 is considered the lightest, and SWS the deepest, stage of non-REM sleep. As the EEG is a summation of neural electrical activity, greater synchronisation of neural firing leads to higher amplitude (i.e., voltage) and slower frequency EEG activity as a person transitions from wake to sleep, and advances into deeper stages of non-REM sleep. (See Figure 1.3.) This is coupled with a declining sensitivity to external stimuli or higher arousal threshold (Carskadon & Dement, 2017).

Stage N1 sleep is a transitional stage between wake and other sleep stages, and is the lightest stage of non-REM sleep (Carskadon & Dement, 2017). It is typically associated with slower EEG activity than wake (i.e., the emergence of 4 – 8 Hz theta activity). (See Figure 1.3.) Stage N1 sleep generally occurs at the commencement of each sleep cycle, or following an awakening from sleep, lasting for approximately one to seven minutes. The proportion of time spent in stage N1 sleep within a sleep cycle increases in the second half of the sleep period, as homeostatic sleep drive dissipates, and awakenings become more frequent. (See Figure 1.2). On average, only two to five percent of the entire sleep period is dedicated to stage N1 sleep (Carskadon & Dement, 2017).

Stage N2 sleep is characterised by the appearance of two distinct EEG phenomena: sleep spindles and K-complexes. Sleep spindles are brief (0.5 – 3.0 second) bursts of higher frequency EEG activity between 11 and 16 Hz (sigma frequency; Andrillon et al., 2011). (See Figure 1.3.) Topographically, sleep spindles or sigma EEG activity are more prominent at centrally located electrode sites (i.e., parietal brain regions; Carskadon & Dement, 2017; Chan et al., 2015; Feinberg & Campbell, 2010). K-complexes are a single delta frequency EEG waveform (0.5 – 4.0 Hz) that occur spontaneously throughout stage N2 sleep (AASM, 2007; Colrain, 2005). They can also be elicited by external stimuli, such as auditory tones. (See Figure 1.3.) K-complexes are thought to utilise the same cortical synchronisation processes as SWS, and their presence in stage N2 sleep have been suggested to be precursors of SWS (Colrain, 2005; Nicholas, Trinder, & Colrain, 2002). On average, 10 to 25 minutes of each sleep cycle is dedicated to stage N2 sleep. Like stage N1 sleep, the proportion of stage N2 sleep within a cycle increases in the second half of the sleep period, as homeostatic sleep drive dissipates. (See Figure 1.2). Across the

entire sleep period, approximately 45 to 55 percent of total sleep time is spent in stage N2 sleep, which is more than any other sleep stage (Carskadon & Dement, 2017).

Stage N3 sleep or SWS is the deepest stage of non-REM sleep. SWS is characterised by low frequency (0.75 – 4.5 Hz) delta activity and high amplitude ($\geq 75 \mu\text{V}$) EEG waveforms, indicating many cortical neurons are firing synchronously. (See Figure 1.3.) EEG frequencies of 0.5 to 4.5 Hz are commonly referred to as slow wave activity (Achermann & Borbely, 2017; Borbely, 2001). SWS and slow wave activity are fundamental markers of sleep homeostasis (Achermann, Dijk, Brunner, & Borbély, 1993; Borbely, 2001). Due to this, a much larger proportion of the sleep cycle is dedicated to SWS in the first half of the sleep period, when homeostatic sleep drive is highest. For example, the first sleep cycle of a healthy adult may be comprised of up to 45 minutes of SWS (Carskadon & Dement, 2017). As homeostatic sleep drive dissipates across the night, the amount of SWS within a sleep cycle declines. It is not uncommon for later sleep cycles to contain very little or no SWS (Carskadon & Dement, 2017). (See Figure 1.2). As a proportion of total sleep time, approximately 10 to 20 percent of the sleep period is dedicated explicitly to SWS. Topographically, slow wave activity is most prominent in frontal brain regions (Finelli, Borbely, & Achermann, 2001).

REM sleep is the most cortically active sleep stage. It is characterised by EEG activity that is most similar to wake, specifically, low amplitude and high frequency beta waveforms (13 to 30 Hz; Carskadon & Dement, 2017). (See Figure 1.3). REM sleep is commonly associated with vivid dreaming (Carskadon & Dement, 2017; Dement & Kleitman, 1957). Despite wake-like neurological activity, REM sleep is associated with skeletal muscle paralysis or atonia (Carskadon &

Dement, 2017). Critical exceptions to this are spontaneous twitches in postural muscles, and bursts of rapid eye movements, thus the name, REM sleep (Carskadon & Dement, 2017). These rapid eye movements are distinct from those during wake as there are fewer in number, and movements are larger and sharper (Marquez-Ruiz & Escudero, 2008). There are two distinct phases of REM sleep: tonic and phasic (Carskadon & Dement, 2017). During phasic REM sleep there are fast successions of rapid eye movements and postural muscle twitches. In contrast, during tonic REM sleep, there are no rapid eye movements or muscle twitches, though cortical patterns remain active and muscle tone low. In the first sleep cycle, only ten minutes or less is typically comprised of REM sleep. Across the night, the amount of time dedicated to REM sleep within each sleep cycle increases. (See Figure 1.2.) The high concentration of REM sleep in the second half of the sleep period, or in the early morning hours, is believed to be primarily regulated by the circadian system (Lee, Swanson, & de la Iglesia, 2009; Wurts & Edgar, 2000).

1.2.1.2 Sleep quality and duration

As well as sleep architecture, there are other critical factors that determine the quality and duration of sleep. Measures of sleep quality are particularly concerned with sleep continuity, for example time taken to fall asleep, number of awakenings from sleep, total time spent asleep, as well as overall sleep efficiency. Like sleep architecture, measures of sleep quality and duration can be determined using a standard PSG assessment (AASM, 2007).

Sleep onset latency refers to the time taken to fall asleep once a person is in bed and lights are turned out. Under normal circumstances, sleep onset latency takes approximately 10 minutes (Carskadon & Dement, 2017). Arousals are very brief awakenings from sleep lasting between 3 and 15 seconds (AASM, 2007). It is both

normal and natural for arousals to occur during sleep, however, an excessive number of arousals are disruptive to sleep and associated with negative health consequences (Knauert, Naik, Gillespie, & Kryger, 2015; Noda, Okada, Hayashi, Yasuma, & Yokota, 1993). Wake after sleep onset is defined as the amount of time spent awake during the sleep period after sleep onset. Again, it is normal to have periods of wake (>15 seconds) following sleep onset, however excessive amounts of wakefulness are considered to be detrimental to health (Medic et al., 2017).

Sleep duration is measured as the amount of time spent asleep following sleep onset (i.e., total sleep time). Although there is a large amount of variability in interindividual sleep need, it is currently recommended that adults receive 7 to 9 hours of sleep per night (Hirshkowitz et al., 2015). Another critical measure of sleep quality is sleep efficiency, or the amount of time spent in bed sleeping versus being awake (Carskadon & Dement, 2017). For example, if a person spends a long period of time in bed, but spends little of that time sleeping, they will have low sleep efficiency. Poor sleep efficiency is common in sleep disorders, such as insomnia (Baglioni et al., 2014), sleep apnea (Zhang et al., 2020), narcolepsy (Takei et al., 2012), periodic leg movement disorder (Sieminski, Pyrzowski, & Partinen, 2017), and restless leg syndrome (Montplaisir et al., 1997). These disorders are associated with shorter sleep durations and greater wake after sleep onset, which may negatively impact health. Disturbances to sleep continuity, or the quality and quantity of sleep, are associated with substantial social, psychological, and physiological health problems (Medic et al., 2017).

1.2.2 Sleep across the lifespan

Age is the largest factor that modifies sleep quality and architecture across the lifespan (Bliwise & Scullin, 2017; Carskadon & Dement, 2017). Sleep duration is longest immediately following birth, before progressively declining across the lifespan (Ohayon, Carskadon, Guilleminault, & Vitiello, 2004; Roffwarg, Muzio, & Dement, 1966). (See Figure 1.4.) This has been suggested as evidence for the importance of sleep during development, as more sleep is needed during critical times of neural and physiological development (Sheldon, 2014).

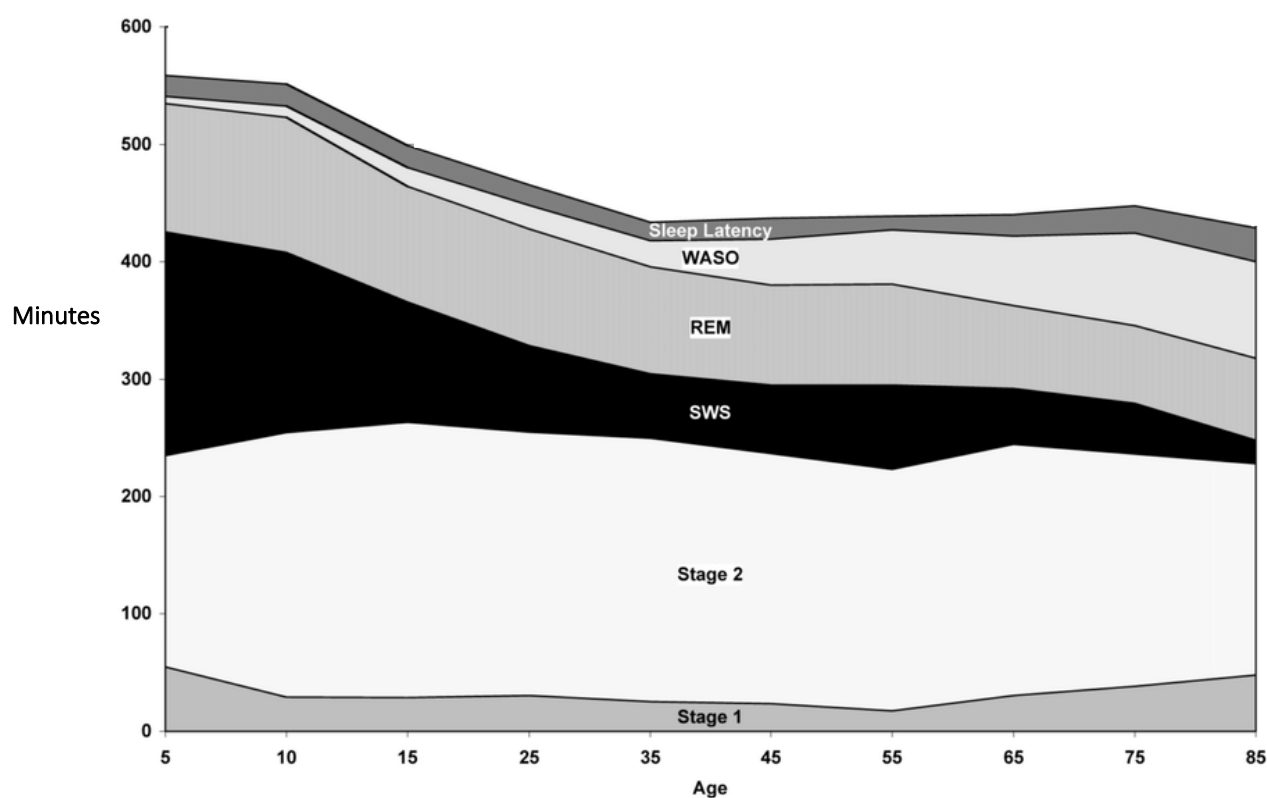


Figure 1.4. Mean minutes of sleep onset latency (sleep latency), wake after sleep onset (WASO), rapid eye movement sleep (REM), stage N3 sleep/slow wave sleep (SWS), stage N2 sleep (Stage 2), and stage N1 sleep (Stage N1) across the lifespan. Adapted from Ohayon et al. (2004).

As soon as neural development allows for the capacity to sleep (approximately 24 – 26 weeks post conception), a developing fetus will spend approximately 90 to 95 percent of the 24-hour period sleeping (Sheldon, 2014; Suwanrath & Suntharasaj, 2010). Newborn infants spend approximately 70 percent of the 24-hour period sleeping, in contrast to adults who spend approximately 25 to 30 percent (Sheldon, 2014). Infant sleep quantity and architecture is believed to reflect the greatest neural changes that occur in the lifetime (Eisermann, Kaminska, Moutard, Soufflet, & Plouin, 2013; Roffwarg, Muzio, & Dement, 1966; Sheldon, 2014). Infants experience shorter sleep cycles than adults (approximately 50-minutes) and enter sleep via REM sleep (Carskadon & Dement, 2017). Approximately 50 percent of an infant sleep cycle is dedicated to REM sleep, and the other 50 percent to the lighter stages of non-REM sleep (Eisermann et al., 2013; Sheldon, 2014). This ratio shifts across the first two years of life, culminating with REM sleep decreasing to approximately 20 to 25 percent of the sleep cycle, and non-REM sleep increasing to approximately 75 to 80 percent (Carskadon & Dement, 2017). SWS with its characteristic delta EEG waveforms first emerges between three and six months of age (Coons & Guilleminault, 1982; Louis, Zhang, Revol, Debilly, & Challamel, 1992; Peirano, Fagioli, Bes, & Salzarulo, 1993; Sheldon, 2014).

SWS proliferates in childhood, peaking prior to the onset of puberty (Carskadon & Dement, 2017; Eisermann et al., 2013). (See Figure 1.4.) This is believed to reflect the continuation of neural development throughout childhood, specifically an increase in synaptic density (Eisermann et al., 2013; Kurth et al., 2010). Coinciding with these sleep and neural changes, homeostatic sleep drive is at its highest (Carskadon & Dement, 2017). During this critical developmental time

period, children will spend approximately 10 to 13 hours of the 24-hour period sleeping (Roffwarg et al., 1966).

The next major bout of sleep changes commence in adolescence and continue into the third decade of life (Hagenauer & Lee, 2013; Hagenauer et al., 2009; Marshall & Tanner, 1969, 1970; Tarokh et al., 2011). Changes in sleep are particularly marked during this time and are thought to reflect aspects of neurological, pubertal, and psychosocial development (Dahl & Lewin, 2002). To highlight the importance of adequate sleep at this age, a review by Curcio and colleagues (2006) indicated that sleep restriction was associated with substantially impaired neurocognitive and academic performance during both secondary and tertiary education. There is also substantial evidence that sleep restriction in young people is related to increased risk-taking behaviour, including sexual activity, physical fighting, suicide, and drug and alcohol use (McKnight-Eily et al., 2011; O'Brien & Mindell, 2005; Wolfson & Carskadon, 1998).

There are two major sleep changes that commence at the onset of adolescence: a circadian phase delay and a decline homeostatic sleep drive (Hagenauer & Lee, 2013; Hagenauer et al., 2009). These physiological changes manifest in behavioural changes, most notably a marked shift to later bedtimes (Baker et al., 2012; Colrain & Baker, 2011). The decline in homeostatic sleep drive commences following the onset of puberty (approximately 10 – 14 years in females and 12 – 16 years in males) and continues into young adulthood (Marshall & Tanner, 1969, 1970; Tarokh et al., 2011). The decline in homeostatic sleep drive is demonstrated by a considerable reduction in SWS and delta EEG activity across adolescence (Baker et al., 2012; Buchmann et al., 2011; Campbell & Feinberg, 2009; Feinberg, de Bie, Davis, & Campbell, 2011). This phenomenon is believed to

primarily reflect the final stages of neural development (Feinberg & Campbell, 2010; Gogtay et al., 2004; Goldstone et al., 2018; Tarokh et al., 2011).

The circadian phase delay refers to a shift in the circadian oscillator of approximately one to three hours, peaking between the ages of 15 to 21 years (Hagenauer & Lee, 2013; Hagenauer et al., 2009; Roenneberg et al., 2004). This is demonstrated by notable delays in sleep timing and melatonin release: a circadian dependent hormone (Crowley, Acebo, & Carskadon, 2007; Crowley et al., 2014; Hagenauer et al., 2009). This behavioural and physiological delay results in adolescents and young adults being more active and alert later in the evening than children and mature adults (Crowley et al., 2007; Goldstein, Hahn, Hasher, Wiprzycka, & Zelazo, 2007). The adolescent delay in circadian sleep timing has been observed across all cultures and mammal species (Hagenauer & Lee, 2013; Hagenauer et al., 2009). This ubiquitous delay is believed to be evolutionarily advantageous as it has been associated with increased socialising behaviour and reproductive success (Crowley et al., 2007; Spear, 2000). Coupled with the reduction in homeostatic sleep drive, the circadian phase delay permits adolescents to maintain wakefulness for longer and commence sleep later in the 24-hour period.

In combination with socio-environmental factors, the homeostatic and circadian sleep changes that occur across adolescence and young adulthood contribute to chronic sleep restriction in this population (Carskadon, 2011; Hagenauer et al., 2009). Despite adolescents' and young adults' endogenous preference for later bedtimes, their total sleep duration is often restricted by inflexible early-morning commitments, such as school or university, employment, and familial responsibilities (Carskadon, 2011; Wittmann, Dinich, Merrow, & Roenneberg, 2006). Evidence of sleep restriction in this age group has been

demonstrated by studies that show adolescents have significantly longer sleep durations on weekends and holidays when there are fewer early morning commitments (Carskadon, 2011; Kim et al., 2011; Leger, Beck, Richard, & Godeau, 2012; Thorleifsdottir, Björnsson, Benediktsdottir, Gislason, & Kristbjarnarson, 2002). Further highlighting this, a large survey (n=9,251) by Leger and colleagues (2012) reported that 40.5 percent of 15-year-old adolescents were currently experiencing sleep deprivation, compared to 16 percent of 11-year-old children. Other environmental factors that can impact adolescent sleep timing and duration include evening light exposure, electronic media devices, social activities, and alcohol use (Dahl & Lewin, 2002; Hagenauer et al., 2009; Spear, 2000). Social and environmental factors, coupled with a lowered homeostatic sleep drive and circadian phase delay, may contribute to sleep restriction in this age group.

After approximately 21 years of age the circadian rhythm begins to advance, resulting in earlier sleep and rise times and a preference for daytime activities (Carskadon & Dement, 2017; Hagenauer et al., 2009). Sleep duration progressively decreases across the lifetime, although a plateau has been observed between approximately 25 and 35 years of age (Bliwise, 1993; Courchesne et al., 2000; Feinberg & Campbell, 2010; Feinberg et al., 2011; Van Cauter, Leproult, & Plat, 2000). The decline in total sleep time typically observed in older adults is believed to reflect age-related neuronal loss, mirrored by a decline in SWS percentage and delta EEG activity (Achermann & Borbely, 2017; Bishop, Lu, & Yankner, 2010; Borbely, 1982b; Floyd, Janisse, Jenuwine, & Ager, 2007; Landolt & Borbély, 2001; Mander, Winer, & Walker, 2017; Ohayon et al., 2004). In contrast, REM sleep and stage N2 sleep percentage are relatively well maintained in healthy older adults (Floyd et al., 2007; Ohayon et al., 2004). There is, however, a notable increase in the proportion of

stage N1 sleep with advancing age (Floyd et al., 2007; Ohayon et al., 2004). (See Figure 1.4.)

As well as sleep architectural changes, older adults experience a profound increase in interindividual variability across all sleep measures, and increased incidence of sleep disorders (Bliwise & Scullin, 2017; Neikrug & Ancoli-Israel, 2010; Suzuki, Miyamoto, & Hirata, 2017). Studies have also shown that older adults experience general sleep disruption, including increased sleep onset latency, arousals, and wake after sleep onset (Bliwise & Scullin, 2017; Carskadon, Brown, & Dement, 1982; Ohayon et al., 2004). There is some argument as to whether these changes are the result of a deterioration of general health and age-related disease, or a deterioration of the mechanisms responsible for sleep (Foley, Ancoli-Israel, Britz, & Walsh, 2004; Mander et al., 2017). Age-related sleep disturbance may be the result of age-related degradations in neural structure and function, leading to a diminished homeostatic sleep drive (Bishop et al., 2010; Colrain et al., 2010; Landolt & Borbély, 2001). This theory is supported by research that has shown age-related prefrontal atrophy and broader cortical thinning, as measured by magnetic resonance imaging (MRI), are associated with lower slow wave activity (Dube et al., 2015; Mander et al., 2013). Mirroring these findings, the amplitude and incidence of spontaneous and elicited K-complexes decline markedly with aging (Colrain & Baker, 2011; Colrain et al., 2010; Crowley, Trinder, & Colrain, 2002). This is also believed to reflect normal age-related neural degradation, as fewer neurons, and poorer connections between neurons, may impair neural synchronicity (Colrain et al., 2010; Colrain et al., 2009b; Crowley et al., 2002). However, some studies suggest that sleep homeostasis is preserved in older age (Bliwise, 1993).

1.2.2.1 Sex differences in sleep across the lifespan

In infancy and childhood there are no notable sex differences in sleep architecture and quality (Carskadon & Dement, 2017). Sex differences in sleep first emerge in adolescence and are related to both pubertal and neural development (Baker & O'Brien, 2017). As previously highlighted, females commence neurodevelopmental changes and the related decline in delta EEG activity earlier than males (Baker et al., 2012; Baker et al., 2016; Pfefferbaum et al., 2016). In adolescence, the incidence of insomnia and general sleep disturbance become more prevalent in females compared to males (Coren, 2009; Fatima, Doi, Najman, & Mamun, 2016; Johnson, Roth, Schultz, & Breslau, 2006). This is believed to be related to the pubertal onset of menses (Johnson et al., 2006). It is well-established that sex hormone fluctuations associated with the menstrual cycle can negatively impact sleep quality (Baker & Driver, 2004; Romans et al., 2015). There is also evidence that the female oral contraceptive pill may raise basal body temperature, and alter normal sleep architecture (Baker, Mitchell, & Driver, 2001). Despite these general findings, objective sex differences in sleep are generally subtle in young adulthood (Baker & O'Brien, 2017; Carskadon & Dement, 2017). It has been theorised that sex differences in objective sleep measures become more apparent when there is a major challenge to the sleep system, such as aging, disease, or excessive alcohol use (Baker & O'Brien, 2017; Colrain et al., 2009b).

There is substantial evidence that females have greater SWS and delta EEG activity across the lifespan, than males (Carrier, Land, Buysse, Kupfer, & Monk, 2001; Dijk, Beersma, & Bloem, 1989; Ehlers & Kupfer, 1997; Latta, Leproult, Tasali, Hofmann, & Van Cauter, 2005; Mourtazaev, Kemp, Zwinderman, & Kamphuisen, 1995; Walsleben et al., 2004). Physiologically, there is evidence that

women have higher regional and global grey matter volumes, and thicker cortical volumes, than men (Gur et al., 1999; Luders, Gaser, Narr, & Toga, 2009). More neurons available for synchronised firing could potentially lead to higher SWS and delta EEG activity in females (Colrain et al., 2009b). It has also been suggested that estrogen, a female sex hormone, may be protective against age-related brain degradation and neuronal loss (Ehlers & Kupfer, 1997; Zarate, Stevnsner, & Gredilla, 2017). In older age, women tend to have longer sleep durations and better sleep quality than men (Baker & O'Brien, 2017; Bixler et al., 2009; Redline et al., 2004). This may be due to their higher requirement or capability to produce SWS, leading to a higher homeostatic sleep drive, as well as the cessation of sex hormone fluctuations following menopause (Baker & O'Brien, 2017). Finally, it is worth noting that females generally have higher EEG spectral power than men in most frequency bands, including alpha, sigma, theta and delta, which may be related to the sex differences highlighted above (Carrier et al., 2001).

1.2.3 Slow wave and rapid eye movement sleep homeostasis

There are multiple neurotransmitter systems involved in the onset, maintenance and offset of both SWS and REM sleep (Lechin et al., 2004; Siegel, 2004). These systems include serotonin (Slater, Jones, & Moore, 1978; Steriade, 2004b; Ursin, 2002), histamine (Ikeda-Sagara et al., 2012), norepinephrine (Mitchell & Weinshenker, 2010; Monti et al., 1991; Thakkar, 2011), acetylcholine (Jasper & Tessier, 1971; Platt & Riedel, 2011; Steriade, 2004a; Vazquez & Baghdoyan, 2001), glutamate (Clement, Sapin, Berod, Fort, & Luppi, 2011; et al.; Stutzmann, Lucas, Blanchard, & Laduron, 1988), and gamma-aminobutyric acid (GABA; Fraigne, Torontali, Snow, & Peever, 2015; Gottesmann, 2002; Lu et al., 2006). Most notably,

it is well established that GABA neurotransmission promotes and facilitates SWS (Walsh, 2009). This is highlighted by research findings that GABA agonist drugs increase SWS (Feld et al., 2013), and GABA antagonists reduce SWS (Gauthier, Arnaud, Gandolfo, & Gottesmann, 1997). In combination with GABA, glutaminergic neurotransmission is fundamental for REM sleep onset and continuation, in combination with acetylcholine (Fragine et al., 2015; Lu et al., 2006; Platt & Riedel, 2011).

SWS and slow wave activity are believed to represent functional measures of homeostatic sleep drive, and thus reflect sleep depth and intensity. This is supported by evidence that arousal thresholds increase as slow wave activity increases (Williams, Hammack, Daly, Dement, & Lubin, 1964). SWS and slow wave activity are highest in the first half of the sleep period, when homeostatic sleep pressure is greatest, dissipating rapidly from sleep onset (Borbely, Baumann, Brandeis, Strauch, & Lehmann, 1981; Webb & Agnew, 1971). Further, it is not uncommon for SWS to be entirely absent from the final sleep cycle, which may indicate the satiation of homeostatic requirements (Carskadon & Dement, 2017). Lastly, short periods of daytime sleep (i.e., naps) reduce subsequent nocturnal SWS, likely reflecting lower homeostatic sleep pressure in the following sleep period (Werth, Dijk, Achermann, & Borbely, 1996).

Conversely, there is substantial evidence that both partial and total sleep deprivation lead to elevated SWS and slow wave activity during a recovery sleep, representing higher homeostatic sleep pressure following sleep loss (Bonnet, 2011; Borbely, 1982b). Following total sleep deprivation there is evidence that the amount of SWS is positively related to the duration of prior wake (Webb & Agnew, 1971). Slow wave activity is also augmented following total sleep deprivation as a function

of prior wake (Borbely et al., 1981; Dijk, Brunner, Beersma, & Borbely, 1990; Dijk, Hayes, & Czeisler, 1993). Researchers have also selectively deprived participants of SWS by playing a loud auditory tone every time a participant enters SWS, but not other sleep stages (Dijk, Beersma, Daan, Bloem, & Van den Hoofdakker, 1987; Gillberg, Anderzen, & Akerstedt, 1991). These studies revealed that total sleep time, SWS and slow wave activity are augmented following the cessation of selective SWS deprivation. These findings provide further evidence that SWS and slow wave activity are functional markers of homeostatic sleep drive (Achermann & Borbely, 2017; Dijk et al., 1987; Gillberg et al., 1991).

There is also substantial evidence that SWS is homeostatically reinstated preferentially to other sleep stages (Achermann & Borbely, 2017; Bonnet, 2011; Borbely et al., 1981; Dijk et al., 1990; Dijk et al., 1993; Moses, Johnson, Naitoh, & Lubin, 1975). This is indicated by research that has investigated the impact of total sleep deprivation on sleep stage and EEG activity during a ‘recovery’ sleep (Bonnet, 2011; Borbely et al., 1981; Dijk et al., 1990; Dijk et al., 1993; Moses et al., 1975). These studies have shown that an immediate rebound in SWS and slow wave activity occurred in the subsequent sleep opportunity following 36 to 40.5 hours of wake in healthy adult participants. The increase in SWS and slow wave activity was most evident in the first three hours of sleep. This rebound occurred at the expense of other sleep stages and faster EEG frequencies (Bonnet, 2011; Borbely et al., 1981; Dijk et al., 1990; Dijk et al., 1993; Moses et al., 1975). The preferential homeostatic reinstatement of SWS suggests that this sleep stage is fundamental to physical health and optimal functioning (Carskadon & Dement, 2017; Dijk, 2009; Horne, 1992).

Currently, several prominent theories attempt to explain the homeostatic importance of SWS (Dijk, 2009; Horne, 1992; Roth, 2009; Tononi & Cirelli, 2006;

Vassalli & Dijk, 2009). For example, there is strong research evidence that SWS is essential for neurological and physiological restoration, growth, and repair (Horne, 1992; Krueger et al., 2016). In humans, growth hormone is secreted in the first sleep cycle during SWS, attributed to bone, muscle, and tissue growth and repair (Feinberg, 2000; Sassin et al., 1969; Van Cauter, 2000). There is also evidence from animal research that the brain's glymphatic system clears macroscopic waste and excess intracellular fluid during SWS (Mendelsohn & Larrick, 2013). In vivo two-photon imaging in mice has demonstrated that interstitial space between cells in the brain is 60 percent greater during SWS than wake, increasing neural activity waste product clearance (Xie et al., 2013). This is further supported by evidence that glymphatic influx in mice is positively correlated with delta EEG activity, and negatively correlated with beta activity (Hablitz et al., 2019). These studies provide evidence for the importance of SWS for neural restoration, growth, and repair (Mendelsohn & Larrick, 2013).

Alternative theories suggest that SWS is fundamental to memory consolidation and synaptic homeostasis (Holz et al., 2012; Tononi & Cirelli, 2006, 2014). During wakefulness, learning and memory consolidation occur via the process of long-term potentiation i.e., the strengthening of synapses through repeated connections and paired firing (Cirelli, 2013; Miyamoto, Hirai, & Murayama, 2017). Due to its highly synchronous pattern of activation, and neurochemical state, it has been hypothesised that SWS regulates synaptic density by downscaling or removing synapses that have not been potentiated during wake (Tononi & Cirelli, 2003, 2006, 2014). SWS homeostasis is cited as evidence for this, as SWS density is highest at sleep onset when synaptic density is highest, and declines across the sleep period as synapses are downscaled from the neural network (Borbely et al., 1981; Dijk et al.,

1990; Dijk et al., 1993; Tononi & Cirelli, 2006, 2014). Furthermore, there is evidence in drosophila flies that synaptic weight increases during waking hours and decreases during sleep, and that the magnitude of change is dependent on learning (Bushey, Tononi, & Cirelli, 2011). It is also of note that GABAergic neurotransmission is both fundamental to memory consolidation, including long-term potentiation, and SWS onset and continuation (Gottesmann, 2002; Katz & Liebler, 1978; Makkar, Zhang, & Cranney, 2010; Myhrer, 2003; Patenaude, Chapman, Bertrand, Congar, & Lacaille, 2003). It is possible that synaptic homeostasis may underly SWS homeostasis, highlighting the importance of this sleep stage for learning and memory.

Further evidence that SWS homeostasis is fundamental to memory consolidation has been provided by the neural network hypothesis (Holz et al., 2012; Tononi & Cirelli, 2006, 2014). Like synaptic homeostasis, this hypothesis suggests that SWS homeostasis may reflect localised cellular sleep required to produce synaptic alterations for learning (Huber et al., 2004; Seibt & Frank, 2019). Research in humans has demonstrated localised homeostatic increases in slow wave activity over neural areas where learning has occurred during wake (Huber et al., 2004; Seibt & Frank, 2019). For example, a hallmark study by Huber and colleagues (2004) administered a motor learning task prior to sleep onset (n=11) and reported higher slow wave activity in the specific brain regions this task activated during wake. Furthermore, the degree of this increase was associated with better next day performance, highlighting the functional role of slow wave activity in learning and memory. There is also evidence that SWS enhancement may improve verbal declarative memory (see Zhang & Gruber, 2019 for review). Finally, as previously highlighted, there is substantial evidence that sleep deprivation results in

considerable impairments in learning and memory (Banks & Dinges, 2007; Krause et al., 2017; Lim & Dinges, 2010; Lo et al., 2012; Van Dongen et al., 2003). Taken together, this research highlights the functional importance of SWS for neural restoration and repair, as well as learning and memory.

Although REM sleep is believed to be primarily regulated by the circadian system, it is also the only other sleep stage to show homeostatic regulation (Achermann & Borbely, 2017; Borbely, 1982b; Lee et al., 2009; Moses et al., 1975; Wurts & Edgar, 2000). As highlighted above, SWS is immediately reinstated during the subsequent sleep period following total sleep deprivation (Achermann & Borbely, 2017; Bonnet, 2011; Borbely et al., 1981; Dijk et al., 1990; Dijk et al., 1993). In contrast, following one night of total sleep deprivation, REM sleep is reinstated at a slower rate, and only after the successful recovery of SWS (Moses et al., 1975). Notably, the homeostatic regulation of REM sleep is most prominent at times when homeostatic SWS pressure is low, such as just prior to wake or when SWS homeostasis has been satiated (Beersma, Dijk, Blok, & Everhardus, 1990; Brunner, Dijk, & Borbely, 1993; Brunner, Dijk, Tobler, & Borbely, 1990). Crucially, REM sleep homeostasis appears to be smaller in magnitude and secondary to SWS homeostasis (Achermann & Borbely, 2017; Moses et al., 1975).

Drive for REM sleep, or REM sleep pressure, can be determined by measuring REM sleep density, duration, and latency (Colrain et al., 2009b; Gillin et al., 1994). Studies that have selectively deprived participants of REM sleep using loud auditory tones have demonstrated a REM sleep rebound or increase during a recovery sleep (Beersma et al., 1990; Brunner et al., 1993; Brunner et al., 1990; Datta & Maclean, 2007; Dement, 1960; Moses et al., 1975). There is also evidence that selective REM sleep deprivation can lead to reduced slow wave activity during a

recovery sleep, which is likely to allow for adequate REM sleep restoration (Beersma et al., 1990; Brunner et al., 1993; Brunner et al., 1990). Taken together, this research highlights that REM sleep is homeostatically regulated, suggesting that this unique cortically active state of sleep is functionally necessary and important (Datta & Maclean, 2007; Dement, 1960).

Several primary functions for REM sleep have been theorised, including memory consolidation (Maquet, 2001; Siegel, 2001), emotional regulation (Rosales-Lagarde et al., 2012; Tempesta, Succi, De Gennaro, & Ferrara, 2018; Vandekerckhove & Wang, 2017), and promoting wakefulness following adequate sleep (Klemm, 2011). Firstly, although REM sleep has been historically hypothesised to be critical for memory consolidation, there is currently insufficient evidence to support this theory (Siegel, 2001; Vertes, 2004; Vertes & Eastman, 2000). This is highlighted by the observation that there are no notable learning or memory deficits evident in human patients taking medications that grossly suppress REM sleep, such as antidepressants (Vertes, 2004; Vertes & Eastman, 2000). Further to this, patients with neural lesions that prevent REM sleep also do not experience significant learning or memory deficits (Siegel, 2001; Vertes, 2004; Vertes & Eastman, 2000). There is more substantial evidence that REM sleep may play a functional role in emotion regulation and processing (Rosales-Lagarde et al., 2012; Tempesta et al., 2018; Vandekerckhove & Wang, 2017). For example, a study by Rosales-Lagarde and colleagues (2012) demonstrated that selective REM sleep deprivation resulted in higher emotional reactivity to threatening visual stimuli. Further to this, REM sleep has higher cholinergic activity than wake and non-REM sleep, which is believed to facilitate emotional memory consolidation (Cunningham, Pardilla-Delgado, Alger, & Payne, 2014; Hasselmo, 1999; Platt & Riedel, 2011; Riedel, Platt, & Micheau, 2003).

Finally, it has been hypothesised that REM sleep might play a functional role in ‘waking-up’ following adequate sleep, or to functionally prime cortical circuits for wakefulness (Klemm, 2011). This theory is supported by evidence that REM sleep EEG activity is highly similar to wake. Furthermore, REM sleep is most concentrated in the second half of the sleep period after sleep homeostasis has been met, and the final awakening from the sleep period often occurs during an episode of REM sleep (Beersma et al., 1990; Brunner et al., 1993; Brunner et al., 1990; Klemm, 2011). Taken together, this evidence suggests that REM sleep may serve a functional role in both emotion regulation and waking behaviour.

In conclusion, the homeostatic regulation of REM sleep and SWS provides substantial evidence for the functional importance of these unique sleep stages. However, it is important to note that sleep stages do not occur in isolation of each other, but rather in a consistent cyclic pattern across the sleep period (Carskadon & Dement, 2017). (See Figure 1.2.) The robustness of this pattern suggests that each of these unique sleep stages are interrelated and mutually dependent. This may suggest that the timing and distribution of each sleep stage across the sleep period may be aligned with important biological and functional processes, and disturbances to normal sleep architecture may be detrimental (Carskadon & Dement, 2017).

1.2.4 Neurophysiology of slow wave sleep

Stage N3 sleep, or SWS, is visually determined using standardised criteria (AASM, 2007). Notably, slow wave and delta EEG spectral frequencies are traditionally defined using slightly different criteria (Achermann & Borbely, 2017; Colrain et al., 2009b). Slow wave activity is generally characterised by spectral EEG frequencies between 0.5 to 4.5 Hz, whereas delta EEG activity typically ranges from

0.75 to 4.5 Hz (Achermann & Borbely, 2017; Borbely, 2001). These general definitions are not always adhered to by researchers, and are sometimes used interchangeably (Achermann & Borbely, 2017). For example, some research studies define slow wave activity as 0.75 to 4.5 Hz (Achermann, Dijk, Brunner, & Borbely, 1993; Dijk, 2009; Dijk, Cajochen, Tobler, & Borbely, 1991), whereas very similar studies define slow wave activity as 0.5 to 4.5 Hz (Achermann & Borbely, 2017; Borbely, 2001).

It is important to note that there is some evidence that slow oscillations less than 1.0 Hz are physiologically distinct from higher slow wave or delta EEG frequencies. This distinction is supported by findings in animal studies indicating cellular correlates differ between slow oscillations less than 1.0 Hz and higher delta frequencies of 1.0 to 4.0 Hz (Nofzinger & Maquet, 2017; Steriade, McCormick, & Sejnowski, 1993; Steriade, Nunez, & Amzica, 1993a, 1993b). This research suggests that slow oscillations are cortically generated, and delta frequencies are both cortically and thalamically generated (Steriade, McCormick, et al., 1993; Steriade, Nunez, et al., 1993a). This is further supported by human research using high-density EEG source modelling demonstrating that slow oscillations and delta waves originate in different brain regions (Murphy et al., 2009; Nofzinger & Maquet, 2017).

Topographically, these studies found that slow oscillations originated over the brainstem, cerebellum, and parahippocampal gyrus, whereas delta EEG activity originated over frontal electrode sites (Murphy et al., 2009; Nofzinger & Maquet, 2017). Due to these findings, some researchers define delta EEG spectral frequency strictly as 1.0 to 4.0 Hz (Colrain et al., 2009b; Nofzinger & Maquet, 2017).

Nevertheless, there is universal consensus that SWS is dominated by high amplitude, low frequency, synchronous EEG activity (Borbely et al., 1981; Dijk et al., 1993).

SWS is produced by the hyperpolarisation and synchronisation of cortical and thalamocortical neurons via changes in membrane potential (Dijk, 1995; Steriade, Dossi, & Nunez, 1991; Steriade, McCormick, et al., 1993). Evidence for the cellular generation of SWS has been provided primarily by research measuring in vivo intracellular and extracellular recordings of neurons in cats (Dijk, 1995; Steriade et al., 1991; Steriade, McCormick, et al., 1993; Volgushev, Chauvette, Mukovski, & Timofeev, 2006). Firstly, this evidence has highlighted that during the transition from wake to non-REM sleep, cortical and thalamocortical neurons undergo hyperpolarisation causing neurons to switch to a burst firing mode (Dijk, 1995; Steriade, McCormick, et al., 1993). Initially, the hyperpolarisation of membrane potentials leads to the production of sleep spindle or sigma EEG activity, characteristic of stage N2 sleep (Dossi, Nunez, & Steriade, 1992; Steriade et al., 1991). However, further hyperpolarisation of thalamocortical and cortical cells leads to the global generation of slow wave or delta EEG activity (Dossi et al., 1992; Steriade et al., 1991; Volgushev et al., 2006). It is important to note that due to the invasive nature of this research, physiological evidence of SWS mechanisms in humans is currently lacking.

Topographically, slow wave activity shows clear frontal predominance, declining notably from frontal to occipital regions of the brain (Dang-Vu et al., 2005; Nir et al., 2011; Werth, Achermann, & Borbely, 1996, 1997). This is highlighted by research findings that slow wave activity is augmented predominately at frontal electrode sites following acute sleep deprivation (Bersagliere, Pascual-Marqui, Tarokh, & Achermann, 2018; Hung et al., 2013; Tinguely, Finelli, Landolt, Borbely, & Achermann, 2006). Functional MRI studies have found that high voltage delta waveforms (75 – 140 μ V) originate in frontal brain regions (Dang-Vu et al., 2008;

Murphy et al., 2009; Nofzinger & Maquet, 2017). This research also described that slow wave activity then travels along an anterior to posterior axis (Murphy et al., 2009). Frontal predominance of delta EEG activity is apparent during wake, non-REM sleep, and REM sleep, highlighting that this phenomenon is not entirely state dependent, although, delta EEG activity is orders of magnitude larger during SWS compared to other states (Achermann & Borbely, 2017; Hung et al., 2013; Tinguely et al., 2006).

Research suggests that the frontal predominance of SWS is related to the neurophysiological structural and functional characteristics of frontal brain areas (Achermann & Borbely, 2017; Dijk, 2009). In humans, the highest density of neural columns is located in frontal and pre-frontal regions of the brain (Elston, 2000; Huttenlocher, 1979; Teffer & Semendeferi, 2012). When these neural columns fire in synchrony, the electrical signal produced by each individual membrane potential is summed together, producing the high amplitude waveforms detected via the EEG. Thus, the more neurons available for synchronous firing, the greater the capacity for SWS, leading to frontal cortices possessing increased capacity to produce delta activity. Similarly, more synchronous firing leads to lower frequency activity as neurons synchronously hyperpolarise following an action potential and must repolarise (or rest) before the next action potential can occur (Steriade, Nunez, et al., 1993a). This manifests in characteristic slow wave activity concentrated in frontal brain regions due to the higher density of neurons in these areas. Thus, slow wave activity and SWS requires large numbers of healthy, well-connected neurons for simultaneous activation and synchronised firing.

1.2.5 Adolescent maturation of sleep and neural processes

Adolescence is a transitional period in the human lifespan characterised by profound neural development (Spear, 2000). Structurally, this is observed as a dramatic reduction in neural grey matter volume, and increases in white matter volume (Paus, 2005). The largest and most rapid changes in adolescent brain development and behaviour occur between approximately 10 to 17 years of age (Feinberg & Campbell, 2010; Lebel & Beaulieu, 2011). However, the final stages of human neural development continue into young adulthood, or until approximately 25 years of age (Arain et al., 2013; Gogtay et al., 2004; Johnson, Blum, & Giedd, 2009; Lebel & Beaulieu, 2011; Miller et al., 2012; Pfefferbaum et al., 2016; Sowell et al., 2003; Sowell, Thompson, Tessner, & Toga, 2001). This highlights the biological similarities of adolescence and young adulthood. Due to their neurodevelopmental similarities, this thesis will collectively refer to human adolescents and young adults as young people. This time period is associated with several critical neurological changes, all of which appear to have a significant impact upon functioning and behaviour.

Firstly, there is a dramatic decline in synaptic density and cerebral metabolic rate across adolescence that continues into young adulthood (Figure 1.5; Feinberg, Thode, Chugani, & March, 1990; Lebel & Beaulieu, 2011). This is the result of an adaptive developmental process called synaptic pruning in which operational synaptic connections are strengthened and maintained, while non-functional synapses are pruned (Feinberg et al., 1990; Steinberg, 2005; Yurgelun-Todd, 2007). Non-functional synapses are removed through phagocytosis performed by microglia, while active synaptic circuits are preserved (Lieberman, McGuirt, Tang, & Sulzer, 2018; Trapp et al., 2007). Synaptic pruning across adolescence and young adulthood

results in reduced neural grey matter and cerebral metabolic rate, reflecting an estimated loss of approximately half of the neural synapses in the brain that proliferated throughout infancy and childhood (Figure 1.5; Collin & van den Heuvel, 2013; Feinberg et al., 1990; Navlakha, Barth, & Bar-Joseph, 2015; Paus, 2010). Effective synaptic pruning results in a steady increase in cognitive capacity and neural processing speed across adolescence and young adulthood (Feinberg et al., 1990; Steinberg, 2005; Yurgelun-Todd, 2007). It has been theorised that the development of some neuropsychological disorders may be the result of ineffective or erroneous synaptic pruning, such as autism (Hansel, 2019), attention deficit hyperactivity disorder (Selemon, 2013), and schizophrenia (de Silva, 2018; Sellgren et al., 2019).

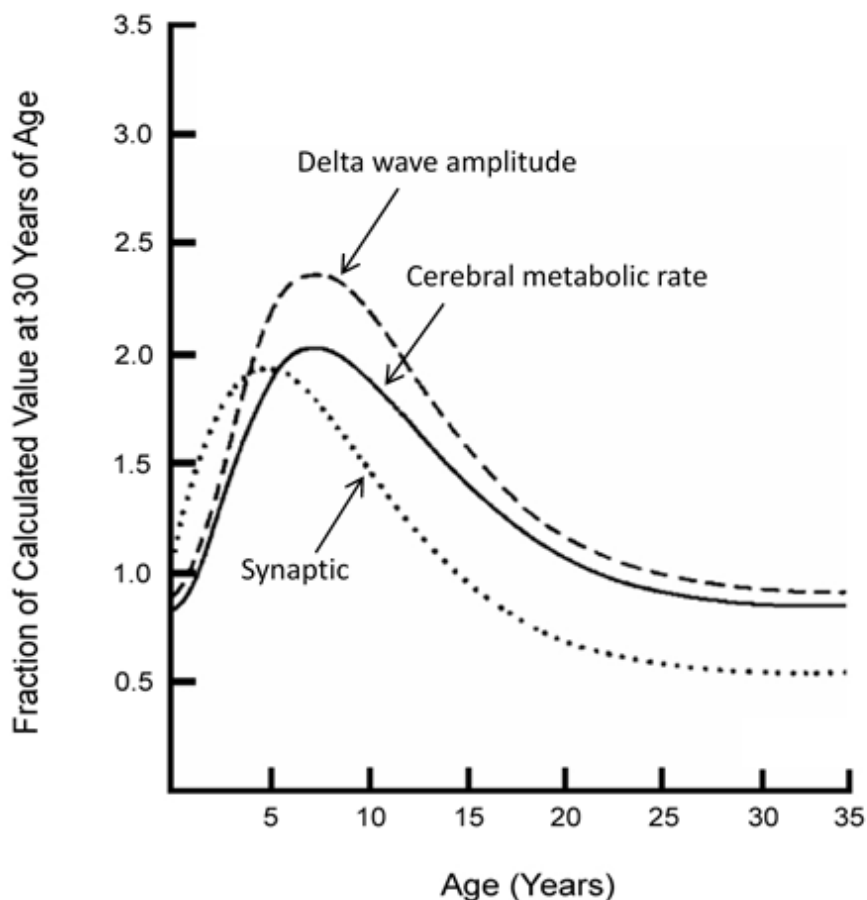


Figure 1.5. Synaptic density, cerebral metabolic rate, and delta wave amplitude; combined gamma distribution models for each measure standardised at 30 years old. Adapted from Feinberg et al. (1990).

The synaptic pathways that are maintained during synaptic pruning are further strengthened by undergoing the biological process of axonal myelination (Chevalier et al., 2015; Deoni et al., 2016; Paus, 2010). Axonal myelination begins in infancy and increases incrementally into young adulthood (Giedd et al., 1999; Lenroot & Giedd, 2006; Miller et al., 2012). Axonal myelination insulates neural axons in a fatty myelin sheath composed of a concentric phospholipid layer, contributing to neural white matter (Bechler, Byrne, & Ffrench-Constant, 2015; Paus, Keshavan, & Giedd, 2008; Yeung et al., 2014). The myelin sheath is produced in the central nervous system by glial cells, specifically oligodendrocytes (Yeung et al., 2014). The insulation of neural axons greatly increases the speed at which action potentials can propagate (Pajevic, Basser, & Fields, 2014). Hence, effective axonal myelination increases the velocity, and enhances the synchrony, of neural impulses between cortical regions, greatly increasing signal processing, and hence cognitive capacity (Fields, 2008b; Nickel & Gu, 2018). Major disruptions to axonal myelination processes or de-myelination, such as that observed in multiple sclerosis, results in impaired neural processing (Love, 2006). More recent evidence suggests that subtle impairments in axonal myelination may be related to serious mental health conditions such as major depressive disorder and schizophrenia (Fields, 2008a).

Critically, neural development commences and progresses at different times and rates in different areas of the brain (Arain et al., 2013; Gogtay et al., 2004; Shaw et al., 2008; Sowell, Trauner, Gamst, & Jernigan, 2002). Both synaptic pruning and axonal myelination occur in a non-linear fashion and suggest a morphometrically organised loss of plasticity (Arain et al., 2013; Gogtay et al., 2004). Phylogenetically older cortices and association tracts develop first, with the development of each

corresponding with the emergence of a primary function, such as vision (Arain et al., 2013; Gogtay et al., 2004; Lebel, Walker, Leemans, Phillips, & Beaulieu, 2008). More evolutionarily recent cortices and tracts associated with secondary higher order functions develop last, such as executive function, attention, and fine motor coordination (Arain et al., 2013; Gogtay et al., 2004). Specifically, synaptic pruning and axonal myelination appears to take place in a caudal to rostral, inferior to posterior, laterally to medial direction, with occipital cortices developing first, and frontal cortices developing last (see Figure 1.6; Arain et al., 2013; Gogtay et al., 2004; Miller et al., 2012). The last brain regions to undergo synaptic pruning include the pre-frontal cortex and higher order association areas, such as the superior temporal gyrus and posterior parietal cortex (Figure 1.6; Gogtay et al., 2004). These do not appear to reach full maturity until well into the third decade of human life (Arain et al., 2013; Best & Miller, 2010; Gogtay et al., 2004; Johnson et al., 2009; Shaw et al., 2008; Sowell et al., 2003; Sowell et al., 2001). The protracted development of these critical areas may explain reduced cognitive control and inhibition, and increased risk-taking behaviour observed in adolescents and young adults (Arain et al., 2013; Liston et al., 2006). Some theories suggest that immature executive function in adolescence and young adulthood may present an evolutionary advantage as lower-order cognition and behaviours more fundamental to survival develop first (Casey, Jones, & Somerville, 2011; Gogtay et al., 2004). Further, reduced inhibition and increased risk-taking behaviour may increase the likelihood of successful mating and reproduction (Casey et al., 2011; Spear, 2000).

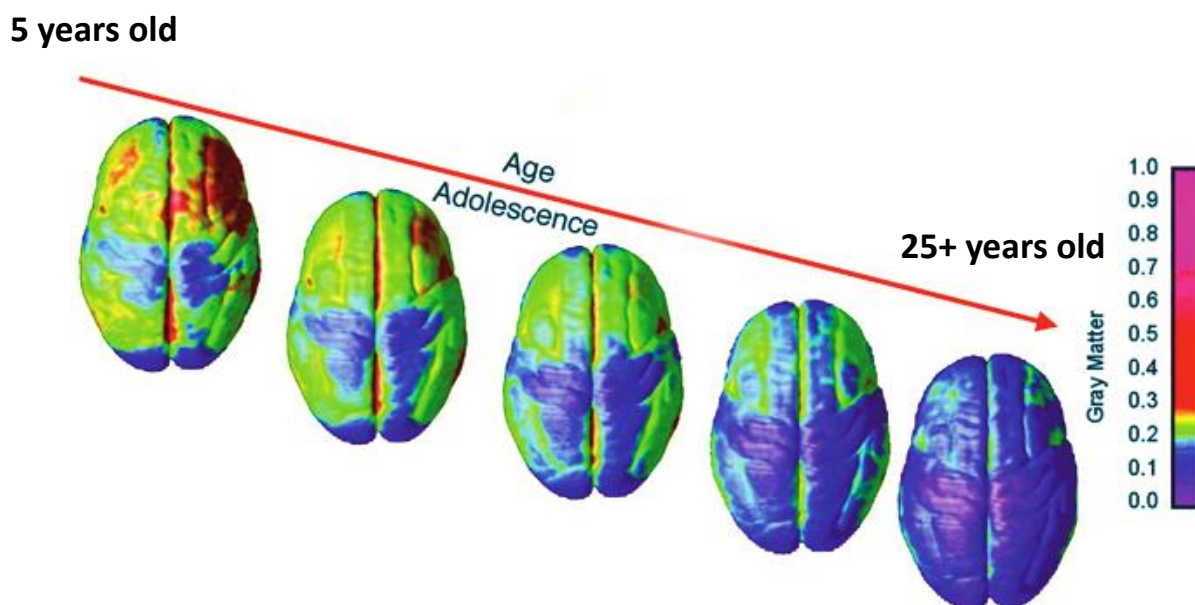


Figure 1.6. Cortical surface grey matter volumes between approximately 5 to 25 years of age (right lateral and top views). Adapted from Gogtay et al. (2004).

Adolescent neural development is accompanied by major and related changes in sleep, most notably a major decline in SWS and delta EEG activity (Baker et al., 2012; Campbell & Feinberg, 2009; Colrain & Baker, 2011; Courchesne et al., 2000; Feinberg & Campbell, 2010; Kurth et al., 2010; Sheldon, 2014). (See Figure 1.5.) Beginning in adolescence there is a 40 percent reduction in visually scored SWS (Colrain & Baker, 2011; Feinberg & Campbell, 2010). This is paralleled by a greater than 65 percent decrease in total slow wave and delta EEG activity (Campbell & Feinberg, 2009; Courchesne et al., 2000; Feinberg & Campbell, 2010; Feinberg et al., 1990; Sheldon, 2014). These changes are believed to reflect the final stages of neural development, manifesting in a substantial decrease in synaptic density, cortical metabolic rate, and delta wave EEG amplitude, displayed in Figure 1.5 (Campbell & Feinberg, 2009). Although the greatest changes occur between the ages of 11 and 17 years, reductions in SWS and delta EEG activity persist well into young

adulthood, mirroring neural development (Feinberg & Campbell, 2010; Tarokh & Carskadon, 2010; Tarokh et al., 2011). Further to this, the changes in SWS and slow wave activity are believed to reflect a decline in homeostatic sleep drive across adolescence and young adulthood (Baker et al., 2012; Buchmann et al., 2011; Campbell et al., 2011; Campbell & Feinberg, 2009; Carskadon, 2011; Feinberg et al., 2011; Hagenauer et al., 2009).

1.2.5.1 Sex differences in adolescent maturation of sleep and neural processes

As highlighted above, there are sex differences in the rate and timing of neural development across adolescence. Both synaptic pruning and axonal myelination commence and complete earlier in females than males (Arain et al., 2013; Kaczkurkin, Raznahan, & Satterthwaite, 2019; Lenroot & Giedd, 2010; Lenroot et al., 2007; Wang et al., 2012). Females also experience a steeper, faster decline in synaptic density and cortical metabolic rate compared to males, whose neural changes appear more gradual (Campbell, Darchia, Khaw, Higgins, & Feinberg, 2005; Kaczkurkin et al., 2019; Lenroot et al., 2007). Taken together, this research suggests that on average females complete brain development earlier than males (Kaczkurkin et al., 2019; Lenroot et al., 2007). Although the precise mechanism is unknown, it has been suggested that sex differences in the timing and progression of neural development may be related to sex hormone exposure, as these changes coincide with the onset of puberty (Harding et al., 2016; Sisk & Zehr, 2005; Vijayakumar, Op de Macks, Shirtcliff, & Pfeifer, 2018). Sex differences in cognition and behaviour also emerge at this time, for example, males show greater risk-taking and aggressive behaviour than females (Schulte, Ramo, & Brown, 2009; Sisk & Zehr, 2005; Turner & McClure, 2003). This could potentially be related to the

protracted neural development observed in males relative to females, as well as hormonal sex differences (Arain et al., 2013; Liston et al., 2006).

The rapid decline in SWS and delta EEG activity observed across adolescence commences earlier in females than males, reflecting the sex differences in neural development described above (Feinberg & Campbell, 2010). Females begin their SWS and delta EEG activity decline at approximately 10 years of age, whereas males begin at approximately 13 years of age (Baker et al., 2012; Baker et al., 2016; Campbell et al., 2005). Females also show a notably steeper decline in SWS and delta EEG activity than males, again mirroring developmental differences in the timing and rate of structural and functional changes to the brain (Campbell et al., 2005). Despite this finding, there is substantial evidence that females generally demonstrate greater SWS and delta EEG activity across the lifespan (Carrier et al., 2001; Dijk et al., 1989; Ehlers & Kupfer, 1997; Latta et al., 2005; Mourtazaev et al., 1995; Walsleben et al., 2004).

1.3 Summary

It is apparent that sleep serves several functional purposes and is necessary for optimal health and functioning. Deficits in sleep quality and duration are associated with adverse physiological and mental health outcomes. Throughout adolescence and young adulthood there are major and related changes to the brain and sleep systems. Most notably, there is a substantial decline in SWS and delta EEG activity, reflecting a developmental decrease in synaptic density. Thus, SWS and delta EEG activity, can be used as non-invasive, functional tools to evaluate neural structure and function. Alcohol is the most commonly consumed psychoactive substance worldwide, and its consumption may negatively impact the neural processes that underpin sleep. As such, an overview of the physiological effects of alcohol will now be examined.

CHAPTER 2

Prevalence and physiological impacts of alcohol use

Alcohol causes a significant health and financial burden on global society (AIHW, 2018; Baumberg, 2006; Collins & Lapsley, 2008a; Collins & Lapsley, 2008b; WHO, 2018). In Australia, alcohol consumption was attributable to 4.6 percent of the total burden of disease and injury in 2011 (AIHW, 2018). In 2018, alcohol use accounted for 5.1 percent of the global total burden of disease and injury (WHO, 2018). Alcohol is also responsible for a substantial financial cost to society, including healthcare, decreased productivity, absenteeism, crime, and premature death (AIHW, 2018; Collins, 2008a; Collins & Lapsley, 2008b). In 2004 and 2005, this cost was estimated to be 10.8 billion dollars in Australia (Collins & Lapsley, 2008b). The high economic and societal costs of alcohol use, both in Australia and worldwide, emphasises the importance of understanding and reducing its negative impacts.

2.1 Prevalence

Alcohol is one of the oldest psychoactive substances consumed by humans (Hart & Ksir, 2011). It remains the most commonly used recreational substance worldwide, particularly in Western societies (WHO, 2018). Alcohol use is highly prevalent in Australia, with approximately 80 percent of the population aged over 15 years consuming at least one alcoholic beverage in the previous 12 months (AIHW, 2017). Per capita, Australians over 15 years of age consume approximately 9.39 litres of pure alcohol per year (ABS, 2018). According to survey data, Australia has some of the highest rates of alcohol use disorders worldwide, with approximately 21.2 percent of the population receiving a diagnosis in their lifetime (Teesson et al., 2010). Across the lifespan women consume less alcohol, and are less likely to develop an alcohol use disorder, than men (AIHW, 2017; Kessler et al., 1994; Khan

et al., 2013; Wilsnack et al., 2000; Wilsnack, Wilsnack, Kristjanson, Vogeltanz-Holm, & Gmel, 2009; Wilsnack, Wilsnack, & Hiller-Sturmhofel, 1994; York & Welte, 1994). However, there is evidence that alcohol use and alcohol use disorders are increasing in women, particularly in younger age groups (Degenhardt, Hall, Teesson, & Lynskey, 2000; Grucza, Norberg, Bucholz, & Bierut, 2008; Keyes, Grant, & Hasin, 2008; SAMHSA, 2017; Slade et al., 2016).

The current Australian guidelines, designed to reduce the risk of immediate alcohol-related harm, are to consume no more than four standard drinks (10 grams of pure alcohol) on a single occasion (NHMRC, 2009, 2013). To reduce the risk of lifetime harm caused by alcohol-related disease or injury, it is recommended that no more than two standard drinks are consumed on any day (NHMRC, 2009, 2013). Current guidelines also state that there is no safe amount of alcohol for pregnant women or young people under the age of 18 years, and advise total abstinence (NHMRC, 2009, 2013). Despite this, 18 percent of Australian adolescents aged 12 to 17 years consumed alcohol in 2016 (AIHW, 2017). Furthermore, 9.1 percent of males, and 6.8 percent of females, aged 12 to 17 years old, exceeded the single occasion risk guidelines for alcohol use once or more per month (AIHW, 2017). This drinking behaviour is commonly referred to as heavy episodic or binge drinking, and is characterised by the irregular consumption of high doses of alcohol; typically five or more standard drinks per drinking occasion (Adan, Benaiges, & Forero, 2016; Naimi, Nelson, & Brewer, 2010; WHO, 2018).

Although the legal drinking age in Australia is 18 years old, alcohol consumption generally commences prior to this age (AIHW, 2017). In Australia, the average age of drinking onset is currently 16.1 years and does not differ between men and women (AIHW, 2017). In 2018, the World Health Organisation (WHO)

reported that 26.5 percent of adolescents aged 15 to 19 years consumed alcohol (WHO, 2018). This research highlighted that approximately 155 million adolescents consume alcohol across the globe (WHO, 2018). Prevalence studies have shown that alcohol use peaks in young adulthood (approximately 18 to 24 years) and then steadily declines across the lifespan (AIHW, 2017; NIAAA, 2008; WHO, 2018). The age group in Australian society most likely to exceed single occasion risk guidelines are young adults aged 18 to 24 years. In 2016, 42 percent of young Australians aged 18 to 24 years old consumed five or more standard drinks per single occasion, once or more per month, and 15 percent consumed more than 11 standard drinks (AIHW, 2017). (See Figure 2.1.) This was notably higher than any other age group, mirroring global findings (AIHW, 2017; WHO, 2018). Furthermore, young adults also experience more frequent and more severe alcohol hangovers, or negative next-day symptoms, than older adults (Tolstrup, Stephens, & Gronbaek, 2014). This likely reflects higher single-occasion alcohol use in this population (AIHW, 2017; Tolstrup et al., 2014; WHO, 2018). Taken together, this epidemiological research highlights that alcohol use is prevalent worldwide and associated with notable health and financial costs to society (AIHW, 2018; Collins & Lapsley, 2008a; WHO, 2018). These findings also highlight that alcohol use commonly commences before neural development is complete, and young people regularly engage in high single-occasion alcohol use, or binge drinking.

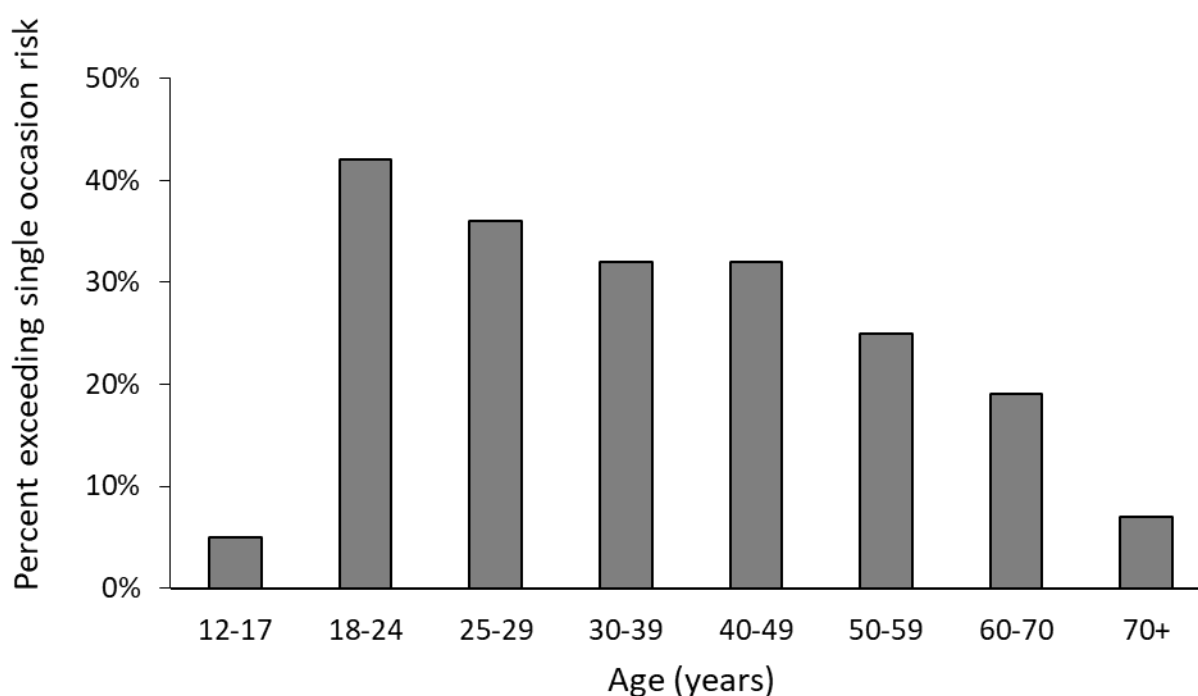


Figure 2.1. Percent of Australians who exceeded single occasion risk guidelines for alcohol consumption (≥ 5 standard drinks) once or more per month by age group in 2016. Adapted from AIHW (2017).

2.2 Physiological effects

2.2.1 Metabolism, absorption, and excretion

Alcohol is most commonly ingested in the form of ethanol. Ethanol, or ethyl alcohol, can be naturally produced by fermenting sugar and yeast (Phillips, 2014). Ethanol is a small, water-soluble molecule that is easily and rapidly absorbed into the blood stream (Cavacuiti & Woodward, 2011). Despite its chemical simplicity, its small size and rapid absorption allows alcohol to affect nearly every aspect of human physiology. Perhaps most critically, ethanol can cross the blood brain barrier and directly impact the central nervous system (Boyle, 2013; Svanberg & Beaunieux, 2015).

After oral ingestion, alcohol is absorbed rapidly through the gastrointestinal tract and enters the blood stream (Cavacuiti & Woodward, 2011). Specifically,

alcohol is absorbed first through the stomach, and then more rapidly through the small intestine (Cederbaum, 2012; Gentry, 2000; Holt, 1981). The rate at which alcohol is absorbed is dependent on several factors, including sex and stomach contents. Firstly, it is well-established that consuming solid, energy-dense food prior to drinking reduces peak blood alcohol concentration (BAC), most likely due to slower gastric emptying (Cederbaum, 2012; Finnigan, Hammersley, & Millar, 1998; Holt, 1981; Horowitz et al., 1989; McFarlane, Pooley, Welch, Rumsey, & Read, 1986; Shultz, Weiner, & Westcott, 1980). Slower gastric emptying allows for more alcohol to be metabolised in the stomach, and delays the entry of alcohol to the small intestine where it is more rapidly absorbed into the blood stream (Cavacuiti & Woodward, 2011; Gentry, 2000; Holt, 1981; McFarlane et al., 1986; Shultz et al., 1980). After consuming the same dose of alcohol, females will attain a 20 to 25 percent higher BAC than a male of the same body mass (Cavacuiti & Woodward, 2011; Goist & Sutker, 1985). This is because women have a smaller pharmacological volume of distribution, caused by proportionally higher body fat percentage and lower total body water, than men (Goist & Sutker, 1985). Women's physiological vulnerability to acute alcohol intoxication is believed to be the primary reason for their lower alcohol intake across the lifespan (Blume, 1986; Wilsnack et al., 2009).

BAC peaks on average one hour after alcohol consumption has ceased before declining linearly (Brunelle, Barrett, & Pihl, 2007; Cederbaum, 2012; Holt, 1981; Mitchell, Teigen, & Ramchandani, 2014; Wilkinson, Sedman, Sakmar, Kay, & Wagner, 1977). (See Figure 2.2.) At moderate to high doses, alcohol is metabolised and eliminated in a pharmacokinetic zero order process at a consistent rate of approximately one standard drink (10 g/kg of ethanol) per hour, independent of the total amount of alcohol consumed (Brunelle et al., 2007; Cederbaum, 2012;

Wilkinson et al., 1977). Figure 2.2 demonstrates this and highlights that alcohol is absorbed and metabolised faster than it is eliminated (Brunelle et al., 2007; Holt, 1981). Approximately 90 percent of alcohol is metabolised and removed hepatically through the liver (Cederbaum, 2012; Zakhari, 2006). A much smaller proportion of alcohol is excreted unmetabolised through sweat, urine, and the lungs (Cederbaum, 2012). Despite differences in mean body mass, men and women metabolise and eliminate alcohol at approximately the same rate, likely due to women having proportionally larger liver volumes than men (Cederbaum, 2012; Kwo et al., 1998).

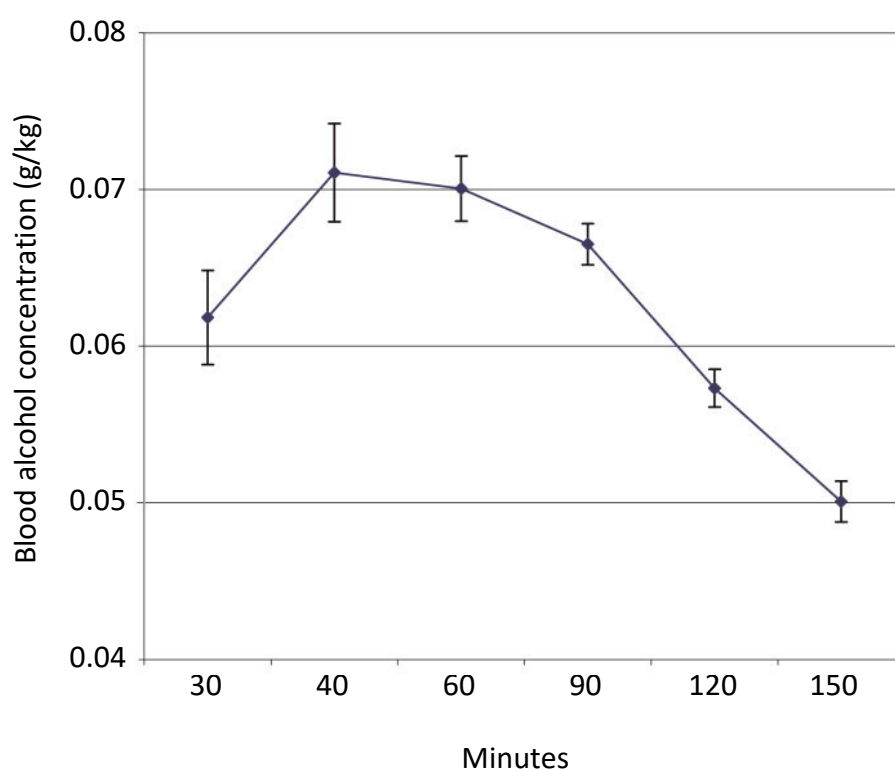


Figure 2.2. Average blood alcohol concentration (g/kg) as a function of time (minutes) following the ingestion of 0.75 g of pure alcohol per kilogram of body weight over 15 minutes at time=0 in 39 males (mean age=23.64 years, standard deviation=3.09 years). Adapted from Brunelle et al. (2007).

In the liver, alcohol is metabolised primarily by two hepatic enzymes; alcohol dehydrogenase and aldehyde dehydrogenase (Edenberg, 2007; NIAAA, 2007; Zakhari, 2006). A genetically determined deficiency in aldehyde dehydrogenase

results in ineffective alcohol metabolism (Edenberg, 2007; Eriksson, 2001; Zakhari, 2006). This genetic polymorphism leads to the accumulation of acetaldehyde, a toxic alcohol metabolite, following alcohol consumption. This causes the alcohol flushing response, or adverse physiological symptoms such as skin redness and nausea, even after small amounts of alcohol are consumed (Eng, Luczak, & Wall, 2007; Zakhari, 2006). The alcohol flushing response is most common in East Asian populations and has been attributed to lower overall rates of alcohol consumption, and lower incidences of alcohol use disorders in these populations (Chang, Hsiao, & Chen, 2017; Eng et al., 2007).

2.2.2 *Effects of acute use*

Following acute ingestion, alcohol has well-established bi-phasic effects on human physiology and behaviour (Boyd, Corbin, Morean, & Martin, 2017; Eckardt et al., 1998; Pohorecky, 1977). At first, as BAC levels begin to rise, alcohol can have stimulatory effects (Eckardt et al., 1998; Pohorecky, 1977). However, alcohol acts primarily as a central nervous system depressant or sedative, particularly at higher doses (Eckardt et al., 1998; Pohorecky, 1977). Alcohols physiological and behavioural effects first emerge approximately 10 minutes following acute consumption (Cederbaum, 2012). Acutely, alcohol affects nearly every aspect of human physiology, including hormonal, gastrointestinal, cardiovascular, immune, respiratory, and central nervous systems (Vonghia et al., 2008). The magnitude of these effects is generally dose dependent (Vonghia et al., 2008). With ingestion of extreme amounts, alcohol can cause unconsciousness and even death due to its depressant effects on respiratory and cardiovascular systems (Jones & Holmgren, 2003; Litovitz, 1986; Svanberg & Beaunieux, 2015; Vonghia et al., 2008).

One of the primary mechanisms through which alcohol alters human functioning and behaviour is through its interaction with inhibitory and excitatory neural signalling in the central nervous system. Acutely, alcohol enhances inhibitory (GABAergic) and suppresses excitatory (glutaminergic) synaptic transmissions (Chastain, 2006; Harrison et al., 2017; Sommer & Spanagel, 2013; Svanberg & Beaunieux, 2015). Although the precise mechanisms are unknown, acute alcohol ingestion appears to facilitate GABAergic neurotransmission, most notably through the enhancement of gamma-aminobutyric acid type A (GABA_A) receptor transmission in the central nervous system (Mihic, 1999). An in vitro investigation using rat neurons showed that acute ethanol exposure increased the frequency and duration of a single GABA_A receptor channel opening (Tatebayashi, Motomura, & Narahashi, 1998). Furthermore, a study in vivisectioned monkey and rat hippocampal tissue slices demonstrated that acute ethanol exposure potentiated GABA_A inhibitory postsynaptic currents (Ariwodola et al., 2003). The enhancement of GABA_A receptor activity leads to reduced neural excitability and increased global inhibition, which likely contributes to the well-established cognitive and behavioural effects of acute alcohol intoxication (Davies, 2003; Lobo & Harris, 2008; Mihic, 1999; Weiner & Valenzuela, 2006). For example, there is evidence that acute alcohol consumption in globally slows information processing in humans (Tzambazis & Stough, 2000). Acute alcohol consumption also results in fatigue and sleepiness, particularly at higher doses (Eckardt et al., 1998; Pohorecky, 1977; Roehrs, Zwyghuizen-Doorenbos, Timms, Zorick, & Roth, 1989). This robust finding is likely driven by alcohol-related GABAergic facilitation, and glutaminergic suppression, as these are the primary neurotransmitter systems responsible for sleep and wake (Roehrs & Roth, 2001a).

In vitro research suggests that acute alcohol exposure facilitates the presynaptic release of GABA in the cerebellum, the brain region primarily responsible for regulating voluntary motor movements (Carta, Mameli, & Valenzuela, 2004). Increased inhibitory signalling in the cerebellum may be responsible for motor impairments during acute alcohol intoxication (Carta et al., 2004). These motor impairments include ataxia, slowed locomotion, impaired eye tracking, and increased reaction time (Eckardt et al., 1998; Peterson, Rothfleisch, Zelazo, & Pihl, 1990; Tagawa et al., 2000; Zoethout, Delgado, Ippel, Dahan, & van Gerven, 2011). For example, in 38 healthy adults, a moderate (breath alcohol concentration; BrAC= .05%) or high (BrAC= .10%) acute alcohol dose led to longer reaction times, and increased errors on a psychomotor vigilance task in a dose-dependent manner (Anderson et al., 2011). Alcohol-related motor impairments have been attributed to increased risk of accidents and injuries during intoxication, including falls and vehicular accidents (Taylor et al., 2010; Waller et al., 1986).

There is evidence that, even at low doses, acute alcohol ingestion reduces the efficacy of glutamate receptors, most notably the N-methyl-D-aspartate (NMDA) receptor (Chastain, 2006). In vitro investigations in animal neurons, most commonly hippocampal, have demonstrated that acute ethanol exposure inhibits NMDA glutaminergic neurotransmission (Ariwodola et al., 2003; Hoffman, Rabe, Moses, & Tabakoff, 1989; Lovinger, White, & Weight, 1989; Weaver et al., 1993). Both excitatory and inhibitory neurotransmitter pathways are heavily implicated in learning and memory processes, most notably long-term potentiation (Chastain, 2006). It has been hypothesised that glutaminergic inhibition, in combination with GABAergic facilitation, may be related to impairments in learning and memory following acute alcohol ingestion (Chastain, 2006; Gonzales & Jaworski, 1997;

Morrisett & Swartzwelder, 1993; Randall, Lee, Meyer, Wittenberg, & Gruol, 1995; White, 2003; White, Matthews, & Best, 2000; Zorumski, Mennerick, & Izumi, 2014). This has been demonstrated by evidence that in vitro ethanol exposure to vivisectioned slices of rat hippocampal tissue inhibits long-term potentiation in these cells (Blitzer, Gil, & Landau, 1990). This finding has since been replicated in vivo (Givens & McMahon, 1995). Laboratory studies in both humans and animals have consistently shown that acute alcohol ingestion impairs working memory and long-term memory consolidation (Chin et al., 2011; Dry, Burns, Nettelbeck, Farquharson, & White, 2012; Mintzer, 2007; Peterson et al., 1990; Soderlund, Grady, Easdon, & Tulving, 2007; Soderlund, Parker, Schwartz, & Tulving, 2005). An investigation in 27 men showed that next-day episodic memory recall was notably impaired following acute alcohol intoxication (BrAC = .069%) during learning (Soderlund et al., 2007). The impacts of acute alcohol consumption on memory are further demonstrated by the well-reported clinical phenomenon of dose-dependent memory loss or ‘blackouts’ during alcohol intoxication (Lee, Roh, & Kim, 2009; Perry et al., 2006; White, 2003).

Animal studies have provided evidence that even low doses of acute alcohol are associated with the release of both dopamine and serotonin in the nucleus accumbens, a brain region intimately involved in mediating reward processing (Chastain, 2006; Yan, 1999; Yoshimoto, McBride, Lumeng, & Li, 1992). This neurological response may underly the self-reported euphoria, reduced stress, and positive mood initially reported following acute alcohol consumption in healthy adults (Geiger & MacKerron, 2016; Levenson, Sher, Grossman, Newman, & Newlin, 1980; Sayette, 1999; Steele & Josephs, 1988). It is likely this neurochemical action contributes to the neurologically rewarding or ‘addictive’ properties of alcohol

(Chastain, 2006). In summary, there is substantial evidence that acute alcohol consumption interacts directly with neurotransmitter systems, which in turn impacts behaviour and cognition in a complex dose-dependent manner.

Following the cessation of acute consumption BAC will return, after time, to zero. This time-period is known as acute alcohol withdrawal, colloquially referred to as the alcohol hangover (Prat, Adan, & Sanchez-Turet, 2009; Swift & Davidson, 1998; Wiese, Shlipak, & Browner, 2000). Acute alcohol withdrawal can persist for up to 24 hours, and is associated with negative physiological, psychological, and behavioural symptoms that increase in severity with higher levels of preceding alcohol consumption (Prat et al., 2009; Swift & Davidson, 1998; Tipple, Benson, & Scholey, 2016; van Schrojenstein Lantman, Mackus, van de Loo, & Verster, 2017; Wiese et al., 2000). These symptoms may include nausea, vomiting, fatigue, tiredness, headaches, diarrhoea, sensitivity to bright light, muscle aches, thirst, and low mood (Prat et al., 2009; Tipple et al., 2016). Motor control and memory impairments also appear to extend into the acute alcohol withdrawal period (Karadayian & Cutrera, 2013; Prat, Adan, Perez-Pamies, & Sanchez-Turet, 2008; Stephens, Ling, Heffernan, Heather, & Jones, 2008; van Schrojenstein Lantman et al., 2017; Verster, van Duin, Volkerts, Schreuder, & Verbaten, 2003). A study in 48 healthy young adults (24 women) showed delayed recall on a word-learning test administered the morning following a high dose of pre-bedtime alcohol (1.4 g/kg), despite a BrAC of .00 percent, suggesting impaired memory retrieval during acute alcohol withdrawal (Verster et al., 2003).

Alcohol hangover symptoms are believed to result from alcohol's detrimental impact on metabolic and biological systems, including gastrointestinal irritation, low blood sugar, dehydration, electrolyte imbalance, vasodilation, and prolonged

exposure to harmful alcohol metabolites, such as acetaldehyde (Prat et al., 2009; Tipple et al., 2016). The discontinuation of alcohol's acute effects on neurotransmitter systems may also contribute to the alcohol hangover (Prat et al., 2009; van Schrojenstein Lantman et al., 2017). For example, the cessation of dopaminergic and serotonergic facilitation during acute alcohol withdrawal may underly low mood (McKinney & Coyle, 2006; van Schrojenstein Lantman et al., 2017). Critically, it has been hypothesised that some alcohol hangover symptoms may be related to alcohol-related sleep disturbances (Chan et al., 2015; McKinney & Coyle, 2006; Prat et al., 2009; Swift & Davidson, 1998; Verster, 2008). Indeed, the most common symptom of acute alcohol withdrawal is fatigue and tiredness (McKinney & Coyle, 2006; Swift & Davidson, 1998; van Schrojenstein Lantman et al., 2017; Wiese et al., 2000). Alcohol-related sleep disturbance may result from acute alcohol withdrawal occurring during the sleep period (Colrain, Nicholas, & Baker, 2014; Roehrs & Roth, 2001a). Further to this, acute alcohol consumption suppresses melatonin release, delaying circadian sleep timing and processes (Prat et al., 2009; Rupp, Acebo, & Carskadon, 2007). In combination, these effects may disrupt the functional properties of sleep, and contribute directly to fatigue and other alcohol hangover symptoms.

2.2.3 Effects of chronic use

Heavy alcohol consumption over an extended time period is associated with well-established negative physiological and neurological consequences (Rehm, 2011). The chronic effects of alcohol use are most commonly researched in people with a past or current alcohol use disorder. Alcohol use disorders are characterised by problematic, compulsive alcohol use, resulting in cognitive and behavioural

symptoms that are thought to be underpinned by alcohol-related neurological degeneration (APA, 2013; Connor, Haber, & Hall, 2016; Freyer, Morley, & Haber, 2016; NIAAA, 2016). Alcohol use disorders are also associated with serious deteriorations in physical health (Lieber, 1998; Molina & Nelson, 2018; Rehm, 2011). This includes liver cirrhosis, gastrointestinal disturbances, such as ineffective digestion and the malabsorption of nutrients, and closely-related neurological disorders, such as Wernicke Korsakoff syndrome (Bode & Bode, 1997; Butterworth, 1995; Lu & Cederbaum, 2008; Martin, Singleton, & Hiller-Sturmhofel, 2003; O'Shea, Dasarathy, McCullough, & Pack, 2010; Pfeiffer, Schmidt, Vidon, Pehl, & Kaess, 1992). Alcohol use disorders are also an independent risk factor for developing cardiovascular diseases such as myocardial infarction, atrial fibrillation, congestive heart failure (Whitman et al., 2017), hypertension (Marques-Vidal et al., 2001), and stroke (Sundell, Salomaa, Vartiainen, Poikolainen, & Laatikainen, 2008). Alcohol has also been defined as a Group 1 carcinogen by the International Agency for Research on Cancer, with research demonstrating alcohol's causative role in the development of human cancers, including breast, liver, oral cavity, pharynx, larynx, and colorectum (Cogliano et al., 2011; LoConte, Brewster, Kaur, Merrill, & Alberg, 2018). It is of note that women diagnosed with alcohol use disorders have a greater susceptibility to alcohol-related disease and injury compared to men (Ashley et al., 1977; Ceylan-Isik, McBride, & Ren, 2010; SAMHSA/CSAT, 2009). This is despite women experiencing shorter time-periods of chronic alcohol use, longer periods of sobriety, and consuming less alcohol overall than men (Colrain et al., 2011; Pfefferbaum, Rosenbloom, Deshmukh, & Sullivan, 2001). This is believed to be attributable to women's physiological vulnerability to acute alcohol intoxication

(Brady & Randall, 1999; Ceylan-Isik et al., 2010; Greenfield et al., 2007; SAMHSA/CSAT, 2009).

At repeated and high doses, chronic alcohol consumption can cause structural and functional changes to the brain (Oscar-Berman & Marinkovic, 2003, 2007; Sullivan, Harris, & Pfefferbaum, 2010; Zahr & Pfefferbaum, 2017; Zahr, Pfefferbaum, & Sullivan, 2017). These changes appear to be dose dependent as they are related to the amount and duration of heavy alcohol use (Harding, Halliday, Ng, Harper, & Kril, 1996). In both men and women, chronic alcohol use is associated with increased cerebrospinal fluid volume and brain volume shrinkage, including reductions in both grey and white neural matter (Colrain et al., 2011; De Bellis et al., 2000; Fein et al., 2002; Fortier et al., 2011; Harper, Smith, & Kril, 1990; Kril, Halliday, Svoboda, & Cartwright, 1997; Pfefferbaum, Adalsteinsson, & Sullivan, 2006a, 2006b; Pfefferbaum, Rosenbloom, Serventi, & Sullivan, 2002; Pfefferbaum & Sullivan, 2002; Pfefferbaum et al., 2000; Pfefferbaum, Sullivan, Rosenbloom, Mathalon, & Lim, 1998; Rohlfing, Sullivan, & Pfefferbaum, 2006; Rosenbloom, Sullivan, & Pfefferbaum, 2003; Sullivan, 2003; Sullivan, Deshmukh, Desmond, Lim, & Pfefferbaum, 2000; Sullivan et al., 2010). These alcohol-related neural changes have been shown both in vivo MRI studies (De Bellis et al., 2000; Moselhy, Georgiou, & Kahn, 2001; Pfefferbaum et al., 2006a; Pfefferbaum et al., 2000; Pfefferbaum, Sullivan, Mathalon, & Lim, 1997; Rohlfing et al., 2006; Rosenbloom et al., 2003), and in vitro post mortem neural cell counts (Harding et al., 1996; Harper, Dixon, Sheedy, & Garrick, 2003; Harper & Kril, 1988; Kril et al., 1997; Sutherland, Sheedy, & Kril, 2014). Critically, frontal and prefrontal brain regions show the greatest volume deficits (Harper, 2009; Harper & Matsumoto, 2005; Kril et al., 1997; Moselhy et al., 2001; Pandey et al., 2018; Pfefferbaum et al., 1997). Unsurprisingly,

these neural changes have been associated with substantial cognitive impairments, particularly in executive functioning (Oscar-Berman & Marinkovic, 2003, 2007; Sullivan et al., 2010; Zahr & Pfefferbaum, 2017; Zahr et al., 2017). These impairments include impaired inhibition (Fox, Hong, & Sinha, 2008; Oscar-Berman, Shagrin, Evert, & Epstein, 1997; Stavro, Pelletier, & Potvin, 2013), impulse control, emotion regulation (Fox et al., 2008; Petit et al., 2015; Stephan et al., 2017), attention, and working memory (Fein, Bachman, Fisher, & Davenport, 1990; Hagen et al., 2016; Maurage, de Timary, Billieux, Collignon, & Heeren, 2014; Oscar-Berman & Marinkovic, 2007; Oscar-Berman et al., 2014; Pandey et al., 2018; Sullivan, Rosenbloom, & Pfefferbaum, 2000). To further highlight this, a meta-analysis by Stephan and colleagues (2017), involving 77 studies and 5,140 participants, concluded that executive function and impulsivity, including planning, problem solving, and inhibitory control, were substantially impaired in people with alcohol use disorders.

Long-term alcohol use disorders are also associated with notable changes to functional white matter. This has been demonstrated using diffusion tensor imaging (DTI) techniques, such as fractional anisotropy, that provide a measure of axonal connectivity, integrity, and degree of myelination (Alba-Ferrara & de Erausquin, 2013; Alexander, Lee, Lazar, & Field, 2007). Specifically, research has generally shown that people with alcohol use disorders have widespread fractional anisotropy deficits, most notable in fronto-temporal regions (Chumin et al., 2018; Monnig et al., 2013a; Monnig, Tonigan, Yeo, Thoma, & McCrady, 2013b; Pandey et al., 2018; Pfefferbaum et al., 2006a; Pfefferbaum & Sullivan, 2002; Pfefferbaum et al., 2000; Zorlu et al., 2014). These findings suggest that the white matter tracts are not as effective at facilitating the transmission of neural signals, slowing neural

communication (Alba-Ferrara & de Erausquin, 2013; Zahr et al., 2017). These deficits may represent axonal loss and/or demyelination related to chronic alcohol use and have been associated with reduced cognitive performance (Johansen-Berg, 2010; Pandey et al., 2018). For example, an investigation by Pandey and colleagues (2018) demonstrated that white matter fractional anisotropy was lower in 30 abstinent men with alcohol use disorders, compared to 30 healthy men. Furthermore, lower fractional anisotropy in these individuals was associated with worsening visuo-spatial memory and problem-solving abilities, measured using the visual span test, and Tower of London test, respectively.

The injurious effects of chronic alcohol exposure on the brain include reduced neuronal dendritic branching, increased oxidative stress, and cell membrane and blood brain barrier damage (Haorah et al., 2008; Harper, 2009; Kril et al., 1997). Animal models of binge alcohol exposure suggest that inflammatory cytokines and activated microglia may play a critical role in chronic alcohol-related neurodegeneration (Zhao et al., 2013). Zhao and colleagues (2013) intermittently administered high doses of alcohol intragastrically to 16 adult rats. They found that increased expression of pro-inflammatory cytokines and hypertrophied microglia was associated with dendritic injury and neural death. Secondary disease resulting from chronic alcohol use may also play a critical role in alcohol-related brain damage, including hepatic encephalopathy resulting from liver cirrhosis (Butterworth, 2003; Gorg et al., 2010; Harper & Kril, 1989), and Wernicke–Korsakoff syndrome resulting from nutrient malabsorption (Butterworth, 1995; Martin et al., 2003). It is worth noting that neural deficits are still evident in people with alcohol use disorders without secondary disease, and most prominent in the

frontal and prefrontal cortex (Harper, 2009; Harper & Matsumoto, 2005; Kril et al., 1997).

Chronic alcohol exposure can modify critical neurotransmitter systems (Banerjee, 2014; Chastain, 2006; Kumar et al., 2009; Ward, Lallemand, & de Witte, 2009). This includes GABA (Kumar et al., 2009), glutamate (Gonzales & Jaworski, 1997), opioid (Bazov et al., 2013; Herz, 1997), dopamine (Ma & Zhu, 2014; Soderpalm, Lof, & Ericson, 2009), and serotonin (Banerjee, 2014; Lovinger, 1997) neurochemical pathways. These systems adapt in response to chronic alcohol exposure in order to maintain neurochemical homeostasis. This results in rebound or opposite neurochemical actions when alcohol is no longer present in the system (Most, Ferguson, & Harris, 2014). The primary mechanisms through which this neuroadaptation occurs is the up or down regulation of pre-synaptic neurotransmitter release and/or post-synaptic receptor density (Most et al., 2014; Roberto & Varodayan, 2017).

Notably, research in both animals and humans has shown that chronic alcohol exposure leads to the adaptation of the primary inhibitory and excitatory neurotransmitter systems in the brain (Gonzales & Jaworski, 1997; Kumar et al., 2009). Acutely, alcohol facilitates GABAergic, and inhibits glutaminergic neurotransmission; however, neuroadaptation following chronic alcohol exposure results in GABAergic suppression, and glutaminergic enhancement (Gonzales & Jaworski, 1997; Kumar et al., 2009; Lovinger, 1997; Roberto & Varodayan, 2017). The downregulation of GABAergic, and upregulation of glutaminergic neurotransmission, has been clearly demonstrated by in vitro and in vivo findings in animal models. Intermittent oral ethanol exposure (6 g/kg per day for 60 days) in 30 Sprague-Dawley rats, compared to controls, resulted in a lasting decrease in GABA_A

receptor-mediated inhibition in vivisectioned hippocampal tissue (Kang, Spigelman, Sapp, & Olsen, 1996). An in vitro study in cultured cerebellar granule cells, collected from a Sprague Dawley rat, showed that continuous 100 percent ethanol exposure to these cells over two to four days increased NMDA post-synaptic receptor transmission (Iorio, Reinlib, Tabakoff, & Hoffman, 1992). Research has also demonstrated that intermittent chronic ethanol exposure using vapour chambers in mice enhances glutaminergic neurotransmission in vivisectioned prefrontal cortex tissue (Kroener et al., 2012; Pleil et al., 2015). A post-mortem investigation of neural gene expression in eight humans diagnosed with an alcohol use disorder found a decrease in GABA_A receptor messenger ribonucleic acid (mRNA), and increased NMDA receptor mRNA, in the hippocampus and prefrontal cortex (Zhou, Yuan, Mash, & Goldman, 2011). This finding suggests a downregulation of GABAergic receptors, and upregulation of glutaminergic receptors, in these brain regions (Roberto & Varodayan, 2017). Taken together, these findings highlight the brain's ability to function and maintain neurochemical homeostasis during periods of high and prolonged alcohol exposure (Kumar et al., 2009; Most et al., 2014). This neurochemical adaptation may also contribute to the experience of alcohol withdrawal syndromes following the cessation of chronic alcohol exposure (Most et al., 2014; Roberto & Varodayan, 2017).

Consistent with these adaptations an abrupt cessation or major reduction in alcohol consumption following a long-term alcohol use disorder is associated with numerous negative physiological, neurological and behavioural consequences, referred to as alcohol withdrawal syndrome (APA, 2013; Bayard, McIntyre, Hill, & Woodside, 2004; Jesse et al., 2017; Kalant, 1977; McKeon, Frye, & Delanty, 2008; Trevisan, Boutros, Petrakis, & Krystal, 1998). The severity of this syndrome is

largely dependent on the duration and intensity of the alcohol use disorder (Bayard et al., 2004; McKeon et al., 2008). It has been suggested that enhanced glutamate-mediated excitability following the cessation of chronic alcohol use may be responsible for most clinical symptoms, including autonomic hyperactivity, delirium tremens, hallucinations, anxiety, psychomotor agitation, tonic-clonic seizures, and insomnia (APA, 2013; Bayard et al., 2004; Jesse et al., 2017; Kalant, 1977; McKeon et al., 2008; Trevisan et al., 1998). Cardiovascular dysregulation during alcohol withdrawal syndrome may be due to the overactivity of the sympathetic nervous system (Bar et al., 2006; Kahkonen, 2004). Hallucinations and hyperactivity may result from augmented glutaminergic and dopaminergic neurotransmission during this time period (Cosgrove et al., 2009). Research suggests that GABAergic suppression, and glutaminergic enhancement, may be responsible for both tonic-clonic seizures and insomnia following the cessation of alcohol use (Brower, 2003; Brower, Krentzman, & Robinson, 2011; Chakravorty, Chaudhary, & Brower, 2016; Hughes, 2009; Rogawski, 2005; Stein & Friedmann, 2005). These adverse symptoms typically last for one to seven days, although some may persist for longer and are referred to as protracted alcohol withdrawal syndrome (Jesse et al., 2017; Trevisan et al., 1998).

There is both physical and neural recovery with extended abstinence in people recovering from alcohol use disorders. Physiological changes during prolonged abstinence include improvements in immune function, and alcohol-related liver injury, such as reduced cirrhosis progression (O'Shea et al., 2010; Pessione et al., 2003). Long-term abstinence is also associated with some improvements in structural and functional integrity of the brain (Pfefferbaum et al., 2014; Zou et al., 2017). Neurological recovery during abstinence may be related to a reduction in

inflammatory cytokines and hypertrophic microglia, and the proliferation of neurotrophic microglia, which have been associated with neural and cognitive recovery in animal models of alcohol use disorders (Zhao et al., 2013). In humans, studies have reported increases in both grey and white matter volume across extended abstinence (Bartsch et al., 2007; Gazdzinski, Durazzo, Mon, Yeh, & Meyerhoff, 2010; Pfefferbaum et al., 1995; van Eijk et al., 2013). Van Eijk and colleagues (2013) reported a rapid recovery in total brain volume using MRI in 49 middle-aged adults (9 women) recovering from an alcohol use disorder. Specifically, there was a global increase in grey matter and reduction in cerebrospinal fluid, following 14 days of abstinence. However, despite this rapid recovery, total brain volume was still lower than a healthy age- and sex-matched comparison group (n=55), suggesting that neural recovery may be protracted (van Eijk et al., 2013). Indeed, there is evidence that some neural changes resulting from chronic alcohol use may be long lasting or even permanent (Fein et al., 2006a; Fein, Shimotsu, Chu, & Barakos, 2009). For example, Fein and colleagues (2006b; 2009) found that grey matter deficits were still detected using MRI following long-term abstinence (6 months to 14 years) in 48 adults (23 women) with a previous alcohol use disorder. Critically, some structural deficits were associated with impairments in cognitive functioning. For example, reduced parietal lobe volume was associated with deficits in visuospatial information processing, using the Clocks, Tic Tac, and Block Design tests (Fein et al., 2009; Fein, Torres, Price, & Di Sclafani, 2006b). This suggests that, although there is notable recovery, some neural and cognitive deficits associated with chronic alcohol use may be enduring.

As well as increases in brain volume, abstinence following an alcohol use disorder has also been associated with improvements in functional neural

connectivity (Monnig et al., 2013a; Pfefferbaum et al., 2014; Zou et al., 2017). In vitro animal models of alcohol use disorders have shown that neural dendritic spine density increases following five months of abstinence, indicating neural reorganisation and improved connectivity (King, Hunter, & Walker, 1988). A human study by Zou and colleagues (2017) assessed 52 adults (7 women) recovering from alcohol use disorders using DTI. They found increases in fractional anisotropy in the right cingulum and hippocampus, following one month of abstinence, compared to one week. This is indicative of improvements in microstructural white matter in these regions, possibly representing remyelination and/or glial cell proliferation (Crews & Nixon, 2009; Sullivan & Pfefferbaum, 2005; Zou et al., 2017). Critically, lower fractional anisotropy in these participants was associated with increased disorder severity, lower mood on the Beck Depression Inventory, and higher impulsivity on the Barratt Impulsiveness Scale (Zou et al., 2017). Furthermore, there is evidence that reduced fractional anisotropy is a biological risk factor for relapse in abstinent individuals with an alcohol use disorder (Pfefferbaum et al., 2014; Zou et al., 2018). It is also worth noting that some functional white matter deficits appear to be long lasting (Monnig et al., 2013a; Pfefferbaum et al., 2014; Zou et al., 2017). A study by Monnig and colleagues (2013a) found that nine remitted adults (2 female), aged approximately 36.4 years, still had lower fractional anisotropy in parietal brain regions following a year or more of abstinence, compared to 15 aged-matched healthy control participants (Monnig et al., 2013a). As this brain region is central to processing visuospatial information, these deficits may also underly the previously described findings of Fein and colleagues (2006b; 2009) that showed long-lasting deficits in visuospatial processing in individuals recovering from alcohol use disorders. In summary, chronic alcohol consumption, such as that observed in long-

term alcohol use disorders, is associated with major and related changes to the brain and cognitive function. Critically, although many of these deficits show recovery following the cessation of heavy drinking, some appear to be long-lasting.

2.2.4 Alcohol use in adolescents and young adults

Adolescence and young adulthood are major developmental time periods, typically encompassing both the final stages of neural development, and the onset and acceleration of alcohol use (AIHW, 2017; Baker et al., 2012; Colrain & Baker, 2011; Feinberg & Campbell, 2010; Gogtay et al., 2004; Hagenauer et al., 2009; Spear, 2002a). Critically, both acute and habitual alcohol use during this crucial developmental period may uniquely and negatively impact the brain and its healthy development (Guerri & Pascual, 2010; Lubman et al., 2007; Sadrian et al., 2013).

2.2.4.1 Effects of acute use

Due to the ethical and legal constraints of administering alcohol to underage adolescents, research in this age group has primarily been conducted in young adults over 18 or 21 years, or using validated animal models of adolescent development (Spear, 2004). However, as adolescents and young adults are neurodevelopmentally similar, research findings are likely relevant to both age groups (Gogtay et al., 2004; Lebel & Beaulieu, 2011; Miller et al., 2012; Pfefferbaum et al., 2016; Sowell, Thompson, Tessner, & Toga, 2001). The high prevalence of acute alcohol consumption in young people may be related to the unique physiological effects of alcohol during development (AIHW, 2017; Spear, 2014; WHO, 2018). Notably, there is growing evidence that young people may be less sensitive to the depressive effects of acute alcohol, and potentially more sensitive to its acute stimulatory effects, compared to neurologically mature adults (Little, Kuhn, Wilson, &

Swartzwelder, 1996; Monti et al., 2005; Moy, Duncan, Knapp, & Breese, 1998; NIAAA, 2004/2005; Novier, Diaz-Granados, & Matthews, 2015; Quoilin, Didone, Tirelli, & Quertemont, 2010; Spear, 2000; Spear, 2014).

Firstly, there is substantial behavioural evidence in animal models that young people may be less responsive to the sedative and motor impairing effects of acute alcohol (Pian, Criado, Walker, & Ehlers, 2008; Silveri & Spear, 1998; Slawecki, 2002; Treloar, Celio, Lisman, Miranda, & Spear, 2017; York & Chan, 1993). The righting reflex is a well-established behavioural measure of physiological sedation and motor coordination in rats (Spear, 2014). Numerous studies have demonstrated that after receiving an intravenous dose of alcohol (1.5 – 5.0 g/kg), adolescent rats were significantly faster at completing a righting reflex after being laid dorsally, compared to mature adult rats (Linsenhardt et al., 2009; Little et al., 1996; Moy et al., 1998; Pian et al., 2008; Quoilin et al., 2010; Silveri & Spear, 1998). Further to this, following a high dose of alcohol (2.0 – 3.0 g/kg), adolescent rats demonstrated less impairments in motor coordination on a tilting-plane test compared to adults (White et al., 2002). A potential mechanism for these robust findings is the protracted development of the inhibitory GABAergic neurotransmitter system across adolescence, observed in both animals (Moy et al., 1998; Yu, Wang, Fritschy, Witte, & Redecker, 2006) and humans (Chugani et al., 2001; Fung et al., 2010; Silveri et al., 2013). A key study by Chugani and colleagues (2013) investigated GABA_A receptor distribution across the lifespan using positron emission topography in 35 participants (15 female) aged between 2 and 50 years. Their findings indicated that subcortical GABA_A receptors reached adult levels between 14 and 17.5 years of age, however, cortical GABA_A receptors did not reach maturity until approximately 18 to 22 years (Chugani et al., 2001). This finding has since been supported by other in

vivo studies in human adolescents (Fung et al., 2010; Silveri et al., 2013). Given that acute alcohol ingestion facilitates inhibitory GABAergic neurotransmission, the immaturity of this system (i.e., fewer cortical GABA_A receptors) could potentially explain less physiological sedation in this developing age group (Moy et al., 1998; Spear, 2014). Concerningly, longitudinal research in adults has shown that lower sensitivity to the depressant effects of alcohol are a well-established risk factor for developing an alcohol use disorder (Schuckit, Smith, Anderson, & Brown, 2004).

Coupled with reduced sensitivity to alcohol's sedative effects, young people may also experience heightened sensitivity to alcohol's physiological stimulatory effects (ANCD, 2013; Dragan, 2015; Kuntsche, Knibbe, Gmel, & Engels, 2005; Monti et al., 2005; Quoilin et al., 2010; Spear, 2002b, 2014). Animal models have provided some evidence that adolescents may experience greater physiological stimulation on the ascending limb of the BAC curve (Quoilin et al., 2010; Stevenson, Besheer, & Hodge, 2008). For example, following a high dose of intravenous alcohol (2.5 – 5.0 g/kg), adolescent rodents had greater locomotor stimulation than adult rodents, an established measure of physiological stimulation (Quoilin et al., 2010; Stevenson et al., 2008). In humans, young people self-report more stimulatory and positive effects from acute alcohol consumption than adults (Harrison, Kelly, Lindsay, Advocat, & Hickey, 2011; Treloar et al., 2017). An increased stimulatory response to acute alcohol in this age group may be related to the heightened sensitivity of the mesolimbic reward system during adolescence and young adulthood (Doremus-Fitzwater, Varlinskaya, & Spear, 2010; Petit, Kornreich, Verbanck, Cimochovska, & Campanella, 2013; Spear, 2011).

There is also evidence that long-term potentiation or neural plasticity may be more disrupted by acute alcohol consumption in young people (Pyapali, Turner,

Wilson, & Swartzwelder, 1999; White & Swartzwelder, 2005). This is supported by in vivo findings that acute ethanol exposure inhibits long-term potentiation at lower doses in adolescent rat hippocampal tissue, compared to mature adults (Pyapali et al., 1999). Studies in animals and humans have shown that young people experience greater acute alcohol-related memory impairments than adults (see White & Swartzwelder, 2005 for review). For example, a human study found that young people aged 21 to 24 years had greater semantic memory impairments following alcohol consumption (0.6 g/kg) compared to participants aged 25 to 29 years, assessed via the Hopkins Verbal Learning Test (n=12; Acheson et al., 1998). There is also evidence in animal models that acute ethanol exposure during the final stages of neural development may impair neurogenesis (Crews, Mdzinarishvili, Kim, He, & Nixon, 2006). Specifically, Crews and colleagues (2006) administered varying doses of ethanol (1.0 – 5.0 g/kg) to adolescent rats, and found that in vitro cell survival, and differentiation of progenitor neurons, was inhibited by acute ethanol exposure, even at low doses. These findings could potentially explain greater learning and memory impairments following acute alcohol exposure in young people.

Finally, research suggests that young people may experience milder acute alcohol withdrawal or ‘hangover’ symptoms compared to adults, after consuming the same alcohol dose (Doremus, Brunell, Varlinskaya, & Spear, 2003; Schramm-Sapota, Walker, Caster, Levin, & Kuhn, 2009; Varlinskaya & Spear, 2006). Several animal studies indicate that after receiving the same dose of alcohol, adolescent rats show faster recovery of acute alcohol withdrawal symptoms compared to mature adults (Brasser & Spear, 2002; Doremus-Fitzwater & Spear, 2007; Varlinskaya & Spear, 2006). Furthermore, adolescent rats did not display indicators of anxiety during acute alcohol withdrawal, with anxiety being notably elevated in adult rats

(Brasser & Spear, 2002; Doremus-Fitzwater & Spear, 2007; Doremus et al., 2003; Varlinskaya & Spear, 2006). This suggests that young people may experience less severe acute alcohol withdrawal than adults, which could potentially contribute to higher single-occasion alcohol use in this age group (Schramm-Sapota et al., 2009). However, despite these findings, epidemiological research in humans has consistently demonstrated that young people experience more frequent and severe alcohol hangovers than adults (Tolstrup et al., 2014). A large cross-sectional study in 51,645 men and women aged 18 to 94 years demonstrated that the incidence and severity of alcohol hangovers decreased with age. As this research did not control for alcohol doses, this finding likely reflects higher and more frequent single-occasion alcohol consumption in young people (Tolstrup et al., 2014). Taken together, there is substantial evidence that young people experience unique physiological and behavioural responses to acute alcohol consumption that differ from adults. This may contribute to higher single-occasion alcohol use in this developing age group (Doremus-Fitzwater et al., 2010; Novier et al., 2015; Schramm-Sapota et al., 2009; Schuckit, 1994; Schuckit et al., 2004).

2.2.4.2 Effects of habitual use

It is well-established that prolonged ethanol exposure during critical developmental time periods can cause lasting changes to the brain, cognition, and behaviour (Guerri & Pascual, 2010; Gupta, Gupta, & Shirasaka, 2016; Hames, 2012; Hong & Krauss, 2017; Lubman et al., 2007; Miller, 2006; Sadrian et al., 2013). To highlight this, chronic prenatal alcohol exposure can result in life-long intractable physiological and neurological impairments, such as fetal alcohol spectrum disorder (Bell et al., 2010; Clarke & Gibbard, 2003; Gupta et al., 2016; Riley, Infante, & Warren, 2011; Sadrian et al., 2013; Streissguth, Landesman-Dwyer, Martin, &

Smith, 1980; Streissguth & O'Malley, 2000). More recently, the impact of habitual alcohol use during the final stages of adolescent neural development has become of interest (Lubman et al., 2007; Miller, 2006; Squeglia, Jacobus, & Tapert, 2009a; Witt, 2010). These effects are typically investigated in young people who habitually exceed single occasional risk guidelines for alcohol use (i.e., binge drink), as well as those diagnosed with alcohol use disorders. Evidence has also been gathered using animal models (Becker & Ron, 2014; Spanagel, 2000). In both humans and animals, heavy alcohol exposure during the final stages of neural development is associated with unique physiological, neurological, and behavioural consequences (Kuntsche & Gmel, 2013; Monti et al., 2005; NIAAA, 2004; Spear, 2014).

2.2.4.2.1 Physiological effects

Unsurprisingly, as in adults, heavy alcohol use has been associated with poorer overall physical health in young people (Clark, Lynch, Donovan, & Block, 2001; Mohamed & Ajmal, 2015; NIAAA, 2004, Oesterle et al., 2004; Okoro et al., 2004). A study by Clark and colleagues (2001) compared the physical health of 128 adolescents diagnosed with an alcohol use disorder, aged 14 to 18 years old, to 131 same-aged control participants. Adolescents experiencing alcohol use disorders had poorer overall physical health, including modestly elevated liver enzymes, suggesting liver injury. A prospective investigation by Oesterle and colleagues (2004) reported that binge drinking during adolescence was associated with worse health problems in young adulthood, including increased risk of obesity and hypertension. The fewest health problems were observed in young adults who did not engage in binge drinking during adolescence. These findings suggest that heavy alcohol use in young people negatively impact physical health (Clark et al., 2001; NIAAA, 2004).

Habitual alcohol consumption may also interfere with physiological growth and development in young people (NIAAA, 2004). There is mounting evidence in animal models that heavy alcohol exposure early in life may delay the onset of puberty through alcohol's interaction with hypothalamic neuroendocrine function (see Dees, Hiney, & Srivastava, 2017 for review). Adolescence and young adulthood are also critical developmental time periods for bone formation and growth (Sampson, 1998). There is substantial evidence in both humans and animals that habitual alcohol use in adolescence impairs bone formation (Hogan, Sampson, Cashier, & Ledoux, 1997; LaBrie, Boyle, Earle, & Almstedt, 2018; Lucas, Fraga, Ramos, & Barros, 2012; Sampson, 1998; Sampson, Chaffin, Lange, & DeFee, 1997). A study by LaBrie and colleagues (2018) demonstrated that frequent binge drinking (four or more drinks per occasion) in adolescence was associated with lower vertebral bone mineral density in 87 young adult women (LaBrie et al., 2018). These findings highlight that, due to ongoing physiological development, young people may experience unique health and developmental consequences as a result of habitual alcohol consumption.

2.2.4.2.2 Neurological effects

Evidence in animal models suggests that heavy ethanol exposure during adolescence may cause unique and lasting changes to the brain. A study by Crews and colleagues (2000) exposed adolescent and adult rats to intermittent intragastric ethanol (mirroring binge drinking) for four consecutive days. They found that ethanol exposure produced significant brain damage at both ages, assessed using the *in vitro* amino cupric silver technique. However, compared to adults, neural damage was greater and more widespread in adolescent rats, particularly in frontal regions. These differences may be due to the ongoing development of these neural areas in

adolescence, as well as unique impairments in neurogenesis resulting from acute ethanol exposure (Crews et al., 2000; Crews et al., 2006; Cservenka & Brumback, 2017; Spear, 2014, 2016). There is also evidence that chronic ethanol exposure in adolescence may cause a long-lasting suppression of neurogenesis. This was demonstrated by Ehlers and colleagues (2013b) who exposed adolescent Wistar rats to moderate doses of intermittent ethanol vapour for 35 consecutive days. In vitro evidence indicated that there was a notable reduction in measures of neurogenesis and progenitor proliferation, even following the cessation of ethanol exposure and the presence of alcohol withdrawal syndrome, in adulthood. Interestingly, neurogenesis suppression was correlated with behavioural disinhibition, a relationship that persisted into adulthood (Ehlers, Desikan, & Wills, 2013a). These studies provide some evidence that ethanol exposure during the final stages of development may cause lasting and unique neural changes (Crews et al., 2006; Cservenka & Brumback, 2017; Guerri & Pascual, 2010; Jacobus & Tapert, 2013; Lubman et al., 2007; Miller, 2006; Sadrian et al., 2013; Spear, 2014; Wilson, Malone, Thomas, & Iacono, 2015).

There is substantial evidence in humans that young people may be particularly susceptible to the impacts of heavy alcohol use on the brain (Bava & Tapert, 2010; Brown & Tapert, 2004; Clark, Thatcher, & Tapert, 2008; Crews, He, & Hodge, 2007; McGorry, Purcell, Goldstone, & Amminger, 2011; Nixon & McClain, 2010). As in adults, adolescents diagnosed with alcohol use disorders show structural brain changes (De Bellis et al., 2000; De Bellis et al., 2005; De Bellis et al., 2008; Tapert et al., 2001). Several MRI studies have shown that adolescents with alcohol use disorders have smaller grey and white matter volumes, compared to same-aged healthy adolescents (De Bellis et al., 2000; De Bellis et al., 2005; Fein et al., 2013;

Medina et al., 2008; Medina, Schweinsburg, Cohen-Zion, Nagel, & Tapert, 2007; Nagel, Schweinsburg, Phan, & Tapert, 2005; Welch, Carson, & Lawrie, 2013). For example, a meta-analysis by Welch and colleagues (2013) analysed five MRI studies in young people (14 – 21 years) and seven studies in adults (21 – 40 years) that compared individuals diagnosed with alcohol use disorders to age-matched healthy participants. They concluded that chronic alcohol use was associated with structural deficits in both age groups, notably in hippocampal and prefrontal brain regions. However, hippocampal deficits were more notable in young people. This meta-analysis also indicated that prefrontal cortex deficits in young people were detected primarily in female participants. These findings suggest that young people, and in particular females, may be more susceptible to certain chronic alcohol-related neural changes. Unexpectedly, two studies investigating functional white matter connectivity using DTI, reported that young people with adolescent onset alcohol use disorders had higher fractional anisotropy than same-aged healthy participants (Cardenas et al., 2013; De Bellis et al., 2008). This contrasts with the adult literature that typically reports lower fractional anisotropy in alcohol use disorders (Chumin et al., 2018; Monnig et al., 2013a; Monnig et al., 2013b; Pandey et al., 2018; Pfefferbaum et al., 2006a; Pfefferbaum & Sullivan, 2002; Pfefferbaum et al., 2000; Zorlu et al., 2014). It is possible that higher fractional anisotropy in young people with an adolescent onset alcohol use disorder may represent a pre-existing vulnerability to chronic alcohol use. For example, earlier myelination may strengthen reward processing, and contribute to the development of alcohol addiction (Cardenas et al., 2013; De Bellis et al., 2008). It is critical to note that these functional white matter changes in young people with alcohol use disorders are still considered abnormal and are coupled with critical structural and cognitive deficits.

There is substantial evidence that young people who habitually engage in heavy alcohol use, but are not diagnosed with an alcohol use disorder, also show differences in brain structure and function, compared to same-aged light drinkers (Cservenka & Bmrumback, 2017; Ewing, Sakhardande, & Blakemore, 2014; Jones, Lueras, & Nagel, 2018; Lees et al., 2018; Lisdahl, Gilbert, Wright, & Shollenbarger, 2013a; Lisdahl, Thayer, Squeglia, McQueeney, & Tapert, 2013b; Luciana, Collins, Muetzel, & Lim, 2013; McQueeney et al., 2009; Petit, Maurage, Kornreich, Verbanck, & Campanella, 2014; Pfefferbaum et al., 2018; Silveri et al., 2016; Squeglia et al., 2009a; Squeglia et al., 2012; Squeglia et al., 2015; Wilson et al., 2015). Wilson and colleagues (2015) investigated morphometric brain differences related to binge drinking in 97 monozygotic twins (49 female), aged 14.0 to 16.8 years. They utilised a within- and between-twin pairs design to determine whether structural differences detected using MRI were the result of binge drinking or a pre-existing condition. The within-twin pairs analysis demonstrated that reduced cortical thickness in the middle temporal gyrus, and reduced ventral diencephalon volume, were the direct result of binge alcohol exposure. The between-twin pairs comparison suggested that cortical volume differences related to binge drinking in the amygdala, cerebellum, and some frontal and temporal regions, may reflect abnormal neural development, and/or represent a pre-existing vulnerability to problematic alcohol use (Wilson et al., 2015). A longitudinal study by Pfefferbaum and colleagues (2018) showed that initiating moderate to heavy alcohol consumption between the ages of 12 and 19 years (n=127; 66 female) was associated with a dose-dependent decline in frontal cortical grey matter. Critically, compared to young people with no or low alcohol consumption (n=356; 176 female), this decline deviated notably from normal adolescent neural development. A longitudinal study by Luciana and colleagues

(2013) measured brain structure and function using MRI and DTI in 55 alcohol-naïve young people aged 14 to 19 years. Participants who commenced habitual alcohol use (n=30; 14 women) showed neurodevelopmental abnormalities at a two-year follow-up, compared to participants who did not drink alcohol. This included reduced cortical thickness in the middle frontal gyrus, protracted white matter development, and reduced fractional anisotropy. A cross-sectional study by McQueeney and colleagues (2009) also reported global reductions in fractional anisotropy in 14 (2 female) binge-drinking young people aged 16 to 19 years, compared to 14 age- and sex-matched light drinkers. These findings suggest that binge drinking may disrupt myelination and/or produce axonal defects that impair white matter structure and function in young people (Luciana et al., 2013; McQueeney et al., 2009). Notably, these findings are inconsistent with reports of higher fractional anisotropy in young people with an adolescent onset alcohol use disorder (Cardenas et al., 2013; De Bellis et al., 2008). This could suggest that sporadic binge ethanol exposure is more detrimental to white matter integrity than chronic exposure, however, further research is required to confirm these findings.

Longitudinal research suggests that neural degradations detected in heavy drinking young people may be long lasting (Cservenka & Brumback, 2017; Hanson, Cummins, Tapert, & Brown, 2011; Heikkinen et al., 2017; Squeglia et al., 2015). Several MRI studies have reported that people who engaged in heavy alcohol use during adolescence had lower grey and white matter volume up to 10 years later, compared to aged-matched participants who did not drink heavily (Cservenka & Brumback, 2017; Hanson et al., 2011; Heikkinen et al., 2017; Squeglia et al., 2015). Furthermore, these deficits were most notable in frontal brain regions (Cservenka & Brumback, 2017; Hanson et al., 2011; Heikkinen et al., 2017; Squeglia et al., 2015).

These robust findings suggest that heavy alcohol exposure during the final stages of brain development leads to lasting structural and functional neural deficits. These deficits may reflect alcohol's neurotoxic effects on the brain and/or a pre-existing vulnerability to heavy alcohol use in young people (Cservenka & Brumback, 2017; Guerri & Pascual, 2010; Jacobus & Tapert, 2013).

There is also evidence that heavy alcohol exposure in young people without alcohol use disorders may lead to neurochemical alterations in the brain (Silveri et al., 2014). An investigation by Silveri and colleagues (2014) used in vivo magnetic resonance spectroscopy to compare intracellular GABA levels in binge- (n=21; 11 female) and light- (n=27; 13 female) drinking young people aged 18 to 24 years old. Their results indicated that young people who engaged in binge drinking had lower frontal lobe, and anterior cingulate cortex, intracellular GABA levels than same-aged light drinkers (Silveri et al., 2014). These findings suggest that binge drinking may lead to the downregulation of GABAergic neurotransmission in these developing brain regions. As alcohol acutely facilitates inhibitory GABAergic communication, repeated heavy exposure may cause a homeostatic downregulation in this system (Gonzales & Jaworski, 1997; Kumar et al., 2009; Lovinger, 1997; Roberto & Varodayan, 2017). As the GABAergic neurotransmitter system is still developing in this age group, it is currently unclear whether these deficits would have the same impact as mature adults (Chugani et al., 2001; Fung et al., 2010; Silveri, 2014; Silveri et al., 2014; Silveri et al., 2013).

2.2.4.2.3 Cognitive effects

Young people diagnosed with alcohol use disorders exhibit robust impairments in cognitive function, which may reflect the underlying neurophysiological changes outlined above (Brown & Tapert, 2004; Brown, Tapert,

Granholm, & Delis, 2000; Medina et al., 2007; Moss, Kirisci, Gordon, & Tarter, 1994; Tapert & Brown, 2000; Tapert, Granholm, Leedy, & Brown, 2002; Tapert et al., 2004; Tarter, Mezzich, Hsieh, & Parks, 1995). A study by Brown and colleagues (2000) found that 33 (19 female) adolescents aged 15 to 16 years diagnosed with alcohol use disorders, had poorer retrieval of verbal and nonverbal information, compared to 24 age- and sex-matched healthy participants. Higher order executive functioning is also compromised in adolescents experiencing alcohol use disorders (Moss et al., 1994; Tapert & Brown, 2000; Tarter et al., 1995). A study by Tapert and colleagues (2000) showed that 101 young people (aged 13 – 19 years) diagnosed with an alcohol use disorder, had poorer performance on neuropsychological tests for attention and information processing, compared to 50 same-aged healthy participants. Critically, these cognitive deficits appear to be long lasting, as they have been detected up to 11 years after the successful treatment of the alcohol use disorder (Hanson et al., 2011; Tapert et al., 2002). Demonstrating this, Tapert and colleagues (2002) examined neuropsychological function longitudinally in 47 (20 female) young people receiving treatment for an alcohol use disorder over 8 years (commencing at 16 years of age). They found attention, learning, and memory retention, was still impaired at the final time point (24 years of age), compared to 26 same-aged control participants. These findings suggest that chronic alcohol use in young people is related to enduring cognitive changes that may potentially reflect underlying neural deficits.

Young people who engage in heavy alcohol use, but are not diagnosed with an alcohol use disorder, also demonstrate long-lasting cognitive impairments (Jones et al., 2018; Silveri et al., 2016; Townshend & Duka, 2005; Winward, Hanson, Tapert, & Brown, 2014; Zeigler et al., 2005). This includes impairments in executive

function, such as attention and inhibitory control (Gil-Hernandez & Garcia-Moreno, 2016; Lannoy et al., 2017; Peeters, Vollebergh, Wiers, & Field, 2014; Scaife & Duka, 2009), and learning and memory (Crego et al., 2009; Heffernan, Clark, Bartholomew, Ling, & Stephens, 2009; Heffernan & O'Neill, 2012; Mota et al., 2013; Nguyen-Louie et al., 2016; Parada et al., 2011). A study by Parada and colleagues (2011) found that 62 (30 female) binge-drinking university students, aged 18 to 20 years, had impairments in verbal declarative memory, as indicated by poorer immediate and delayed recall, compared to 60 (29 female) same-aged participants who did not binge drink (Parada et al., 2011). A prospective study by Squeglia and colleagues (2009) investigated neuropsychological functioning over three years in 76 (29 female) adolescents prior to the onset of alcohol use (commencing at 12 to 14 years of age). They demonstrated that the initiation of moderate to heavy alcohol use was associated with the development of neuropsychological impairments approximately three years later, including deficits in visuospatial memory and sustained attention. These findings have also been replicated in young adults (Mota et al., 2013). Critically, these cognitive differences did not appear to be pre-existing as they were not present at baseline (Mota et al., 2013; Squeglia, Spadoni, Infante, Myers, & Tapert, 2009b). These cognitive deficits may be related to the underlying neurological impairments described above. It has also been theorised that some neuropsychological impairments associated with heavy drinking may be related to the alcohol hangover (Squeglia et al., 2009b). Neurocognitive deficits in young people are especially concerning due to their unique academic, cognitive, and social pressures, such as completing high school, entering university, and/or the workforce (AIHW, 2017; Brown & Tapert, 2004; WHO, 2018). It is possible that impairments

in executive function may further perpetuate heavy drinking behaviours in this developing age group (McCarty et al., 2004; Oesterle et al., 2004).

2.2.4.2.4 Pre-existing differences

There is evidence that some neural and cognitive deficits present in heavy-drinking young people may exist prior to the onset of alcohol use (Crews et al., 2007; Cservenka & Brumback, 2017). It is well recognised that young people with a family history of alcohol use disorders are at higher risk of developing an alcohol use disorder (Lieb et al., 2002; Merikangas et al., 1998). Furthermore, these individuals display unique neural and cognitive deficits prior to the onset of alcohol consumption. Research has consistently shown that alcohol naïve children and adolescents with a family history of alcohol use disorders have lower cortical grey and white matter density, and reduced functional white matter connectivity, compared to same-aged young people with no family history (Acheson et al., 2014; Benegal, Antony, Venkatasubramanian, & Jayakumar, 2007; Cservenka, 2016; Henderson et al., 2018; Herting, Fair, & Nagel, 2011; Spadoni, Simmons, Yang, & Tapert, 2013; Squeglia, Jacobus, Brumback, Meloy, & Tapert, 2014; Venkatasubramanian et al., 2007). These pre-existing neural deficits are most prominent in frontal brain regions, and are accompanied by impairments in cognitive function, including impaired executive function (Nigg et al., 2004), working memory (Cservenka, Herting, & Nagel, 2012; Spadoni, Norman, Schweinsburg, & Tapert, 2008), self-regulation (Sher, Walitzer, Wood, & Brent, 1991), inhibitory control, and increased risk-taking (Dougherty et al., 2015; Kamarajan et al., 2015). These effects are independent of maternal alcohol consumption. It has been suggested that these neural and cognitive deficits may have both a genetic (Hu et al., 2005; Mayfield, Harris, & Schuckit, 2008; Merikangas, 1990; Meyers & Dick, 2010; Schuckit &

Smith, 2000) and environmental (Barnow, Schuckit, Lucht, John, & Freyberger, 2002; Light, Irvine, & Kjerulf, 1996; Meyers & Dick, 2010) basis. For example, research has highlighted a common genetic profile between alcohol use disorders and externalising psychological disorders (e.g., conduct disorder, antisocial behaviour), which are both characterised by high risk taking and disinhibited behaviour, including risky alcohol use (Meyers & Dick, 2010). It has been theorised that pre-existing cognitive deficits may contribute to the onset and continuation of heavy alcohol use in young people with a family history of alcohol use disorders (Nigg et al., 2004). Furthermore, protracted neural and cognitive development across adolescence and young adulthood in general, has been hypothesised to contribute to higher single-occasion alcohol use in this population (AIHW, 2017; Hermens et al., 2013; McCarty et al., 2004; Nixon, 2013; Oesterle et al., 2004; Peeters et al., 2015; Peeters et al., 2014; Tarter et al., 2003; WHO, 2018). However, there is still substantial evidence that heavy alcohol use can directly impact neural integrity and cognition in young people (Guerri & Pascual, 2010; Lubman et al., 2007; Sadrian et al., 2013). Taken together, the reviewed findings provide strong research evidence that there is a bi-directional relationship between alcohol use, neural structure and function, and cognition in young people (Arain et al., 2013; Bava & Tapert, 2010; Clark et al., 2008; Crews et al., 2007; Matthews, 2010).

2.2.4.2.5 Alcohol withdrawal syndrome

There is evidence that young people recovering from alcohol use disorders may experience less severe alcohol withdrawal syndrome than mature adults (Harford, Yi, Faden, & Chen, 2009; Martin, Kaczynski, Maisto, Bukstein, & Moss, 1995; Morris, Kelso, Liput, Marshall, & Nixon, 2010; Stewart & Brown, 1995). A study by Martin and colleagues (1995) in 181 young people (aged 13 – 21 years)

diagnosed with alcohol use disorders found that only 23 percent reported symptoms of alcohol withdrawal syndrome. A large population study by Hardford and colleagues (2009) showed that young people aged 12 to 25 years (n=80,663) were less likely to report alcohol withdrawal syndrome symptoms than adults aged 26 years or older (n=52,568). Furthermore, research has shown that the likelihood of reporting alcohol withdrawal syndrome symptoms increases with age (Pabst, Kraus, Piontek, & Baumeister, 2012). This may reflect shorter time-periods of chronic alcohol use, a binge pattern of consumption, and/or ongoing neural development, in young people. There is evidence in animal models that adolescents experience fewer, and less severe, tonic-clonic seizures following the abrupt cessation of chronic alcohol consumption, compared to mature adults (Acheson, Richardson, & Swartzwelder, 1999). This may reflect the immaturity of GABAergic neurotransmitter systems in young people, as this system is primarily responsible for synchronised burst firing during a seizure (Acheson et al., 1999; Chugani et al., 2001; Moy et al., 1998; Silveri, 2014; Yu et al., 2006). Taken together, these findings provide further evidence that young people may respond uniquely to both acute and habitual alcohol exposure, potentially due to continuing neural development. In summary, heavy alcohol consumption in young people, even in the absence of an alcohol use disorder, is associated with interrelated structural, functional, cognitive, and neurochemical alterations.

2.3 Summary

Adolescents and young adults consume higher amounts of alcohol than any other age group. Due to protracted neural development at this age, young people may experience less physiological sedation, and more stimulation, following acute alcohol consumption. Heavy alcohol use is associated with detrimental neural and cognitive effects in young people. This is concerning given the unique socio-environmental pressures that impact this age group. These deficits may reflect alcohol's neurotoxic effects on the developing brain and/or a pre-existing vulnerability to heavy alcohol use. Adequate, high quality sleep is essential for healthy development and well-being. Alcohol's impacts on sleep may be particularly harmful in young people due to their ongoing development, and high levels of alcohol use. As such, the effects of acute and habitual alcohol use on sleep will now be examined.

CHAPTER 3

Impacts of alcohol use on sleep

Alcohol is the oldest pharmacological sedative consumed by humans and has historically been used for general anaesthesia (Hames, 2012; Hart & Ksir, 2011; Roehrs & Roth, 2001a). Although alcohol's acute sleep-promoting effects have long been established, it is only comparatively recently that alcohol's sleep disrupting effects have become apparent (Brower, 2003; Colrain et al., 2014; Ebrahim et al., 2013; Feige et al., 2006; Roehrs & Roth, 2001a). Acute alcohol use results in immediate alterations to normal sleep, and chronic consumption has been attributed to severe and enduring sleep deficits. Alcohol appears to alter sleep through its complex interactions with inhibitory and excitatory neurotransmitter systems, and other neural pathways associated with sleep (Sommer & Spanagel, 2013; Svanberg & Beaunieux, 2015). As sleep is a measure of neural structure and function, long-term changes in sleep may reflect alcohol-related neural damage and adaptation (Colrain et al., 2014; Colrain et al., 2009b).

3.1 Acute use

Pharmacologically, sleep-regulatory systems appear to be directly affected by acute alcohol ingestion (Cavacuiti & Woodward, 2011; Kwasnicka & Auerbach, 2011). There is a comprehensive literature available on the acute effects of alcohol on sleep physiology in a healthy adult population (Aldrich, 1998; Arnedt et al., 2011; Colrain et al., 2014; Ebrahim et al., 2013; Feige et al., 2006; MacLean & Cairns, 1982; Roehrs & Roth, 2001a; Stein & Friedmann, 2005). Alcohol consumption prior to sleep results in dose-dependent, biphasic effects that manifest as sedation in the first half of the sleep period, and disturbance in the second half (Roehrs, 1991; Roehrs et al., 1989). However, current evidence now suggests that sleep quality is

also substantially compromised in the first half of the sleep period (Chan et al., 2015; Van Reen, Jenni, & Carskadon, 2006).

BAC peaks approximately one hour after the cessation of alcohol consumption, and then declines linearly as it is metabolised and excreted (Cavacuiti & Woodward, 2011). This pattern is robust and unaffected by sleep onset (Cavacuiti & Woodward, 2011; Colrain et al., 2014; Rundell, Lester, Griffiths, & Williams, 1972). Sleep is affected differentially during the rising and falling phases of the BAC curve, and following elimination or acute withdrawal (Roehrs & Roth, 2001a; Stein & Friedmann, 2005). The primary mechanisms through which alcohol impacts sleep is most likely its acute interactions with the GABAergic and glutaminergic neurotransmitter systems (Gonzales & Jaworski, 1997; Kumar et al., 2009; Lovinger, 1997). Both systems are intricately involved in the maintenance of wakefulness, sleep, and the distribution of sleep stages across the sleep period (Amzica & Steriade, 1998; Roehrs & Roth, 2001a; Siegel, 2004). In the literature, doses of pre-bedtime alcohol typically range from 0.16 to 1.10 g/kg (approximately 1 – 6 standard drinks), resulting in peak BACs up to .105 percent (Colrain et al., 2014; Ebrahim et al., 2013; Roehrs & Roth, 2001a). At these doses, due to the consistent rate of alcohol metabolism, alcohol is usually eliminated from the body within a normal sleep period of approximately eight hours (Eckardt et al., 1998; Hirshkowitz et al., 2015; Roehrs & Roth, 2001b).

In adults, pre-bedtime alcohol initially acts as a sedative, or promotes sleep, in a dose-dependent manner (Arnedt et al., 2011; Colrain et al., 2014; Feige et al., 2006; MacLean & Cairns, 1982; Roehrs & Roth, 2001a; Roehrs et al., 1989; Stein & Friedmann, 2005; Van Reen et al., 2006). In the first half of the sleep period, as alcohol continues to be absorbed and metabolised, there are shorter sleep onset

latencies, fewer arousals, less wake after sleep onset, higher sleep efficiency, increased REM sleep onset latencies, less REM sleep, and more SWS, compared to a placebo condition (Arnedt et al., 2011; Dijk, Brunner, Aeschbach, Tobler, & Borbely, 1992; Feige et al., 2006; MacLean & Cairns, 1982; Miyata et al., 2004; Prinz, Roehrs, Vitaliano, Linnoila, & Weitzman, 1980; Roehrs et al., 1989; Rundell et al., 1972; Sagawa et al., 2011; Stein & Friedmann, 2005; Van Reen et al., 2006; Yules, Lippman, & Freedman, 1967). These effects were clearly demonstrated by Feige and colleagues (2006) who intravenously administered a placebo (BAC= .00%), low (BAC= .03%) and high (BAC= .10%) dose of alcohol prior to sleep in 10 healthy adults (5 women) over three non-consecutive nights. They showed that sedation increased with higher doses of pre-sleep alcohol. For example, in the first half of the sleep period, SWS increased by 11.0 percent of total sleep time following the high alcohol dose, and 1.6 percent following the low dose, compared to the placebo condition. Studies have also reported an initial increase in delta EEG activity as measured via spectral analysis (Dijk et al., 1992; Landolt, Roth, Dijk, & Borbely, 1996; Van Reen et al., 2006). Van Reen and colleagues (2006) orally administered a moderate dose of alcohol (peak BAC= .05%) 90 minutes prior to sleep in seven adult women, compared to a placebo beverage. They found that non-REM delta EEG spectral power was higher following alcohol consumption in the first two hours sleep, compared to placebo. Taken together, these objective findings provide evidence that alcohol initially acts to promote sleep in adults.

The mechanism most likely driving these initial sedative effects is alcohol's pharmacological facilitation of inhibitory GABAergic neurotransmission, and suppression of excitatory glutaminergic neurotransmission (Chastain, 2006; Harrison et al., 2017; Kumar et al., 2009; Sommer & Spanagel, 2013; Svanberg & Beaunieux,

2015). It is well established that drugs that facilitate GABAergic neurotransmission are hypnotic or sleep-promoting, and increase SWS (Feld et al., 2013; Gottesmann, 2002; Walsh, 2009). GABA facilitation may be responsible for alcohol's sleep-promoting effects in the first half of the sleep period when BAC is highest, such as less wakefulness, more SWS, and higher delta EEG spectral power (Koob & Colrain, 2019). Glutaminergic neurotransmission appears to be central for wakefulness, and REM sleep onset and continuation (Datta, Spoley, & Patterson, 2001; Fraigne et al., 2015; Kodama, Lai, & Siegel, 1998; Lu et al., 2006). Glutaminergic suppression may further contribute to alcohol's initial sleep-promoting effects, including less wakefulness and REM sleep (Gonzales & Jaworski, 1997; Knowles, Laverty, & Kuechler, 1968). Alcohol's acute impacts on the circadian system may also underly some of these sedative effects. Notably, acute alcohol consumption delays the release of the circadian hormone melatonin (Prat et al., 2009; Rupp et al., 2007). As REM sleep is predominantly regulated by the circadian system, this hormonal delay may also postpone REM sleep timing and intensity (Lee et al., 2009; Wurts & Edgar, 2000). These physiological and pharmacological effects of acute alcohol ingestion may contribute to its initial sedative or sleep-promoting effects.

Research has shown that tolerance to the sleep-promoting effects of alcohol develop following repeated consumption over multiple nights (Ebrahim et al., 2013; Feige et al., 2006; Prinz et al., 1980; Roehrs & Roth, 2018; Rundell et al., 1972). Roehrs and Roth (2018) investigated the impact of alcohol administration (dose 0.6 g/kg) over six-consecutive nights in eight adults (4 women) diagnosed with insomnia. They reported that between nights two and six of repeated alcohol administration, all-night sleep efficiency decreased significantly by 15.6 percent, and SWS by 2.7 percent. Feige and colleagues (2006) investigated alcohol administration

over three consecutive nights (peak BAC= .10%) and reported that SWS remained augmented in the first half of the sleep period over all three nights, compared to baseline. This finding was supported by Prinz and colleagues (1980) who found that SWS remained elevated over eight nights of repeated alcohol administration (peak BAC= .10%) in five adult men but returned to baseline levels on the ninth night. It is currently unclear whether tolerance develops to alcohol's acute REM sleep suppressing effects (Colrain et al., 2014). Both Feige and colleagues (2006), and Prinz and colleagues (1980), reported that REM sleep percentage remained below baseline following up to nine nights of repeated alcohol consumption. In contrast, Rundell and colleagues (1972) studied three consecutive nights of alcohol administration (dose 0.9 g/kg) in 17 men, and showed that REM sleep was suppressed only on the first night of alcohol administration, but not the second or third. Taken together, these findings provide evidence that tolerance to some of alcohol's acute sleep-promoting effects may develop relatively quickly in healthy adults. These effects may reflect the adaptation of neurotransmitter systems to the presence of repeated, high doses of alcohol before sleep.

There is growing evidence that the initial sleep-promoting effects of acute alcohol may not be beneficial, but instead disrupt the restorative processes of sleep (Koob & Colrain, 2019). This is supported by findings that alcohol consumption prior to sleep also produces serious hormonal and electrophysiological abnormalities (Colrain et al., 2014; Dijk et al., 1992; Landolt et al., 1996; Prinz et al., 1980; Van Reen et al., 2016). Firstly, in both humans and animals, acute alcohol consumption inhibits growth hormone release during sleep (Dees, Dissen, Hiney, Lara, & Ojeda, 2000; Prinz et al., 1980). In normal sleep, growth hormone is released during the first episode of SWS in the sleep period (Feinberg, 2000; Horne, 1992; Sassin et al.,

1969). Prinz and colleagues (1980) highlighted that despite observing augmented SWS, growth hormone release did not occur following pre-sleep alcohol consumption (peak BAC = .10%). Concerningly, this inhibition was still evident following nine consecutive nights of repeated alcohol administration, suggesting that tolerance to this hormonal abnormality may not develop. Research has also reported atypical increases in alpha EEG spectral power following alcohol consumption prior to sleep (Dijk et al., 1992; Landolt et al., 1996; Rundell et al., 1972; Van Reen et al., 2006). Van Reen and colleagues (2006) noted an increase in alpha and delta EEG frequency during non-REM sleep following a high dose of alcohol (peak BAC = .10%). This increase was largest in the first two hours of sleep, and at frontal electrode sites, where SWS is most pronounced (Van Reen et al., 2006). Alpha EEG activity is typical of wakefulness, and not usually evident during SWS, so may represent an endogenous arousal occurring in the deepest stage of non-REM sleep (Pivik & Harman, 1995; Riemann et al., 2010). These findings suggest that acute alcohol consumption may seriously interfere with the functional properties of sleep.

The co-occurrence of alpha and delta EEG spectral power is an established clinical phenomenon referred to as alpha-delta sleep, and has been associated with daytime symptoms, such as headaches, fatigue, and sleepiness (Guilleminault et al., 2006; Hauri & Hawkins, 1973). Alpha-delta sleep is commonly detected in medical conditions associated with chronic pain, such as fibromyalgia (Horne & Shackell, 1991; Lineberger, Means, & Edinger, 2007; Mahowald & Mahowald, 2000; Menefee et al., 2000; Moldofsky, 2001; Roizenblatt, Moldofsky, Benedito-Silva, & Tufik, 2001), and has also been associated with psychiatric disorders, including depression and suicidal ideation (Agargun et al., 1997; Armitage, 1995; Dolsen et al., 2017; Jaimchariyatam, Rodriguez, & Budur, 2011; Kupfer, Reynolds, & Ehlers, 1989),

insomnia (Riedner et al., 2016; Riemann et al., 2010), chronic fatigue (Guilleminault et al., 2006), dementia (Crowley, Sullivan, Adalsteinsson, Pfefferbaum, & Colrain, 2005), and post-traumatic stress disorder (Woodward, Murburg, & Bliwise, 2000). Alpha-delta sleep can also be elicited experimentally in healthy adults by playing loud auditory tones, or administering a pain stimulus, during SWS (Drewes, Nielsen, Arendt-Nielsen, Birket-Smith, & Hansen, 1997; Moldofsky, 2001; Moldofsky & Scarisbrick, 1976; Moldofsky, Scarisbrick, England, & Smythe, 1975; Ooms, Zempel, Holtzman, & Ju, 2017; Van Der Werf et al., 2009). These collective findings provide evidence that alpha-delta sleep is a direct consequence of extremely disruptive stimuli occurring during sleep, which may compromise sleep's restorative nature. This is supported by robust findings that people experience detrimental daytime symptoms following alpha-delta sleep (Guilleminault et al., 2006; Hauri & Hawkins, 1973). The presence of alpha-delta sleep following acute alcohol consumption may represent a paradoxical arousal that counteracts the restorative actions of SWS and delta EEG activity (Hauri & Hawkins, 1973). Indeed, it has been theorised that alpha-delta sleep may contribute to the next-day alcohol hangover (Chan et al., 2015).

Substantial objective evidence has been presented that acute alcohol consumption prior to sleep initially acts to promote critical and positive properties of sleep in adults. Despite these robust findings, there is mounting evidence that acute alcohol-related sleep promotion may not be beneficial due to the physiological abnormalities also present during this time. These findings provide evidence that acute alcohol consumption may interfere with the fundamental restorative properties of sleep.

3.1.1 Withdrawal from acute use

During the acute withdrawal period, alcohol ultimately acts to disturb sleep (Roehrs & Roth, 2001a). This typically occurs in the second half of the sleep period as alcohol consumed prior to sleep is metabolised and eliminated (Eckardt et al., 1998; Rundell et al., 1972). In the second half of the sleep period, following pre-sleep alcohol consumption, there are more arousals, more wake after sleep onset, lower sleep efficiency, less total sleep time (Arnedt et al., 2011; Landolt et al., 1996; MacLean & Cairns, 1982; Rohsenow et al., 2010), and SWS suppression (Arnedt et al., 2011; MacLean & Cairns, 1982; Rohsenow et al., 2010; Van Reen et al., 2006; Yules et al., 1967), compared to placebo consumption. It is worth noting that some studies have reported an increase or ‘rebound’ in REM sleep in the second half of the sleep period (MacLean & Cairns, 1982; Roehrs & Roth, 2001a; Sagawa et al., 2011), however, other studies have not (Arnedt et al., 2011; Roehrs, 1999, 1991; Rundell et al., 1972). A large study by Arnedt and colleagues (2011) investigated the effects of acute alcohol consumption (peak BAC= .10%) on sleep in 93 adults (59 women). In the second half of the sleep period, compared to a placebo condition, there was 10 minutes less total sleep time, 4.2 percent lower sleep efficiency, and 4.7 percent less SWS. However, they did not report a secondary increase in REM sleep. Two studies have investigated the impact of acute alcohol withdrawal on nocturnal sleep by allowing BAC to return to zero before sleep onset (Landolt et al., 1996; Rouhani, Tran, Leplaidur, Durlach, & Poenaru, 1989). Landolt and colleagues (1996) studied a high afternoon dose of alcohol (peak BAC= .09%) in 10 men, and Rouhani and colleagues (1989) studied a low dose (peak BAC= .03%) in 14 adults (7 women), compared to a placebo condition. Both studies reported more arousals, more wake after sleep onset, and less REM sleep, across the entire sleep period. Additionally,

Rouhani and colleagues (1989) reported less overall SWS percentage, and Landolt and colleagues (1996) identified higher non-REM alpha and delta EEG spectral power, compared to placebo. Taken together, these findings demonstrate that pre-sleep alcohol consumption ultimately leads to gross secondary sleep disturbance during the acute withdrawal period. However, findings regarding REM sleep remain inconclusive (see Colrain et al., 2014 for review).

Though the precise mechanism remains unknown, several mechanisms have been proposed for the secondary sleep disrupting effects of pre-sleep alcohol consumption. Firstly, sleep disturbances during the acute withdrawal period may result from the accumulation of alcohol's toxic metabolites during the metabolism and elimination process (Feige et al., 2006; Roehrs & Roth, 2001b). These effects may also be the result of the discontinuation of alcohol's acute GABAergic facilitation, and glutaminergic inhibition (Feige et al., 2006; Roehrs & Roth, 2001b). For example, more wakefulness and less SWS in the second half of the sleep period, may be related to a secondary homeostatic suppression of inhibitory neurotransmission, and enhanced excitation (Roehrs & Roth, 2001a). Although findings regarding REM sleep during acute withdrawal remain inconclusive, reports that REM sleep remains suppressed across the entire sleep period may be explained by alcohol's acute suppression of melatonin, leading to delayed REM sleep onset and intensity (Prat et al., 2009; Rupp et al., 2007). Taken together, the reviewed findings highlight that alcohol consumption prior to sleep ultimately leads to serious degradations in sleep quality and architecture, particularly during the acute withdrawal phase. These alcohol-related sleep disturbances have been theorised to contribute to the next-day alcohol hangover (Chan et al., 2015; McKinney & Coyle, 2006; Prat et al., 2009; Swift & Davidson, 1998; Verster, 2008).

3.2 Chronic use

Chronic alcohol use, such as that observed in people with long-term alcohol use disorders, is associated with an increased incidence of sleep disorders and archetypal sleep disturbance (Angarita, Emadi, Hodges, & Morgan, 2016; Brower, 2003; Brower, Aldrich, Robinson, Zucker, & Greden, 2001; Chakravorty et al., 2016; Colrain et al., 2014; Conroy, Arnedt, & Brower, 2011; Stein & Friedmann, 2005). It has been estimated that as many as 91 percent of patients who have been diagnosed with an alcohol use disorder report experiencing sleep problems (Cohn, Foster, & Peters, 2003). In alcohol use disorders sleep abnormalities are pervasive and are experienced during phases of active drinking, in association with alcohol withdrawal syndrome, and even following sustained recovery or extended abstinence (Angarita et al., 2016; Brower, 2003; Chakravorty et al., 2016; Cohn et al., 2003). The most common comorbid sleep disorders include insomnia (Brower et al., 2001), obstructive sleep apnea (Le Bon et al., 1997), and periodic limb movement disorder (Aldrich & Shipley, 1993; see Chakravorty et al., 2016 for review).

Insomnia, or difficulty initiating or maintaining sleep, is the most commonly reported sleep disorder in people with a current or past alcohol use disorder (Brower, 2003; Brower et al., 2001; Chakravorty et al., 2016; Roehrs & Roth, 2001b, 2018; Weissman, Greenwald, Nino-Murcia, & Dement, 1997). It has been suggested that insomnia may result from hyperarousal occurring during the intended sleep period (Chakravorty et al., 2016; Drake, Roehrs, & Roth, 2003). In the general population there is a notably higher incidence of insomnia in women compared to men (Suh, Cho, & Zhang, 2018; Zhang & Wing, 2006), however, there are no prevalence differences in insomnia between men and women diagnosed with alcohol use disorders (Brower, 2003; Brower et al., 2001; Chakravorty et al., 2016). It has been

theorised that the strong relationship between sleep disturbance and chronic alcohol use is bi-directional. For example, adults experiencing difficulties sleeping, such as insomnia, may self-medicate with alcohol due to its initial sleep-promoting effects (Brower, 2003; Brower et al., 2001). As previously noted, tolerance to alcohol's acute sedative effects develop relatively quickly, meaning progressively higher doses are needed to achieve the same sleep-promoting effects (Roehrs, Papineau, Rosenthal, & Roth, 1999; Roehrs & Roth, 2001b, 2018). This was demonstrated by Roehrs and colleagues' (2018) second experiment, in which 12 adults diagnosed with insomnia (6 women) were asked to self-administer alcoholic or non-alcoholic beverages prior to sleep at home for one week following either six consecutive nights of pre-sleep administration (dose 0.6 g/kg), or placebo (dose 0.0 g/kg). Results showed that six participants who were pre-treated with alcohol for the previous six nights self-administered more alcoholic beverages prior to sleep in the following week, than six participants who were not pre-treated with acute alcohol. Roehrs and colleagues (2018) suggested that dose escalation due to the development of tolerance may be one pathway through which individuals experiencing sleep difficulties, such as insomnia, may develop an alcohol use disorder (Roehrs & Roth, 2001a; Roehrs & Roth, 2001b). This hypothesis suggests that some sleep disturbances, or disorders, may pre-exist or even contribute to chronic alcohol use in adults (Roehrs & Roth, 2001b, 2018; Roehrs, 1991; Roehrs et al., 1989).

Acute alcohol use is associated with substantial sleep disturbance in people currently experiencing an alcohol use disorder (Chakravorty et al., 2016; Gross, Goodenough, Hastey, & Lewis, 1973; Gross & Hastey, 1975; Hartwell, Bujarski, Glasner-Edwards, & Ray, 2015; Roehrs & Roth, 2001b). In a large sample of 295 individuals with a current alcohol use disorder (age range 21 – 65 years; mean age

31.0 ± 10.5 years), but not seeking treatment, 76 percent had Pittsburgh Sleep Quality Index scores greater than five, indicating poor global sleep quality (Hartwell et al., 2015). There was a negative relationship between alcohol use disorder severity and global sleep quality, and positive relationship with daily sleep disturbance, providing subjective evidence that sleep disturbance is experienced while patients are actively drinking (Hartwell et al., 2015). Surprisingly, alcohol use disorder severity was positively associated with sleep efficiency, a result that may be explained by objective sleep findings (Hartwell et al., 2015). Thus, limited PSG studies have demonstrated that currently drinking individuals with an alcohol use disorder experience longer sleep onset latencies, less total sleep time, more SWS, longer REM sleep onset latencies, and less REM sleep percentage, than during abstinence (Gross et al., 1973; Gross & Hastey, 1975). Unfortunately, wake after sleep onset and sleep efficiency were not reported in these studies. The positive relationship between subjective sleep efficiency and alcohol use disorder severity may potentially be explained by dose-dependent increases in SWS, and decreases in REM sleep, with higher daily acute alcohol consumption. It is worth noting that people with a current alcohol use disorder commonly report being unable to fall asleep without consuming alcohol, but still experience longer sleep onset latencies and shorter total sleep times when actively drinking (Gross et al., 1973; Gross & Hastey, 1975). This likely reflects the adaptation of neurotransmitter systems to the continuous presence of high doses of alcohol, or the development of tolerance to the initial sleep promoting effects of acute consumption (Chakravorty et al., 2016; Roehrs & Roth, 2001b). As previously highlighted, this phenomenon may contribute to alcohol dose escalation in these individuals (Mello & Mendelson, 1970; Roehrs & Roth, 2001b, 2018).

Naturalistic studies have shown that individuals with a current alcohol use disorder generally alternate between short dyssynchronous episodes of sleep and alcohol consumption, across a 24-hour period (Mello & Mendelson, 1970). Based on the PSG findings above, and the preferential reinstatement of SWS following sleep restriction, it is reasonable to suggest that these short sleep periods would be primarily comprised of non-REM sleep (Chakravorty et al., 2016; Gross et al., 1973; Gross & Hastey, 1975; Roehrs & Roth, 2001b). These consolidated bouts of sleep may also be related to alcohol's acute biphasic effects, manifesting as sedation as BACs rise, followed by major sleep disruption or total truncation, as BACs decline and return to zero. The irregular sleep timing observed in actively drinking individuals with alcohol use disorders, and ongoing REM sleep suppression, may be related to circadian rhythm abnormalities (Danel, Cottencin, Tisserand, & Touitou, 2009). In addition to neurotransmitter system alterations, there are major structural and functional neural changes associated with chronic long-term alcohol use, which may also contribute to sleep disturbances in this population (Chakravorty et al., 2016; Roehrs & Roth, 2001b).

3.2.1 *Withdrawal from chronic use*

Successful recovery from an alcohol use disorder requires sustained abstinence from acute alcohol consumption. Following the immediate cessation of alcohol consumption, there are characteristic disturbances to sleep quality and architecture that are experienced during acute (approximately one to two weeks of abstinence) and protracted (approximately two to eight weeks of abstinence) alcohol withdrawal syndromes (Angarita et al., 2016; Brower et al., 2001; Chakravorty et al., 2016; Roehrs & Roth, 2001b). During detoxification, or acute alcohol withdrawal

syndrome, up to 92 percent of patients report subjective sleep disturbances (Steinig, Foraita, Happe, & Heinze, 2011). A large study by Kolla and colleagues (2014) investigated subjective sleep disturbance in 119 patients (49 women) recovering from alcohol use disorders, aged 50.6 ± 13.2 years. They reported that 69.3 percent of patients had a global Pittsburgh Sleep Quality Index greater than five at the commencement of treatment, indicating major sleep disturbance. Following four weeks of treatment, the prevalence of subjective sleep disturbance still remained high, but declined to 49.1 percent (Kolla et al., 2014). A similar study in 57 patients (19 women) recovering from alcohol use disorders reported that the average global Pittsburgh Sleep Quality Index was still greater than five following 12 weeks of abstinence (Cohn et al., 2003). These findings provide evidence that subjective sleep disturbance is highly prevalent during early recovery from an alcohol use disorder.

There is also substantial objective evidence that sleep disturbances persist during acute and protracted alcohol withdrawal syndromes (Brower et al., 2001; Chakravorty et al., 2016; Roehrs & Roth, 2001b). This includes longer sleep onset latencies, lower sleep efficiency, less total sleep time (Aldrich, Brower, & Hall, 1999; Brower, 2001; Drummond, Gillin, Smith, & DeModena, 1998; Gillin et al., 1990a; Gross et al., 1973; Gross & Hastey, 1975; Le Bon et al., 1997; Moeller et al., 1993; Snyder & Karacan, 1985; Wagman & Allen, 1975; Williams & Rundell, 1981), more stage N1 sleep, more stage N2 sleep, less SWS (Brower, 2003; Gross et al., 1973; Gross & Hastey, 1975; Johnson, Burdick, & Smith, 1970; Wagman & Allen, 1975; Williams & Rundell, 1981), shorter REM sleep onset latencies, and more REM sleep (Gillin et al., 1990a; Gillin, Smith, Irwin, Kripke, & Schuckit, 1990b; Snyder & Karacan, 1985; Williams & Rundell, 1981). These findings were clearly demonstrated in a seminal study by Williams and Rundell (1981) that

assessed sleep PSG during early abstinence or protracted alcohol withdrawal syndrome. They compared 48 men recovering from alcohol use disorders, following 3 to 33 years of chronic alcohol use, aged 23 to 63 years, to 20 age-matched healthy men. Following approximately three weeks of abstinence, patients had on average 13.8 minutes longer sleep onset latencies, 88.1 more arousals, 8.9 percent more stage N1 sleep, 6.0 percent less SWS, 36.1 minutes shorter REM sleep onset latencies, and 4.7 percent more REM sleep, across the entire sleep period (Williams & Rundell, 1981). Research also suggests that SWS percentage may be low, or entirely absent, during the first few weeks of abstinence, or acute alcohol withdrawal syndrome (Wagman & Allen, 1975; Williams & Rundell, 1981). These findings provide substantial objective evidence that sleep is severely disrupted during the early stages of recovery from an alcohol use disorder. This likely reflects underlying alcohol-related changes to the neural and hormonal systems that regulate sleep.

Sleep changes observed during alcohol withdrawal syndromes are generally opposite to those observed following acute alcohol consumption. For example, in healthy adults, acute alcohol consumption initially leads to improved sleep quality, augmented SWS, and decreased REM sleep. However, during early abstinence, adults recovering from alcohol use disorders experience dramatic reductions in sleep quality and SWS, and augmented REM sleep. This may reflect the downregulation of GABAergic neurotransmitter systems, and upregulation of glutaminergic, following prolonged periods of high acute alcohol consumption (Brower, 2001, 2003; Brower et al., 2001; Chakravorty et al., 2016; Roehrs & Roth, 2001b). It has been theorised that this neurochemical adaptation may promote wakefulness due to the hyperarousal of the central nervous system (Chakravorty et al., 2016). Further to this, changes in neural integrity and connectivity related to chronic alcohol use may contribute to

sleep disturbances during early abstinence. For example, alcohol-related grey and white matter degradation may impair the brain's ability to synchronise and produce high voltage SWS. Circadian rhythm abnormalities in this population following the cessation of alcohol use may also contribute to sleep disturbances (Danel et al., 2009; Kuhlwein, Hauger, & Irwin, 2003). For example, an investigation by Kuhlwein and colleagues (2003) showed that 11 adult men recovering from alcohol use disorders experienced a circadian phase delay during protracted alcohol withdrawal syndrome (25.6 ± 6.4 days abstinent). This was demonstrated by a 90-minute delay in the secretion of melatonin, measured via intravenous catheter nocturnal blood sampling, compared to 10 age-matched healthy men. A study by Danel and colleagues (2009) reported that seven patients (1 female) recovering from an alcohol use disorder had irregular circadian rhythms across the first 15 days of abstinence. Although there was no healthy comparison group, their circadian rhythms appeared to be desynchronised, as indicated by morning and evening urinary six-sulfatoxymelatonin sampling. Circadian disturbances during early abstinence may also contribute to delayed sleep onset, increased wakefulness, and REM sleep abnormalities. Taken together, these findings suggest that sleep disturbances during early abstinence may reflect underlying alcohol-related neurological and hormonal changes.

There is evidence that the magnitude of sleep deficits experienced during early abstinence may be predictive of relapse to alcohol use (Adamson & Burdick, 1973; Brower, Aldrich, & Hall, 1998; Clark et al., 1998; Drummond et al., 1998; Gillin et al., 1994; Williams & Rundell, 1981). A longitudinal study by Brower and colleagues (1998) followed 74 men and women undergoing treatment for an alcohol use disorder over a 12-month period, during which time 36 patients relapsed. PSG was first assessed at approximately one month of abstinence (31.5 ± 15.5 days)

during the protracted alcohol withdrawal period. Patients who relapsed to alcohol use had longer sleep onset latencies, lower SWS percentage, and shorter REM sleep onset latencies at this time-point, compared to patients who remained abstinent. Furthermore, a logistic regression analysis highlighted that the magnitude of these deficits predicted relapse prior to 12 months. Brower and colleagues (1998) suggested that these sleep disturbances may reflect underlying neurophysiological and cognitive dysfunctions that may contribute to relapse. Further, providing additional support, these results have been reliably replicated (Adamson & Burdick, 1973; Clark et al., 1998; Drummond et al., 1998; Gillin et al., 1994; Williams & Rundell, 1981). In summary, early abstinence following an alcohol use disorder is associated with substantial disturbances to normal sleep that may reflect underlying alcohol-related neural and physiological changes, and may even predict relapse to alcohol use during recovery.

3.2.2 Sustained recovery/extended abstinence after chronic use

Following sustained recovery from an alcohol use disorder, some sleep quality and architecture disturbances persist into long-term abstinence. These deficits largely mirror those observed during early abstinence, or alcohol withdrawal syndromes, but extend well-beyond this time period. These protracted sleep deficits include longer sleep onset latencies, sleep fragmentation (i.e., more awakenings and arousals), less total sleep time (Adamson & Burdick, 1973; Drummond et al., 1998; Williams & Rundell, 1981), less SWS (Adamson & Burdick, 1973; Allen, Wagman, Funderburk, & Wells, 1980; Brower et al., 1998; Colrain et al., 2009b; Drummond et al., 1998; Imatoh, Nakazawa, Ohshima, Ishibashi, & Yokoyama, 1986; Williams & Rundell, 1981), more REM sleep, higher REM sleep density, and shorter REM sleep

onset latencies (Benca, Obermeyer, Thisted, & Gillin, 1992; Brower et al., 2011; Clark et al., 1998; Colrain et al., 2009b; Drummond et al., 1998; Gillin et al., 1994; Imatoh et al., 1986; Williams & Rundell, 1981), compared to healthy age-matched adults. These differences have been detected following up to three years of abstinence (Angarita et al., 2016; Brower et al., 1998; Brower et al., 2001; Chakravorty et al., 2016; Roehrs & Roth, 2001b). As previously highlighted, the magnitude of these deficits may predict relapse to alcohol use (Adamson & Burdick, 1973; Brower et al., 1998; Clark et al., 1998; Drummond et al., 1998; Gillin et al., 1994; Williams & Rundell, 1981). Critically, longitudinal studies have shown some recovery in these measures over extended periods of abstinence (Adamson & Burdick, 1973; Drummond et al., 1998; Imatoh et al., 1986; Williams & Rundell, 1981).

The rate and degree of recovery appears to vary for different objective sleep measures over extended abstinence. This was demonstrated by Williams and Rundell (1981) who reassessed sleep PSG after 3 months (n=46), 9 months (n=24), 15 months (n=8), and 21 months (n=6) of abstinence in men and women recovering from alcohol use disorders, compared to healthy age-matched control participants. They reported that sleep onset latency, wake after sleep onset, and REM sleep percentage, appeared to normalise following one to two years of abstinence. However, at 21 months of abstinence, though some improvements were observed, participants still had more arousals, more sleep stage changes, and lower SWS percentage, compared to healthy age-matched control participants. These findings have largely been replicated by other researchers (Adamson & Burdick, 1973; Drummond et al., 1998; Imatoh et al., 1986; Williams & Rundell, 1981). Objective sleep improvements may reflect neural adaptation and restoration across extended

abstinence. However, it is critical to note that in each of these longitudinal investigations a substantial number of participants either withdrew or returned to alcohol use, leading to smaller, potentially biased, samples at longer follow-up time points (Adamson & Burdick, 1973; Drummond et al., 1998; Williams & Rundell, 1981). As there is evidence that some sleep deficits may predict relapse to alcohol use, it is possible that some alcohol-related sleep disturbances may be more severe and/or enduring in vulnerable individuals (Adamson & Burdick, 1973; Brower et al., 1998; Clark et al., 1998; Drummond et al., 1998; Gillin et al., 1994; Williams & Rundell, 1981). Although it appears that most sleep disturbances show some recovery over extended abstinence, the extent and magnitude of this recovery may not be total (Adamson & Burdick, 1973; Williams & Rundell, 1981).

There is substantial evidence that there are long-lasting deficits in SWS and ongoing sleep fragmentation even with sustained abstinence (Adamson & Burdick, 1973; Colrain et al., 2009b; Drummond et al., 1998; Imatoh et al., 1986; Williams & Rundell, 1981). There are mixed findings regarding the normalisation of REM sleep following extended abstinence. Although some studies have reported a normalisation in REM sleep percentage following one to two years of abstinence (Imatoh et al., 1986; Williams & Rundell, 1981), other studies have reported long-lasting REM sleep augmentation, including shorter REM sleep onset latencies, and higher REM sleep percentage (Colrain et al., 2009b; Drummond et al., 1998). A large cross-sectional study by Colrain and colleagues (2009b) compared sleep architecture and EEG power spectra in 42 abstinent adults (15 women) diagnosed with an alcohol use disorder (30 to 719 days since last drink; mean 196.3 ± 189.2) to 42 age- and sex-matched control participants (23 women). They found that abstinent participants had higher REM sleep percentage, shorter REM sleep onset latencies, less SWS

percentage, and lower non-REM delta EEG spectral power, than healthy control participants. Differences in non-REM delta power were greatest at frontal electrode sites, where this frequency is preferentially generated. Consistent with the normal sleep literature, women had higher overall non-REM delta EEG power compared to men, irrespective of diagnosis (Baker & O'Brien, 2017; Carskadon & Dement, 2017; Dijk et al., 1989; Ehlers & Kupfer, 1997; Mourtazaev et al., 1995; Walsleben et al., 2004). However, women recovering from alcohol use disorders still had notably lower non-REM delta EEG power than age- and sex-matched control participants. This suggests that chronic alcohol use impacts sleep in a similar manner for men and women. Colrain and colleagues (2009b) concluded that these sleep deficits may reflect alcohol-related structural and functional changes to the brain and sleep systems, most prominent in frontal regions. These findings provide evidence that some degradations in sleep following an alcohol use disorder may be persistent and reflect underlying alcohol-related neural changes.

Ongoing deficits in SWS, delta EEG activity, and sleep fragmentation, following recovery from an alcohol use disorder, may reflect long-term changes in the homeostatic regulation of sleep (Brower et al., 2001; Colrain et al., 2014; Conroy et al., 2011; Martindale, Hurley, & Taber, 2017; Thakkar, Sharma, & Sahota, 2015). Research has consistently demonstrated a downregulation in homeostatic sleep drive following recovery from an alcohol use disorder (Armitage, Hoffmann, Conroy, Arnedt, & Brower, 2012; Brower et al., 2011; Colrain et al., 2014; Irwin et al., 2002; Thakkar et al., 2015). Armitage and colleagues (2012), and Brower and colleagues (2011), showed that abstinent men and women diagnosed with an alcohol use disorder had a blunted homeostatic response to a three-hour delay in bedtime, as indicated by less SWS, lower delta EEG spectral power, and a slower dissipation of

these measures across the sleep period, compared to healthy control participants. Irwin and colleagues (2002) reported that following one night of partial sleep deprivation (time in bed restricted to 3 hours) there were no increases in SWS or delta EEG spectral power during the subsequent recovery sleep period, in 46 abstinent men with an alcohol use disorder. These differences reflect a reduced homeostatic sleep drive or pressure, and may contribute to less SWS, lower delta EEG frequency, and more sleep fragmentation during periods of prolonged abstinence (Angarita et al., 2016; Brower et al., 2001; Colrain et al., 2014; Conroy et al., 2011; Thakkar et al., 2015). Diminished homeostatic sleep drive in people with long-term alcohol use disorders may reflect underlying neurochemical, structural, and functional brain changes related to chronic alcohol use.

Degradations in K-complexes have also been observed during sustained recovery following an alcohol use disorder (Brower et al., 2001; Colrain, Crowley, Nicholas, Padilla, & Baker, 2009a; Nicholas, Sullivan, Pfefferbaum, Trinder, & Colrain, 2002a; Roehrs & Roth, 2001b). Research has consistently reported a reduced K-complex incidence, and lower K-complex amplitude, during long-term abstinence, compared to age- and sex-matched healthy adults (Colrain et al., 2009a; Colrain et al., 2011; Nicholas et al., 2002a). These deficits were most notable over frontal scalp sites where K-complexes are most prominent (Colrain, 2005; Nicholas, Trinder, & Colrain, 2002b). As previously described, a K-complex is believed to represent an isolated delta EEG waveform (Colrain, 2005; Nicholas et al., 2002b). This suggests that the enduring deficits in SWS, and delta EEG spectral power, described above, may also be detected when examining a discrete instance of delta EEG activity. These collective findings suggest that chronic alcohol use may produce long-lasting impairments in the brain's capacity to elicit synchronous neural firing.

This may reflect long-term changes in the neurophysiological mechanisms responsible for neural synchronisation and firing, and/or alcohol-related degradations in neural integrity and connectivity (Colrain et al., 2009a; Colrain et al., 2014; Colrain et al., 2011; Colrain et al., 2009b; Nicholas et al., 2002a).

3.2.3 Acute alcohol consumption during early abstinence after chronic use

Several historical studies have investigated the acute effects of alcohol on sleep during the early stages of abstinence in men recovering from alcohol use disorders (Allen, Wagman, & Funderburk, 1977; Allen et al., 1980; Brower, 2001; Gross et al., 1973; Gross & Hastey, 1975; Wagman & Allen, 1975). Although this experimental design is no longer implemented for ethical reasons, these studies orally administered alcohol to men receiving inpatient treatment for alcohol use disorders during the first few weeks of abstinence, and measured subsequent sleep PSG. During early abstinence, or acute alcohol withdrawal syndrome, the effects of acute alcohol consumption on sleep are largely similar to healthy adults, although there are some fundamental differences (Brower, 2001, 2003). As in healthy adults, these studies have demonstrated that acute alcohol consumption during early abstinence leads to increased SWS, longer REM sleep onset latencies, and less REM sleep (Allen et al., 1977; Allen et al., 1980; Brower, 2001; Gross et al., 1973; Gross & Hastey, 1975; Wagman & Allen, 1975; Zarcone, 1978). However, in contrast to healthy adults, sleep onset latencies increased, and total sleep time decreased, in men recovering from alcohol use disorders (Allen et al., 1980; Brower, 2001; Gross et al., 1973; Gross & Hastey, 1975). These differences may reflect chronic alcohol-related changes to the brain and sleep systems, including the downregulation of inhibitory neurotransmitter systems, and upregulation of excitatory systems, as outlined above

(Brower, 2001, 2003; Brower et al., 2001; Chakravorty et al., 2016; Roehrs & Roth, 2001b). This may result in tolerance to the initial sedative effects of acute alcohol and explain this unique response during early abstinence.

Some studies have investigated the impact of repeated alcohol administration over multiple nights on sleep PSG during early abstinence in men receiving treatment for alcohol use disorders (Allen et al., 1977; Brower, 2001, 2003; Gross & Hastey, 1975; Wagman & Allen, 1975). These studies showed that tolerance to the sedative or sleep-promoting effects of acute alcohol, such as augmented SWS, develops within only four to five days of consecutive administration. A small investigation by Allen and colleagues (1977) administered approximately eight standard drinks per day, over three to seven days, in three men undergoing treatment for an alcohol use disorder. They reported that tolerance to the SWS promoting effects of acute alcohol developed faster in patients who had lower SWS percentage prior to commencing. This was also associated with poorer treatment outcomes. A larger study by Gross and colleagues (1975) investigated the effects of repeated alcohol administration on sleep in 12 men aged 26 to 48 years undergoing treatment for an alcohol use disorder. They measured baseline SWS percentage after three to five weeks of total abstinence, compared to four consecutive days of acute alcohol administration (dose 1.6 g/kg – 3.2 g/kg) across which SWS was averaged. They found that participants whose baseline SWS was less than 20 percent of total sleep time, showed either no changes, or lower SWS percentage, following acute alcohol consumption on average. In contrast, participants whose baseline SWS was greater than 20 percent of total sleep time showed higher average SWS following acute consumption (Gross & Hastey, 1975). Low baseline SWS during early abstinence may signify an impaired neural capacity to produce SWS in these patients. These

findings could suggest that acute alcohol consumption cannot enhance SWS if these sleep and neural systems are substantially impaired. In other words, acute alcohol ingestion may only facilitate SWS if the underlying neural structures can elicit and support this EEG activity. Regarding EEG power spectra, Wagman and Allen (1975) showed that acute alcohol administration in 20 abstinent men recovering from alcohol use disorders enhanced both delta and alpha EEG frequency. Interestingly, following repeated administration of varying doses over approximately two weeks, alpha EEG frequency remained elevated, suggesting that tolerance to this electrophysiological abnormality may not develop. Taken together, these findings indicate that, as in healthy adults, sleep following acute alcohol consumption may not be restorative, and elicit alpha-delta sleep, in men with long-term alcohol use disorders.

3.3 Adolescents and young adults

Adolescents and young adults experience the ongoing development of neural mechanisms critical for sleep while consuming higher amounts of alcohol than any other age group (AIHW, 2017; Churchwell & Yurgelun-Todd, 2011; Degenhardt et al., 2013; Hagenauer et al., 2009; Sowell et al., 2004; Tarokh et al., 2011; WHO, 2018). For this reason, it is imperative to consider the effects of alcohol use on sleep in this developing cohort. As previously described, there is substantial evidence to suggest that both acute and habitual alcohol exposure during the final stages of neural development may have detrimental impacts on a range of neurophysiological systems (Guerri & Pascual, 2010; Jacobus & Tapert, 2013; Lubman et al., 2007; Miller, 2006; Sadrian et al., 2013). Given their unique patterns of alcohol

consumption, it is critical to better understand the impacts of both acute and habitual alcohol consumption on sleep in young people.

3.3.1 Acute use

Due to the ethical and legal constraints of administering alcohol to human adolescents below the legal drinking age, no studies have investigated the acute effects of alcohol consumption on sleep in people below 18 years old. A limited number of studies have been conducted in late adolescents aged 18 to 21 years, a population in which adolescent neurological development is still ongoing (Chan, Trinder, Andrewes, Colrain, & Nicholas, 2013; Chan, Trinder, Colrain, & Nicholas, 2013; Williams, MacLean, & Cairns, 1983). Research utilising adolescent animal models have also added knowledge in this area (Ehlers et al., 2013a; Pian et al., 2008; Silveri & Spear, 1998, 1999).

Research undertaken in animals suggests that adolescents experience fewer sedative effects following acute alcohol administration compared to mature adults (Ehlers et al., 2013a; Pian et al., 2008; Silveri & Spear, 1998). Two studies have found total sleep time to be significantly shorter in adolescent rats, compared to mature adults, after receiving an equivalent intravenous dose of alcohol (3.5 – 5.0 g/kg; Pian et al., 2008; Silveri & Spear, 1998). Animal studies have also shown that adolescents experience smaller increases in delta EEG frequency following acute alcohol administration, compared to adults (Ehlers et al., 2013a; Pian et al., 2008). Less total sleep time and lower delta EEG activity may indicate that adolescents experience less physiological sedation than adults. Indeed, this is supported by findings during wake that intoxicated adolescent rodents are faster at completing a righting reflex than adult rodents, signifying lower sedation (Linsenbardt et al., 2009;

Little et al., 1996; Moy et al., 1998; Pian et al., 2008; Quoilin et al., 2010; Silveri & Spear, 1998). A study by Ehlers and colleagues (2013a) has also reported differences in objective sleep between adolescent and adult rats during the acute alcohol withdrawal period. Specifically, compared to adults, adolescents had a larger decline in delta EEG frequency in the subsequent sleep period 20 hours after alcohol was administered (dose 3.5 g/kg) and BAC was zero (Ehlers et al., 2013a). Although further evidence is needed, lower delta EEG frequency may indicate that adolescents experience greater sleep disturbances than adults during acute alcohol withdrawal. Collectively, these findings may reflect neurological developmental differences between adolescents and mature adults. Specifically, the immaturity of the GABAergic neurotransmitter system, and the augmentation of the glutaminergic and mesolimbic reward systems, during adolescence and young adulthood (Doremus-Fitzwater et al., 2010; Ehlers et al., 2013a; Petit et al., 2013; Pian et al., 2008; Spear, 2011, 2014). Taken together, this line of research in animals suggests that adolescents may respond differently to acute alcohol consumption, and more specifically, be less susceptible to its initial sedative or sleep-promoting effects, a phenomenon that is clearly established in the adult literature (Ehlers et al., 2013a; Pian et al., 2008; Silveri & Spear, 1998). There is some evidence to suggest that adolescents may experience exaggerated sleep disturbance during the acute alcohol withdrawal period, although this is yet to be verified (Ehlers et al., 2013a).

Only two studies have explicitly investigated the effects of acute alcohol consumption on sleep in an exclusively late adolescent cohort aged 18 to 21 years (Chan et al., 2015; Chan et al., 2013; Williams et al., 1983). Williams and colleagues (1983) investigated the effects of a high dose of pre-bedtime alcohol (mean BrAC at lights out $.08 \pm .01\%$) on sleep PSG, compared to a placebo beverage (BrAC $.00 \pm$

.00%), in eight female late adolescents (mean age 19.5 years). Chan and colleagues (2013, 2015) completed a similar but larger investigation in 24 late adolescents (mean age 19.1 ± 1.0 years), including both males ($n=12$) and females ($n=12$). The mean BrAC at lights out for Chan and colleagues' (2013, 2015) investigation was $.08 \pm .02$ percent following alcohol ingestion, and $.00 \pm .00$ percent following placebo. For both investigations, it was anticipated that the intended peak BAC of .10 percent would be achieved within the first hour of sleep. These studies recruited only light-drinking participants with no history of binge drinking or family history of alcohol use disorders. Though both studies measured and analysed sleep quality and architecture (Chan et al., 2013; Williams et al., 1983), Chan and colleagues (2015) also completed a spectral analysis of the sleep EEG. In accordance with the general literature, and well-established bi-phasic effects of alcohol, most sleep measures were analysed by comparing the first versus second halves of the sleep period, in both the alcohol and placebo conditions. Additionally, Chan and colleagues (2013, 2015) analysed their data by sleep cycles. Overall, the findings of these studies were largely consistent, generally reporting the typical biphasic effects of acute alcohol consumption on sleep described in mature adults (Chan et al., 2015; Chan et al., 2013; Colrain et al., 2014; Williams et al., 1983).

In the first half of the sleep period, following pre-sleep alcohol consumption, both studies in late adolescents reported 5.2 to 14.4 percent more SWS, and 6.7 to 12.7 percent less REM sleep, on average, compared to a placebo beverage (Chan et al., 2013; Williams et al., 1983). Chan and colleagues (2013) reported that REM sleep onset latency was 27.5 minutes longer on average following acute alcohol ingestion, compared to placebo. Although mean REM sleep onset latency was also longer in Williams and colleagues' (1983) study by 31.5 minutes, this was not

significant, perhaps due to low statistical power. Additionally, Chan and colleagues (2013) reported 1.7 fewer arousals per hour following pre-sleep alcohol, in the first half of the sleep period. However, this sleep quality measure was not analysed by half night in Williams and colleagues' (1983) investigation. These sleep quality and architecture findings have also been consistently reported in mature adults (Arnedt et al., 2011; Dijk et al., 1992; Feige et al., 2006; MacLean & Cairns, 1982; Miyata et al., 2004; Prinz et al., 1980; Roehrs et al., 1989; Rundell et al., 1972; Sagawa et al., 2011; Stein & Friedmann, 2005; Van Reen et al., 2006; Yules et al., 1967). Lastly, following acute alcohol ingestion, Chan and colleagues (2015) reported more non-REM delta (~20%) and alpha (~400%) EEG spectral power in the first sleep cycle, compared to placebo. These differences were greatest at frontal electrode sites and denote the presence of alpha-delta sleep (Chan et al., 2015). These findings suggest that light-drinking late adolescents experience alpha-delta sleep following a high dose of alcohol before bed (Chan et al., 2015). This mirrors findings in mature adults, and suggests that pre-sleep alcohol may also substantially compromise the restorative properties of sleep in this population (Chan et al., 2015; Dijk et al., 1992; Landolt et al., 1996; Rundell et al., 1972; Van Reen et al., 2006).

In the second half of the sleep period, both studies reported 3.9 to 13.2 percent lower SWS following pre-sleep alcohol consumption, compared to placebo, in late adolescents (Chan et al., 2013; Williams et al., 1983). Williams and colleagues (1983) also found 11.6 percent more stage N1 sleep on average in the second half of the sleep period, that was not observed by Chan and colleagues (2013). Additionally, Chan and colleagues (2013) reported an average of 1.7 more awakenings, 13.3 minutes more wake after sleep onset, and approximately 4.2 percent less sleep efficiency, following alcohol compared to placebo ingestion. These

sleep quality measures were not analysed by half night in Williams and colleagues' (1983) study. Critically, neither study reported an increase or rebound in REM sleep in the second half of the sleep period, a phenomenon that is sometimes reported, albeit inconsistently, in the adult literature (MacLean & Cairns, 1982; Roehrs & Roth, 2001a; Sagawa et al., 2011). Both studies reported less overall REM sleep following acute alcohol consumption compared to placebo, across the entire sleep period. In addition, both studies reported that all-night wake after sleep onset was higher following alcohol consumption in late adolescents (Chan et al., 2013; Williams et al., 1983). Taken together, these findings indicate that sleep is substantially compromised by acute alcohol consumption during the final stages of human neural development (Chan et al., 2013; Williams et al., 1983). Changes in sleep quality and architecture resulting from pre-sleep alcohol ingestion in late adolescents are largely similar to those reported in the adult literature (Arnedt et al., 2011; Landolt et al., 1996; MacLean & Cairns, 1982; Roehrs, 1999, 1991; Rohsenow et al., 2010; Rundell et al., 1972; Van Reen et al., 2006; Yules et al., 1967).

The most notable discrepancy between these two adolescent studies, and the adult literature, was in sleep onset latency (Chan et al., 2013; Williams et al., 1983). Consistent with the adult literature, Williams and colleagues (1981) reported that sleep onset latency was on average 11.8 minutes shorter following alcohol consumption compared to placebo. However, Chan and colleagues (2013) reported no differences in sleep onset latency between the alcohol and placebo conditions. This inconsistency may reflect disparities in sex and sample size in these studies, as Williams and colleagues (1983) only included a small sample of eight female participants. However, due to this discrepant finding it is currently unclear whether alcohol impacts sleep onset latency in young people. As evidence in animal models

suggests adolescents experience less sedation following acute alcohol administration, this may also be the case in humans (Ehlers et al., 2013a; Pian et al., 2008; Silveri & Spear, 1998; Slawecki, 2002; Spear, 2002b; York & Chan, 1993). For example, Chan and colleagues (2013) did not report any initial improvements in wake after sleep onset, or sleep efficiency, in the first half of the sleep period, findings that are commonly reported in the adult literature. This may provide further evidence that human adolescents are indeed less susceptible to the sedative effects of alcohol. However, further research is required before conclusions can be drawn.

Finally, in order to discern the acute effects of alcohol consumption on sleep alone, uncomplicated by interactions with chronic use, both studies investigated light-drinking late adolescents only (Chan et al., 2013; Williams et al., 1983). However, such a sample is unlikely to reflect the general population as heavy habitual alcohol use is common in this age group (AIHW, 2017; Degenhardt et al., 2013; WHO, 2011, 2018). To date, no studies have investigated the impacts of acute alcohol consumption on objective sleep in heavy-drinking late adolescents. A large study by Patrick and colleagues (2018) in 667 young people aged under 21 years investigated self-report sleep following an evening of binge alcohol consumption (males: ≥ 5 standard drinks; females: ≥ 4) compared to low or no alcohol consumption (males: 0 – 4 standard drinks; females: 0 – 3). Self-report sleep was measured daily for the duration of the study via three questions that measured sleep duration, sleep quality, and next-day tiredness. This repeated-measures investigation took place over approximately one year and included 25,616 days of data in total. They found that following an acute alcohol binge, sleep quality and duration were lower, and next-day tiredness was higher, compared to an evening of low or no alcohol consumption. Interestingly, these negative effects did not dissipate in individuals who regularly

engaged in binge drinking. Although further evidence is required, this finding suggests that tolerance to the acute effects of alcohol on sleep may not develop with a binge pattern of alcohol consumption. In summary, although acute alcohol appears to disrupt sleep in a similar manner to mature adults, young people may experience less sensitivity to alcohol's initial sleep-promoting effects. However, further human research in this age group is required to confirm this. Furthermore, additional research is needed to elucidate the interactions between acute and habitual alcohol use on sleep, as heavy drinking is common in young people.

3.3.2 *Habitual use*

There is substantial evidence from self-report studies that heavy habitual alcohol use is related to reduced sleep quality and duration in adolescents and young adults without an alcohol use disorder (Bartel, Gradisar, & Williamson, 2015; Ehlers, Wills, & Gilder, 2018b; Johnson & Breslau, 2001; Kenney, LaBrie, Hummer, & Pham, 2012; Kenney, Paves, Grimaldi, & LaBrie, 2014; Marmorstein, 2017; Miller, DiBello, Lust, Carey, & Carey, 2016; Morioka et al., 2013; Nguyen-Louie et al., 2018; Pieters, Van Der Vorst, Burk, Wiers, & Engels, 2010; Popovici & French, 2013; Sivertsen, Skogen, Jakobsen, & Hysing, 2015; Warren, Riggs, & Pentz, 2017; Wong, Brower, Fitzgerald, & Zucker, 2004; Wong, Robertson, & Dyson, 2015; Zhabenko et al., 2016). Whilst heavy alcohol use may cause sleep disturbances due to its established neurophysiological effects, there is also evidence that sleep problems may precede the onset of heavy drinking in young people (Bartel et al., 2015; Colrain et al., 2014; Nguyen-Louie et al., 2018; Pasch, Latimer, Cance, Moe, & Lytle, 2012; Patrick et al., 2018; Sivertsen et al., 2015; Warren et al., 2017; Wong & Brower, 2012; Wong et al., 2004; Wong, Brower, Nigg, & Zucker, 2010; Wong et

al., 2015). As in mature adults, the relationship between heavy alcohol use and sleep disturbance in young people appears to be complex and bi-directional.

Several prospective studies suggest that poor subjective sleep precedes, or even predicts, the onset of alcohol use and alcohol-related problems in young people (Bartel et al., 2015; Miller, Janssen, & Jackson, 2017; Nguyen-Louie et al., 2018; Pasch et al., 2012; Sivertsen et al., 2015; Wong & Brower, 2012; Wong et al., 2004; Wong et al., 2010; Wong et al., 2015). A study by Wong and colleagues (2004) reported that maternal ratings of childhood sleep problems at 3 to 5 years of age, predicted early alcohol use onset between 12 and 14 years of age, in 257 males. Similarly, in 292 (94 female) young people, self-reported sleep problems between 11 and 17 years, predicted alcohol-related problems in late adolescence (18 to 20 years; Wong et al., 2010). Finally, a large study in 6,504 young people demonstrated that shorter sleep durations, and difficulties sleeping, in adolescence predicted alcohol-use problems in young adulthood (Wong et al., 2015). Taken together these findings suggest that, as in adults, some sleep deficits may pre-exist, and possibly contribute to, the onset of heavy alcohol use in young people. In adults, the prospective relationship between sleep disturbance and heavy alcohol use is generally explained by alcohol's initial acute sleep-promoting effects, coupled with the development of tolerance (Brower, 2003; Roehrs & Roth, 2001b, 2018). However, given that young people may be less susceptible to alcohol's acute sedative effects, this is perhaps unlikely to motivate alcohol use in this younger age group. Instead, antecedent sleep disturbances in young people, such as chronic sleep restriction, may result in, or reflect, underlying impairments in executive functions, contributing to increased risk taking, and higher alcohol use (Carskadon, 2011; Hasler, Soehner, & Clark, 2015; Pasch et al., 2012; Pieters et al., 2010).

There is objective evidence that some sleep disturbances may precede the onset of alcohol use in young people. Studies have shown EEG power spectra differences in alcohol-naïve young people with a family history of alcohol use disorders (Tarokh & Carskadon, 2010; Tarokh et al., 2012). A family history is a well-established risk factor for developing an alcohol use disorder (Meyers & Dick, 2010). Tarokh and Carskadon (2010) reported that 13 children (5 female) with a family history of alcohol use disorders, aged 9 to 10 years, had less non-REM delta EEG spectral power than 17 age- and sex-matched children with no family history. Tarokh and colleagues (2012) replicated this finding in adolescents with a family history of alcohol use disorders, aged 15 to 19 years, compared to age-matched control participants. Interestingly, discrepancies in non-REM delta EEG frequency became larger with increasing age. Research has also shown that children and young adults with a family history of alcohol use disorders have augmented alpha EEG frequency during sleep, an effect that was unrelated to either acute or habitual alcohol consumption (Dahl et al., 2003; Ehlers & Phillips, 2003). These collective sleep deficits may reflect underlying genetic and/or neurodevelopmental differences, such as less neural grey matter, in young people with a family history of alcohol use disorders (Acheson et al., 2014; Benegal et al., 2007; Cservenka, 2016; Henderson et al., 2018; Herting et al., 2011; Spadoni et al., 2013; Squeglia et al., 2014; Venkatasubramanian et al., 2007). For example, less frontal grey matter may reduce the brain's capacity to elicit synchronous delta EEG activity. Pre-existing neural deficits may contribute to the onset and acceleration of alcohol use in this population as they are associated with impairments in executive function, and increased risk-taking behaviour (Dougherty et al., 2015; Kamarajan et al., 2015; Nigg et al., 2004). It is critical to note that these studies did not report differences in visually scored

sleep quality or architecture (Dahl et al., 2003; Ehlers & Phillips, 2003; Tarokh & Carskadon, 2010; Tarokh et al., 2012). This suggests that sleep deficits related to family history of alcohol use disorders in young people are subtle. Furthermore, these studies did not assess whether participants went on to engage in heavy alcohol use or develop an alcohol use disorder (Tarokh & Carskadon, 2010; Tarokh et al., 2012).

There is considerable evidence that heavy alcohol consumption in adolescence is related to subjective sleep disturbance (Arria, Dohey, Mezzich, Bukstein, & Van Thiel, 1995; Clark et al., 2001; Ehlers et al., 2018b; Johnson & Breslau, 2001; Kenney et al., 2012; Kenney et al., 2014; Marmorstein, 2017; Morioka et al., 2013; Pieters et al., 2010; Popovici & French, 2013; Warren et al., 2017; Wong et al., 2004; Zhabenko et al., 2016). Heavy drinking throughout adolescence has been associated with poor subjective sleep quality in young adulthood (Ehlers et al., 2018b). Ehlers and colleagues (2018b) found that a history of binge drinking in adolescence was related to reduced global sleep quality, as measured by the Pittsburgh Sleep Quality Index, in 800 participants (448 female) aged between 18 and 30 years with no history of alcohol use disorders. A large-scale cross-sectional study by Morioka and colleagues (2013) investigated habitual alcohol consumption and self-reported sleep disturbance in 98,967 (50,073 female) Japanese adolescents. This investigation revealed a dose-dependent relationship between habitual alcohol use and sleep disturbances. Specifically, sleep duration and continuity decreased, and sleep onset latency increased, with more drinking days per month, and more alcohol per drinking occasion. Finally, sleep disruption is one of the most robust self-reported symptoms of an adolescent onset alcohol use disorder (Arria et al., 1995; Clark et al., 2001). It is possible that some subjective sleep

complaints in actively drinking young people may represent the acute sleep disrupting actions of alcohol. However, these sleep disturbances may also reflect underlying alcohol-related changes to the brain and sleep systems that have also been reported in heavy-drinking young people (see Section 2.2.4.2).

There is substantial evidence that ethanol exposure in utero during the early stages of human neural development can result in life-long neurological and cognitive deficits, as well as disturbances to sleep (Bell et al., 2010; Clarke & Gibbard, 2003; Riley et al., 2011; Streissguth et al., 1980; Streissguth & O'Malley, 2000). Sleep fragmentation and low sleep efficiency has been identified in children and adolescents diagnosed with fetal alcohol spectrum disorder (Goril, Zalai, Scott, & Shapiro, 2016). These sleep deficits are long-lasting, with research showing that ethanol exposure in utero is associated with SWS fragmentation (experiencing only short, interrupted bouts of SWS) in mature adulthood (Tayade, 2015; Wilson et al., 2016). SWS fragmentation in fetal alcohol spectrum disorder is positively correlated with cognitive impairment, suggesting that ongoing SWS disruption may contribute to cognitive dysfunction in this cohort (Wilson et al., 2016). This research highlights that alcohol exposure during critical stages of neural development has the potential to cause lasting changes to the brain and sleep systems (Wilson et al., 2016).

Research using animal models has shown that chronic alcohol exposure during adolescence may also produce long-lasting neurophysiological changes detectable in sleep (Criado, Wills, Walker, & Ehlers, 2008; Ehlers & Criado, 2010; Ehlers, Sanchez-Alavez, & Wills, 2018a). Criado and colleagues (2008) exposed 22 male adolescent Wistar rats to 95 percent ethanol vapour for 12 hours a day for five consecutive weeks. Following five weeks of abstinence, and recovery from alcohol withdrawal syndrome, sleep EEG was measured in mature adulthood. Criado and

colleagues (2008) reported less total SWS, less SWS within a sleep cycle, and less delta EEG frequency, compared to 18 age- and experimentally-matched controls with no alcohol exposure (Criado et al., 2008). This finding has since been replicated in an investigation by Ehlers and colleagues (2018a) that utilised identical procedures. These lasting sleep changes may be unique to alcohol exposure during adolescence i.e., the final stages of neural development (Criado et al., 2008; Ehlers et al., 2018a). Although these studies did not include an adult comparison group, an investigation using identical procedures showed that chronic alcohol exposure in adult Wistar rats did not result in long-lasting sleep changes following recovery from alcohol withdrawal syndrome (Ehlers & Slawecki, 2000). Taken together, these findings suggest that heavy alcohol exposure in young people may produce unique, long-lasting deficits in SWS and delta EEG frequency (Criado et al., 2008; Ehlers & Criado, 2010; Ehlers et al., 2018a). These findings, however, have not yet been tested or confirmed in humans.

There is very little human research available on the impact of habitual alcohol use on objective sleep measures in young people (Colrain et al., 2014). A pilot study by Nicholas and colleagues (2011) investigated the incidence and amplitude of evoked K-complexes during sleep in late adolescent males, six of whom were heavy drinkers (19.49 ± 1.1 years) and seven light (19.47 ± 1.2 years). K-complexes, although spontaneously occurring, can also be elicited during sleep by an external stimulus (e.g., an auditory tone). These K-complexes constitute a single delta EEG frequency waveform (Colrain, 2005; Nicholas et al., 2002b). Nicholas and colleagues (2011) reported that heavy-drinking late-adolescent males had fewer auditory evoked K-complexes than same-aged light drinkers in stage N2 sleep and SWS. Furthermore, heavy drinkers had slower N550 latencies during SWS. In other words,

it took longer for heavy drinkers to reach the K-complex amplitude peak, compared to light drinkers. These findings suggest that despite their relatively short drinking histories, heavy-drinking late adolescents may experience a reduced neural capacity to synchronise delta EEG frequency (Nicholas et al., 2011). Although these findings were largely consistent with those reported in adults with long-term alcohol use disorders, Nicholas and colleagues (2011) reported no differences in evoked K-complex amplitude height between heavy- and light-drinking late-adolescent males (Colrain et al., 2009a; Colrain et al., 2011; Nicholas et al., 2002a). These collective findings suggest that although heavy-drinking late adolescents may experience some evoked K-complex impairments, they are not yet to the same extent as those observed in adults with long-term alcohol use disorders.

Limited research suggests that heavy alcohol use during adolescence may be related to electrophysiological abnormalities during wake in young adulthood (Ehlers et al., 2007). Ehlers and colleagues (2007) measured event-related potentials or the electrophysiological response to a facial discrimination task in 125 young adults (73 female) aged 18 to 25 years, with or without a history of binge drinking during adolescence. In this study, a history of binge drinking was defined as consuming more than five standard drinks per drinking occasion once or more per month, for a minimum of six months, prior to 18 years of age. Ehlers and colleagues (2007) reported young adults with a history of binge drinking had shorter P350 latencies, and lower P450 amplitudes, than young adults without a history. They postulated that this may represent an acceleration of neural loss that occurs naturally across adolescence and young adulthood related to excessive alcohol use, and/or frontal lobe disinhibition. Taken together, these findings indicate that young people who habitually engage in heavy alcohol use may experience abnormalities in EEG

synchronisation, during both wakefulness and sleep (Ehlers et al., 2007; Nicholas et al., 2011).

To date, only one study has investigated the effects of habitual alcohol use on objective sleep quality and architecture in young people (Cohen-Zion et al., 2009). Cohen-Zion and colleagues (2009) investigated the impacts of habitual alcohol and marijuana consumption on sleep PSG in 49 young people (15 female) aged 16.3 to 21.4 years. This sample included 29 habitual polysubstance users who had consumed approximately 39.4 ± 41.3 standard alcoholic drinks, and 204.1 ± 232.1 inhalations of marijuana, in the previous 30 days, and 20 age- and sex-matched control participants who consumed 2.4 ± 4.5 standard alcoholic drinks on average, and 0.0 ± 0.0 inhalations of marijuana. Sleep recordings took place on two occasions: the first following approximately one or two days of abstinence from alcohol and marijuana consumption, and the second following approximately 28 days of monitored abstinence. A regression analysis including all 49 participants was performed for previous 30-day alcohol and marijuana consumption, and sleep quality and architecture measures. For the initial sleep recording, alcohol intake in the previous 30 days independently predicted longer sleep onset latencies, and higher REM sleep pressure, signified by shorter REM sleep onset latencies and a trend for higher REM sleep percentage. However, previous 30-day marijuana consumption, but not alcohol, independently predicted lower SWS percentage. For the second sleep recording, approximately 28 days later, habitual alcohol consumption no longer predicted any differences in measures of sleep quality and architecture. These findings are difficult to interpret as they are likely severely confounded by marijuana or polysubstance use. However, they do provide preliminary evidence that habitual alcohol use in young people may impact sleep quality and architecture, even in the absence of pre-

sleep alcohol consumption. Interestingly, longer sleep onset latencies, and higher REM sleep pressure, has also been reported in abstinent adults recovering from long-term alcohol use disorders (Brower, 2003; Chakravorty et al., 2016; Colrain et al., 2014; Roehrs & Roth, 2001b). However, inconsistent with the alcohol use disorder literature, SWS was not associated with habitual alcohol consumption. Cohen-Zion and colleagues' (2009) findings suggest that recovery from habitual alcohol-related sleep deficits occurs relatively quickly (i.e., within 28 days) in this younger age group, but again, polysubstance use may have confounded this. Further studies are needed to investigate the potential effects of habitual alcohol use on objective sleep quality and architecture in young people.

There are several physiological and neurochemical mechanisms through which habitual heavy drinking in young people could impact normal sleep. As in mature adults, this may include alcohol-related structural and functional brain changes, as well as the adaptation of neurotransmitter systems (Brower, 2003; Colrain et al., 2014). There is substantial evidence that heavy alcohol use during the final stages of human neural development results in lasting changes in neural integrity and connectivity, including grey and white matter atrophy, and functional brain changes (Crews, Vetreno, Broadwater, & Robinson, 2016; Cservenka & Brumback, 2017; Ewing et al., 2014; Jones et al., 2018; Lees et al., 2018; Lisdahl et al., 2013a; McQueeney et al., 2009; Petit et al., 2014; Pfefferbaum et al., 2018; Silveri et al., 2016; Squeglia et al., 2009a; Squeglia et al., 2012; Squeglia et al., 2015; Wilson et al., 2015). Alcohol-related neural damage may underly the sleep findings described in the limited adolescent literature in humans (Nicholas et al., 2011) and animals (Criado et al., 2008; Ehlers et al., 2018a), such as less SWS percentage, delta EEG frequency, and evoked K-complex incidence. For example, fewer neurons

and/or impaired connections between neurons, is likely to impair the brain's capacity to synchronise neuronal firing and elicit high voltage, slow frequency EEG activity. These sleep deficits could also be exacerbated by the downregulation of inhibitory neurotransmitter systems, and upregulation of excitatory systems, which has also been observed in heavy-drinking young people (Silveri et al., 2014). It is also important to reiterate that as brain development has not yet finalised in adolescence and young adulthood, heavy alcohol exposure might disrupt or alter normal brain development, which could in turn be observed in sleep measures (Ehlers & Criado, 2010; Guerri & Pascual, 2010; Jacobus & Tapert, 2013; Lubman et al., 2007; Miller, 2006; Sadrian et al., 2013). As sleep is a functional measure of neurological state, changes in sleep architecture and quality may represent underlying neural changes related to heavy alcohol use in young people. Finally, given the clear bi-directional relationship between sleep disturbance and heavy alcohol use, it is also possible that some neural and sleep deficits in young people may be pre-existing.

3.3.3 *Acute and habitual alcohol use*

There is preliminary evidence that heavy-drinking young people may experience altered responses to the electrophysiological effects of acute alcohol consumption. For example, there is evidence in animal models that chronic alcohol exposure during adolescence alters the electrophysiological response to acute alcohol consumption during wake in adulthood (Slawecki, 2002). Slawecki (2002) exposed Sprague Dawley rats to 95 percent ethanol vapour for 12 hours per day for five days in adolescence. They then measured their electrophysiological EEG response to intravenous alcohol administration (1.0 – 1.5 g/kg) after maturing to adulthood, compared to age-matched controls with no adolescent ethanol exposure. They

showed rats with binge ethanol exposure in adolescence had blunted EEG responses to high doses of acute alcohol, which was demonstrated by reduced EEG variability. They suggested this may reflect enduring neuromodulation resulting from binge ethanol exposure during adolescence, dampening the response to acute alcohol in adulthood (Slawecki, 2002). Although it was not assessed, it is possible this unique electrophysiological response may also have been present prior to mature adulthood, and during sleep. However, further research is required to determine this.

To date, no human research has investigated the acute effects of alcohol consumption on sleep in young people who habitually engage in heavy alcohol use. Thus, at present it is unclear whether acute alcohol ingestion will alter sleep differentially in heavy- and light-drinking young people. It is possible that the effects of acute alcohol consumption on sleep in heavy-drinking young people would be similar to those reported in adults with long-term alcohol use disorders, such as augmented SWS (Allen et al., 1977; Allen et al., 1980; Brower, 2001; Gross et al., 1973; Gross & Hastey, 1975; Wagman & Allen, 1975). This response may reflect the adaptation of neurotransmitter systems to repeated high doses of acute alcohol, or the development of tolerance. However, given young people's binge drinking patterns, and comparatively short drinking histories, it is currently unclear whether tolerance to alcohol's acute effects on sleep would develop in this cohort. To highlight this, adults with long-term alcohol use disorders generally consume high amounts of alcohol daily, allowing tolerance to develop relatively quickly (Brower, 2001, 2003; Roehrs & Roth, 2001b; Rubinsky, Dawson, Williams, Kivlahan, & Bradley, 2013; Sobell & Sobell, 2008). In contrast, daily alcohol consumption in young people is very rare (AIHW, 2017). Instead, young people typically adopt a binge drinking pattern, consuming high amounts of alcohol on the weekend and abstaining from

alcohol during the week (AIHW, 2017; Del Boca, Darkes, Greenbaum, & Goldman, 2004; Heeb, Gmel, Rehm, & Mohler-Kuo, 2008; Kuntsche & Gmel, 2013; Kuntsche & Labhart, 2012). This sporadic pattern of heavy drinking could mean that tolerance to alcohol's acute sleep effects may develop differently, or not at all, in this younger age group. Indeed, this theory is supported by previously described evidence that binge-drinking young people still consistently report subjective sleep disruption following acute alcohol consumption (Patrick et al., 2018). However, human research is needed to determine whether habitual alcohol use interacts with acute alcohol ingestion to impact objective sleep in young people.

3.4 Summary

Sleep is essential for maintaining optimal health and wellbeing. Acute pre-sleep alcohol consumption leads to characteristic, bi-phasic changes to sleep quality and architecture. This manifests initially as sedation or sleep promotion, coupled with electrophysiological and hormonal abnormalities, followed by secondary sleep disruption. There is some evidence that young people may experience less sedation than mature adults, although further human research is needed to confirm this. Chronic alcohol use, such as that observed in alcohol use disorders, is associated with distinct and enduring patterns of sleep disturbance. Importantly, the relationship between heavy alcohol use and sleep disruption appears to be bi-directional. There is currently limited human research available on the effects of habitual alcohol use on objective sleep measures in late adolescent humans. It is imperative that this is investigated further, as the impacts of acute and habitual alcohol use on sleep, and their interaction, could have unique and negative consequences for the health and development of young people.

CHAPTER 4

The present study

4.1 Rationale

The final stages of human neural development, and the interrelated sleep changes, commence in adolescence and span into young adulthood (Churchwell & Yurgelun-Todd, 2011; Hagenauer et al., 2009; Johnson et al., 2009; Sowell, Thompson, Holmes, Jernigan, & Toga, 1999; Sowell et al., 2004; Tarokh et al., 2011). Thus, adolescence and young adulthood are biologically similar developmental time periods in the lifespan (Arain et al., 2013; Gogtay et al., 2004; Johnson et al., 2009; Lebel & Beaulieu, 2011; Miller et al., 2012; Pfefferbaum et al., 2016; Sowell et al., 2003; Sowell et al., 2001). Young people habitually consume higher amounts of alcohol per drinking occasion than any other age group globally (AIHW, 2017; NIAAA, 2008; WHO, 2018). As such, the onset and escalation of alcohol use usually commences in the lifespan before brain development and sleep changes finalised. This is especially concerning given that evidence suggests alcohol exposure during the final stages of brain development may be neurotoxic and detrimental to daily functioning (Guerri & Pascual, 2010; Jacobus & Tapert, 2013; Lubman et al., 2007; Miller, 2006; Sadrian et al., 2013).

Sleep is fundamental to healthy development and wellbeing, and its measures are reflective of neural integrity and chemical state (Brand & Kirov, 2011; Carskadon, Acebo, & Jenni, 2004; Colrain et al., 2011; Colrain et al., 2009b; Dahl & Lewin, 2002; Wolfson & Carskadon, 1998). There is a well-established, bi-directional relationship between alcohol use and subjective sleep disturbance in young people (Bartel et al., 2015; Colrain et al., 2014; Nguyen-Louie et al., 2018; Pasch et al., 2012; Patrick et al., 2018; Sivertsen et al., 2015; Warren et al., 2017; Wong & Brower, 2012; Wong et al., 2004; Wong et al., 2010; Wong et al., 2015). The mechanisms driving this bi-directional relationship in this developing population

are not yet well understood. Firstly, there is evidence that sleep disturbance may contribute to the onset and acceleration of alcohol use in young people. Secondly, there is evidence that acute and habitual alcohol use in young people may directly and adversely impact sleep. Unfortunately, there is only limited research available on the effects of acute and habitual alcohol use on objective measures of sleep in young people. Furthermore, there is currently no human research in this age group that has investigated the interaction between acute and habitual alcohol use on objective sleep.

In late adolescents, acute alcohol consumption prior to sleep leads to characteristic disturbances to normal sleep quality and architecture, similar to those reported in adults (Chan et al., 2015; Chan et al., 2013; Williams et al., 1983). However, young people may experience some unique effects, such as less initial sedation, that warrant further investigation (Chan et al., 2013). Although there is currently limited evidence available in humans, animal models suggest that habitual alcohol exposure in young people may cause unique, long-lasting disturbances to normal sleep (Criado et al., 2008; Ehlers et al., 2018a). These sleep disturbances may reflect underlying neural damage and/or neurochemical adaptation in young people. Both acute and habitual alcohol exposure during the final stages of neural development may impact the brain and sleep systems uniquely to adults (Chan et al., 2015; Chan et al., 2013; Criado et al., 2008; Ehlers et al., 2013a; Slawecki, 2002). Furthermore, alcohol-related sleep disturbances in young people could have unique and negative consequences for health, development, and function. Thus far, no studies have investigated the effects of acute and habitual alcohol use on objective sleep measures in a representative population of male and female late-adolescent

humans. Therefore, it is of paramount importance that the effects of acute and habitual alcohol consumption on sleep in late-adolescent humans are examined.

4.2 Aims

Considering the preceding background, the present study aimed to investigate the effects of both acute and habitual alcohol consumption on objective sleep quality, architecture, and EEG power spectra in male and female late adolescents, aged between 18 and 21 years old. (See Section 5.2 for study design.)

4.3 Hypotheses

1. Acute pre-sleep alcohol consumption will modulate sleep quality, architecture, and EEG power spectra such that, compared to the placebo condition, there will be:
 - a) Fewer arousals, less wake after sleep onset, higher sleep efficiency, longer REM sleep onset latencies, less REM sleep, more SWS, and higher delta and alpha EEG spectral power in the first half of the sleep period.
 - b) More arousals, more wake after sleep onset, lower sleep efficiency, less SWS, and lower delta and alpha EEG spectral power in the second half of the sleep period.
2. Habitual alcohol consumption will impact sleep quality, architecture, and EEG power spectra such that, compared to same-aged light drinkers, heavy-drinking late adolescents will have:
 - a) Longer sleep onset latencies, more wake after sleep onset, lower sleep efficiency, less SWS, shorter REM sleep onset latencies, more REM sleep, and lower delta EEG spectral power.

CHAPTER 5

Methodology

5.1 Participants

5.1.1 Recruitment

Participants for this study were recruited via a three-step process (Figure 5.1). Participants were initially recruited via poster advertisement at the University of Melbourne and online (see Appendix A). Following an expression of interest, participants completed a general health questionnaire to determine suitability for the experiment, and screen for major confounding health and sleep problems (Appendix B). Eligible participants were subsequently invited to take part in a detailed screening interview.

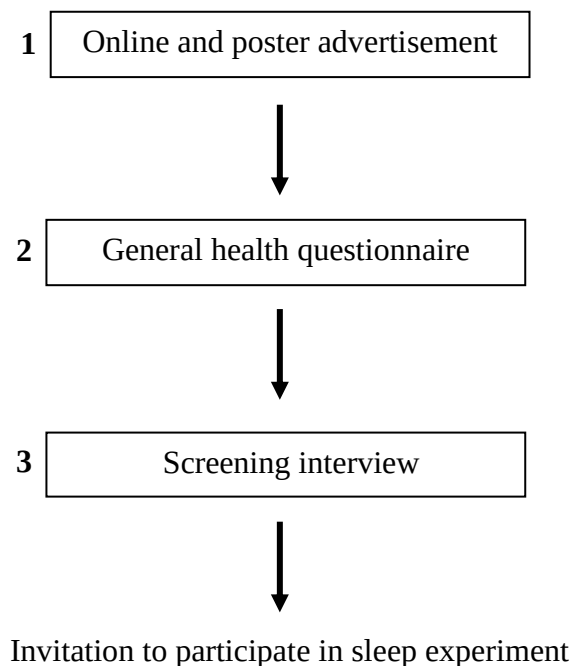


Figure 5.1. Three-step recruitment process participants underwent to determine suitability for inclusion in the sleep experiment.

5.1.1.1 General health questionnaire

The general health questionnaire assessed prospective participants' age, habitual alcohol use, general health and lifestyle factors known to affect sleep, as well as suitability for alcohol consumption (Appendix B). In this primary stage of the

recruitment process participants were included if they were aged between 18 and 21 years old; consumed alcohol; and were in a healthy weight range, defined as a body mass index (BMI) between 18 and 30. For ethical reasons, alcohol naïve participants and those abstaining from alcohol were excluded. Participants with a previous or current sleep disorder, sleeping difficulties (e.g., regular napping, extremely delayed sleep phase), major physical or psychological illness, or a substantial head injury, were excluded due to their potential effects on sleep (Kemple, O'Toole, & O'Toole, 2016; Thaxton & Myers, 2002) and interactions with alcohol use (Buckman et al., 2015; Glatter, Myers, & Chiamvimonvat, 2012). Participants were also excluded if they reported taking part in lifestyle factors known to affect sleep architecture and quality, including heavy caffeine consumption (>450 mg/day; Clark & Landolt, 2017), smoking (McNamara et al., 2014), transmeridian travel or 'jetlag' in the previous three months (Cingi, Emre, & Muluk, 2018), shift work (Boivin & Boudreau, 2014), and current major life stress (Benham, 2010; Geiker et al., 2018; Mezick et al., 2009).

5.1.1.2 Screening interview

This interview assessed ethnicity, physiological sensitivity to the effects of alcohol, socio-economic status, family history of alcohol use disorders, current alcohol and drug use, and lifetime history of alcohol consumption. For women, menstrual phase and use of hormonal birth control were also documented.

5.1.1.2.1 Materials and procedure

During the screening interview, an additional general questionnaire was used to assess participants' ethnicity, alcohol sensitivity or 'flushing response', and menstrual phase in women (Appendix B). Socio-economic status was assessed using the two-factor index of social position (Hollingshead, 1957; Hollingshead, 1971;

Appendix B). This index defines five levels of social class, where one is considered the highest level and five the lowest (Hollingshead, 1957). Lifetime alcohol consumption was estimated using a structured interview described in Pfefferbaum, Rosenbloom, Crusan, and Jernigan (1988; Appendix B). Family history of alcohol use disorders was verified using the family tree questionnaire for assessing family history of alcohol use problems (Mann, Sobell, Sobell, & Pavan, 1985; Appendix B). Recent habitual alcohol use was determined using a guided 30-day retrospective alcohol intake questionnaire, administered using a timeline follow-back procedure (Sobell & Sobell, 2008; Sobell, Sobell, Klajner, Pavan, & Basian, 1986; Appendix B). For this procedure, participants were asked to report the type, size, and commercial brand of each individual alcoholic beverage that they had consumed in the previous 30 days. In circumstances where the commercial brand could not be recalled, the alcohol percentage was estimated using the Australian Government Department of Health national standard (AGDH, 2010). If alcoholic beverages had been consumed in a commercially licensed venue it was assumed they were standard size. For alcoholic beverages that had been consumed in an unlicensed venue, such as a private residence, volume of the beverage was estimated based on the participant's recollection of the size and type of the receptacle utilised. The number of standard drinks (10g alcohol/standard drink) for each alcoholic beverage was calculated using a formula provided by the Australian Government Department of Health (2012), see Figure 5.2.

$$\text{Volume of Container (L)} \times \% \text{ Alcohol by Volume} \times 0.789 = \text{Number of Standard Drinks}$$

Notes: L= litres; 0.789 = specific gravity of ethyl alcohol; Standard drinks= 10 grams of alcohol; % Alcohol by Volume= mL/100ml

Figure 5.2. Formula for calculating the number of standard drinks in an alcoholic beverage (AGDH, 2012).

Using the 30-day retrospective alcohol intake questionnaire, the total number of standard drinks consumed in the previous 30 days, and amount per week, was calculated for each participant (NHMRC, 2009). A 30-day retrospective medication and recreational drug use questionnaire was also administered in this manner.

5.1.1.2.2 Inclusion and exclusion criteria

Flushing symptoms. Physiological alcohol sensitivity, or the ‘flushing response’, is particularly prominent in East Asian populations (~36% in China, Korea, and Japan; Eng et al., 2007). It is predominantly due to a genetic polymorphism in aldehyde dehydrogenase, an enzyme that is fundamental in the metabolic pathway for the breakdown of alcohol (Eriksson, 2001; Zakhari, 2006). This polymorphism results in ineffective alcohol metabolism, causing a build-up of acetaldehyde. This manifests as physiological symptoms of intoxication after consuming only small amounts of alcohol (Wolff, 1972). Symptoms include vasodilation, increased skin temperature, facial flushing, tachycardia, bronchoconstriction, nausea, and headaches (Eriksson, 2001). If participants reported regularly experiencing symptoms of alcohol flushing after consuming only one or two standard alcoholic drinks, they were excluded from the sleep study.

Irregular menstrual cycles or birth control. Hormonal fluctuations associated with menstrual phase (most notably during the luteal phase) are known to negatively impact sleep (Baker & Driver, 2004; Baker et al., 2001; Romans et al., 2015). Due to this, women who had irregular menstrual cycles, or had recently commenced/ceased taking hormonal birth control, were excluded.

Early initiation of alcohol use. Individuals who first initiated alcohol use before 14 years of age were excluded from the study as this is a well-known

independent risk factor for developing an alcohol use disorder (Grant & Dawson, 1997; Hingson, Heeren, & Winter, 2006a).

Family history of alcohol use disorders. Participants with a family history of alcohol use disorders were excluded as this is also a risk factor for developing an alcohol use disorder, and is also known to impact sleep architecture (Elliott, Carey, & Bonafide, 2012; Merikangas & Avenevoli, 2000; Powers, Berger, Fuhrmann, & Fendrich, 2017; Tarokh & Carskadon, 2010; Tarokh et al., 2012). A positive family history was defined as one first (parent and/or sibling) or two second (grandparent and/or parent's siblings) degree relatives with an alcohol use disorder (Mann et al., 1985).

Medications and drugs. Sleep can be affected by some medications such as antidepressants (Holshoe, 2009), sedatives (Watson, Baghdoyan, & Lydic, 2010), antihistamines (Randall, Roehrs, & Roth, 2008), and recreational drugs such as marijuana and cocaine (Garcia & Salloum, 2015). If participants were currently consuming medications or drugs known to affect sleep, or had a history of habitual use, they were excluded from the study.

Categorisation of heavy and light drinkers. Based upon NHMRC (2009) guidelines, participants were categorised as either heavy or light habitual drinkers. Those who did not fall into one of these categories based on the information collected in the screening interview were excluded. (See sections below.)

5.2 Design

The effects of acute and habitual alcohol consumption on sleep in male and female late adolescents were studied using a randomised crossover single-blind, mixed-model design. Acute condition (pre-sleep alcohol vs. placebo consumption)

and half night (PSG measures recorded in the first vs. second half of the sleep period) were the repeated-measures factors. Sex (male vs. female) and habitual alcohol use (heavy vs. light drinking) were the between-subjects factors. Participants were blinded to the type of beverage administered (alcohol or placebo) for both acute experimental conditions.

Participants were categorised as either light or heavy habitual drinkers (NHMRC, 2009). Light drinkers were defined as participants who consumed less than seven standard drinks per week in the previous 30 days, with no more than two occasions in which they consumed more than four standard drinks. Heavy drinkers were defined as participants who consumed more than 14 standard drinks in at least two of the previous four weeks.

5.3 General laboratory procedures

5.3.1 Recruitment, payment, and consent

Participants completed the primary general health questionnaire either online or in person (Appendix B). The screening interview and sleep study were conducted at the Melbourne School of Psychological Sciences Sleep Laboratory, University of Melbourne, Australia. Participants were provided with the screening interview plain language statement, and consent form, prior to attending the interview. Following the screening interview, eligible participants were contacted and provided with the plain language statement for the sleep study. (See Appendix A.) To ensure informed consent, participants were invited to visit the Sleep Laboratory to view the equipment and discuss experimental procedures. All participants gave informed written consent prior to their participation in both the screening interview and sleep studies and were free to withdraw at any stage of the recruitment process or sleep experiment.

Participants were reimbursed for their time; they received \$A10 for taking part in the screening interview and \$A75 for each night of the sleep study. All aspects of the study's procedure conformed to the Declaration of Helsinki and received approval from the Human Ethics Committee of the University of Melbourne (HREC #1239050.3).

5.3.2 Experimental procedures

For the sleep experiment, participants were asked to attend the sleep laboratory overnight for three non-consecutive nights within a two-week period. The three nights consisted of an adaptation sleep night, followed by the two acute experimental nights: placebo and alcohol conditions. (See Figure 5.3.) On average, there were 4 ± 3 (mean $\pm$ standard deviation; range 2 – 11) nights between the experimental conditions.

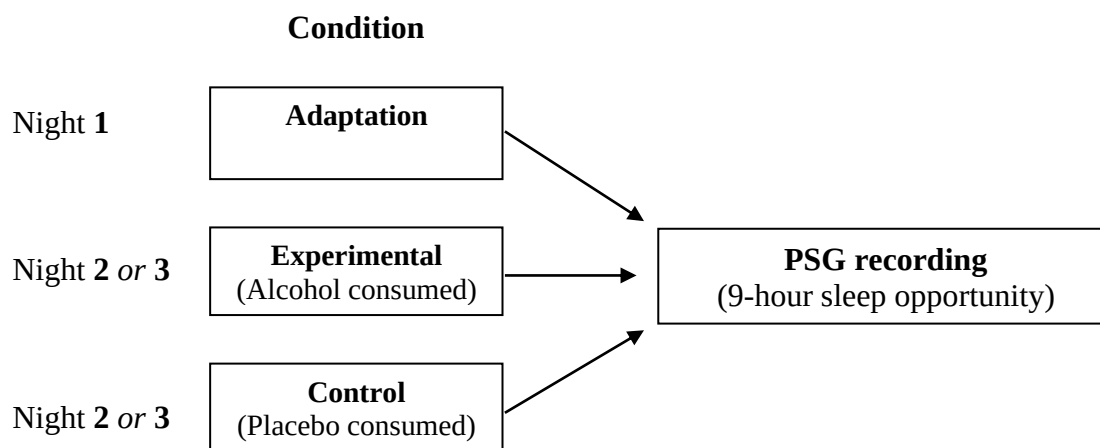


Figure 5.3. The three nights of the sleep experiment were all completed within a two-week period. The second two experimental nights were non-consecutive and counterbalanced over participants. The 9-hour sleep recording consisted of standard polysomnography (PSG).

In order to increase the precision and accuracy of current habitual alcohol consumption, the experimenter obtained an additional guided 30-day retrospective alcohol history on each night of the sleep study. (See 4.1.1.2 Screening Interview.) A 30-day medication and drugs diary was also completed to confirm participants continued to meet inclusion criteria throughout the study. (See Appendix B).

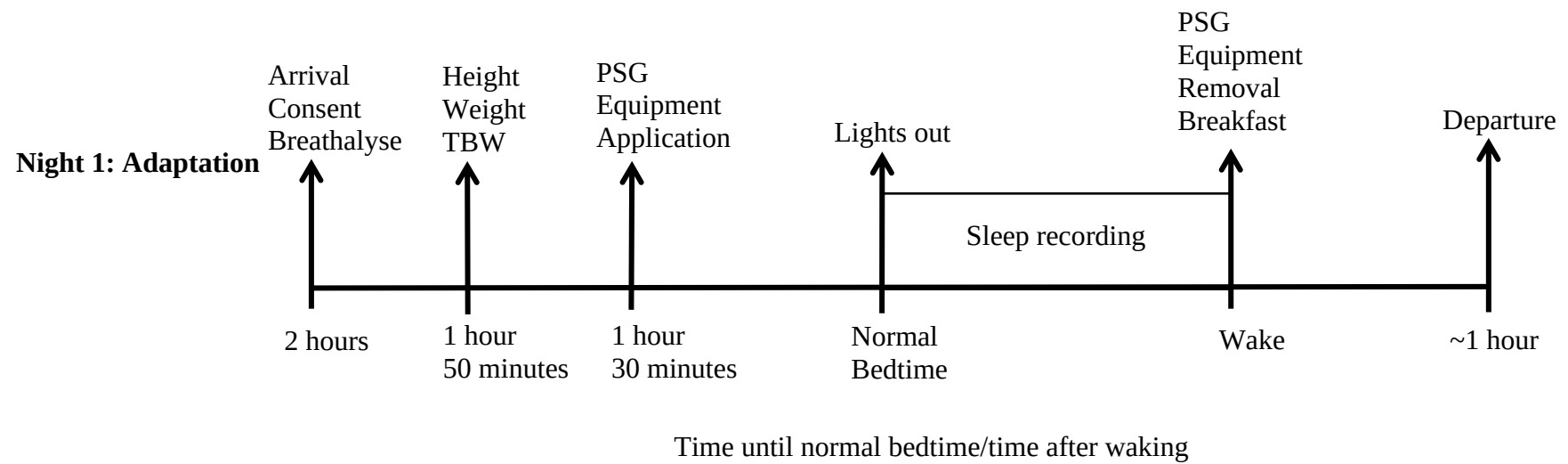
The first night of the sleep study was an adaptation night which also served to screen for occult sleep disorders, an exclusion criterion. Undiagnosed sleep disorders, such as restless leg syndrome and obstructive sleep apnoea, were determined using standard PSG. (See 4.3.1.3.2 Respiratory and body movement monitoring equipment.) The second and third nights were counterbalanced experimental nights: one involving pre-sleep alcohol administration dosed to obtain a peak BrAC of .10 percent (vodka and orange juice) and one involving a non-alcoholic placebo beverage (orange juice with a straw dipped in vodka). Participants were blinded to the acute conditions.

For one week prior to the adaptation night, and for the duration of the sleep study, participants maintained a regular sleep-wake schedule and completed a sleep diary. Prior to the experimental nights, participants were asked to abstain from alcohol for 48 hours, and from caffeine and food after lunchtime on the day of the study. If they reported non-compliance with these requests the experimental nights were rescheduled. On arriving at the laboratory for each session, participants were breathalysed using a handheld breathalyser (Alchosense® Precision, Andatech®, Melbourne, Australia) to ensure a BrAC of .00 percent to participate. No participants had a positive BrAC upon arrival for the experiment.

As sleep quality can vary as a function of menstrual phase, all women took part in the sleep experiment during the mid-follicular phase of their menstrual cycle

(days 3 – 14, where day 1 was the first day of menstruation; Baker & Driver, 2004, 2007; Baker et al., 2001; Romans et al., 2015). Given that hormonal fluctuations occurring during menstruation are known to disturb sleep, women using hormonal birth control took part in the sleep experiment only whilst consuming active hormones (Baker et al., 2001; Romans et al., 2015).

On the initial adaptation night, participants arrived approximately two hours prior to their normal bedtime. Once PSG recording equipment was attached, participants went to bed at their normal bedtime and were allowed to wake at a time of their choosing. (See Figure 5.4 for a detailed timeline.)



Nights 2 & 3: Experimental (alcohol or placebo; order counterbalanced)

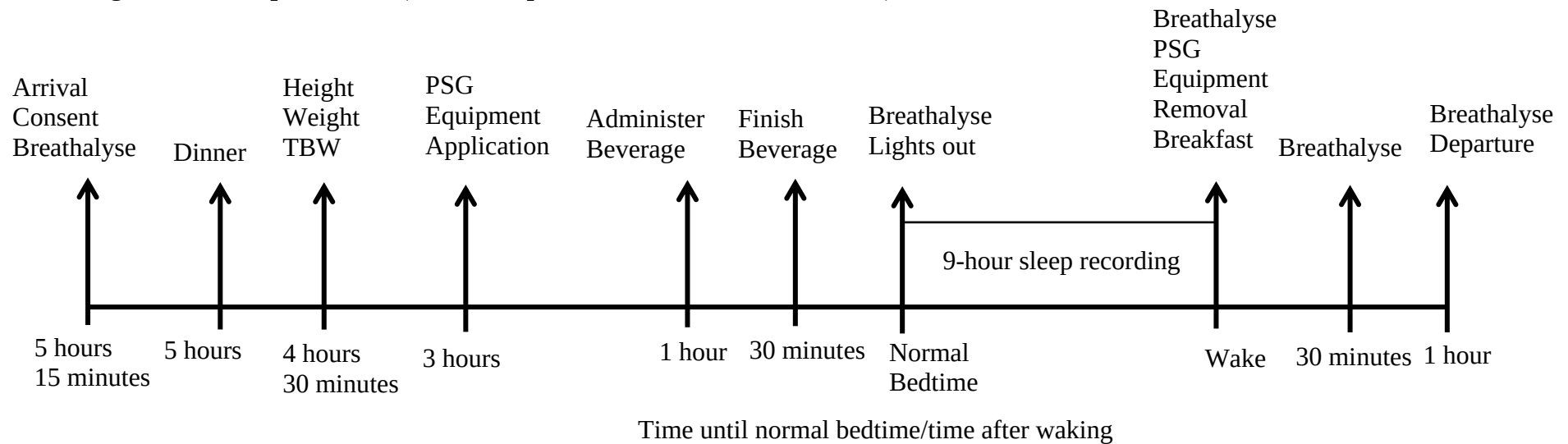


Figure 5.4. Detailed procedure timeline for all three nights of the sleep experiment. This consisted of an adaptation night (top pane), and two experimental nights: alcohol condition, and a placebo condition (bottom pane). Notes: TBW= total body water, PSG= polysomnography.

On the two experimental nights, participants arrived at the laboratory 5 hours and 15 minutes before their usual bedtime. (See Figure 5.4 for detailed timeline.) Five hours prior to bedtime, participants consumed a standardised evening meal (400g of pasta served with an optional salad), which was to assist with consistency in alcohol absorption rates across participants (Cavacuiti & Woodward, 2011; Paton, 2005). With the exception of their evening meal, participants were asked to maintain their normal diet on the day prior to, and during, the sleep studies. Following dinner, participant height and weight was measured, and their percentage of total body water was calculated using commercially available bathroom scales (Tanita BC541 InnerScan®). This information was used to calculate the alcohol dose required to achieve a peak BAC of .10 percent, using a previously published formula (Curtin & Fairchild, 2003; see Figure 5.5). This formula accounted for both individual and sex-differences in alcohol metabolism, allowing participants to achieve the same peak BrAC with personalised doses of alcohol (Cavacuiti & Woodward, 2011; Goist & Sutker, 1985). (See Section 2.2.1.) The total volume of the beverage was determined according to body mass, such that a person who weighed 70kg would consume 400ml of liquid.

$$\text{Alcohol dose (g)} = (10 \times \text{BAC} \times \text{TBW})/0.8 + 10 \times \text{MR} \times (\text{DDP} + \text{TBP}) \times (\text{TBW}/0.8)$$

Notes: BAC = blood alcohol concentration; TBW = total body water; MR = alcohol metabolism rate; DDP = duration of drinking period; TBP = time to peak BAC

Figure 5.5. Formula for calculating the alcohol dose required to achieve target blood alcohol concentration (BAC) of .10 percent (Curtin & Fairchild, 2003).

Three hours prior to the participant's regular bedtime, application of PSG equipment commenced. (See Section 5.3.3.) One hour prior to bedtime the beverage was administered and consumed evenly over 30 minutes. This was monitored by an

experimenter and assisted by the use of a 30-minute countdown timer (<http://www.online-stopwatch.com/countdown/>: Last Accessed April 2018). Consumption of the beverage concluded 30 minutes before participants' normal bedtime. BAC was expected to peak 30 to 45 minutes following this, such that the target concentration of .10 percent was likely achieved within the first hour of sleep (Curtin & Fairchild, 2003). At their normal bedtime, participants were breathalysed, and lights were turned out. Participants were asked to switch off electronic devices (e.g., mobile phones) before lights out to prevent interference with recording equipment or sleep continuity. The sleep recording then commenced, and participants were given a 9-hour sleeping opportunity (or time in bed). The recording was monitored throughout the night by an experimenter.

After waking, participants were breathalysed, and PSG equipment was removed. They were offered breakfast and provided with shower facilities. Participants were asked to remain in the laboratory until two consecutive BrAC recordings (30 minutes apart) of .00 percent were received. Participants were offered transport to and from the laboratory for all nights.

5.3.3 Equipment and application

Brain and cardiac electrophysiology, as well as muscle movement and respiration, were monitored using PSG, the gold-standard of objective sleep assessment (Kryger, Roth, & Dement, 2017; Kushida et al., 2005). Before application, all electrode sites were first prepared by exfoliating the skin using a cotton tip and Lemon Prep® Abrasive Skin Prepping Lotion (Mavidon™, Lake Worth, Florida, USA). Dislodged dirt, oil, and dead skin were then removed using an alcohol swab and gauze (or gauze only if the participant reported skin sensitivity).

Electrocardiogram (ECG) Medi-Trace® electrodes (Kendall Healthcare™, Miami, Florida, USA) were self-adhesive and applied after skin preparation. Face electrodes were filled with Signa-gel® electrode gel (Parker Laboratories™, Fairfield, New Jersey, USA), a highly conductive multi-purpose electrolyte, before being attached to the skin using double sided adhesive electrode collars and surgical tape. EEG electrodes were secured to the scalp under a thin piece of gauze using Collodion USP® glue (Mavidon™, Lake Worth, Florida, USA), and filled with Signa-Gel®. The following morning, EEG electrodes were detached from the scalp using Collodion Remover (Mavidon™, Lake Worth, Florida, USA). Electrodes and body sensors attached with tape were gently removed. Once removed, all electrodes were cleaned using anti-bacterial detergent and left to air dry. According to international guidelines, the risk of cross-contamination using these procedures was minimal (Putnam, Johnson, & Roth, 1992). None of these procedures involved direct contact with blood or other bodily fluids.

5.3.3.1 Electrophysiological measurements

Six Grass® gold-cup electroencephalogram (EEG) electrodes were placed over frontal (F3, F4), central (C3, C4) and occipital (O1, O2) regions of the scalp, determined by the international 10/20 system (Jasper, 1958; Figure 5.6). Eight electrodes were attached to the face including; a recording reference and ground electrode (forehead), left and right electro-oculogram (EOG), left (A1) and right (A2) earlobes, and a pair of electrodes (or electromyogram; EMG) over the submental muscle (Figure 5.7). EOG electrodes were placed approximately one centimetre from the outer canthi (eye crease) of the left and right eye. As noted, EEG electrodes were recorded using a single forehead electrode (reference). For sleep staging, EEG and EOG electrodes were digitally re-referenced to the contralateral earlobe (left earlobe

[A1] re-referenced: F4, C4, O2, right EOG, and right earlobe [A2] re-referenced: F3, C3, O1, left EOG). EOG and EMG electrodes were used to assist with sleep scoring (determining wake or sleep stages).

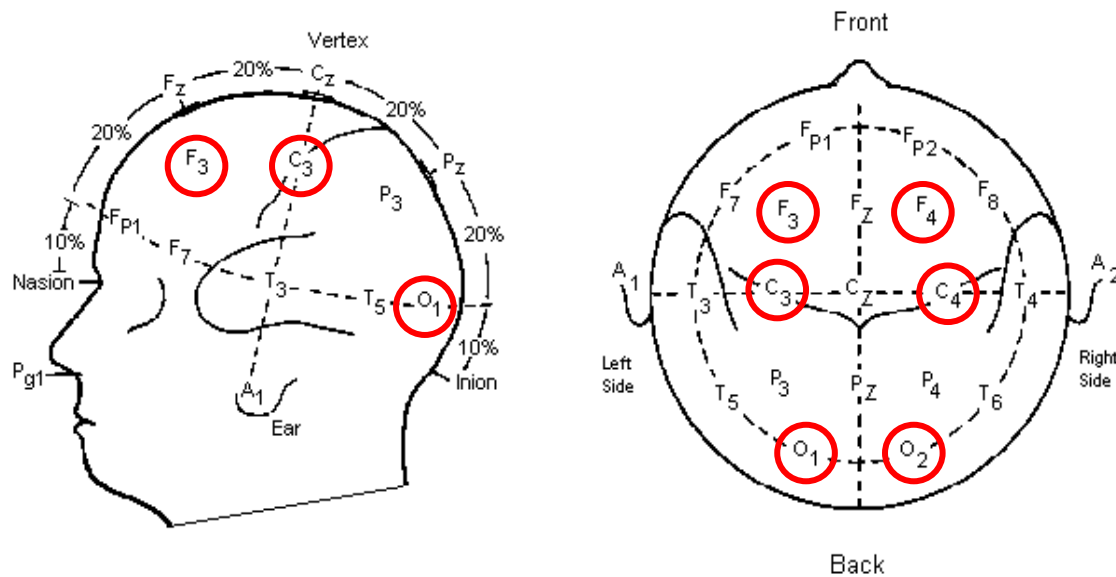


Figure 5.6. Positioning of electroencephalogram (EEG) scalp electrodes according to the international 10/20 system (electrode positions used in the present study are circled in red; Jasper, 1958).

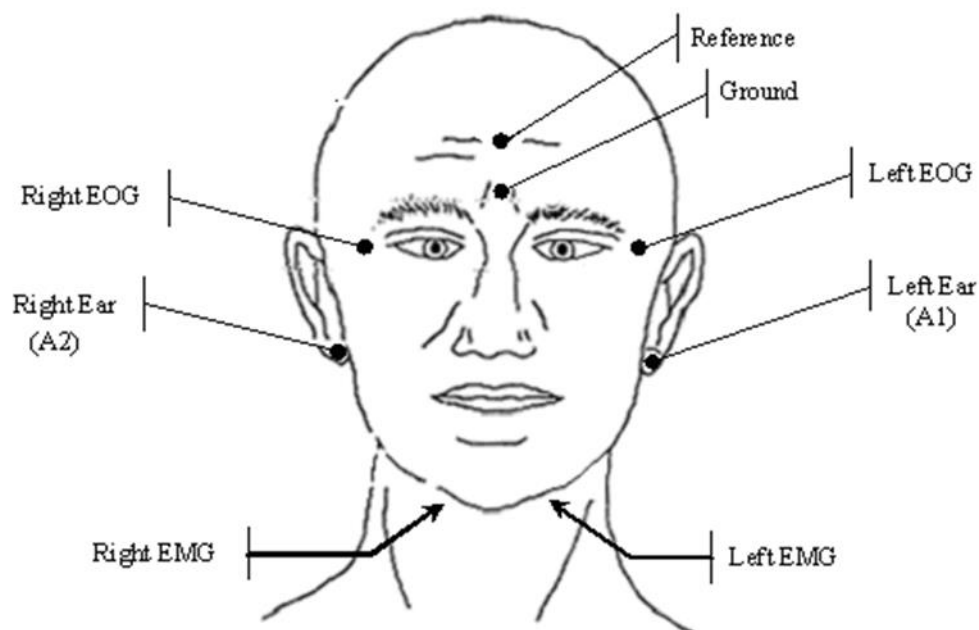


Figure 5.7. Positioning of face electrodes (Chan, 2013).

5.3.3.2 Respiratory and body movement monitoring equipment

Four devices were attached for the detection of sleep disordered breathing. (See Figure 5.8 for equipment positioning.) These included an oro-nasal thermistor to assess airflow (positioned underneath the nasal openings), thoracic and abdominal respiratory effort bands, and a finger pulse oximeter (Compumedics® Ltd., Abbotsford, Australia). Respiratory events were assessed using standardised AASM (2007) criteria. A body position sensor was attached to the centre of the thoracic respiratory effort band to monitor sleeping position. Periodic limb movements were identified using EMG sensors taped over the anterior tibialis muscle on both the left and right lower leg. A piezoelectric vibration sensor, taped two centimetres to the left or right of the laryngeal prominence (Adam's apple), was used to detect snoring. All respiratory and body movement sensors were attached for all three nights of the sleep study. (Figure 5.8 shows correct placement for all sensors.) An ECG was used to measure heart rate, recorded with a standard Einthoven lead II (one electrode placed above the right clavicle, and the other on the lower left rib cage; see Figure 5.8). The following morning, equipment was removed and then cleaned using alcohol swabs.

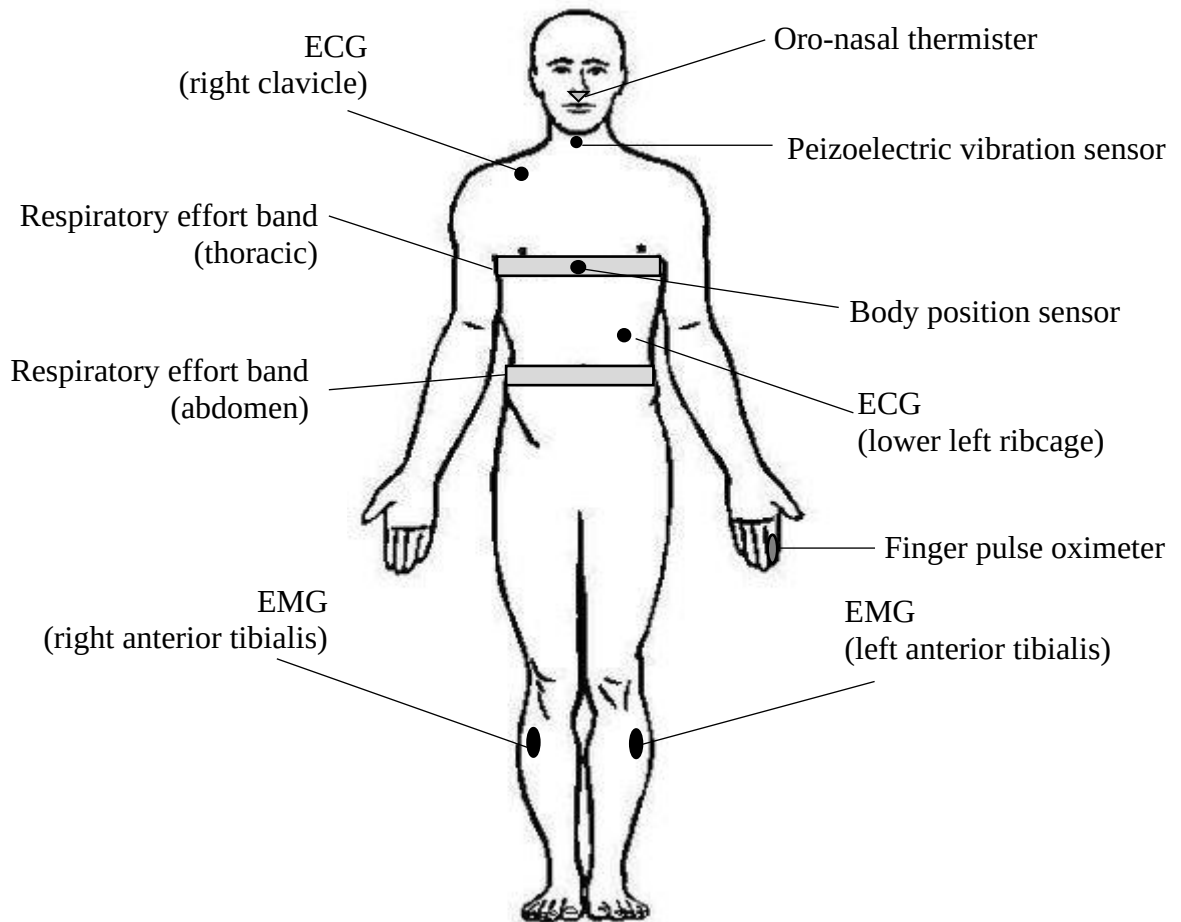


Figure 5.8. Location of body sensors for the detection of undiagnosed sleep disorders, and electrocardiogram (ECG). (EMG=electromyogram; Chan, 2013).

5.4 Data acquisition and analysis

5.4.1 Data acquisition

Clinical grade digital amplifier systems from the same manufacturer (E-Series, Siesta, and Graef PSG amplifiers; Compumedics® Ltd., Abbotsford, Australia) were used to record and amplify PSG (including EEG) signals. The particular amplifier system used was dependent on its availability in the laboratory at the time of the sleep study. All recording parameters, however, were identical across systems. (See 4.4.2 Data analysis for a summary of amplifier configuration.) Within each participant, it was ensured that the same recording system (and bedroom) was

used for the two experimental nights. Each of these systems were positioned near the participant's head, on a bedside table. As required by regulatory standards, each system contained circuitry that isolated connected participants from mains power. For all amplifier systems, ECG, EEG, EOG and EMG signals were sampled at 512 Hz. Respiratory and body movement sensors were sampled according to standard clinical AASM guidelines (2007). EEG and PSG signals were saved to a host computer and displayed live using ProFusion PSG 3 software (Compumedics® Ltd., Abbotsford, Australia). At the time of recording signals were filtered appropriately for visual scoring (AASM, 2007). For all EEG, face and ECG electrodes, electrical impedance (resistance) was less than 10 Kilo-Ohms ($k\Omega$).

5.4.2 Data analysis

5.4.2.1 Sleep disordered breathing and body movement

For all three nights, data were visually assessed using standard AASM (2007) criteria to detect the presence of sleep disordered breathing and/or periodic limb movements (e.g., restless leg syndrome). A threshold of five apnea-hypopnea, or periodic limb movement, events per hour were considered pathological. One participant was excluded for having more than five apnea-hypopnea events per hour during their adaptation night. No participants were excluded due to periodic limb movements.

5.4.2.2 Sleep quality and architecture

Each sleep recording was independently scored by two experienced researchers blind to acute condition, to assess measures of sleep quality and architecture. (See Table 5.1 for a variable summary.) Visual scoring of EEG, EOG and EMG recordings was conducted using standard AASM (2007) criteria.

Discrepancies between scorers were resolved by an independent adjudicator who was also blinded to acute condition.

Table 5.1

Sleep quality and architecture dependent variables extracted from experimental participant sleep polysomnography data.

Sleep quality	Sleep architecture
Sleep onset latency (minutes)	Sleep stage 1 (%)
Wake after sleep onset (WASO; minutes)	Sleep stage 2 (%)
Arousal index (number of events per hour)	Slow wave sleep (SWS; %)
Sleep efficiency (%)	SWS latency (minutes)
	Rapid eye movement (REM) sleep (%)
	REM sleep latency (minutes)

Sleep onset latency was defined as the time (in minutes) between ‘lights out’ and three consecutive 30-second epochs of stage N1 sleep, or one 30 second epoch of stage N2 sleep, slow wave sleep (N3), or REM sleep. Sleep cycle length was determined using the rules described in Table 5.2. Rule three was employed as adolescents and young adults do not always experience a distinct or clear period of REM sleep at the conclusion of their first sleep cycle (Table 5.2; Trinder, Stevenson, Paxton, & Montgomery, 1982). As there was a nine-hour sleeping opportunity, the cut-off point for the half night analysis was four and a half hours from sleep onset. This was also consistent with the first half cut-off point in Chan and colleagues’ (2013) investigation. This cut-off would have provided enough time for more than half of the ingested alcohol to be metabolised and eliminated from the body, allowing for comparisons with the second half of the sleep period (Rouhani et al., 1989; Rundell et al., 1972; Stone, 1980; Williams et al., 1983). Total sleep time was not included as a dependent variable for analysis as this was intentionally curtailed at approximately nine hours of time in bed.

Table 5.2

Rules employed to determine sleep cycle length in young adults based on: Trinder and colleagues (1982).

	A sleep cycle was defined as the time (in minutes) from the beginning of the
1.	non-rapid eye movement (NREM) period (any stage of NREM sleep following sleep onset) to the end of the subsequent rapid eye movement (REM) period.
2.	The completion of a sleep cycle was retrospectively determined by an absence of REM sleep for more than 15 minutes.
	For the first sleep cycle, the REM period was judged to have occurred if any
3.	REM sleep characteristics were observed at an appropriate interval, but no 30 second epochs were officially scored as REM sleep.

5.4.2.3 Electroencephalogram spectral analysis

Power spectral analysis was conducted using Curry 7® software (Compumedics Neuroscan™, Abbotsford, Australia). Data from all EEG electrode sites (F3, F4, C3, C4, O1 and O2) were digitally re-referenced to the contralateral ‘linked’ ear lobe (A1 or A2), and applied with a zero phase Hann bandpass filter between 0.3 and 30 Hz, with a 0.6 and 8 Hz slope respectively. Spectral power was calculated for each of the five EEG frequency bands, beta (16 – 30 Hz), sigma (12 – <16 Hz), alpha (8 – <12 Hz), theta (4 – <8 Hz), and delta (0.5 – <4 Hz) for each visually scored sleep stage in the first and second half of the sleep period.

As previously conducted by Chan and colleagues (2015), Fast Fourier transforms were used in power spectral analysis to calculate stationary process in a time series by decomposing that series into composite sine and cosine waves. Each of the five EEG frequency bands were assigned to a 0.125 Hz bin and allocated a power value by integrating and squaring the area under the wave for that frequency band (squared EEG amplitude; squared microvolts; μV^2). Power values calculated by power spectral analysis reflect both incidence and amplitude of waves within a given frequency band. Spectral power for all artefact and arousal free 5-second EEG segments were averaged across each 30-second sleep epoch. These were then

averaged for each separate sleep stage for the first and second half of the sleep period.

5.4.2.4 Final statistical analyses

An a priori power analysis was conducted according to the method outlined by Keppel (1982), with effect sizes ranging between 0.8 to 1.0 (Chan et al., 2013). The power analysis indicated a sample size of 24 (two groups of 12 participants) was adequate to detect both within and between group main effects, as well as interaction effects, for acute condition and habitual alcohol use, with a power between 0.8 and 0.9. The study was not powered to detect further interactions with sex (male vs. female) due to minimal sex differences being reported in the literature for the effects of both acute and habitual alcohol use on sleep in this age group (Chan et al., 2015; Chan et al., 2013; Cohen-Zion et al., 2009; Colrain et al., 2009b).

Statistical analysis was completed using IBM SPSS Statistics for Windows Version 25.0 (IBM CorpTM, New York, USA). Differences in participant demographics between groups related to sex and habitual alcohol use were assessed using a two-way between subjects analysis of variance (ANOVA). In order to test the impact of acute and habitual alcohol use on sleep in 18 to 21 year old male and female late adolescents, 2 (habitual alcohol use; heavy vs. light drinking) by 2 (acute condition; alcohol vs. placebo) by 2 (half night; first half vs. second half of the sleep period) by 2 (sex; male vs. female) mixed-model ANOVAs were conducted on each sleep quality and architecture variable (Table 5.1). For spectral analysis, left and right EEG electrode sites were averaged to derive a single power value for frontal, central, and occipital sites for analysis. EEG spectra data were analysed using 2 (heavy vs. light drinking) by 2 (alcohol vs. placebo) by 2 (first half vs. second half of the sleep period) by 2 (male vs. female) by 3 (frontal, central, and occipital EEG

electrode sites) mixed-model ANOVAs for each of the five EEG frequency bands (beta, alpha, sigma, theta, and delta) in each visually scored sleep stage. Standard IBM SPSS (IBM CorpTM, New York, USA) covariance structures were used and no random effects were added. Both paired and independent samples t-tests were used to interpret interaction effects when appropriate. Two-tailed t-tests were reported unless the result pertained to a directional hypothesis, in which case one-tailed tests were reported. An alpha-level of .05 was set for all statistical tests.

For each within-subjects effect, Box's test of equality of covariance matrices was used to assess whether homogeneity was violated. However, given the high sensitivity of this test and similar sample sizes between groups, the significance threshold was set at $p < .001$ as recommended by Tabachnick and Fidell (2001; 2007). If Box's test was violated at $p < .001$, the conservative Pillai's Trace criterion was used to account for this (Tabachnick & Fidell, 2001). For between-subjects effects, Levene's test of equality of error variances was used to test homogeneity. If Levene's test was violated appropriate corrections to degrees of freedom so that equal variances were not assumed were employed.

Correlational analyses were performed to explore potential associations between measures of sleep quality and architecture with habitual alcohol use, including lifetime history of alcohol consumption, 30-day retrospective alcohol consumption, and number of years drinking. Before conducting correlational analyses normality of variables was tested using the Shapiro-Wilk statistic. This statistic was only reported when normality was violated. When both variables were normally distributed, a Pearson's correlation was conducted (Hauke & Kossowski, 2011). When one or both variables were not normally distributed, a non-parametric Spearman's correlation was conducted and reported (Bishara & Hittner, 2012, 2015;

Hauke & Kossowski, 2011; Zimmerman & Zumbo, 1993). As number of years drinking may potentially be confounded by age, partial correlations controlling for age were used with this variable. Correlations coefficients of 0.1 to 0.3 were considered small, 0.3 to 0.5 moderate, and 0.5 to 1.0 large associations (Hemphill, 2003).

For each mixed-model ANOVA, effect size was measured using partial eta squared (η_p^2). For t-tests, Cohen's *d* was calculated as a measure of effect size (Cohen, 1988; Larner, 2014). Effect sizes of 0.2 to 0.3 were considered small, 0.5 medium, and more than 0.8 large (Cohen, 1988; Cohen, 1992). Partial eta squared (η_p^2) was used to measure effect sizes for all mixed model ANOVA results (Field, 2009). According to Cohen (1988), an η_p^2 of 0.01 to 0.05 is a small effect, 0.06 to 0.12 a medium effect, and more than 0.13 a large effect (Cohen, 1988; Richardson, 2011).

CHAPTER 6

Results

6.1 Participant demographics

Participants were 46 (26 female) volunteers with a mean age of 19.61 ± 1.0 years (mean $\pm$ standard deviation; SD). See Figure 6.1 for a flow diagram of participant recruitment and attrition numbers.

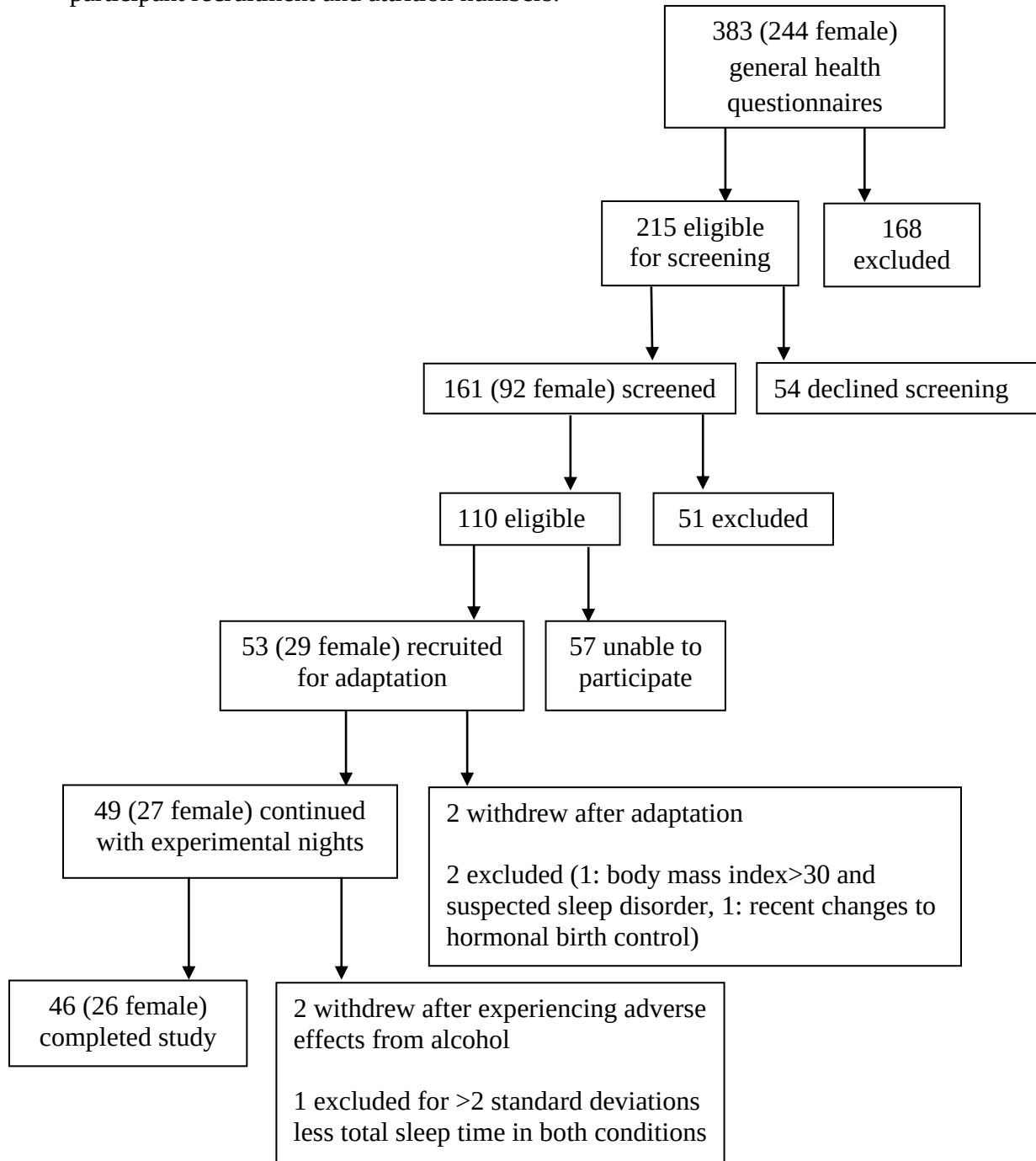


Figure 6.1. Participant recruitment and attrition for each recruitment phase. See Section 5.1.1 for inclusion and exclusion criteria.

Following the completion of the experiment, one participant was excluded from the final analysis as they had more than two standard deviations less total sleep time in both conditions (placebo: 4.15 hours and alcohol: 5.76 hours) than the sample mean (placebo: 8.00 hours [standard deviation; SD=48.43 minutes] and alcohol: 7.67 hours [SD=48.33 minutes]). Figure 6.2 and Table 6.1 display sample size and demographics for the participants who completed the study. Heavy and light drinkers were categorised using the criteria outlined in Section 5.2. To ensure groups were representative and comparable an equivalent number of heavy- and light-drinking females and males were recruited.

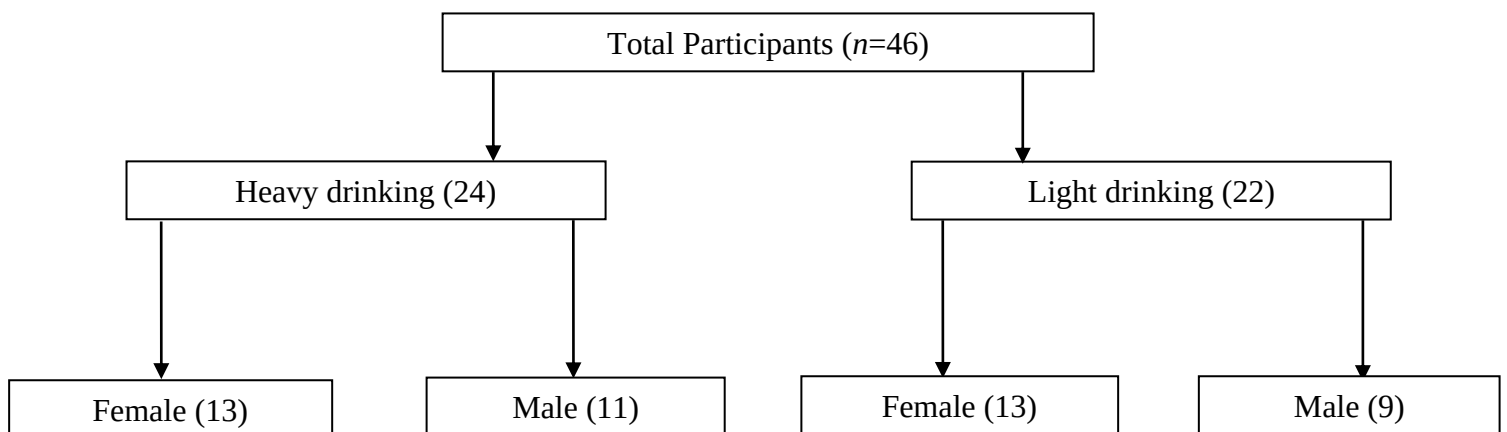


Figure 6.2. Final participant sample size (n) broken down into groups by habitual alcohol use and sex of the participants who completed the sleep experiment.

Table 6.1

Final participant demographics broken down by sex and habitual alcohol use. Mean ($\pm$ standard deviation). NB, SD=standard drinks (10 g of alcohol). BMI= body mass index. BrAC=breath alcohol concentration.

	Heavy-drinking female (n=13)	Heavy-drinking male (n=10)	Light-drinking female (n=13)	Light-drinking male (n=9)
Age (years)	19.15 (0.90)	20.09 (0.70)	19.38 (1.19)	20.00 (0.87)
Height (metres)	1.65 (0.07)	1.83 (0.05)	1.65 (0.05)	1.77 (0.06)
Weight (kg)	60.23 (8.14)	76.16 (6.75)	63.79 (6.76)	67.32 (2.21)
BMI (kg/m ²)	22.14 (2.18)	22.78 (1.78)	23.59 (2.37)	21.61 (1.66)
Total body water (%)	50.93 (3.28)	59.03 (2.68)	49.64 (3.38)	62.12 (3.22)
Alcohol dose (g/kg)	0.73 (0.05)	0.85 (0.04)	0.72 (0.05)	0.89 (0.05)
BrAC at lights out (%)	0.08 (0.02)	0.08 (0.02)	0.07 (0.01)	0.08 (0.02)
Lifetime alcohol (SD)	1813.64 (1694.69)	2863.27 (2304.17)	264.06 (299.23)	299.39 (296.27)
30-day alcohol diary (SD)	81.91 (25.63)	133.44 (78.77)	12.25 (8.03)	13.47 (10.33)
Age drinking commenced	16.43 (1.11)	16.94 (1.19)	17.76 (1.34)	17.60 (1.53)
Number of years drinking	3.18 (1.68)	3.52 (1.43)	2.24 (1.72)	2.50 (1.19)
Socio-economic status score	1.46 (0.66)	1.74 (0.71)	1.85 (0.56)	2.22 (0.83)

6.1.1 Habitual alcohol use

By design, groups differed in the number of standard drinks (10 g of alcohol) consumed in the previous 30-days, $F(1, 46)=59.31$, $p < .001$, $\eta_p^2 = .59$. As expected, groups also differed in their estimated lifetime history of alcohol consumption, $F(1, 46)=22.36$, $p < .001$, $\eta_p^2 = .35$. On average, heavy drinkers commenced alcohol consumption earlier in their lifetime than light drinkers, $F(1, 46)=6.78$, $p = .013$, $\eta_p^2 = .14$. Heavy drinkers had also been consuming alcohol for a longer time period than light drinkers on average, $F(1, 46)=4.47$, $p = .040$, $\eta_p^2 = .10$. Heavy-drinking participants had lower socio-economic status scores than light-drinking participants, signifying a higher socio-economic status, $F(1, 46)=7.97$, $p = .007$, $\eta_p^2 = .16$. No

other demographic differences between heavy and light drinkers were observed. (See Table 6.1.)

6.1.2 Sex

On average, male participants were older than female participants, $F(1, 46)=7.55$, $p=.009$, $\eta_p^2=.15$. As anticipated, females were significantly shorter in height – $F(1, 46)=75.02$, $p<.001$, $\eta_p^2=.64$, weighed less – $F(1, 46)=21.20$, $p<.001$, $\eta_p^2=.34$, and had less total body water – $F(1, 46)=118.87$, $p<.001$, $\eta_p^2=.74$, than males. However, there were no sex differences in BMI, $F(1, 46)=1.18$, $p=.284$, $\eta_p^2=.03$. Due to the anticipated differences in total body water, on average females received smaller doses of alcohol than males, $F(1, 46)=112.10$, $p<.001$, $\eta_p^2=.85$ (Curtin & Fairchild, 2003). However, as expected, there were no differences in BrAC at lights out between males and females, $F(1, 46)=2.54$, $p=.119$, $\eta_p^2=.06$. On average, females had consumed less alcohol in the previous 30-days than males, $F(1, 46)=4.59$, $p=.038$, $\eta_p^2=.10$. For females, 16 were taking hormonal birth control (the combined birth control pill, Depo-Provera injection, or NuvaRing®), and 10 were not using hormonal contraception. There were no differences in any demographic variable between females currently taking hormonal contraception and those not. (See Table 6.1.)

6.1.3 Habitual alcohol use and sex interactions

There was an interaction between habitual alcohol use and sex for weight, $F(1, 46)=8.61$, $p=.005$, $\eta_p^2=.17$. Heavy-drinking males weighed more than light-drinking males, $t(18)=3.02$, $p=.007$, $d=1.36$, however there were no differences in weight between heavy- and light-drinking females, $t(24)=1.21$, $p=.237$, $d=0.48$.

There was also an interaction between habitual alcohol use and sex for total body water, $F(1, 46)=5.40$, $p=.025$, $\eta_p^2=.11$. Heavy-drinking males had less total body water than light-drinking males, $t(18)=2.35$, $p=.030$, $d=1.05$, but again there were no differences between heavy- and light-drinking females, $t(24)=0.99$, $p=.332$, $d=0.39$. These effects explained the interaction between habitual alcohol use and sex for the pre-sleep alcohol dose (g/kg), $F(1, 46)=5.32$, $p=.026$, $\eta_p^2=.11$, where, due to differences in total body water, heavy-drinking males received lower doses of alcohol than light-drinking males, $t(18)=2.43$, $p=.026$, $d=1.08$. There were no differences in alcohol dose between heavy- and light-drinking females, $t(24)=0.92$, $p=.367$, $d=0.36$. There was an interaction between habitual alcohol use and sex for BMI, $F(1, 46)=5.57$, $p=.038$, $\eta_p^2=.10$. Light-drinking females had a higher BMI than light-drinking males, $t(20)=2.16$, $p=.043$, $d=0.97$, however there were no differences between heavy-drinking males and females, $t(20)=0.79$, $p=.440$, $d=0.32$. Finally, there was an interaction between habitual alcohol use and sex for 30-day alcohol consumption, $F(1, 46)=4.18$, $p=.047$, $\eta_p^2=.09$. Heavy-drinking females consumed less alcohol in the previous 30 days than heavy-drinking males, $t(20)=2.23$, $p=.036$, $d=0.88$. There was no difference in 30-day alcohol consumption between light-drinking males and females, $t(20)=0.31$, $p=.759$, $d=0.13$. No other demographic differences between heavy- and light-drinking females and males were observed. (See Table 6.1.) In summary, the demographics of the sample selected were typical of this age group.

6.1.4 Alcohol dosing

The mean pre-sleep alcohol dose administered was 0.79 (SD=0.90) g/kg. This resulted in a mean BrAC at lights out of 0.08 ± 0.01 percent. (See Table 6.1.)

6.2 Acute and habitual effects of alcohol on sleep quality and architecture

The following section presents the descriptive and inferential statistics for the acute (alcohol vs. placebo) and habitual (heavy vs. light drinking) effects of alcohol on visually scored measures of sleep quality and architecture. Interactions between acute and habitual alcohol effects, and sex, are also presented. Table 6.2 displays the means and standard deviations for all sleep quality and architecture variables for heavy- and light-drinking females and males in the first and second halves of the sleep period following alcohol or placebo consumption. To enhance clarity, and for brevity, unless the results pertained directly to a hypothesis, only significant effects have been reported.

Table 6.2

Means ($\pm$ standard deviations) for sleep onset latency, wake after sleep onset (WASO), arousal index, sleep efficiency, stage N1 sleep (N1), stage N2 sleep (N2), stage N3/slow wave sleep (N3/SWS), rapid eye movement (REM) sleep, and SWS and REM sleep latency, for heavy- and light-drinking females and males in the first and second halves of the sleep period.

	Heavy drinker								Light drinker							
	Placebo				Alcohol				Placebo				Alcohol			
	Female		Male		Female		Male		Female		Male		Female		Male	
	1 st half	2 nd half	1 st half	2 nd half	1 st half	2 nd half	1 st half	2 nd half	1 st half	2 nd half	1 st half	2 nd half	1 st half	2 nd half	1 st half	2 nd half
Sleep onset latency (minutes)	20.73 (19.22)		20.68 (1.43)		24.96 (14.47)		20.59 (19.17)		18.96 (9.99)		22.44 (10.25)		20.92 (14.37)		12.50 (5.00)	
WASO (minutes)	7.39 (7.51)	15.81 (16.74)	19.36 (21.59)	19.41 (14.92)	17.00 (18.46)	24.19 (27.85)	12.73 (14.13)	50.32 (38.87)	16.77 (21.62)	13.81 (12.70)	7.78 (4.22)	13.83 (8.25)	4.35 (4.75)	41.69 (33.26)	16.44 (22.03)	43.11 (32.11)
Arousal index (events per hour)	9.15 (3.94)	11.26 (4.68)	10.87 (3.29)	10.06 (5.92)	6.27 (2.60)	15.40 (5.09)	7.36 (2.28)	13.57 (4.29)	8.79 (4.11)	8.89 (1.07)	9.91 (2.72)	9.57 (4.34)	6.81 (2.09)	12.78 (3.90)	6.05 (1.22)	12.65 (3.15)
Sleep efficiency (%)	97.13 (2.85)	93.84 (6.47)	92.19 (8.79)	92.24 (5.79)	93.44 (6.98)	90.43 (10.97)	95.00 (5.55)	79.96 (15.81)	93.59 (8.23)	94.73 (4.73)	96.94 (1.68)	94.59 (3.40)	98.30 (1.90)	83.90 (12.95)	93.73 (8.52)	83.65 (12.32)
N1 (%)	3.19 (2.07)	6.07 (3.12)	4.07 (2.18)	8.05 (3.00)	2.90 (1.30)	10.75 (5.42)	2.98 (3.49)	8.97 (3.14)	3.96 (2.30)	6.08 (3.15)	3.42 (1.37)	7.80 (4.62)	2.43 (2.16)	9.25 (6.28)	3.59 (2.87)	8.94 (3.78)
N2 (%)	42.61 (7.78)	59.86 (6.81)	47.50 (8.42)	56.57 (7.66)	45.93 (5.83)	58.35 (5.88)	40.56 (3.75)	56.10 (12.53)	36.22 (7.78)	53.73 (5.85)	46.43 (9.78)	52.41 (6.16)	39.72 (9.70)	54.09 (8.37)	49.36 (7.71)	56.32 (8.00)
SWS (N3; %)	41.18 (10.49)	8.52 (3.94)	35.14 (10.10)	7.36 (5.84)	41.23 (7.28)	5.75 (4.48)	47.74 (6.19)	6.57 (4.64)	46.49 (8.75)	11.33 (6.28)	38.26 (9.29)	8.76 (4.72)	48.07 (8.71)	7.77 (6.46)	41.15 (8.00)	3.08 (3.62)
REM sleep (%)	13.04 (5.21)	25.55 (5.02)	13.29 (4.49)	28.04 (5.44)	9.94 (2.62)	26.92 (4.95)	8.72 (4.88)	26.60 (11.75)	13.33 (3.95)	28.87 (5.74)	11.87 (3.27)	31.04 (5.08)	9.80 (5.11)	28.88 (6.11)	5.91 (3.69)	31.72 (10.67)
SWS latency (minutes)	11.35 (4.57)		15.68 (6.06)		11.54 (3.60)		10.82 (5.62)		18.58 (22.92)		11.72 (1.82)		10.04 (4.49)		17.50 (18.88)	
REM latency (minutes)	73.08 (17.69)		87.18 (37.47)		104.69 (27.75)		107.36 (41.90)		90.65 (31.08)		82.83 (25.71)		110.69 (44.71)		152.72 (54.94)	

6.2.1 Acute alcohol effects on sleep quality and architecture

6.2.1.1 Sleep quality

There were no main or interaction effects of acute alcohol consumption (alcohol vs. placebo) on sleep onset latency (minutes), $F(1, 42)=0.13$, $p=.720$, $\eta_p^2=.003$. There was a main effect of acute alcohol consumption on wake after sleep onset, such that participants had more wake after sleep onset following pre-sleep alcohol compared to placebo, $F(1, 42)=11.69$, $p=.001$, $\eta_p^2=.22$. There was also a main effect of half night (first versus second half of the sleep period), $F(1, 42)=25.84$, $p<.001$, $\eta_p^2=.38$, which was driven by an interaction between half night and acute condition, $F(1, 42)=18.36$, $p<.001$, $\eta_p^2=.30$. Following alcohol there was more wake after sleep onset (minutes) in the second half of the night compared to the first half, $t(45)=5.10$, $p<.001$, $d=1.02$, but there were no half night differences following placebo, $t(45)=1.02$, $p=.316$, $d=0.18$. In the first half of the sleep period there were no differences in wake after sleep onset between the alcohol and placebo conditions, $t(45)=0.19$, $p=.850$, $d=0.04$. In contrast, in the second half of the sleep period, wake after sleep onset was higher following alcohol consumption compared to placebo, $t(45)=4.40$, $p<.001$, $d=0.91$. (See Table 6.3.)

Acute pre-sleep alcohol consumption had an effect on arousal index. Firstly, the main effect of half night on arousal index, $F(1, 42)=51.59$, $p<.001$, $\eta_p^2=.55$, was driven by an interaction between half night and acute condition, $F(1, 42)=48.07$, $p<.001$, $\eta_p^2=.53$. There were more arousals per hour in the second half of the sleep period compared to the first half in the alcohol condition, $t(45)=9.58$, $p<.001$, $d=2.09$, but there were no half night differences in the placebo condition, $t(45)=0.56$, $p=.577$, $d=0.09$. In the first half of the sleep period, compared to placebo, there were fewer arousals per hour following alcohol consumption, $t(45)=6.95$, $p<.001$, $d=1.00$.

However, in the second half of the sleep period there were more arousals per hour following alcohol consumption than placebo, $t(45)=5.58$, $p<.001$, $d=0.87$. (See Table 6.3.)

There was a main effect of acute alcohol consumption on sleep efficiency, $F(1, 42)=11.49$, $p<.002$, $\eta_p^2=.22$. Participants had lower sleep efficiency following alcohol consumption compared to placebo. There was also a main effect of half night, $F(1, 42)=25.69$, $p=.001$, $\eta_p^2=.38$ which was driven by an interaction between half night and acute condition, $F(1, 42)=18.08$, $p<.001$, $\eta_p^2=.30$. Following alcohol consumption sleep efficiency was lower in the second half of the sleep period compared to the first half, $t(45)=5.09$, $p<.001$, $d=1.02$. However, there were no half night differences in the placebo condition, $t(45)=1.00$, $p=.325$, $d=0.18$. In the first half of the sleep period there were no differences in sleep efficiency between the alcohol and placebo conditions, $t(45)=0.24$, $p=.811$, $d=0.05$. In contrast, in the second half of the sleep period, sleep efficiency was lower following alcohol consumption compared to placebo, $t(45)=4.38$, $p<.001$, $d=0.91$. (See Table 6.3.) In summary, alcohol consumption prior to sleep impacted sleep quality. These effects were most concentrated in the second half of the sleep period.

Table 6.3

Means ($\pm$ standard deviations) for sleep onset latency, wake after sleep onset (WASO), arousal index, and sleep efficiency for acute condition (alcohol vs. placebo) by half night (first vs. second half of the sleep period).

	Placebo		Alcohol	
	1 st half	2 nd half	1 st half	2 nd half
Sleep onset latency (minutes)	20.55 (13.02)		20.34 (14.68)	
WASO (minutes)	12.98 (16.58)	15.72 (13.64)	12.29 (15.99)	39.09 (33.48)
Arousal index (arousals per hour)	9.61 (3.61)	9.97 (4.26)	6.64 (2.15)	13.68 (4.25)
Sleep efficiency (%)	94.91 (6.52)	93.86 (5.25)	95.24 (6.15)	84.75 (13.22)

6.2.1.2 Sleep architecture

Following acute pre-sleep alcohol consumption, participants had more stage N1 sleep percentage compared to placebo, $F(1, 42)=6.47, p=.015, \eta_p^2=.13$. There was a main effect of half night, $F(1, 42)=120.69, p<.001, \eta_p^2=.74$, and interaction between half night and acute condition, $F(1, 42)=22.55, p<.001, \eta_p^2=.35$. In both the alcohol and placebo conditions, participants had more stage N1 sleep in the second half of the sleep period than in the first half [alcohol condition: $t(45)=9.93, p<.001, d=1.73$, placebo condition: $t(45)=7.88, p<.001, d=1.14$]. However, following alcohol consumption participants had less stage N1 sleep in the first half, $t(45)=2.24, p=.030, d=0.33$, and more stage N1 sleep in the second half of the sleep period, $t(45)=4.41, p<.001, d=0.62$, compared to placebo. (See Table 6.4 and Figure 6.3.)

As expected, acute pre-sleep alcohol consumption had no effect on stage N2 sleep. There was a main effect of half night on stage N2 sleep percentage, $F(1, 42)=100.36, p<.001, \eta_p^2=.71$. Regardless of acute condition, there was more stage N2 sleep in the second half of the sleep period compared to the first. (See Table 6.4 and Figure 6.3.) There was no main effect of acute alcohol consumption on SWS latency (minutes), $F(1, 42)=3.46, p=.070, \eta_p^2=.06$. (See Table 6.4 and Figure 6.4.) However, there was a main effect of half night, $F(1, 42)=821.61, p<.001, \eta_p^2=.95$, and an interaction between half night and acute condition for SWS percentage, $F(1, 42)=15.71, p<.001, \eta_p^2=.27$. In both the alcohol and placebo conditions there was more SWS in the first half of the sleep period than in the second half [alcohol condition: $t(45)=29.76, p<.001, d=5.70$, placebo condition: $t(45)=18.38, p<.001, d=3.85$]. However, following acute alcohol consumption participants had more SWS in the first half, $t(45)=2.82, p=.007, d=0.44$, and less SWS in the second half of the

sleep period, $t(45)=3.01$, $p=.004$, $d=0.59$, compared to placebo. (See Table 6.4 and Figure 6.3.)

There was a main effect of acute alcohol consumption on REM sleep latency (minutes), whereby REM sleep latency was longer in the alcohol condition compared to the placebo, $F(1, 42)=21.16$, $p<.001$, $\eta_p^2=.34$. (See Table 6.4 and Figure 6.4.)

There was also a main effect of acute alcohol consumption on REM sleep percentage, $F(1, 42)=8.16$, $p=.007$, $\eta_p^2=.16$. Following alcohol consumption participants had less REM sleep compared to placebo. As anticipated, there was a main effect of half night on REM sleep, $F(1, 42)=412.56$, $p<.001$, $\eta_p^2=.91$, as well as an interaction between half night and acute condition, $F(1, 42)=6.81$, $p=.013$, $\eta_p^2=.14$. In both the alcohol and placebo conditions participants had more REM sleep in the second half of the sleep period compared to the first half [alcohol condition: $t(45)=13.89$, $p<.001$, $d=2.91$, placebo condition: $t(45)=14.64$, $p<.001$, $d=3.09$].

Notably, in the first half of the sleep period participants had less REM sleep following alcohol consumption compared to placebo, $t(45)=5.05$, $p<.001$, $d=0.96$, however, there were no differences between acute conditions in the second half of the sleep period, $t(45)=0.14$, $p=.892$, $d=0.03$. (See Table 6.4 and Figure 6.3.) In summary, alcohol consumption prior to sleep altered normal sleep architecture compared to placebo consumption.

Table 6.4

Means ($\pm$ standard deviations) for percentage of stage N1 sleep (N1), stage N2 sleep (N2), stage N3/slow wave sleep (N3/SWS), rapid eye movement (REM) sleep, and minutes of SWS and REM sleep latency, for acute condition (alcohol vs. placebo) by half night (first vs. second half of the sleep period).

	Placebo		Alcohol	
	1 st half	2 nd half	1 st half	2 nd half
N1 (%)	3.66 (2.02)	6.88 (3.45)	3.06 (2.50)	9.47 (4.77)
N2 (%)	42.71 (9.25)	55.88 (7.05)	43.56 (7.74)	56.21 (8.76)
SWS (N3; %)	40.66 (10.31)	9.08 (5.34)	44.70 (8.11)	6.08 (5.07)
REM sleep (%)	12.95 (4.25)	28.16 (5.52)	8.82 (4.34)	28.33 (8.43)
SWS latency (minutes)	14.50 (12.81)		10.84 (4.29)	
REM latency (minutes)	83.33 (28.64)		116.42 (44.70)	

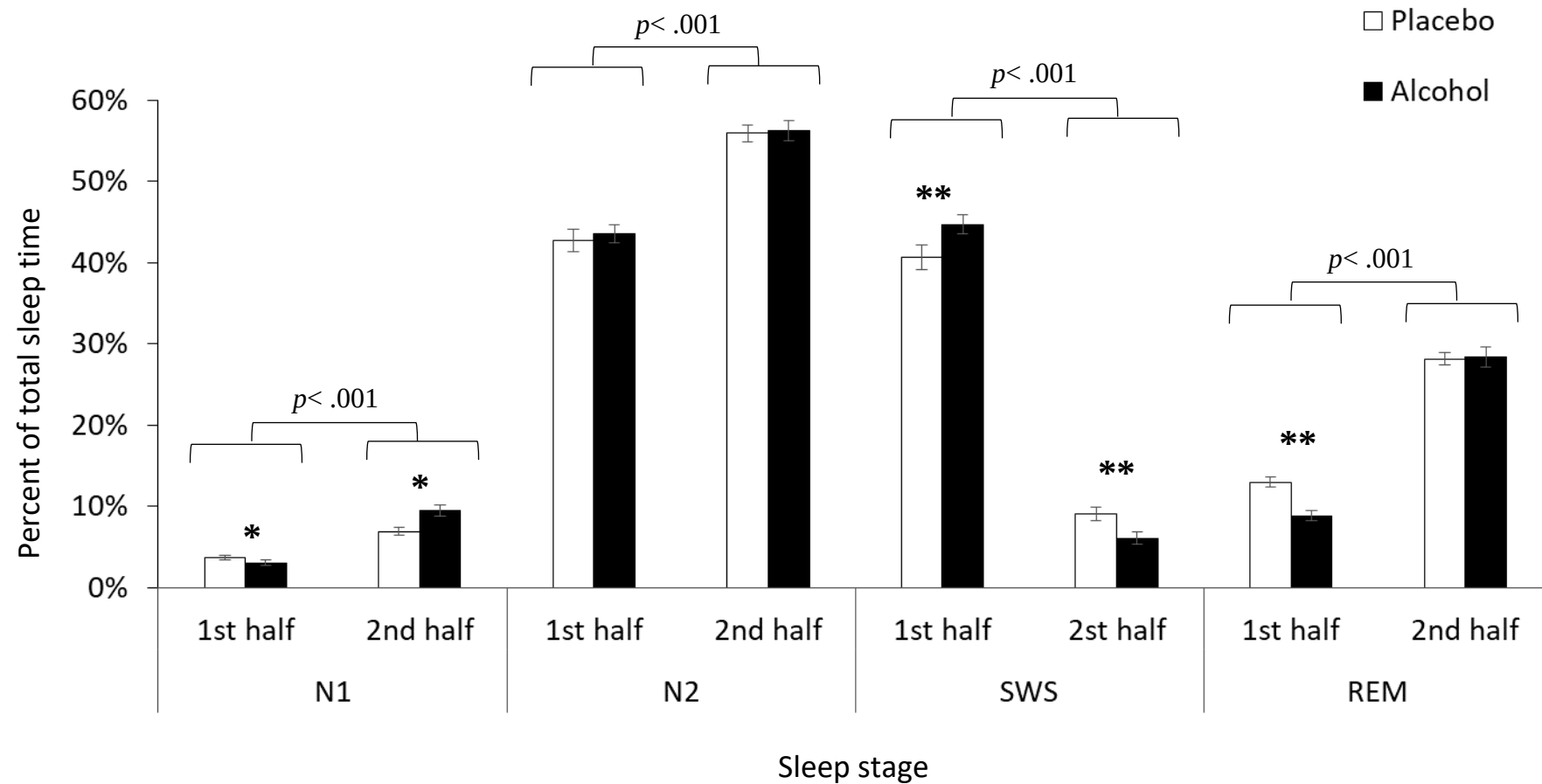


Figure 6.3. Means ($\pm$ standard errors) for percentage of total sleep time for stage N1 sleep (N1), stage N2 sleep (N2), stage N3/slow wave sleep (SWS), and rapid eye movement (REM) sleep by half night and acute condition, placebo: white bars, alcohol: black bars. Horizontal lines represent main half night comparisons and asterisks represent significant interaction effects. * $p < .05$. ** $p < .001$.

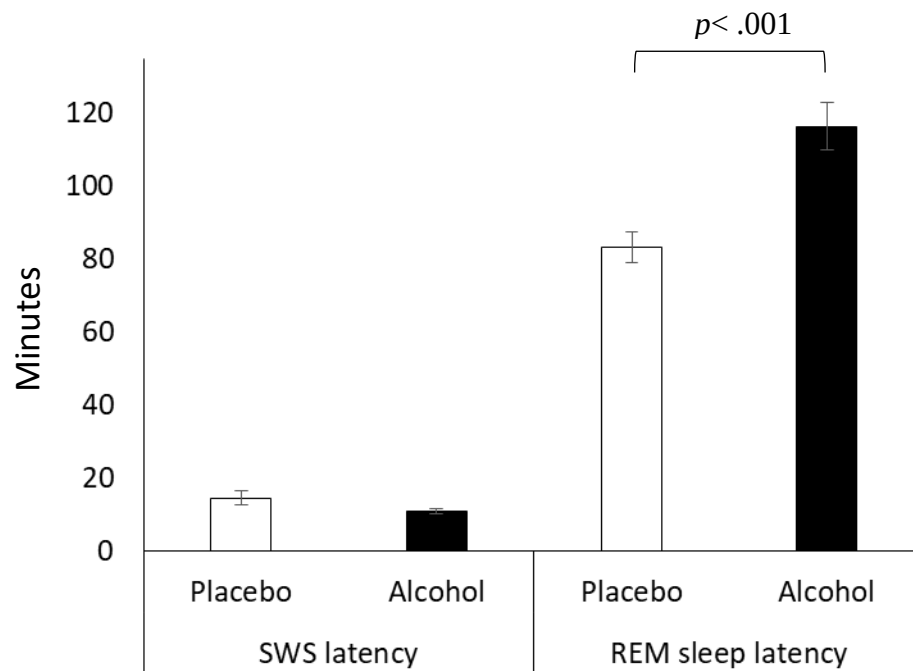


Figure 6.4. Means ($\pm$ standard errors) for slow wave sleep (SWS) and rapid eye movement (REM) sleep latency (minutes) in alcohol (black bars) and placebo (white bars) conditions. The horizontal line represents the main effect of acute condition (alcohol vs. placebo).

6.2.2 Habitual alcohol effects on sleep quality and architecture

There was no main effect of habitual alcohol use for sleep onset latency, $F(1, 42)=4.59$, $p=.038$, $\eta_p^2=.10$, wake after sleep onset, $F(1, 42)=0.89$, $p=.350$, $\eta_p^2=.02$, sleep efficiency, $F(1, 42)=0.18$, $p=.676$, $\eta_p^2=.05$, or SWS percentage, $F(1, 42)=1.49$, $p=.229$, $\eta_p^2=.03$. There was a main effect of habitual alcohol use (heavy vs. light drinking) for REM sleep latency, $F(1, 42)=4.59$, $p=.038$, $\eta_p^2=.10$. On average, heavy drinkers had shorter REM sleep latencies than light drinkers. (See Table 6.5 and Figure 6.6.) There was also an interaction between habitual alcohol use and half night for REM sleep percentage, $F(1, 42)=6.28$, $p=.016$, $\eta_p^2=.13$. In the second half of the sleep period, heavy drinkers had less REM sleep than light drinkers overall, however, there was no difference in the first half of the sleep period. (See Table 6.5 and Figure 6.5.) There were no other main or interaction effects of habitual alcohol use for sleep quality or architecture. (See Table 6.5 and Figure 6.5.)

Table 6.5

Means ($\pm$ standard deviations) for sleep onset latency, wake after sleep onset (WASO), arousal index, sleep efficiency, stage N1 sleep (N1), stage N2 sleep (N2), stage N3/slow wave sleep (N3/SWS), rapid eye movement (REM) sleep, and SWS and REM sleep latency for habitual alcohol use (heavy vs. light drinker) by half night (first vs. second half of the sleep period).

	Heavy drinker		Light drinker	
	1 st half	2 nd half	1 st half	2 nd half
Sleep onset latency (minutes)	21.83 (15.90)		18.93 (11.05)	
WASO (minutes)	13.96 (16.27)	26.81 (28.57)	11.19 (16.19)	28.05 (27.70)
Arousal index (events per hour)	8.36 (3.49)	12.64 (5.29)	7.87 (3.12)	10.95 (3.63)
Sleep efficiency (%)	94.51 (6.41)	89.37 (11.41)	95.70 (6.20)	89.23 (10.66)
N1 (%)	3.40 (2.34)	8.38 (4.01)	3.32 (2.24)	7.95 (4.71)
N2 (%)	44.16 (7.03)	57.84 (8.30)	42.03 (9.81)	54.09 (7.05)
SWS (N3; %)	41.31 (9.49)	7.06 (4.70)	44.18 (9.27)	8.15 (6.06)
REM sleep (%)	11.27 (4.68)	26.73 (7.01)	10.47 (4.85)	29.90 (6.87)
SWS latency (minutes)	12.27 (5.17)		10.43 (4.07)	
REM latency (minutes)	92.73 (33.95)		107.67 (46.44)	

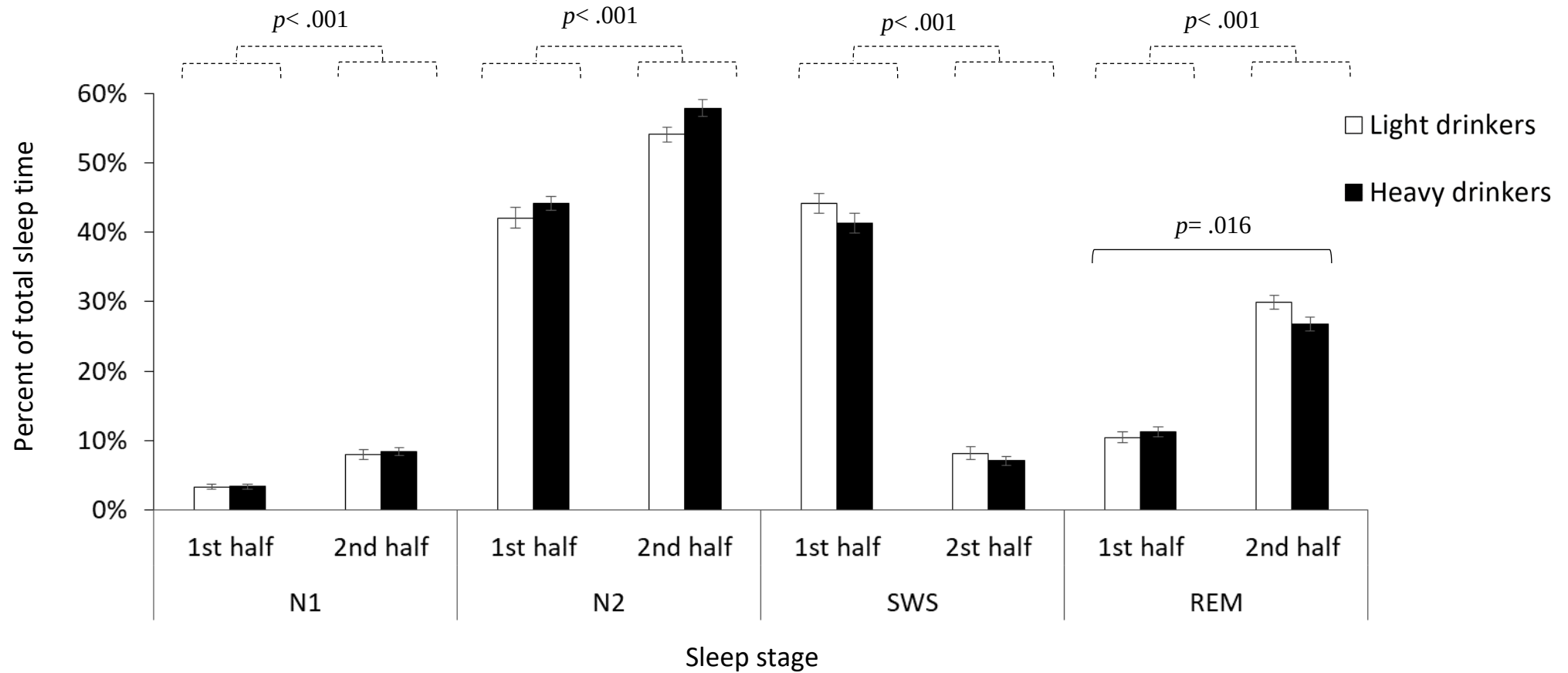


Figure 6.5. Means ($\pm$ standard errors) for percentage of total sleep time for stage N1 sleep (N1), stage N2 sleep (N2), stage N3/slow wave sleep (SWS), and rapid eye movement (REM) sleep by half night and habitual alcohol use, light drinkers: white bars, heavy drinkers: black bars. Horizontal perforated lines represent the main effects of half night and solid horizontal line represents the interaction between habitual alcohol use and half night.

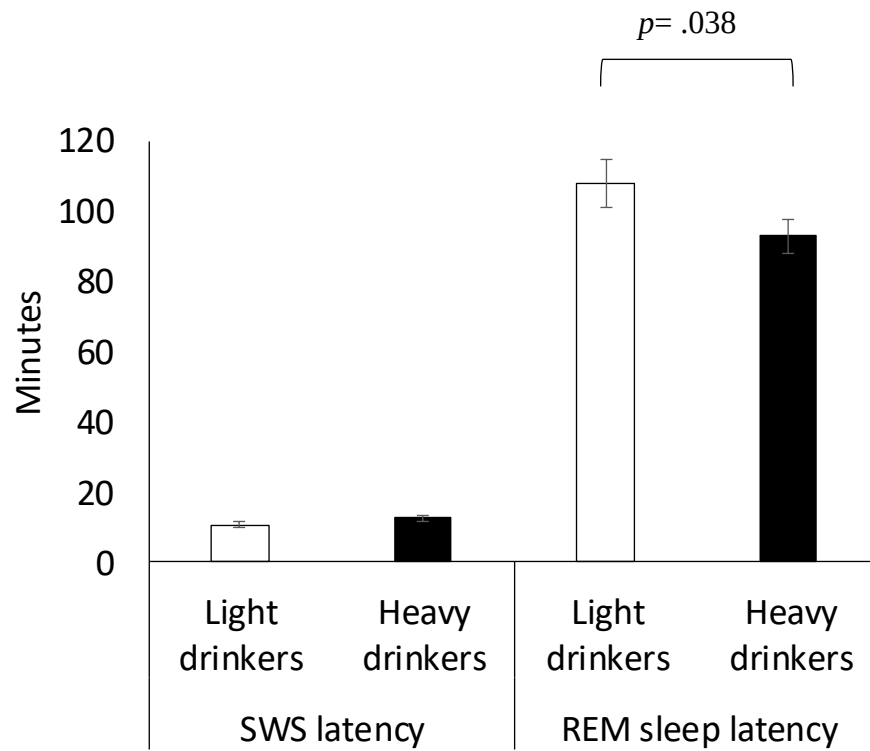


Figure 6.6. Means ($\pm$ standard errors) for slow wave sleep (SWS) and rapid eye movement (REM) sleep latency (minutes) in heavy drinkers (black bars) and light drinkers (white bars). The horizontal line represents the main effect of habitual alcohol use (heavy vs. light drinking).

6.2.3 *Acute and habitual alcohol interactions on sleep quality and architecture*

There was an interaction between acute (alcohol vs. placebo) and habitual alcohol use (heavy vs. light drinking) for stage N2 sleep percentage, $F(1, 42)=6.92$, $p=.012$, $\eta_p^2=.12$. Heavy drinkers had more stage N2 sleep in the placebo condition than light drinkers, $t(44)=2.80$, $p=.008$, $d=0.82$, but there were no differences in the alcohol condition, $t(44)=0.61$, $p=.548$, $d=0.18$. (See Table 6.6.) There was also an interaction between acute and habitual alcohol use for SWS percentage, $F(1, 42)=6.14$, $p=.017$, $\eta_p^2=.13$. Heavy drinkers had less SWS than light drinkers in the placebo condition, $t(44)=2.01$, $p=.026$, $d=0.59$, however in the alcohol condition there were no SWS differences between heavy and light drinkers, $t(44)=0.12$, $p=.909$, $d=0.03$. (See Table 6.6). There were no interactions between acute and habitual alcohol use for any other measure of sleep quality or architecture. (See Table 6.6.)

Table 6.6

Means ($\pm$ standard deviations) for sleep onset latency, wake after sleep onset (WASO), arousal index, sleep efficiency, stage N1 sleep (N1), stage N2 sleep (N2), stage N3/slow wave sleep (N3/SWS), rapid eye movement (REM) sleep, and SWS and REM sleep latency for habitual alcohol use (heavy vs. light drinker), acute condition (alcohol vs. placebo) and half night (first vs. second half of the sleep period).

	Heavy drinker				Light drinker			
	Placebo		Alcohol		Placebo		Alcohol	
	1 st half	2 nd half	1 st half	2 nd half	1 st half	2 nd half	1 st half	2 nd half
Sleep onset latency (minutes)	20.71 (15.17)		22.96 (16.20)		20.39 (10.01)		17.48 (12.06)	
WASO (minutes)	12.88 (16.41)	17.46 (15.70)	15.04 (16.41)	36.17 (35.19)	13.09 (17.16)	13.82 (11.04)	9.30 (15.32)	42.27 (32.02)
Arousal index (events per hour)	9.94 (3.68)	10.71 (5.20)	6.77 (2.47)	14.56 (4.73)	9.24 (3.58)	9.17 (2.82)	6.50 (1.79)	12.72 (3.53)
Sleep efficiency (%)	94.86 (6.64)	93.11 (6.09)	94.16 (6.28)	85.63 (14.14)	94.96 (6.53)	94.67 (4.15)	96.43 (5.92)	83.79 (12.40)
N1 (%)	3.59 (2.12)	6.98 (3.16)	3.20 (2.57)	9.78 (4.33)	3.74 (1.95)	6.78 (3.81)	2.90 (2.48)	9.13 (5.29)
N2 (%)	44.85 (8.28)	58.35 (7.25)	43.47 (5.60)	57.32 (9.36)	40.40 (9.87)	53.19 (5.87)	43.67 (9.70)	55.00 (8.10)
SWS (N3; %)	38.41 (10.55)	7.99 (4.82)	44.21 (7.44)	6.13 (4.48)	43.21 (9.68)	10.28 (5.72)	45.24 (8.94)	6.02 (5.75)
REM sleep (%)	13.16 (4.79)	26.69 (5.26)	9.38 (3.78)	26.77 (8.54)	12.73 (3.68)	29.76 (5.46)	8.21 (4.89)	30.04 (8.17)
SWS latency (minutes)	13.33 (5.63)		11.21 (4.54)		15.77 (17.70)		10.43 (4.07)	
REM latency (minutes)	79.54 (28.73)		105.92 (34.16)		87.45 (28.62)		127.89 (52.34)	

6.2.4 Sex and alcohol interaction effects on sleep quality and architecture

There were two parallel four-way interactions between sex, acute and habitual alcohol use, and half night for both wake after sleep onset, $F(1, 42)=6.64$, $p=.014$, $\eta_p^2=.14$, and sleep efficiency, $F(1, 42)=6.70$, $p=.013$, $\eta_p^2=.14$. These interactions indicated that there was generally more wake after sleep onset, and lower sleep efficiency, in the alcohol condition compared to placebo across all groups, but with the exception that heavy-drinking males and light-drinking females had less wake after sleep onset, and higher sleep efficiency, in the first half of the alcohol condition. (See Table 6.2 and Figure 6.7.)

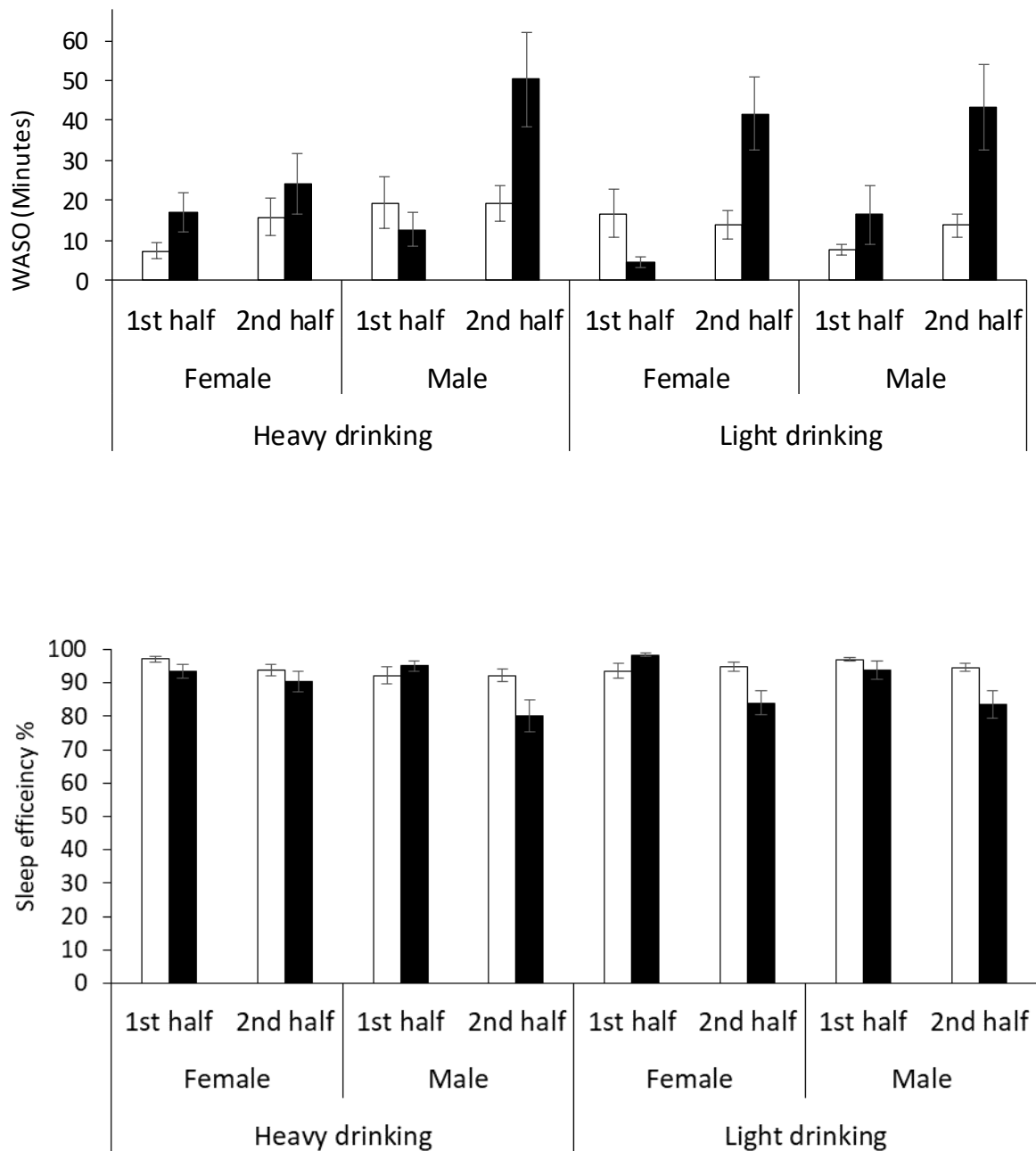


Figure 6.7. Four-way interactions between sex (female vs. male), habitual alcohol use (heavy vs. light drinking), acute condition (alcohol vs. placebo), half night (first vs. second half of the sleep period) for wake after sleep onset (WASO) in minutes (top pane; four-way interaction, $p = .014$) and sleep efficiency (bottom pane; four-way interaction, $p = .013$).

There was an interaction between sex and habitual alcohol use for stage N2 sleep, $F(1, 42)=5.45$, $p=.024$, $\eta_p^2=.12$. This interaction indicated that overall, light-drinking females had less stage N2 sleep than heavy-drinking females [placebo condition: $t(24)=2.98$, $p=.007$, $d=1.17$; alcohol condition: $t(24)=2.77$, $p=.011$, $d=1.08$], however this pattern was not observed in males [placebo $t(18)=0.93$, $p=.365$, $d=0.42$; alcohol condition: $t(18)=2.61$, $p=.018$, $d=1.18$]. (See Table 6.2.)

There was a main effect of sex on SWS percentage, $F(1, 42)=4.56$, $p=.039$, $\eta_p^2=.10$, which was driven by an interaction between sex and acute condition, $F(1, 42)=6.00$, $p=.019$, $\eta_p^2=.13$. Females had more SWS than males in the placebo condition, $t(44)=2.84$, $p=.007$, $d=0.85$, however, there were no differences in the alcohol condition, $t(44)=0.16$, $p=.870$, $d=0.05$. There was also an interaction between sex and habitual alcohol use for SWS, $F(1, 42)=4.67$, $p=.037$, $\eta_p^2=.10$, which was driven by an interaction between sex, habitual alcohol use, and acute condition, $F(1, 42)=7.51$, $p=.009$, $\eta_p^2=.15$. Heavy-drinking females had less SWS in the alcohol condition compared to the placebo, $t(12)=2.31$, $p=.040$, $d=0.34$, whereas heavy-drinking males had more SWS in the alcohol condition than the placebo, $t(10)=5.36$, $p<.001$, $d=1.74$. There were no differences in overall SWS between the alcohol and placebo conditions for either light-drinking females, $t(12)=0.11$, $p=.918$, $d=0.03$, or light-drinking males, $t(8)=0.25$, $p=.831$, $d=0.12$. The interaction also indicated that heavy-drinking females had less SWS than light-drinking females in both the placebo, $t(24)=1.77$, $p=.045$, $d=0.70$, and alcohol, $t(15.90)=1.87$, $p=.040$, $d=0.74$, conditions. Heavy-drinking females also had less SWS than heavy-drinking males following alcohol, $t(22)=3.39$, $p=.003$, $d=1.38$, but no differences following placebo, $t(22)=1.95$, $p=.065$, $d=0.80$. Light-drinking males had less SWS than heavy-drinking males in the alcohol condition, $t(18)=3.34$, $p=.004$, $d=1.52$, but

showed no differences in the placebo condition, $t(18)=1.05$, $p= .328$, $d=0.45$. (See Table 6.2.) There were no interactions between sex, acute and/or habitual alcohol use for any other measures of sleep quality or architecture. (See Table 6.2.)

6.2.5 Correlations

Estimated lifetime history of alcohol consumption, previous 30-day retrospective alcohol intake, and number of years drinking were each individually correlated with all visually scored sleep architecture and quality variables. This analysis was completed in the entire sample ($n=46$), as well as heavy- ($n=24$) and light-drinking participants ($n=22$) separately. Normality was assessed and accounted for via the process outlined in Section 5.4.2 Data analysis. For the entire sample, normality was violated for lifetime history of alcohol consumption, $W= .73$, $p< .001$, and 30-day retrospective alcohol consumption, $W= .78$, $p< .001$. Normality was also violated for wake after sleep onset, $W= .73$, $p< .001$, and sleep efficiency, $W= .79$, $p< .001$, in the placebo condition.

There was a positive correlation in the placebo condition whereby as lifetime history of alcohol consumption increased, wake after sleep onset (minutes) also increased, $\rho= .376$, $p= .010$. There was also a positive correlation whereby as 30-day retrospective alcohol consumption increased, wake after sleep onset in the placebo condition also increased, $\rho= .312$, $p= .035$. Finally, there was a positive correlation highlighting that as number of years drinking increased, wake after sleep onset also increased, $\rho= .413$, $p= .004$. It is worth noting that although age was also positively correlated with wake after sleep onset, $\rho= .291$, $p= .049$, this relationship was weaker than number of years drinking. Further to this, a partial correlation demonstrated that

the positive correlation between number of years drinking and wake after sleep onset was still present whilst controlling for age, $\rho = .307$, $p = .020$.

There was a negative correlation whereby as lifetime history of alcohol consumption increased, sleep efficiency declined in the placebo condition, sleep, $\rho = -.388$, $p = .008$. There was also a negative correlation showing that as 30-day retrospective alcohol consumption increased, sleep efficiency in the placebo condition declined, $\rho = -.327$, $p = .027$. These findings were mirrored by a negative correlation whereby as number of years of drinking increased, sleep efficiency in the placebo condition decreased, $\rho = -.413$, $p = .004$. Supporting this, a partial correlation demonstrated that the negative relationship between number of years drinking and sleep efficiency was still significant after controlling for age, $\rho = -.324$, $p = .015$.

There was a negative correlation whereby as 30-day retrospective alcohol use increased, SWS percentage in the placebo condition decreased, $\rho = -.261$, $p = .040$. There was also a negative correlation highlighting that as number of years of drinking increased, SWS percentage in the placebo condition decreased, $r^2 = -.255$, $p = .044$. However, it is worth noting that the negative relationship between age and SWS percentage was stronger than number of years drinking, $r^2 = -.290$, $p = .025$. Indeed, whilst controlling for age the relationship between number of years drinking and SWS percentage was no longer significant, $r = .110$, $p = .474$. There was a positive correlation whereby as 30-day retrospective alcohol use increased, stage N2 sleep percentage in the placebo condition increased, $\rho = .250$, $p = .047$. Lastly, there was a negative correlation whereby as 30-day retrospective alcohol consumption increased, REM sleep latency in the alcohol condition decreased, $\rho = -.315$, $p = .033$.

6.2.5.1 Heavy-drinking late adolescents

In heavy-drinking participants, normality was violated for lifetime history of alcohol consumption, $W = .84$, $p = .002$, 30-day retrospective alcohol consumption, $W = .69$, $p < .001$, and wake after sleep onset in the placebo condition, $W = .85$, $p = .002$. In heavy drinkers, there was a positive correlation whereby as lifetime history of alcohol consumption increased wake after sleep onset in the placebo condition also increased, $\rho = .534$, $p = .007$. There was also a positive correlation whereby as 30-day retrospective alcohol consumption increased, wake after sleep onset in the placebo condition also increased, $\rho = .576$, $p = .003$. Finally, there was a positive correlation showing that as number of years drinking increased for heavy drinkers, wake after sleep onset in the placebo condition also increased, $\rho = .465$, $p = .022$. However, a partial correlation showed that whilst controlling for age there was no association between number of years drinking and wake after sleep onset, $\rho = .079$, $p = .718$.

There was a negative correlation whereby as lifetime history of alcohol consumption increased, sleep efficiency in the placebo condition decreased, $\rho = -.537$, $p = .007$. There was also negative correlation whereby as previous 30-day retrospective alcohol consumption increased, sleep efficiency in the placebo condition decreased, $\rho = -.572$, $p = .003$.

There was a positive correlation highlighting that as number of years drinking increased for heavy drinkers, stage N2 sleep percentage in the placebo condition increased, $r^2 = .420$, $p = .041$. In heavy drinkers only, age was not significantly correlated with stage N2 sleep, $r^2 = .062$, $p = .774$. Supporting this, a partial correlation demonstrated that the negative relationship between number of years drinking and sleep efficiency was still significant after controlling for age, $r = .519$,

$p = .011$. There was a negative correlation highlighting that as number of years of drinking increased, SWS percentage in the placebo condition decreased, $r^2 = -.369$, $p = .038$. Again, it is worth noting that the negative relationship between age and SWS percentage was still marginally stronger than number of years drinking in heavy drinkers, $r^2 = -.383$, $p = .033$. However, a partial correlation demonstrated that whilst controlling for age there was no association between number of years drinking and SWS, $r = -.158$, $p = .471$.

6.2.5.2 *Light-drinking late adolescents*

Normality was violated for lifetime history of alcohol consumption in light-drinking participants, $W = .84$, $p = .002$. There was a positive correlation showing that as lifetime alcohol consumption increased, REM sleep latency in the placebo condition also increased in light drinkers, $\rho = .524$, $p = .012$. There was a positive correlation showing that as 30-day retrospective alcohol use increased, REM sleep latency in the placebo condition also increased, $r^2 = .612$, $p = .002$. Finally, there was a positive correlation showing that as 30-day retrospective alcohol consumption increased in light drinkers, REM sleep latency in the placebo condition also increased, $r^2 = .426$, $p = .048$.

There was a positive correlation highlighting that as lifetime alcohol consumption increased, REM sleep percentage in the alcohol condition also increased, $\rho = .503$, $p = .017$. There was a positive correlation highlighting that as 30-day retrospective alcohol consumption increased, REM sleep percentage in the alcohol condition also increased, $r^2 = .437$, $p = .042$. Lastly, there was a positive correlation highlighting that as number of years drinking increased for light drinkers, REM sleep percentage in the alcohol condition increased, $r^2 = .469$, $p = .028$. However, a partial correlation demonstrated that whilst controlling for age there was no association between number of years drinking and REM sleep percentage, $r = .405$, $p = .068$.

6.3 Acute and habitual effects of alcohol on sleep EEG power spectra

The final section presents the descriptive and inferential statistics for the acute and habitual effects of alcohol on sleep EEG power spectra. Interactions between acute and habitual alcohol use, and sex, have also been included. Computerised spectral analysis of the sleep EEG was undertaken to demonstrate the effects of acute and habitual alcohol use that would likely be missed using traditional visual scoring alone (Colrain et al., 2009b). Tables 6.7 to 6.11 and Figures 6.8 to 6.12 display the EEG spectral power for heavy- and light-drinking female and male late adolescents in the first and second halves of the sleep period for each frequency band, acute condition, sleep stage, and across each electrode site. Power spectral plots for 1 to 30 Hz frequency EEG activity are displayed in Appendix C.

For all spectral power frequency bands, main and interaction effects were observed for sleep stage, half night, electrode site, and sex. (See Appendices D, E, and G.) These were consistent with the effects reported in the literature investigating normal sleep in males and females (Achermann & Borbély, 2017; Baker & O'Brien, 2017; Bersagliere et al., 2018; Carrier et al., 2001; Carskadon & Dement, 2017; Dijk, et al., 1989; Latta et al., 2005; Mourtazaev et al., 1995; Nir et al., 2011). For brevity and because the current investigation focussed on the effects of alcohol use on sleep, only main effects and interactions involving acute and habitual alcohol use are reported below. Results pertaining to all other main effects and interactions are included in Appendices D, E, and G.

Table 6.7

Means ($\pm$ standard deviations) for beta spectral power (microvolts squared; μV^2) during stage N1 sleep (N1), stage N2 sleep (N2), stage N3/slow wave sleep (SWS), and rapid eye movement (REM) sleep, at frontal (F), central (C), and occipital (O) electrode sites, in heavy- and light-drinking females and males after alcohol or placebo in the first and second halves of the sleep period.

Stage	Site	Heavy drinkers								Light drinkers							
		Placebo				Alcohol				Placebo				Alcohol			
		1 st Half		2 nd Half		1 st Half		2 nd Half		1 st Half		2 nd Half		1 st Half		2 nd Half	
		Female	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female	Male
N1	F	15.70	10.88	12.33	7.96	9.87	8.48	8.34	8.91	12.55	14.47	11.70	13.44	9.58	14.12	9.05	15.68
		(11.58)	(5.11)	(7.48)	(3.85)	(4.67)	(4.74)	(3.31)	(4.69)	(6.97)	(9.19)	(5.71)	(6.87)	(6.01)	(6.61)	(9.57)	(13.26)
	C	17.50	11.05	13.24	7.38	9.62	7.58	9.26	8.24	11.58	14.72	11.18	13.61	9.28	16.91	9.85	13.92
		(14.98)	(7.73)	(8.33)	(3.25)	(3.68)	(3.63)	(5.40)	(5.67)	(6.56)	(10.86)	(5.25)	(8.43)	(5.78)	(15.00)	(12.63)	(9.53)
	O	7.88	6.76	6.04	5.14	6.19	6.14	5.12	5.04	7.06	5.58	6.73	6.34	6.26	6.11	5.82	6.97
		(3.51)	(2.77)	(1.94)	(1.89)	(2.51)	(4.14)	(1.38)	(2.49)	(3.04)	(1.53)	(2.79)	(5.10)	(2.76)	(3.08)	(3.23)	(5.10)
N2	F	3.79	3.70	3.27	3.29	3.40	4.44	3.52	3.42	3.82	2.80	4.13	5.85	3.78	3.46	3.57	2.95
		(0.96)	(1.94)	(0.82)	(1.60)	(0.92)	(2.37)	(0.93)	(1.54)	(1.68)	(1.08)	(3.93)	(9.57)	(2.03)	(1.57)	(1.53)	(1.23)
	C	3.75	3.42	3.39	2.96	3.21	3.67	3.58	3.14	4.00	2.59	3.88	5.62	3.98	2.91	3.66	2.66
		(0.79)	(1.35)	(0.84)	(1.11)	(0.63)	(1.53)	(1.19)	(1.30)	(2.02)	(0.87)	(3.54)	(9.27)	(2.99)	(0.88)	(2.09)	(0.96)
	O	3.86	3.15	3.31	2.80	3.68	3.28	3.46	2.83	3.72	2.49	3.19	5.18	3.60	2.70	3.41	2.59
		(1.20)	(0.82)	(1.14)	(0.75)	(1.12)	(0.88)	(1.17)	(0.80)	(1.56)	(1.10)	(1.43)	(8.81)	(1.63)	(1.32)	(1.38)	(1.11)
SWS	F	2.22	2.29	2.60	2.26	2.18	2.42	2.01	2.44	2.37	1.80	3.27	1.77	2.31	1.70	2.13	2.01
		(0.61)	(1.15)	(0.86)	(1.41)	(0.73)	(1.29)	(1.45)	(1.61)	(0.86)	(0.58)	(3.81)	(0.63)	(0.98)	(0.66)	(1.45)	(0.80)
	C	2.33	2.38	2.72	2.28	2.14	2.22	1.95	2.46	2.59	1.77	3.20	1.64	2.65	1.64	2.50	1.83
		(0.54)	(0.99)	(0.73)	(1.32)	(0.55)	(0.92)	(1.28)	(1.57)	(1.15)	(0.54)	(3.46)	(0.53)	(1.72)	(0.66)	(2.17)	(0.66)
	O	2.75	2.26	2.66	2.09	2.42	2.18	2.10	2.19	2.71	1.89	2.51	1.66	2.56	1.86	2.35	1.90
		(1.02)	(0.50)	(1.00)	(0.98)	(0.75)	(0.58)	(1.49)	(1.00)	(1.12)	(1.00)	(0.88)	(0.58)	(1.04)	(1.08)	(1.43)	(0.72)
REM	F	4.14	5.71	3.77	4.59	5.02	8.66	3.71	6.16	5.51	6.32	5.84	5.19	6.26	10.38	5.06	5.80
		(1.13)	(3.33)	(1.17)	(2.59)	(1.64)	(5.99)	(0.97)	(3.86)	(3.88)	(5.02)	(5.05)	(3.35)	(4.69)	(9.74)	(3.76)	(4.78)
	C	3.48	3.75	3.20	3.13	3.86	4.91	3.15	3.99	4.17	3.98	4.48	3.27	4.27	6.15	3.89	3.82
		(0.71)	(1.51)	(0.74)	(1.09)	(0.89)	(2.77)	(0.76)	(1.88)	(2.70)	(2.57)	(3.76)	(1.60)	(2.32)	(4.53)	(2.08)	(2.16)
	O	4.04	3.63	3.35	2.92	4.44	3.86	3.53	3.07	4.07	2.93	3.45	2.54	4.10	3.75	3.66	2.85
		(1.23)	(1.24)	(1.01)	(0.75)	(1.34)	(1.38)	(1.16)	(0.78)	(1.86)	(1.19)	(1.82)	(0.81)	(2.14)	(2.18)	(1.91)	(1.18)

Table 6.8

Means ($\pm$ standard deviations) for alpha spectral power (microvolts squared; μV^2) during stage N1 sleep (N1), stage N2 sleep (N2), stage N3/slow wave sleep (SWS), and rapid eye movement (REM) sleep, at frontal (F), central (C), and occipital (O) electrode sites, in heavy- and light-drinking females and males after alcohol or placebo in the first and second halves of the sleep period.

Stage	Site	Heavy drinkers								Light drinkers							
		Placebo				Alcohol				Placebo				Alcohol			
		1 st Half		2 nd Half		1 st Half		2 nd Half		1 st Half		2 nd Half		1 st Half		2 nd Half	
		Female	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female	Male
N1	F	9.64	8.09	9.19	6.78	9.87	9.40	7.73	7.66	9.35	6.24	8.53	8.27	9.47	6.71	7.65	6.11
		(4.63)	(3.64)	(3.65)	(2.96)	(5.90)	(7.25)	(2.83)	(3.68)	(3.05)	(1.48)	(3.46)	(8.56)	(3.48)	(2.04)	(2.82)	(1.65)
	C	11.90	10.79	12.00	10.19	11.28	12.42	10.13	11.59	11.46	7.12	11.15	10.03	11.26	7.83	10.33	7.46
		(4.38)	(5.51)	(4.30)	(5.44)	(6.32)	(8.57)	(3.68)	(6.03)	(4.31)	(2.07)	(5.37)	(8.29)	(4.30)	(2.06)	(4.48)	(2.16)
	O	19.37	16.92	21.17	18.41	19.61	21.52	18.25	17.79	18.04	11.46	18.14	15.33	18.32	12.99	16.98	10.54
		(7.99)	(7.58)	(10.80)	(10.56)	(14.60)	(20.49)	(8.23)	(9.28)	(9.99)	(7.04)	(10.35)	(11.12)	(13.58)	(10.51)	(9.44)	(4.94)
N2	F	16.69	10.38	14.36	13.70	20.58	18.73	14.48	12.95	17.38	10.38	14.85	11.32	18.55	12.19	14.21	8.80
		(7.25)	(4.02)	(7.97)	(5.56)	(12.29)	(10.22)	(7.41)	(5.22)	(5.17)	(4.02)	(5.61)	(9.53)	(7.06)	(5.80)	(5.31)	(2.85)
	C	16.07	14.99	14.30	13.34	19.75	18.05	14.09	13.70	16.08	8.87	13.73	10.49	18.39	10.44	13.71	8.22
		(6.28)	(7.32)	(6.76)	(6.13)	(10.95)	(9.94)	(6.40)	(6.44)	(5.23)	(2.88)	(5.27)	(9.17)	(8.72)	(3.39)	(5.35)	(1.77)
	O	17.90	14.94	16.03	13.22	22.90	18.27	16.70	13.22	16.77	7.69	14.29	10.08	20.95	9.60	14.65	7.87
		(7.25)	(7.81)	(6.31)	(6.43)	(15.05)	(9.95)	(8.65)	(7.23)	(10.18)	(2.58)	(8.84)	(9.64)	(17.56)	(3.61)	(10.23)	(2.48)
SWS	F	20.95	25.39	20.24	19.81	35.72	48.32	16.55	21.27	25.67	14.49	21.19	10.80	42.94	27.45	16.55	12.90
		(9.69)	(14.73)	(13.01)	(13.12)	(28.03)	(40.45)	(15.95)	(13.76)	(11.41)	(7.35)	(7.61)	(4.30)	(32.60)	(21.73)	(11.34)	(6.05)
	C	16.68	16.89	17.17	14.75	22.69	26.34	12.80	16.54	20.28	9.47	18.63	8.19	29.92	15.35	15.29	9.78
		(7.19)	(8.31)	(10.07)	(9.37)	(13.21)	(17.39)	(10.51)	(10.46)	(9.98)	(3.27)	(8.06)	(2.72)	(22.95)	(9.23)	(11.15)	(3.41)
	O	17.35	13.56	17.00	12.11	19.66	15.82	14.32	11.63	17.91	7.25	16.65	6.44	21.35	9.28	13.59	6.94
		(5.96)	(5.91)	(6.55)	(7.05)	(9.49)	(7.74)	(10.74)	(5.51)	(11.46)	(2.47)	(11.16)	(2.37)	(18.04)	(4.10)	(12.32)	(2.90)
REM	F	7.69	5.87	6.94	5.75	9.11	8.11	7.24	7.02	7.85	4.73	7.30	4.49	8.90	5.95	7.52	4.86
		(3.57)	(2.12)	(2.98)	(2.04)	(4.35)	(4.33)	(2.81)	(3.07)	(2.97)	(0.91)	(3.40)	(0.86)	(3.38)	(1.94)	(3.21)	(0.85)
	C	8.83	7.32	7.76	6.95	10.57	10.81	8.05	8.72	9.90	5.68	8.59	5.19	10.74	6.91	8.77	5.43
		(3.52)	(3.18)	(2.49)	(3.03)	(5.14)	(5.75)	(3.04)	(4.14)	(5.68)	(1.27)	(4.39)	(1.39)	(4.52)	(1.96)	(4.07)	(0.92)
	O	19.61	18.06	15.14	12.98	23.41	22.10	16.07	13.56	20.24	11.53	14.87	9.12	21.96	16.04	15.18	9.19
		(11.17)	(13.85)	(6.80)	(6.45)	(16.15)	(14.55)	(9.03)	(8.58)	(11.64)	(6.06)	(9.15)	(4.39)	(16.71)	(12.60)	(10.52)	(3.54)

Table 6.9

Means ($\pm$ standard deviations) for sigma spectral power (microvolts squared; μV^2) during stage N1 sleep (N1), stage N2 sleep (N2), stage N3/slow wave sleep (SWS), and rapid eye movement (REM) sleep, at frontal (F), central (C), and occipital (O) electrode sites, in heavy- and light-drinking females and males after alcohol or placebo in the first and second halves of the sleep period.

Stage	Site	Heavy drinkers								Light drinkers							
		Placebo				Alcohol				Placebo				Alcohol			
		1 st Half		2 nd Half		1 st Half		2 nd Half		1 st Half		2 nd Half		1 st Half		2 nd Half	
		Female	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female	Male
N1	F	5.69 (2.43)	5.31 (2.61)	4.82 (1.37)	3.67 (1.77)	5.86 (2.26)	6.55 (5.00)	4.05 (1.13)	4.00 (1.97)	5.18 (1.78)	5.40 (2.32)	4.40 (2.07)	5.03 (4.39)	5.65 (2.26)	5.81 (2.32)	3.94 (1.85)	4.39 (1.70)
	C	6.04 (2.48)	5.13 (2.02)	5.05 (1.26)	3.66 (1.32)	5.64 (2.64)	5.71 (4.05)	4.28 (0.96)	4.27 (2.08)	5.25 (1.95)	5.45 (2.22)	4.46 (1.82)	5.17 (4.26)	5.86 (2.64)	5.77 (2.73)	4.48 (2.17)	4.40 (1.43)
	O	6.33 (2.38)	5.24 (1.63)	5.11 (1.56)	4.18 (1.20)	6.28 (2.78)	5.56 (2.72)	4.62 (1.26)	4.43 (2.01)	5.83 (2.32)	4.05 (1.82)	4.75 (1.95)	4.56 (4.50)	5.69 (2.63)	4.53 (2.46)	4.59 (1.85)	3.91 (1.70)
N2	F	12.43 (5.87)	11.56 (5.30)	14.15 (7.43)	11.73 (4.88)	12.85 (6.91)	10.74 (5.53)	15.66 (8.22)	10.97 (4.66)	11.15 (5.17)	6.72 (2.28)	11.58 (6.17)	8.84 (7.31)	9.43 (4.70)	6.16 (2.32)	11.92 (6.77)	6.65 (2.37)
	C	13.36 (6.61)	12.42 (4.93)	15.12 (7.88)	13.15 (4.86)	13.57 (6.01)	12.05 (6.09)	15.50 (6.28)	13.11 (6.00)	11.66 (4.78)	8.45 (2.73)	12.28 (5.88)	10.40 (7.00)	11.73 (5.02)	7.45 (3.06)	12.58 (6.52)	8.20 (2.72)
	O	9.42 (3.12)	8.67 (4.25)	8.95 (3.10)	8.33 (4.71)	9.82 (2.58)	7.65 (3.14)	9.12 (2.22)	7.46 (3.18)	8.42 (4.10)	5.07 (2.39)	7.28 (3.61)	6.43 (5.82)	7.49 (3.79)	4.90 (2.49)	7.05 (3.23)	4.86 (2.05)
SWS	F	9.73 (5.13)	9.68 (4.74)	11.35 (5.87)	10.08 (6.16)	9.23 (5.40)	8.76 (4.91)	11.53 (10.78)	10.62 (5.91)	9.08 (5.26)	5.32 (1.93)	12.07 (7.42)	5.93 (2.61)	7.98 (4.20)	4.50 (1.91)	8.05 (4.95)	5.83 (2.84)
	C	9.81 (4.88)	9.50 (3.81)	11.22 (5.41)	10.08 (5.65)	9.09 (4.22)	8.85 (4.47)	10.08 (8.59)	11.61 (7.36)	8.96 (4.15)	5.71 (1.92)	12.12 (7.01)	6.38 (2.35)	8.43 (4.01)	4.69 (1.89)	7.89 (4.28)	6.14 (2.47)
	O	6.81 (2.23)	5.93 (2.44)	6.81 (2.70)	5.55 (3.30)	6.46 (1.75)	5.02 (1.95)	5.47 (3.55)	6.05 (3.58)	6.09 (3.06)	3.33 (1.37)	6.16 (3.10)	3.09 (1.13)	5.53 (2.76)	2.88 (1.27)	4.60 (3.12)	3.12 (1.02)
REM	F	2.90 (1.17)	2.47 (1.17)	2.25 (0.65)	2.09 (0.83)	3.37 (1.12)	4.39 (2.76)	2.26 (0.75)	2.64 (1.33)	3.45 (1.95)	1.97 (0.50)	2.82 (2.08)	1.60 (0.37)	4.12 (2.17)	2.89 (1.33)	2.68 (1.11)	1.68 (0.39)
	C	2.99 (1.11)	2.43 (0.92)	2.36 (0.65)	2.13 (0.80)	3.33 (1.08)	3.45 (1.81)	2.39 (0.79)	2.75 (1.53)	3.28 (1.73)	1.90 (0.49)	2.77 (1.87)	1.57 (0.34)	3.87 (1.78)	2.39 (0.74)	2.89 (1.48)	1.65 (0.25)
	O	5.24 (2.59)	3.77 (1.19)	3.67 (1.37)	3.00 (0.81)	5.34 (1.76)	4.47 (1.50)	3.71 (1.45)	3.34 (0.97)	4.78 (2.67)	2.78 (1.69)	3.37 (1.87)	2.20 (1.11)	4.83 (2.60)	3.49 (2.34)	3.59 (1.87)	2.41 (1.24)

Table 6.10

Means ($\pm$ standard deviations) for theta spectral power (microvolts squared; μV^2) during stage N1 sleep (N1), stage N2 sleep (N2), stage N3/slow wave sleep (SWS), and rapid eye movement (REM) sleep, at frontal (F), central (C), and occipital (O) electrode sites, in heavy- and light-drinking females and males after alcohol or placebo in the first and second halves of the sleep period.

Stage	Site	Heavy drinkers								Light drinkers							
		Placebo				Alcohol				Placebo				Alcohol			
		1 st Half		2 nd Half		1 st Half		2 nd Half		1 st Half		2 nd Half		1 st Half		2 nd Half	
		Female	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female	Male
N1	F	27.87	20.89	23.71	18.52	29.97	22.57	23.59	17.85	28.59	18.97	24.15	21.12	32.24	22.32	24.55	20.91
		(11.63)	(6.20)	(9.33)	(5.36)	(19.08)	(8.71)	(11.23)	(6.02)	(12.28)	(6.48)	(10.62)	(21.44)	(22.82)	(11.33)	(15.61)	(12.77)
	C	28.53	21.68	24.11	18.35	26.15	22.70	22.63	18.14	31.36	18.51	26.04	20.29	32.11	21.12	26.41	19.74
		(9.59)	(10.35)	(7.88)	(5.22)	(12.92)	(9.48)	(8.09)	(6.07)	(16.30)	(7.43)	(14.55)	(21.14)	(23.06)	(8.89)	(17.69)	(12.21)
	O	26.40	26.00	29.26	20.77	28.21	26.73	30.34	21.49	31.11	16.38	29.18	21.71	36.38	18.81	31.21	20.73
		(6.99)	(18.33)	(11.84)	(8.35)	(14.05)	(16.01)	(12.56)	(8.50)	(17.90)	(5.68)	(15.78)	(22.58)	(26.28)	(6.75)	(20.08)	(13.68)
N2	F	46.73	36.75	37.27	30.62	53.21	38.87	38.11	30.08	48.10	25.63	36.80	29.18	56.67	30.85	37.45	23.21
		(19.23)	(9.42)	(13.63)	(8.88)	(34.81)	(10.61)	(17.48)	(8.80)	(20.29)	(6.47)	(14.31)	(26.79)	(34.01)	(14.56)	(18.68)	(7.92)
	C	44.65	35.95	37.87	30.29	47.69	37.36	37.10	30.75	51.26	23.67	40.51	28.01	57.72	27.32	40.42	22.58
		(14.45)	(9.77)	(10.80)	(7.46)	(23.22)	(9.95)	(11.55)	(9.96)	(26.26)	(4.54)	(18.23)	(26.15)	(35.98)	(7.96)	(20.08)	(6.18)
	O	39.03	31.88	42.45	29.60	44.40	33.92	43.30	29.05	44.68	19.65	41.67	27.79	53.56	21.18	42.16	21.34
		(13.41)	(12.19)	(20.67)	(7.66)	(22.54)	(16.60)	(20.58)	(10.54)	(25.76)	(6.54)	(25.94)	(28.57)	(40.93)	(6.16)	(28.93)	(9.20)
SWS	F	89.11	68.28	63.57	48.55	96.08	76.10	52.44	45.62	103.00	45.76	73.93	32.94	119.01	52.21	58.21	38.82
		(30.68)	(22.05)	(19.82)	(22.50)	(53.43)	(29.65)	(41.11)	(22.48)	(48.33)	(8.42)	(28.91)	(6.10)	(86.33)	(17.19)	(26.93)	(12.39)
	C	74.83	54.31	57.82	40.02	74.16	55.75	44.82	38.70	90.72	37.21	71.30	28.53	95.38	40.37	56.27	32.68
		(20.42)	(13.95)	(14.14)	(16.96)	(29.78)	(17.76)	(31.64)	(18.59)	(50.12)	(5.84)	(33.87)	(4.05)	(69.29)	(8.23)	(45.66)	(5.08)
	O	70.00	49.63	60.00	36.76	67.62	45.02	51.75	33.56	75.05	32.16	63.49	26.97	77.97	31.38	51.93	26.41
		(25.35)	(13.51)	(26.68)	(17.35)	(28.00)	(10.91)	(40.86)	(18.19)	(41.12)	(11.21)	(37.78)	(8.86)	(57.88)	(8.10)	(47.40)	(8.63)
REM	F	32.16	21.56	27.23	21.31	39.52	29.43	28.01	22.89	31.75	16.82	27.18	15.69	40.21	24.06	28.57	18.42
		(16.62)	(5.36)	(10.88)	(5.84)	(25.97)	(10.33)	(12.32)	(7.22)	(13.83)	(5.36)	(11.74)	(4.15)	(24.47)	(10.53)	(16.69)	(4.97)
	C	29.85	20.41	26.35	19.55	33.54	27.78	26.21	21.44	30.85	14.21	26.77	13.65	37.41	20.11	28.78	16.25
		(13.33)	(5.37)	(8.20)	(4.48)	(17.66)	(9.93)	(9.66)	(5.88)	(14.66)	(3.65)	(13.61)	(3.23)	(23.48)	(6.52)	(18.99)	(4.00)
	O	25.59	20.80	23.88	17.68	33.42	31.73	25.83	19.90	30.99	11.63	23.59	11.31	41.31	19.30	25.43	12.89
		(11.54)	(14.19)	(9.56)	(7.56)	(18.29)	(24.69)	(11.38)	(10.76)	(17.85)	(4.13)	(12.71)	(4.27)	(25.50)	(9.00)	(15.02)	(3.49)

Table 6.11

Means ($\pm$ standard deviations) for delta spectral power (microvolts squared; μV^2) during stage N1 sleep (N1), stage N2 sleep (N2), stage N3/slow wave sleep (SWS), and rapid eye movement (REM) sleep, at frontal (F), central (C), and occipital (O) electrode sites, in heavy- and light-drinking females and males after alcohol or placebo in the first and second halves of the sleep period.

Stage	Site	Heavy drinkers								Light drinkers							
		Placebo				Alcohol				Placebo				Alcohol			
		1 st Half		2 nd Half		1 st Half		2 nd Half		1 st Half		2 nd Half		1 st Half		2 nd Half	
		Female	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female	Male
N1	F	199.61 (100.99)	158.57 (68.23)	185.15 (93.29)	182.04 (99.19)	149.77 (91.40)	192.13 (249.55)	140.98 (56.34)	128.15 (66.05)	180.40 (60.21)	164.81 (46.48)	194.19 (140.79)	221.57 (312.72)	197.78 (77.27)	248.03 (188.99)	153.60 (68.98)	256.57 (243.49)
	C	229.09 (258.58)	119.21 (52.47)	166.93 (75.43)	151.72 (83.25)	129.09 (78.90)	180.66 (221.95)	139.89 (68.62)	126.17 (75.67)	162.15 (94.15)	137.91 (39.01)	265.58 (440.33)	227.68 (311.66)	159.04 (72.59)	138.30 (138.31)	150.62 (71.58)	242.17 (253.98)
	O	150.45 (76.50)	348.02 (599.19)	304.14 (187.34)	199.94 (132.39)	151.88 (109.47)	185.18 (209.52)	241.28 (226.78)	138.43 (70.87)	156.28 (80.50)	281.77 (364.48)	320.50 (418.97)	266.24 (341.92)	209.46 (129.09)	395.99 (715.47)	166.33 (97.75)	335.59 (362.90)
N2	F	535.64 (244.93)	455.16 (178.73)	468.42 (255.88)	378.34 (150.66)	496.27 (264.30)	359.08 (128.09)	430.25 (200.10)	350.95 (141.11)	450.47 (102.50)	338.63 (93.78)	349.45 (127.69)	301.43 (205.80)	427.45 (126.31)	301.73 (77.88)	348.26 (97.62)	251.06 (103.17)
	C	368.32 (149.81)	291.73 (75.94)	358.49 (168.35)	281.58 (84.76)	344.51 (152.29)	253.44 (62.54)	325.25 (134.79)	262.50 (77.44)	316.00 (78.57)	230.89 (79.20)	279.83 (102.49)	247.18 (198.97)	298.54 (86.67)	220.06 (44.69)	266.17 (73.91)	194.85 (65.10)
	O	194.49 (71.64)	152.70 (45.19)	205.52 (111.41)	153.71 (54.30)	221.91 (101.10)	145.07 (34.77)	213.70 (123.82)	137.75 (38.81)	184.55 (86.44)	123.34 (32.44)	175.71 (93.18)	171.41 (204.50)	213.20 (109.46)	122.46 (38.20)	188.03 (99.99)	112.14 (44.67)
SWS	F	2324.12 (1201.24)	1672.16 (696.82)	1314.89 (654.33)	1015.98 (414.54)	2473.29 (1416.19)	1849.75 (687.09)	1073.64 (843.11)	962.48 (420.86)	2265.75 (735.51)	1168.02 (354.99)	1195.19 (302.36)	688.69 (130.14)	2345.31 (935.51)	1379.23 (468.57)	940.03 (602.89)	1065.18 (611.88)
	C	1739.66 (735.83)	1224.10 (323.95)	1103.43 (508.43)	819.34 (349.21)	1927.47 (842.24)	1470.14 (384.19)	856.72 (628.85)	748.30 (360.54)	1769.44 (738.16)	901.12 (315.10)	1014.26 (302.77)	571.85 (107.37)	1862.28 (918.70)	1096.59 (305.12)	748.22 (514.60)	855.46 (418.13)
	O	1043.12 (391.85)	795.05 (272.00)	691.37 (408.91)	500.57 (301.14)	1346.06 (527.35)	886.71 (240.14)	568.72 (450.96)	395.10 (231.03)	1113.69 (514.68)	563.95 (201.51)	672.94 (345.28)	351.82 (111.56)	1205.17 (715.25)	663.54 (162.09)	497.61 (417.18)	489.87 (223.11)
REM	F	132.76 (67.80)	104.84 (25.24)	125.53 (62.12)	97.33 (23.09)	150.84 (97.73)	111.04 (33.60)	123.53 (64.45)	105.19 (30.14)	139.27 (42.15)	80.83 (28.35)	132.59 (44.93)	73.49 (18.60)	180.40 (165.39)	94.14 (29.41)	135.29 (39.34)	79.24 (21.91)
	C	113.50 (50.91)	81.37 (13.20)	98.81 (35.17)	74.59 (14.56)	122.47 (68.42)	97.32 (32.64)	98.35 (47.59)	79.27 (18.24)	112.17 (32.98)	64.59 (22.87)	98.35 (37.21)	55.29 (14.81)	150.50 (130.09)	78.91 (19.28)	99.22 (32.37)	60.01 (17.01)
	O	128.37 (82.16)	83.27 (27.87)	109.91 (60.66)	73.16 (23.34)	165.31 (95.12)	123.77 (47.64)	114.16 (61.93)	79.89 (32.52)	123.67 (72.38)	63.49 (23.04)	108.63 (78.08)	54.35 (17.73)	203.89 (141.62)	84.93 (36.04)	107.34 (63.45)	58.13 (26.10)

Figure 6.8. Means ($\pm$ standard errors) for beta spectral power (microvolts squared; μV^2) in stage N1 sleep (N1), stage N2 sleep (N2), stage N3/slow wave sleep (SWS), rapid eye movement sleep (REM) for heavy-drinking (HD) and light-drinking (LD) females (F) and males (M), after alcohol (black bars) and placebo (white bars) in the first (left panes) and second (right panes) halves of the sleep period at frontal (top panes), central (middle panes), and occipital (bottom panes) electrode sites.

□ Placebo ■ Alcohol

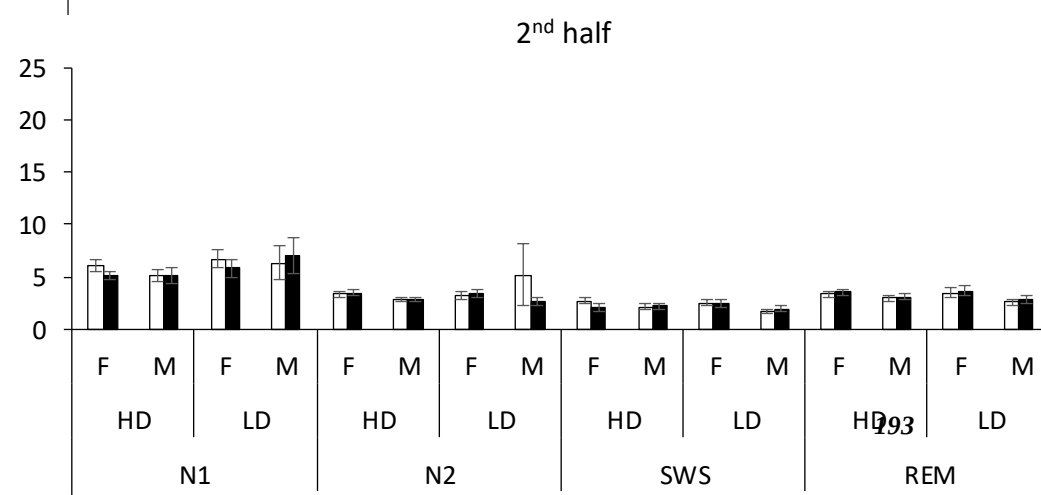
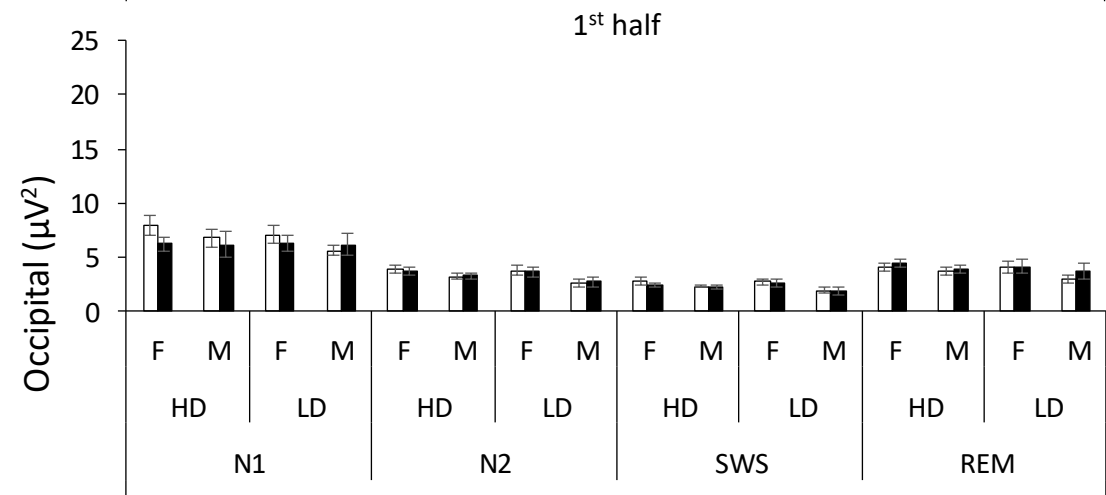
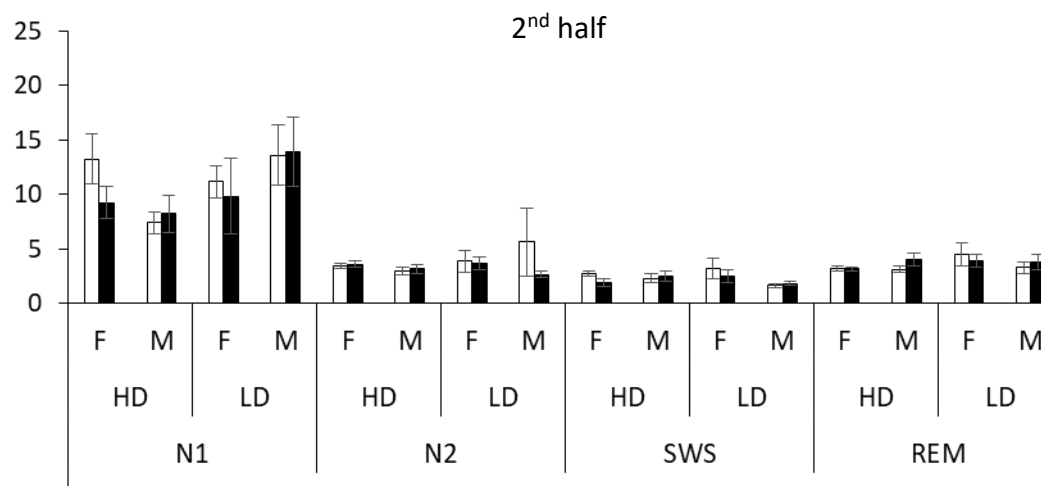
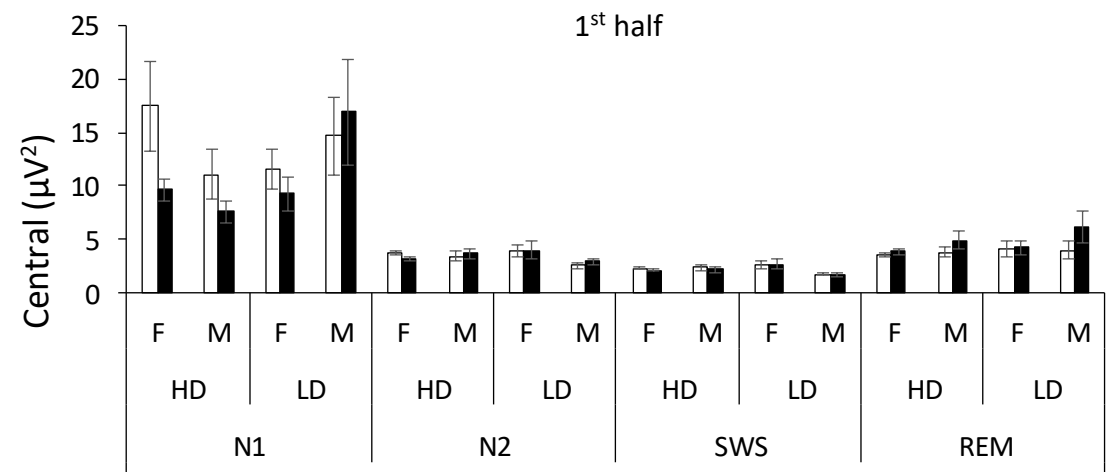
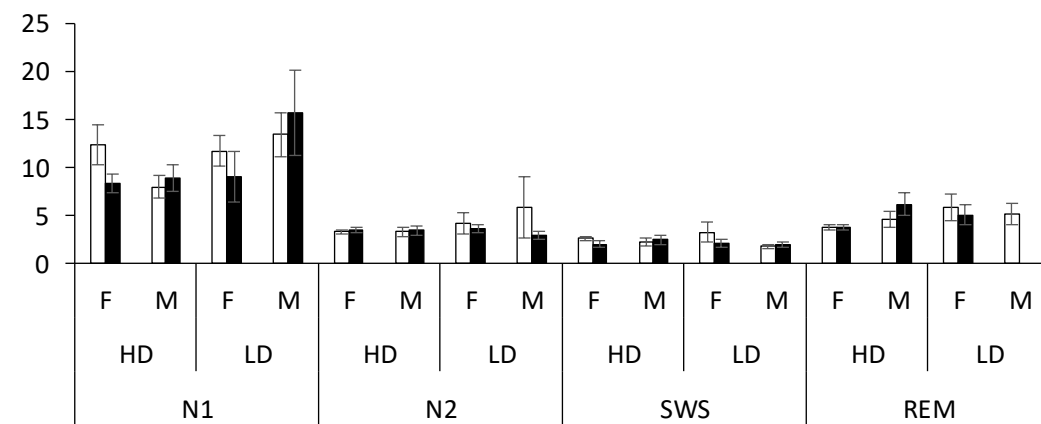
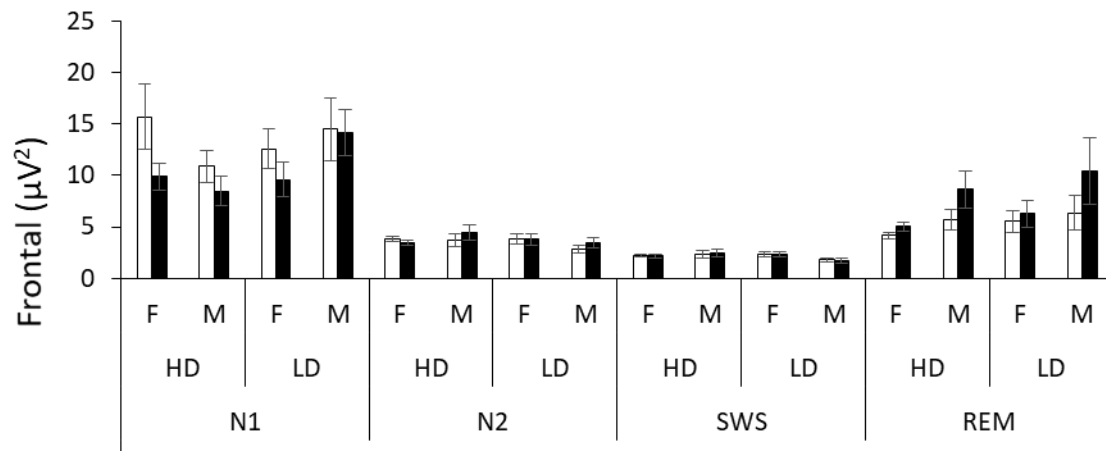


Figure 6.9. Means ($\pm$ standard errors) for alpha spectral power (microvolts squared; μV^2) in stage N1 sleep (N1), stage N2 sleep (N2), stage N3/slow wave sleep (SWS), rapid eye movement sleep (REM) for heavy-drinking (HD) and light-drinking (LD) females (F) and males (M), after alcohol (black bars) and placebo (white bars) in the first (left panes) and second (right panes) halves of the sleep period at frontal (top panes), central (middle panes), and occipital (bottom panes) electrode sites.

□ Placebo ■ Alcohol

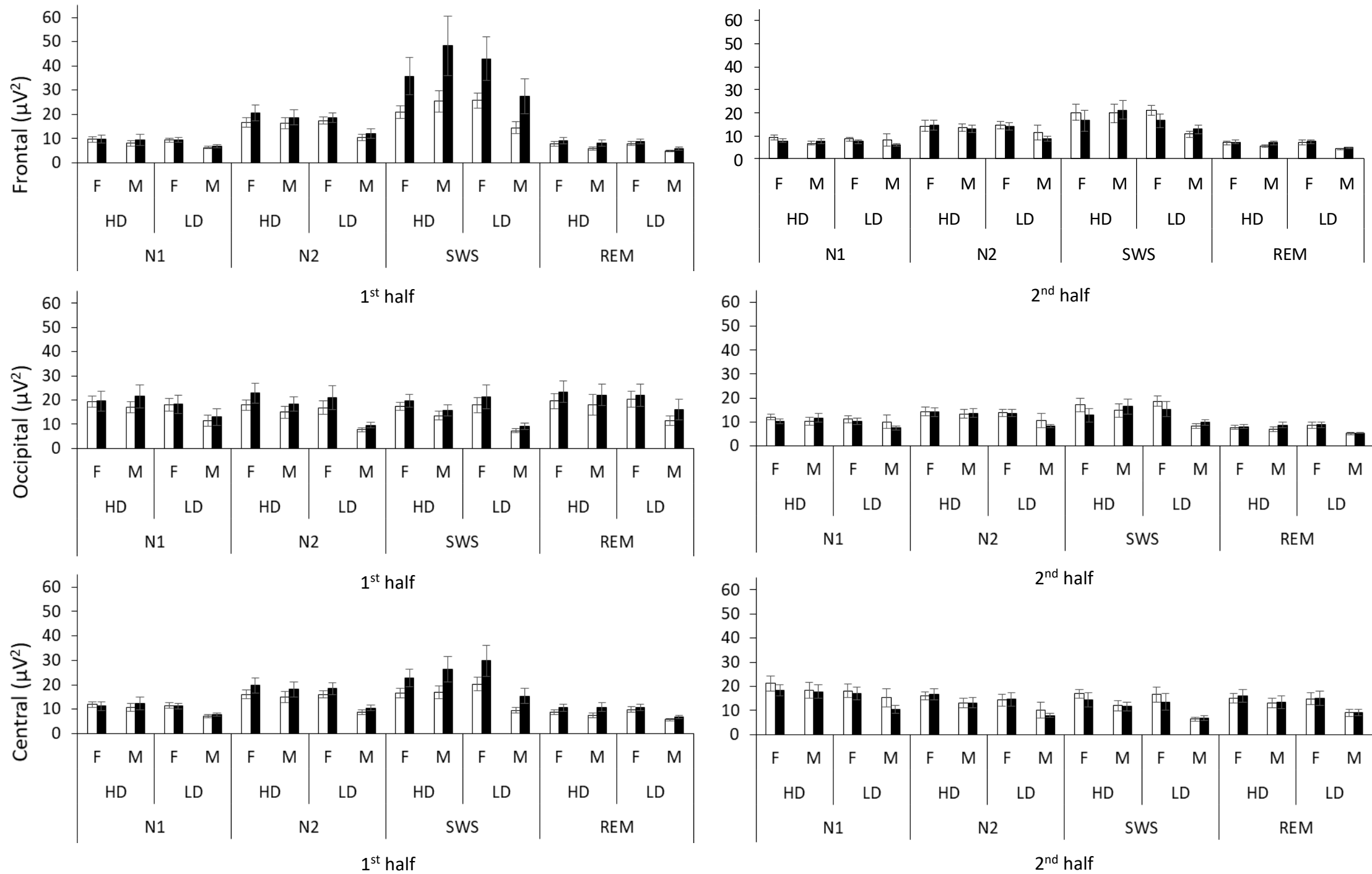


Figure 6.10. Means ($\pm$ standard errors) for sigma spectral power (microvolts squared; μV^2) in stage N1 sleep (N1), stage N2 sleep (N2), stage N3/slow wave sleep (SWS), rapid eye movement sleep (REM) for heavy-drinking (HD) and light-drinking (LD) females (F) and males (M), after alcohol (black bars) and placebo (white bars) in the first (left panes) and second (right panes) halves of the sleep period at frontal (top panes), central (middle panes), and occipital (bottom panes) electrode sites.

□ Placebo ■ Alcohol

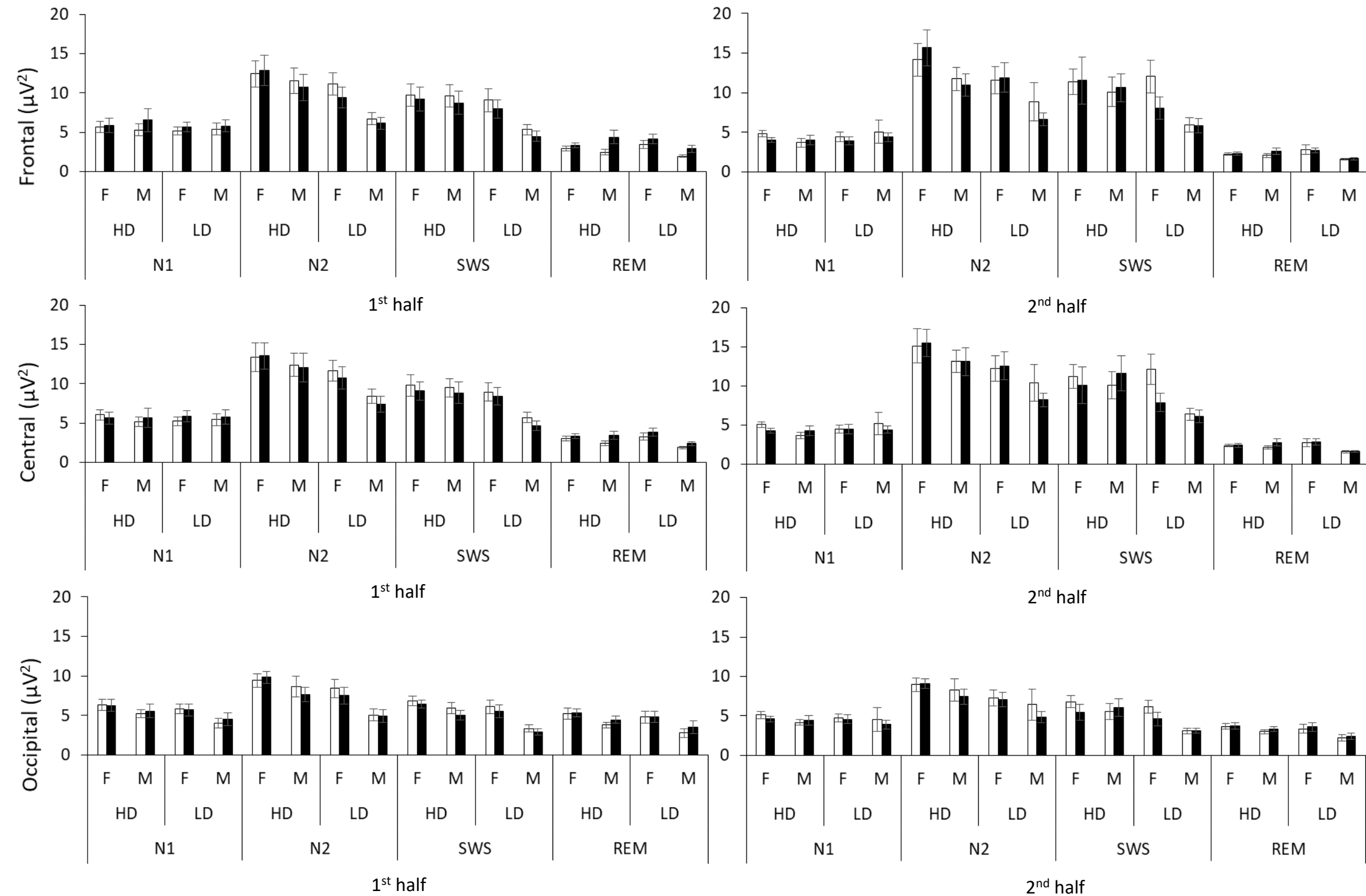


Figure 6.11. Means ($\pm$ standard errors) for theta spectral power (microvolts squared; μV^2) in stage N1 sleep (N1), stage N2 sleep (N2), stage N3/slow wave sleep (SWS), rapid eye movement sleep (REM) for heavy-drinking (HD) and light-drinking (LD) females (F) and males (M), after alcohol (black bars) and placebo (white bars) in the first (left panes) and second (right panes) halves of the sleep period at frontal (top panes), central (middle panes), and occipital (bottom panes) electrode sites.

□ Placebo ■ Alcohol

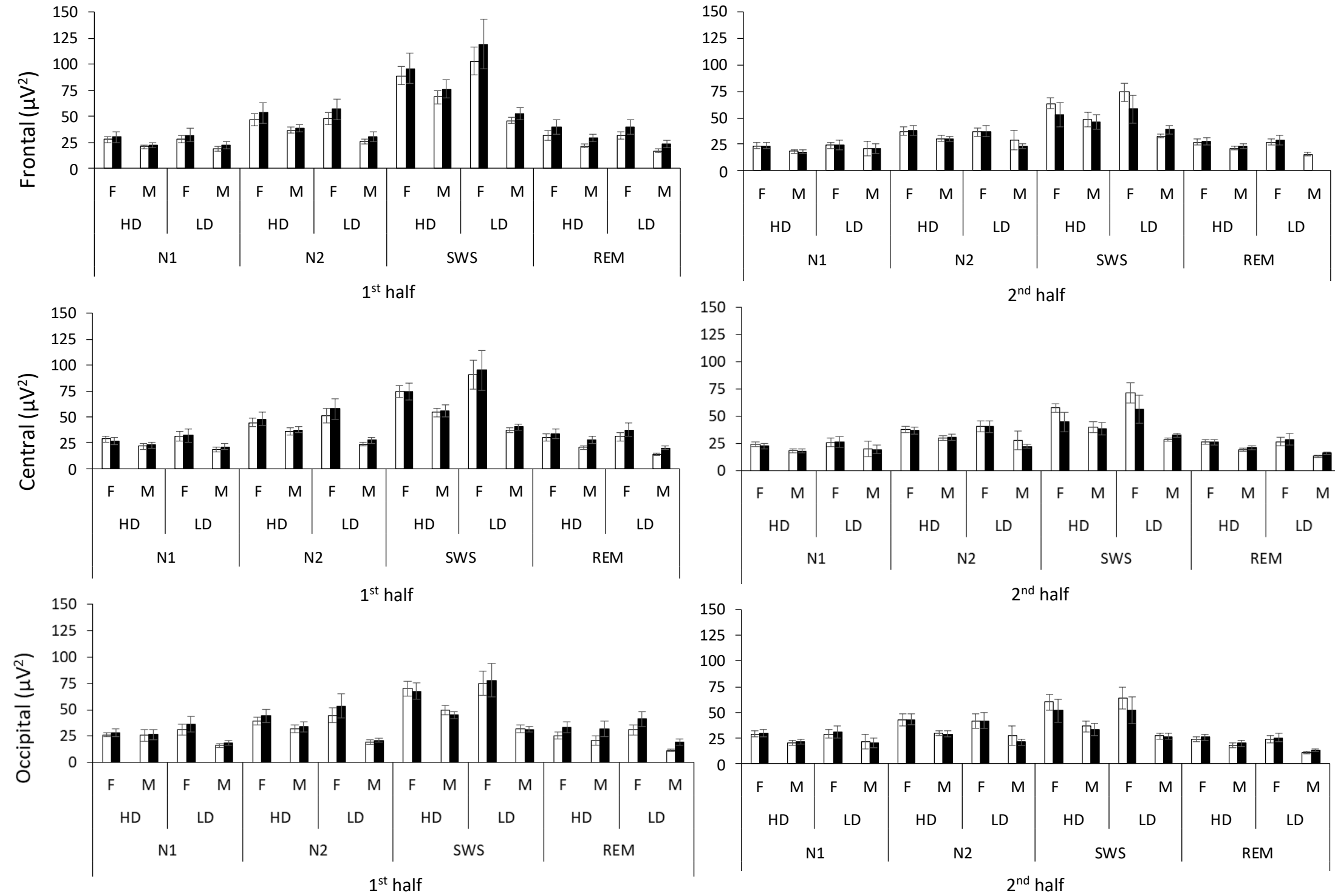
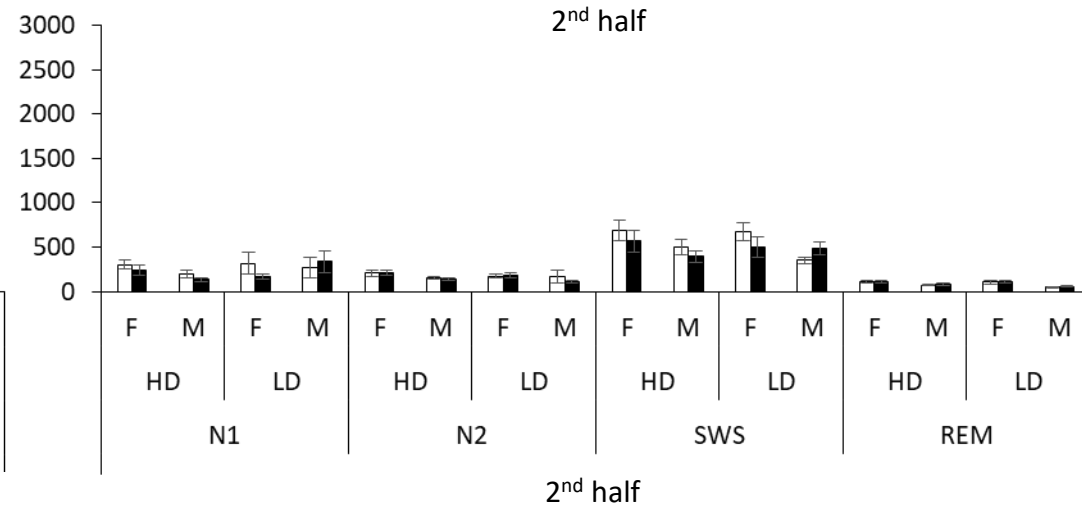
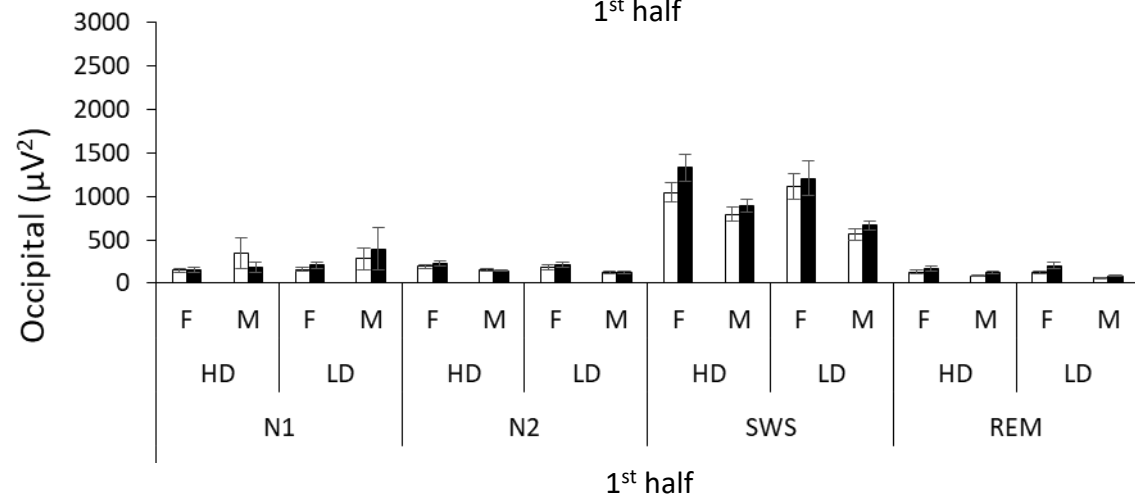
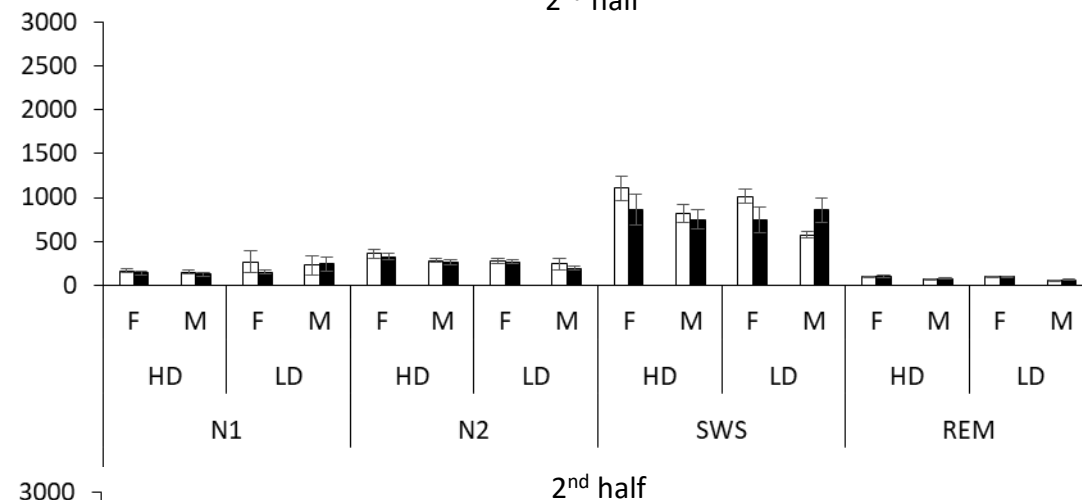
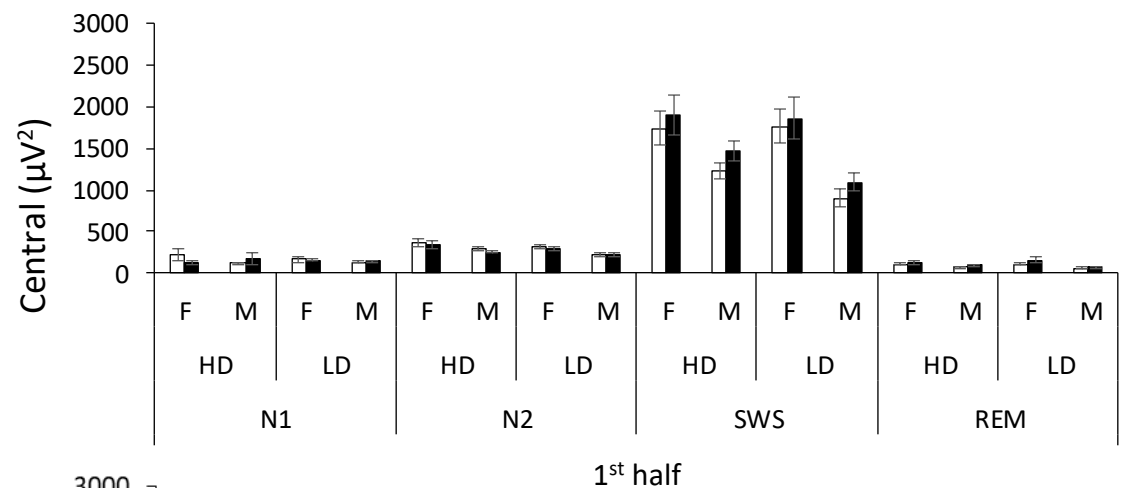
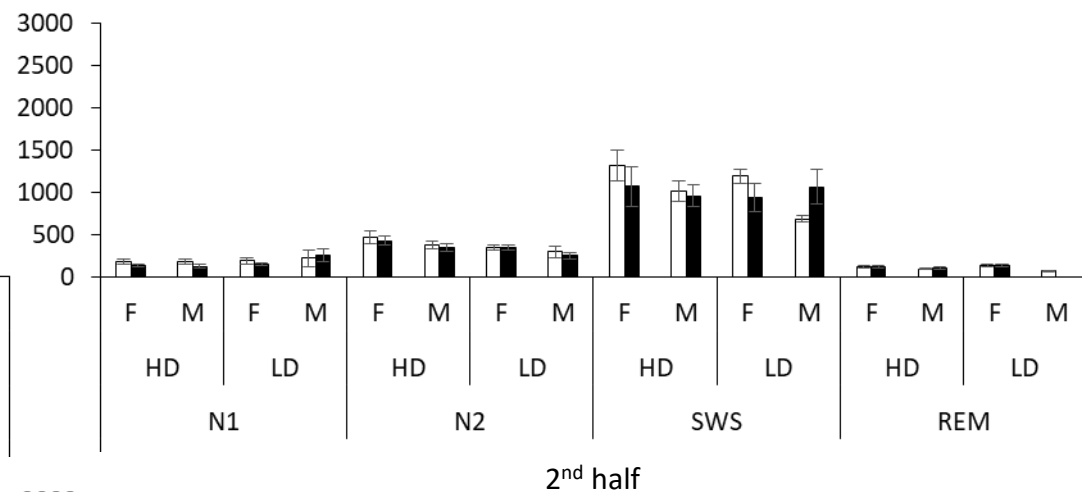
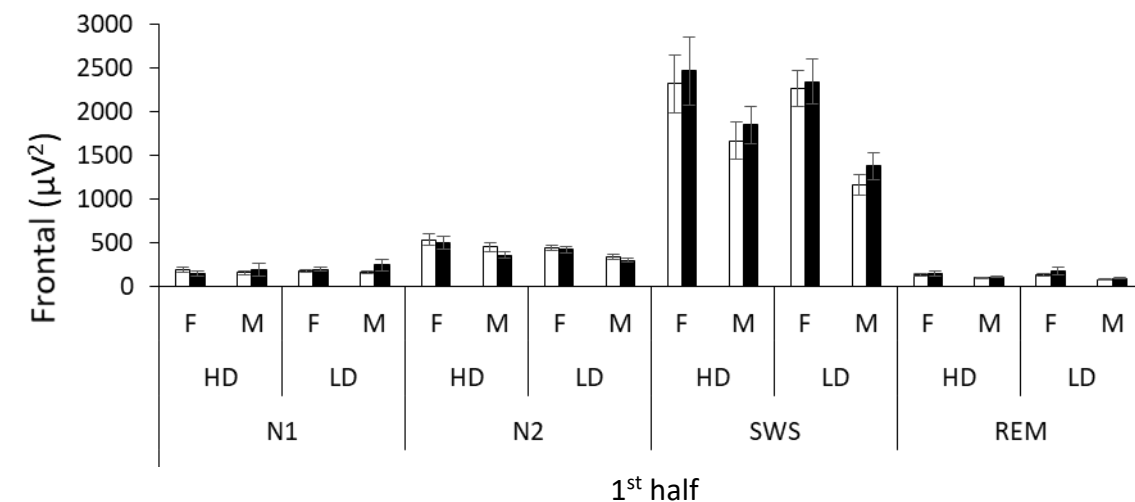


Figure 6.12. Means ($\pm$ standard errors) for delta spectral power (microvolts squared; μV^2) in stage N1 sleep (N1), stage N2 sleep (N2), stage N3/slow wave sleep (SWS), rapid eye movement sleep (REM) for heavy-drinking (HD) and light-drinking (LD) females (F) and males (M), after alcohol (black bars) and placebo (white bars) in the first (left panes) and second (right panes) halves of the sleep period at frontal (top panes), central (middle panes), and occipital (bottom panes) electrode sites

□ Placebo ■ Alcohol



6.3.1 Acute alcohol effects on sleep EEG power spectra

In stage N1 sleep, there was a main effect of acute condition (alcohol vs. placebo) for beta spectral power, $F(1, 42)=4.71$, $p=.036$, $\eta_p^2=.10$, $\beta=.56$. Beta power during stage N1 sleep was lower following alcohol consumption than placebo. (See Table 6.7 and Figure 6.8.) Acute pre-sleep alcohol consumption also had an effect on alpha spectral power in stage N1 sleep. In stage N1 sleep, there was an interaction between acute condition and half night, $F(1, 42)=7.77$, $p=.008$, $\eta_p^2=.16$, $\beta=.77$, that was driven by a three-way interaction between condition, half night and electrode site, $F(1, 42)=5.68$, $p=.017$, $\eta_p^2=.12$, $\beta=.69$, for alpha power during stage N1 sleep. At frontal electrode sites, in stage N1 sleep, alpha power was lower in the second half of the sleep period compared to the first half following alcohol consumption, $t(45)=3.31$, $p=.002$, $d=0.40$, but not placebo, $t(45)=0.43$, $p=.672$, $d=0.07$. Further, no half night differences were observed at central [alcohol: $t(45)=1.56$, $p=.127$, $d=0.16$, placebo: $t(45)=0.57$, $p=.574$, $d=0.07$] or occipital electrode sites [alcohol: $t(45)=1.87$, $p=.067$, $d=0.19$, placebo: $t(45)=1.94$, $p=.059$, $d=0.11$]. (See Table 6.8 and Figure 6.9.) There were no other main or interaction effects in stage N1 sleep for EEG power spectra. (See Appendix E.)

In stage N2 sleep, there was a main effect of acute condition for alpha spectral power, whereby power was higher overall in the alcohol condition than in the placebo condition, $F(1, 42)=4.20$, $p=.047$, $\eta_p^2=.09$, $\beta=.52$. There was also an interaction between acute condition and half night for alpha power during stage N2 sleep, which did not drive the main effect, $F(1, 42)=16.49$, $p<.001$, $\eta_p^2=.28$, $\beta=.98$. In the first half of the sleep period, in stage N2 sleep, alpha power was higher following alcohol consumption than following placebo [frontal: $t(45)=3.63$, $p=.001$, $d=0.29$, central: $t(45)=4.43$, $p<.001$, $d=0.34$, occipital: $t(45)=3.38$, $p=.002$, $d=0.33$].

There were no differences in alpha power between acute conditions in the second half of the sleep period in stage N2 sleep [frontal: $t(45)=1.32$, $p=.195$, $d=0.13$, central: $t(45)=0.69$, $p=.493$, $d=0.07$, occipital: $t(45)=0.18$, $p=.856$, $d=0.02$]. (See Table 6.8 and Figure 6.9.) There was also an interaction between half night and acute condition for theta spectral power during stage N2 sleep, $F(1, 42)=7.50$, $p=.009$, $\eta_p^2=.15$, $\beta=.76$. Theta power was higher during stage N2 sleep following alcohol consumption compared to placebo, in the first half of the sleep period [frontal: $t(45)=2.52$, $p=.016$, $d=0.25$, central: $t(45)=2.06$, $p=.045$, $d=0.17$, occipital: $t(45)=1.93$, $p=.061$, $d=0.20$]. However, there were no differences between conditions in the second half of the sleep period [frontal: $t(45)=0.52$, $p=.606$, $d=0.06$, central: $t(45)=0.73$, $p=.467$, $d=0.08$, occipital: $t(45)=0.48$, $p=.632$, $d=0.05$]. (See Table 6.10 and Figure 6.11.)

During stage N2 sleep, there was a main effect of acute condition on delta spectral power, whereby delta power was lower overall following alcohol consumption than placebo, $F(1, 42)=4.84$, $p=.033$, $\eta_p^2=.10$, $\beta=.58$. This main effect was not driven by the proceeding interactions. There was an interaction between acute condition and electrode site for delta power during stage N2 sleep, $F(1, 42)=6.26$, $p=.004$, $\eta_p^2=.13$, $\beta=.86$, which was driven by an interaction between condition, half night and electrode site, $F(1, 42)=6.93$, $p=.006$, $\eta_p^2=.14$, $\beta=.81$. Following alcohol consumption, delta power in stage N2 sleep was lower in the second half of the sleep period compared to the first half, at all three electrode sites [frontal: $t(45)=3.72$, $p=.001$, $d=0.32$, central: $t(45)=2.14$, $p=.038$, $d=0.10$, occipital: $t(45)=2.06$, $p=.045$, $d=0.14$], whereas following placebo consumption, half night differences in delta power were observed at frontal sites only [frontal: $t(45)=4.53$, $p<.001$, $d=0.39$, central: $t(45)=0.89$, $p=.385$, $d=0.17$, occipital: $t(45)=0.74$, $p=.463$,

$d=0.11$]. Interestingly, the interaction also indicated that in the first half of the sleep period, delta power during stage N2 sleep was higher in the placebo condition than the alcohol condition at frontal [$t(45)=2.54, p=.014, d=0.27$] and central [$t(45)=2.26, p=.029, d=0.21$] electrode sites, but not occipital [$t(45)=1.82, p=.076, d=0.17$], whereas in the second half of the sleep period delta power was higher in the placebo condition at central sites only [frontal: $t(45)=1.49, p=.143, d=0.16$, central: $t(45)=2.03, p=.048, d=0.23$, occipital: $t(45)=0.76, p=.451, d=0.09$]. (See Table 6.11 and Figure 6.12.) There were no other main or interaction effects in stage N2 sleep for EEG power spectra. (See Appendix E.)

In SWS, there was a main effect of acute condition for alpha spectral power, whereby alpha power was higher in the alcohol condition than in the placebo condition, $F(1, 42)=11.35, p=.002, \eta_p^2=.21, \beta=.91$. For alpha power during SWS, there was also an interaction between condition and half night, $F(1, 42)=29.50, p<.001, \eta_p^2=.41, \beta>.99$, and an interaction between condition and electrode site, $F(1, 42)=21.06, p<.001, \eta_p^2=.33, \beta=.99$, which did not drive the main effect. These interactions were driven by a three-way interaction between condition, half night and electrode site, $F(1, 42)=33.64, p<.001, \eta_p^2=.46, \beta>.99$. In the first half of the sleep period, alpha power during SWS was higher following alcohol consumption than it was following placebo [frontal: $t(45)=5.36, p<.001, d=0.72$, central: $t(45)=5.12, p<.001, d=0.58$, occipital: $t(45)=2.70, p=.010, d=0.25$]. However, the magnitude of this difference was largest at frontal electrode sites, and smallest at occipital. No differences between acute conditions were observed for alpha power during SWS in the second half of the sleep period [frontal $t(45)=1.27, p=.209, d=0.14$, central: $t(45)=1.41, p=.166, d=0.15$, occipital: $t(45)=1.71, p=.095, d=0.18$]. (See Table 6.8 and Figure 6.9.)

For theta spectral power during SWS, there was an interaction between acute condition and half night, $F(1, 42)=8.48$, $p = .006$, $\eta_p^2 = .17$, $\beta = .81$, as well as an interaction between condition and electrode site, $F(1, 42)=3.87$, $p = .025$, $\eta_p^2 = .08$, $\beta = .67$. These effects were driven by a three-way interaction between condition, half night and electrode site for theta power during SWS, $F(1, 42)=15.20$, $p < .001$, $\eta_p^2 = .27$, $\beta = .99$. In the first half of the sleep period, theta power during SWS was higher following alcohol consumption compared to placebo at frontal electrode sites, $t(45)=2.36$, $p = .023$, $d=0.19$, but not at central, $t(45)=0.85$, $p = .398$, $d=0.05$, or occipital sites, $t(45)=0.35$, $p = .729$, $d=0.03$. In the second half of the sleep period, theta power during SWS was lower following alcohol consumption compared to the placebo at central electrode sites, $t(45)=2.23$, $p = .031$, $d=0.66$, but not at frontal, $t(45)=1.78$, $p = .082$, $d=0.23$, or occipital sites, $t(45)=1.69$, $p = .098$, $d=0.20$. (See Table 6.10 and Figure 6.11.) For delta spectral power, there was an interaction between acute condition and half night during SWS, $F(1, 42)=7.79$, $p = .008$, $\eta_p^2 = .16$, $\beta = .78$. In the first half of the sleep period, delta power during SWS was higher following alcohol consumption than it was following placebo [frontal: $t(45)=1.94$, $p = .030$, $d=0.13$, central: $t(45)=3.00$, $p = .004$, $d=0.23$, occipital: $t(45)=2.70$, $p = .010$, $d=0.29$], however, no differences between alcohol and placebo were observed in the second half of the sleep period [frontal: $t(45)=0.94$, $p = .354$, $d=0.14$, central: $t(45)=1.57$, $p = .123$, $d=0.24$, occipital: $t(45)=1.58$, $p = .120$, $d=0.24$]. (See Table 6.11 and Figure 6.12.) There were no other main or interaction effects in SWS for EEG power spectra. (See Appendix E.)

In REM sleep, there was a main effect of acute condition for beta spectral power, whereby overall beta power was higher in the alcohol condition than the placebo condition, $F(1, 42)=9.60$, $p = .003$, $\eta_p^2 = .19$, $\beta = .86$. This main effect was

not driven by the proceeding interactions. For beta power during REM sleep, there was an interaction between acute condition and half night, $F(1, 42)=20.20$, $p < .001$, $\eta_p^2 = .33$, $\beta = .99$, as well as an interaction between condition and electrode site, $F(1, 42)=6.31$, $p = .010$, $\eta_p^2 = .13$, $\beta = .77$. These interactions were driven by an interaction between condition, half night and electrode site, $F(1, 42)=20.49$, $p < .001$, $\eta_p^2 = .33$, $\beta > .99$. During REM sleep, in the first half of the sleep period, beta power was higher following alcohol consumption compared to placebo at all electrode sites [frontal: $t(45)=3.91$, $p < .001$, $d=0.40$, central: $t(45)=2.99$, $p = .005$, $d=0.35$, occipital: $t(45)=2.49$, $p = .016$, $d=0.21$], however, in the second half of the sleep period, beta power was higher following alcohol consumption compared to placebo at occipital electrode sites only [frontal: $t(45)=0.69$, $p = .497$, $d=0.45$, central: $t(45)=0.44$, $p = .663$, $d=0.07$, occipital: $t(45)=2.42$, $p = .020$, $d=0.08$]. (See Table 6.7 and Figure 6.8.)

In REM sleep, there was a main effect of acute condition for alpha spectral power, whereby overall alpha power was higher in the alcohol condition than the placebo condition, $F(1, 42)=10.28$, $p = .003$, $\eta_p^2 = .20$, $\beta = .88$. There was also an interaction between condition and half night for alpha power during REM sleep, $F(1, 42)=8.96$, $p = .005$, $\eta_p^2 = .18$, $\beta = .83$, which did not drive the main effect. This indicated that alpha power was higher following alcohol consumption compared to placebo in the first half of the sleep period during REM sleep [frontal: $t(45)=4.32$, $p < .001$, $d=0.44$, central: $t(45)=4.06$, $p < .001$, $d=0.42$, occipital: $t(45)=2.46$, $p = .018$, $d=0.26$].

However, no differences were observed in alpha power during REM sleep in the second half of the sleep period [frontal: $t(45)=1.81$, $p = .077$, $d=0.19$, central: $t(45)=1.88$, $p = .067$, $d=0.18$, occipital: $t(45)=0.73$, $p = .469$, $d=0.06$]. (See Table 6.8 and Figure 6.9.)

During REM sleep, there was a main effect of acute condition for sigma spectral power, $F(1, 42)=9.14$, $p=.004$, $\eta_p^2=.18$, $\beta=.84$. Sigma power was higher in the alcohol condition compared to the placebo condition in REM sleep. This effect did not appear to be driven by the proceeding interaction effects. There was an interaction between condition and half night, $F(1, 42)=23.40$, $p<.001$, $\eta_p^2=.36$, $\beta>.99$, which was driven by an interaction between condition, half night and electrode site, $F(1, 42)=10.67$, $p<.001$, $\eta_p^2=.20$, $\beta=.97$, for sigma power during REM sleep. In the first half of the sleep period, sigma power during REM sleep was higher following alcohol consumption than placebo at frontal, $t(45)=4.44$, $p<.001$, $d=0.56$, and central electrode sites, $t(45)=3.24$, $p=.002$, $d=0.43$, but not occipital sites, $t(45)=1.67$, $p=.102$, $d=0.16$, whereas there were no differences between conditions in the second half of the sleep period [frontal: $t(45)=0.63$, $p=.533$, $d=0.10$, central: $t(45)=1.09$, $p=.283$, $d=0.17$, occipital: $t(45)=1.78$, $p=.082$, $d=0.13$]. (See Table 6.9 and Figure 6.10.)

During REM sleep, there was a main effect of acute condition for theta spectral power, whereby theta power was higher in the alcohol condition than the placebo condition, $F(1, 42)=19.92$, $p<.001$, $\eta_p^2=.32$, $\beta=.99$. This effect was not driven by the following interactions. For theta power during REM sleep, there was an interaction between condition and half night, $F(1, 42)=34.26$, $p<.001$, $\eta_p^2=.45$, $\beta>.99$, which was driven by an interaction between condition, half night and electrode site, $F(1, 42)=5.61$, $p=.009$, $\eta_p^2=.12$, $\beta=.79$. In the first half of the sleep period, theta power during REM sleep was higher following alcohol consumption than placebo at all three electrode sites [frontal, $t(45)=5.07$, $p<.001$, $d=0.45$, central, $t(45)=4.53$, $p<.001$, $d=0.38$, occipital: $t(45)=5.02$, $p<.001$, $d=0.50$], whereas in the second half of the sleep period theta power was higher following alcohol

consumption at central electrode sites only [frontal: $t(45)=2.01$, $p=.050$, $d=0.14$, central: $t(45)=2.09$, $p=.043$, $d=0.13$, occipital: $t(45)=1.96$, $p=.056$, $d=0.17$]. (See Table 6.10 and Figure 6.11.)

In REM sleep, there was a main effect of acute condition for delta spectral power, whereby delta power was higher in the alcohol condition than in the placebo condition, $F(1, 42)=10.59$, $p=.002$, $\eta_p^2=.20$, $\beta=.89$. There was also an interaction between condition and half night for delta power during REM sleep, $F(1, 42)=7.36$, $p=.010$, $\eta_p^2=.15$, $\beta=.76$, which did not drive the main effect. In the first half of the sleep period, delta power during REM sleep was higher following alcohol consumption than placebo [frontal: $t(45)=1.63$, $p=.111$, $d=0.25$, central: $t(45)=2.10$, $p=.041$, $d=0.31$, occipital: $t(45)=5.84$, $p<.001$, $d=0.55$], whereas there were no differences between the alcohol and placebo condition in the second half of the sleep period [frontal: $t(45)=0.70$, $p=.489$, $d=0.07$, central: $t(45)=0.68$, $p=.500$, $d=0.06$, occipital: $t(45)=0.79$, $p=.432$, $d=0.06$]. There was also an additional interaction between acute condition and electrode site for delta power during REM sleep, $F(1, 42)=4.03$, $p=.042$, $\eta_p^2=.09$, $\beta=.55$. Following alcohol consumption, delta power during REM sleep was higher overall at occipital [first half: $t(45)=5.84$, $p<.001$, $d=0.55$, second half: $t(45)=0.79$, $p=.432$, $d=0.06$] and central [first half: $t(45)=2.10$, $p=.041$, $d=0.31$, second half: $t(45)=0.68$, $p=.500$, $d=0.06$] electrode sites compared to placebo, however there were no differences between conditions at frontal electrode sites [first half: $t(45)=1.63$, $p=.111$, $d=0.25$, second half: $t(45)=0.70$, $p=.489$, $d=0.07$]. (See Table 6.11 and Figure 6.12.) There were no other main or interaction effects in REM sleep for EEG power spectra. (See Appendix E.)

6.3.2 *Habitual alcohol effects on sleep EEG power spectra*

There was no main effect of habitual alcohol use on delta EEG spectral power during SWS, $F(1, 42)=1.15$, $p=.289$, $\eta_p^2=.03$, $\beta=.18$. (See Table 6.11 and Figure 6.12.) There was, however, a main effect of habitual alcohol use on sigma spectral power during SWS, $F(1, 42)=5.08$, $p=.029$, $\eta_p^2=.11$, $\beta=.60$. Overall, heavy drinkers had higher sigma power than light drinkers in SWS. (See Table 6.9 and Figure 6.10.) This effect was also observed in stage N2 sleep, $F(1, 42)=5.78$, $p=.021$, $\eta_p^2=.12$, $\beta=.65$. (See Table 6.9 and Figure 6.10.) There were no other main or interaction effects related to habitual alcohol use for EEG power spectra (Appendix F).

6.3.3 *Sex and alcohol interaction effects on sleep EEG power spectra*

6.3.3.1 *Acute alcohol effects and sex interactions*

There was a significant interaction between sex and acute alcohol consumption for beta spectral power during stage N1 sleep, $F(1, 42)=5.14$, $p=.029$, $\eta_p^2=.11$, $\beta=.60$. Females had less beta power following alcohol consumption than placebo during stage N1 sleep [first half - frontal: $t(25)=2.32$, $p=.029$, $d=0.57$, central: $t(25)=2.29$, $p=.031$, $d=0.57$, occipital: $t(25)=2.25$, $p=.034$, $d=0.43$; second half - frontal: $t(25)=2.03$, $p=.054$, $d=0.49$, central: $t(25)=1.28$, $p=.212$, $d=0.32$, occipital: $t(25)=1.41$, $p=.170$, $d=0.38$]. However, no differences between acute conditions for beta power were observed in males during stage N1 sleep [first half – frontal: $t(19)=0.72$, $p=.478$, $d=0.22$, central: $t(19)=0.35$, $p=.731$, $d=0.09$, occipital: $t(19)=0.20$, $p=.848$, $d=0.04$; second half – frontal: $t(19)=0.84$, $p=.399$, $d=0.19$, central: $t(19)=0.36$, $p=.720$, $d=0.08$, occipital: $t(19)=6.76$, $p=.508$, $d=0.06$]. (See Table 6.7 and Figure 6.8.) There were no other interactions between acute condition and sex during stage N1 sleep. (See Appendix G.)

For sigma spectral power in stage N2 sleep, there was a four-way interaction between sex, acute condition, half night and electrode site, $F(1, 42)=4.15$, $p=.030$, $\eta_p^2=.09$, $\beta=.63$. Firstly, females had higher sigma power overall than males during stage N2 sleep, although no main effect was observed, $F(1, 42)=3.95$, $p=.053$, $\eta_p^2=.09$, $\beta=.49$. Regardless of acute condition, females had higher sigma power in the second half of the sleep period, compared to the first half, though this effect diminished at occipital electrode sites. In males there were minimal half night differences in sigma spectral power in stage N2 sleep. Following alcohol consumption, males had lower sigma power on average in stage N2 sleep. Acute alcohol consumption prior to sleep appeared to have little impact on sigma power in females. (See Table 6.9 and Figure 6.10.) There were no other interactions between acute condition and sex during stage N2 sleep. (See Appendix G.)

In SWS, for theta spectral power there was an interaction between sex, acute condition and half night, $F(1, 42)=5.41$, $p=.025$, $\eta_p^2=.11$, $\beta=.62$. Firstly, in SWS there was a main effect of sex, whereby females had greater theta power than males, regardless of condition, in both the first and second half of the sleep period, $F(1, 42)=12.53$, $p=.001$, $\eta_p^2=.23$, $\beta=.93$. Additionally, for females, in the first half of the sleep period there were no differences in theta power during SWS following pre-sleep alcohol compared to placebo consumption [frontal: $t(25)=1.65$, $p=.111$, $d=0.20$, central: $t(25)=0.47$, $p=.641$, $d=0.04$, occipital: $t(25)=0.05$, $p=.960$, $d=0.01$], however, in the second half of the sleep period theta power was generally lower following alcohol consumption than placebo [frontal: $t(25)=2.05$, $p=.051$, $d=0.38$, central: $t(25)=2.65$, $p=.014$, $d=0.42$, occipital: $t(25)=1.62$, $p=.117$, $d=0.26$]. This pattern was reversed in males, where theta power during SWS was generally higher in the first half of the sleep period following alcohol consumption than placebo

[frontal: $t(19)=2.64$, $p= .016$, $d=0.30$, central: $t(19)=1.49$, $p= .151$, $d=0.15$, occipital: $t(19)=1.29$, $p= .210$, $d=0.21$], whereas in the second half of the sleep period there were no differences between conditions [frontal: $t(19)=0.37$, $p= .719$, $d=0.06$, central: $t(19)=0.48$, $p= .634$, $d=0.08$, occipital: $t(19)=0.53$, $p= .604$, $d=0.14$]. (See Table 6.10 and Figure 6.11.)

For delta spectral power during SWS, there was an interaction between sex, acute condition and electrode site, $F(1, 42)=6.16$, $p= .003$, $\eta_p^2= .13$, $\beta= .88$. Firstly, in SWS there was a main effect of sex for delta EEG spectral power, highlighting that females had higher overall delta power than males, regardless of condition, $F(1, 42)=9.08$, $p= .004$, $\eta_p^2= .18$, $\beta= .84$. Highlighting this, compared to males, females had higher delta power overall in the placebo condition during SWS at all electrode sites [first half – frontal: $t(44)=3.41$, $p= .001$, $d=1.04$, central: $t(44)=3.84$, $p< .001$, $d=1.19$, occipital: $t(44)=3.42$, $p= .001$, $d=1.05$; second half – frontal: $t(44)=2.92$, $p= .009$, $d=0.89$, central: $t(44)=3.23$, $p= .002$, $d=0.98$, occipital: $t(43.02)=2.74$, $p= .009$, $d=0.89$]. The magnitude of this sex difference appeared largest at frontal electrode sites, and smallest at occipital sites. In the alcohol condition, females still generally had higher overall delta power than males during SWS, however, the magnitude of the difference between males and females was notably smaller [first half – frontal: $t(44)=2.49$, $p= .017$, $d=0.77$, central: $t(36.30)=2.98$, $p= .005$, $d=0.85$, occipital: $t(33.11)=3.49$, $p= .001$, $d=0.98$; second half – frontal: $t(44)=0.01$, $p= .992$, $d=0.002$, central: $t(44)=0.04$, $p= .966$, $d=0.01$, occipital: $t(39.66)=0.97$, $p= .336$, $d=0.28$]. There were no other interactions between acute condition and sex during SWS. (See Appendix G.)

Finally, during REM sleep, there was an interaction between sex and acute condition for beta spectral power, $F(1, 42)=6.59$, $p= .014$, $\eta_p^2= .14$, $\beta= .71$. This was

driven by an interaction between sex, condition, and electrode site, $F(1, 42)=6.06$, $p=.012$, $\eta_p^2=.13$, $\beta=.74$. For males, beta power was higher following alcohol consumption compared to placebo, however, the magnitude of this difference was greatest at frontal electrode sites and smallest at occipital [first half – frontal: $t(19)=3.69$, $p=.002$, $d=0.22$, central: $t(19)=3.49$, $p=.002$, $d=0.56$, occipital: $t(19)=2.32$, $p=.032$, $d=0.33$; second half – frontal: $t(19)=2.65$, $p=.016$, $d=0.33$, central: $t(19)=3.30$, $p=.004$, $d=0.43$, occipital: $t(19)=2.47$, $p=.023$, $d=0.26$]. For females, there were no differences between acute conditions [first half – frontal: $t(25)=1.98$, $p=.059$, $d=0.25$, central: $t(25)=0.78$, $p=.441$, $d=0.13$, occipital: $t(25)=1.25$, $p=.255$, $d=0.13$; second half – frontal: $t(25)=0.75$, $p=.463$, $d=0.13$, central: $t(25)=0.65$, $p=.520$, $d=0.14$, occipital: $t(25)=1.42$, $p=.169$, $d=0.13$]. (See Table 6.7 and Figure 6.8.) There were no other interactions between acute condition and sex during REM sleep. (See Appendix G.)

6.3.3.2 Habitual alcohol effects and sex interactions

During stage N1 sleep, there was a three-way interaction between sex, habitual alcohol use and electrode site for beta spectral power, $F(1, 42)=4.71$, $p=.013$, $\eta_p^2=.10$, $\beta=.76$. On average, heavy-drinking males had less beta spectral power in stage N1 sleep than light-drinking males at frontal and central electrode sites, however there were minimal differences at occipital sites. There were no differences between heavy- and light-drinking females in beta power during stage N1 sleep at any electrode site. (See Table 6.7 and Figure 6.8.)

For theta spectral power, there was a four-way interaction between sex, habitual alcohol use, half night, and electrode site during stage N1 sleep, $F(1, 42)=5.22$, $p=.017$, $\eta_p^2=.11$, $\beta=.70$, and REM sleep, $F(1, 42)=5.87$, $p=.012$, $\eta_p^2=.12$, $\beta=.74$. These interactions suggested that heavy-drinking males had higher theta

spectral power in both stage N1 and REM sleep, than light-drinking males in the first half of the sleep period, although these differences were most notable at occipital electrode sites. These effects were no longer apparent in the second half of the sleep period. There were no notable differences in theta spectral power between heavy and light-drinking females in stage N1 or REM sleep. (See Table 6.10 and Figure 6.11.) There were no other interaction effects for sex and habitual alcohol use for EEG power spectra. (See Appendix H.)

CHAPTER 7

Discussion

The current study found that in the first half of the sleep period following acute alcohol consumption, both heavy- and light-drinking late adolescents had fewer arousals, less stage N1 sleep, more SWS, longer REM sleep onset latencies, and less REM sleep, compared to placebo consumption. These findings were in support of the hypothesis that predicted sedation in the first half of the sleep period following acute alcohol consumption. However, contrary to this prediction, no differences between the alcohol and placebo conditions were reported for SWS onset latency, wake after sleep onset, or sleep efficiency in the first half of the sleep period. There were also no differences in sleep onset latency between the alcohol and placebo conditions. As predicted, in the first half of the sleep period there was higher alpha and delta EEG spectral power following alcohol consumption in SWS and REM sleep, compared to placebo. Unexpectedly, while alpha power was higher, delta power was lower in stage N2 sleep following pre-sleep alcohol. In the second half of the sleep period, there were more arousals, more wake after sleep onset, lower sleep efficiency, more stage N1 sleep, and less SWS, following acute alcohol consumption compared to placebo, in both heavy- and light-drinking late adolescents. These findings were in support of the hypothesis that acute alcohol consumption before sleep would result in major sleep disruption in the second half of the sleep period. In contrast to the predictions, there were no differences in alpha or delta spectral power in the second half of the sleep period between the alcohol and placebo conditions.

Higher levels of alcohol consumption in the previous 30 days and across the lifetime, and greater number of years drinking, were associated with more wake after sleep onset, and lower sleep efficiency, in the placebo condition. This was consistent with the prediction that heavy drinkers would experience worse sleep quality than same-aged light drinkers. Somewhat surprisingly, there were no overall differences

in sleep onset latency, number of arousals, wake after sleep onset, or sleep efficiency between heavy- and light-drinking young adults. In the placebo condition, as predicted, heavy drinkers had less all-night visually scored SWS, and more stage N2 sleep, than same-aged light drinkers. Providing further support, higher levels of alcohol consumption in the previous 30 days was associated, albeit weakly, with lower SWS percentage in the placebo condition. Furthermore, higher levels of alcohol consumption in the previous 30 days were moderately associated with higher stage N2 sleep percentage in the placebo condition. As anticipated, heavy-drinking late adolescents had shorter REM sleep onset latencies, compared to same-aged light drinkers, irrespective of experimental condition. Although there were no differences in total REM sleep percentage between heavy and light drinkers, there were disparities in the distribution of REM sleep across the sleep period. Specifically, heavy drinkers had less REM sleep percentage in the second half of the sleep period compared to light drinkers, in both conditions. Heavy-drinking late adolescents did not have lower delta EEG spectral power in SWS, or any other sleep stage, compared to same-aged light drinkers. This finding was not in support of the hypothesis that heavy drinkers would demonstrate a reduced ability to synchronise and produce delta EEG activity during sleep. Although it was not predicted, the current study showed that heavy-drinking late adolescents had higher sigma EEG spectral power in stage N2 sleep and SWS, than same-aged light drinkers, regardless of experimental condition.

Finally, there was an unpredicted interaction between sex, acute alcohol use, and habitual alcohol use, for all-night SWS percentage. This interaction showed that heavy-drinking females had less all-night SWS following acute alcohol consumption, compared to placebo. In contrast, compared to the placebo condition, heavy-drinking

males had more total SWS in the alcohol condition. There were no overall differences in SWS percentage between the alcohol and placebo condition for light-drinking males or females. This finding suggests that acute and habitual alcohol use may interact with sex to impact SWS.

Taken together, the findings of the current study demonstrated that acute alcohol consumption prior to sleep results in substantial sleep disturbance in both heavy- and light-drinking late adolescents. These findings were largely consistent with the limited literature available in this age group, and distinct to previous findings reported in adults, suggesting that acute alcohol use may impact sleep uniquely in young people. The current investigation also revealed that, despite their relatively short drinking histories, heavy-drinking late adolescents experience disturbances to normal sleep, irrespective of pre-sleep alcohol consumption. Although there were some similarities between the current findings and those presented in the adult literature, the results reported emphasise the importance of investigations in this developmentally distinct, and largely understudied, age group.

7.1 Acute effects of alcohol on sleep in young people

The findings of the current investigation largely replicated those reported in the late adolescent literature (Chan et al., 2015; Chan et al., 2013; Williams et al., 1983). Firstly, research has consistently reported that, as seen in mature adults, pre-sleep alcohol consumption in late adolescence leads to sedation in the first half of the sleep period when BAC is highest. Consistent with the current findings, previous research has reported fewer arousals, less stage N1 sleep, and longer REM sleep onset latencies (Chan et al., 2013); less REM sleep, and more SWS (Chan et al., 2013; Williams et al., 1983); and more delta EEG spectral power (Chan et al., 2015).

The current study also reported lower beta power in stage N1 sleep; higher theta power in stage N2 sleep, SWS, and REM sleep; and higher delta power during SWS and REM sleep, in the first half of the sleep period, providing further evidence of sedation following pre-sleep alcohol consumption. These findings are unique to the current study as it is presently the only investigation in this age group to examine the impacts of acute alcohol consumption on EEG spectral power within each individual sleep stage. Taken together, these findings provide evidence that acute alcohol consumption prior to sleep leads to elevated measures of sedation in late adolescents, similar to those observed in the adult literature.

Although the precise mechanism is unknown, the initial sedative effects of acute alcohol consumption are most likely the result of alcohol's pharmacological facilitation of inhibitory neurotransmitter systems, and suppression of excitatory systems (Chastain, 2006; Feige et al., 2006; Harrison et al., 2017; Roehrs & Roth, 2001a; Sommer & Spanagel, 2013; Svanberg & Beaunieux, 2015). It is well established that inhibitory GABAergic neurotransmission facilitates sleep onset and continuity, in particular SWS and delta EEG activity (Chastain, 2006; Feld et al., 2013; Harrison et al., 2017; Saper, Scammell, & Lu, 2005; Sommer & Spanagel, 2013; Svanberg & Beaunieux, 2015; Walsh, 2009). Further to this, excitatory glutaminergic neurotransmission promotes wakefulness, as well as REM sleep onset and continuation (Datta et al., 2001; Gonzales & Jaworski, 1997; Knowles et al., 1968; Kodama, Lai, & Siegel, 1998). GABAergic enhancement, and glutaminergic suppression, following acute alcohol consumption, may explain findings of objective sleep promotion in the first half of the sleep period when BAC would be highest, reported in the current study and in the general literature (Chan et al., 2015; Chan, 2013; Roehrs & Roth, 2001a; Williams et al., 1983). A circadian delay, or inhibited

melatonin release, following pre-sleep alcohol consumption may also contribute to these sedative effects, particularly the postponement of REM sleep timing (Prat et al., 2009; Rupp et al., 2007).

It is worth noting some differences between the late adolescent and adult literature regarding alcohol's acute sedative effects. Consistent with the current findings, research in this age group suggests that human adolescents may experience less sedation following pre-sleep alcohol consumption, compared to mature adults (Chan et al., 2013; Williams et al., 1983). Firstly, both the current study and Chan and colleagues (2013) reported an absence of changes in sleep onset latency, wake after sleep onset, and sleep efficiency in the first half of the sleep period in late adolescents aged 18 to 21 years. It is worth noting that Williams and colleagues (1983) did not compare the first and second half of the sleep period for wake after sleep onset or sleep efficiency in their study. However, all studies in this age group have reported an absence of changes in SWS onset latency following pre-sleep alcohol consumption (Chan et al., 2013; Williams et al., 1983). Uniquely, the current study identified lower delta power in stage N2 sleep following acute alcohol consumption in late adolescents. These findings are in contrast to robust reports in the adult literature of global sedation following acute alcohol consumption, including longer sleep onset latency, shorter SWS onset latency, less wake after sleep onset, higher sleep efficiency, and augmented non-REM delta EEG spectral power (Arnedt et al., 2011; Dijk et al., 1992; Feige et al., 2006; MacLean & Cairns, 1982; Van Reen et al., 2006). The unique findings reported in this younger age group are unlikely to reflect a floor effect as the averages of these sleep quality measures appeared typical. For example, the average sleep onset latency for the current study was approximately 20.6 (placebo) and 20.3 (alcohol) minutes, and for Chan and colleagues (2013) it was

approximately 16.9 (placebo) and 14.3 (alcohol) minutes, which are considered typical for sleep PSG (Carskadon & Dement, 2017). Although Williams and colleagues (1983) reported a significant 11.8-minute reduction in sleep onset latency following alcohol consumption, this discrepancy was potentially confounded by their small single-sex sample of eleven light-drinking women. Thus, the current findings may provide objective evidence that young people experience diminished sensitivity to the initial sedative effects of acute alcohol consumption.

There is substantial evidence in the animal literature to suggest that immature animals experience reduced sensitivity to the initial sedative effects of acute alcohol consumption, compared to mature adults, during both sleep and wake (Linsenbardt et al., 2009; Little et al., 1996; Moy et al., 1998; Pian et al., 2008; Quoilin et al., 2010; Silveri & Spear, 1998; White et al., 2002; York & Chan, 1993). The proposed mechanism is the delayed development of inhibitory GABAergic neurotransmitter systems across adolescence and young adulthood, present in both animals (Moy et al., 1998; Silveri, 2014; Spear, 2014; Yu et al., 2006) and humans (Chugani et al., 2001; Fung et al., 2010; Silveri et al., 2013). Several *in vivo* imaging studies in humans have demonstrated that GABAergic neurotransmission does not reach full maturity until early adulthood (Chugani et al., 2001; Fung et al., 2010; Silveri et al., 2013). For instance, Chugani and colleagues (2001) investigated GABA_A receptor distribution in humans between the ages of 2 and 50 years of age using positron emission topography (n=35). Their findings indicated that cortical GABA_A receptors do not reach full maturity until approximately 18 to 22 years of age (Chugani et al., 2001). Immaturity of the inhibitory neurotransmitter system may potentially explain the findings observed in the current investigation and previous literature (Arain et al., 2013; Chan et al., 2013; Moy et al., 1998; Silveri, 2014; Spear, 2014; Williams et al.,

1983). For example, the protracted development of the inhibitory system in young people, expressed as fewer cortical GABA_A receptors, may dampen alcohol's acute pharmacological inhibitory action, as there are fewer receptors available to act on or to facilitate inhibition (Moy et al., 1998; Spear, 2014). This could potentially result in less objective sedation following pre-sleep alcohol consumption in this younger age group.

If young people do experience less sedation following acute alcohol ingestion, they may be less likely to use alcohol as a sleep aid. Sedation or sleep promotion following acute alcohol consumption is a motivating, or reinforcing, factor that is commonly cited in the adult literature (Brower, 2003; Brower, Aldrich, Robinson, Zucker, & Greden, 2001; Roehrs & Roth, 2001b). However, based on the current findings, young people appear to be less sensitive to alcohol's acute sleep promoting effects. It is therefore possible that objective sleep promotion is unlikely to motivate acute alcohol use in this age group (AIHW, 2017; Crews et al., 2007; Spear, 2014; WHO, 2018). Thus, the use of alcohol to aid sleep in young people requires further investigation. Concerningly, reduced sensitivity to the acute sedative effects of alcohol, as observed in the current investigation, has also been implicated as a risk factor for the development of an alcohol use disorder (Schuckit, 1994; Schuckit et al., 2004). Researchers have hypothesised that low responsiveness to alcohol's acute sedative effects may promote the transition from light to heavy drinking, as higher doses of alcohol can be consumed per drinking occasion, and larger doses are needed to achieve psychopharmacological effects (Schuckit, 1998; Schuckit & Smith, 2000; Schuckit et al., 2004). This unique biological insensitivity may contribute to the notably higher single-occasion alcohol use observed in young people globally (AIHW, 2017; Spear, 2014; WHO, 2018). Taken together, these

findings provide evidence that young people may be less susceptible to the initial sedative effects of acute alcohol consumption on objective measures of sleep. This suggests that objective sleep promotion is unlikely to drive high levels of alcohol consumption in young people. Furthermore, this developmental insensitivity could potentially influence ongoing alcohol use and even contribute to the development of an alcohol use disorder. Future research is required to explore this possibility.

The current study provided support for Chan and colleagues' (2015) finding of augmented non-REM alpha and delta EEG spectral power following pre-sleep alcohol consumption in 18- to 21-year-old late adolescents. Specifically, following alcohol consumption prior to sleep (peak BAC= .10%), Chan and colleagues (2015) reported higher non-REM alpha power across the first three sleep cycles, and higher non-REM delta power in the first sleep cycle. Following pre-sleep alcohol ingestion, the current investigation reported higher alpha and delta power during SWS and REM sleep, in the first half of the sleep period. As previously highlighted, although alpha power was higher during stage N2 sleep, delta power was unexpectedly lower, in the first half of the sleep period. The same pattern of results reported in the two studies suggests that elevations in alpha power in the first half of the sleep period following alcohol consumption are greater in magnitude than those observed in delta power. It has been suggested that this electrophysiological peculiarity represents a unique form of sleep disturbance that would likely go undetected using traditional measures of visual sleep scoring (Pivik & Harman, 1995). This clinical phenomenon is referred to as alpha-delta sleep, and has also been reported in the adult literature (Koob & Colrain, 2019; Landolt et al., 1996; Rundell et al., 1972; Van Reen et al., 2006).

The presence of alpha-delta sleep following acute alcohol consumption may signify that the restorative properties of sleep have been compromised (Guilleminault et al., 2006; Hauri & Hawkins, 1973; Moldofsky, 2001). Indeed, alpha-delta sleep has been detected in people experiencing numerous physiological and mental health conditions, including fibromyalgia (Horne & Shackell, 1991; Lineberger et al., 2007; Mahowald & Mahowald, 2000; Menefee et al., 2000; Moldofsky et al., 1975; Roizenblatt et al., 2001), depression (Armitage, 1995; Jaimchariyatam et al., 1989), suicidal ideation (Agargun et al., 1997; Dolsen et al., 2017), insomnia (Riedner et al., 2016; Riemann et al., 2010), chronic fatigue (Guilleminault et al., 2006), dementia (Crowley et al., 2005), and post-traumatic stress disorder (Woodward et al., 2000). As well as alpha-delta sleep, a common theme uniting these debilitating health conditions is unrestful and unrefreshing sleep (Moldofsky, 2001). These health conditions are also associated with negative daytime symptoms that may be a consequence of non-restorative sleep, including fatigue, sleepiness, reduced alertness, musculoskeletal pain, diminished energy, low mood, and cognitive impairments (Moldofsky, 2001). Alpha-delta sleep, and these associated negative daytime symptoms, can also be elicited in healthy individuals by presenting loud auditory or pain stimuli during SWS (Drewes et al., 1997; Moldofsky, 2001; Moldofsky & Scarisbrick, 1976; Moldofsky et al., 1975; Older et al., 1998; Ooms et al., 2017; Van Der Werf et al., 2009). For example, a study by Drewes and colleagues (1997) administered nocturnal pain stimuli during SWS to 10 men aged 22.2 ± 1.4 years over three experimental nights. This resulted in higher alpha power during SWS. The negative next-day symptoms that have been reported following experimentally-elicited alpha-delta sleep include fatigue, low mood, musculoskeletal pain, and memory impairments (Moldofsky, 2001; Moldofsky & Scarisbrick, 1976;

Moldofsky et al., 1975; Older et al., 1998; Van Der Werf et al., 2009). This body of evidence indicates that alpha-delta sleep is associated with unrefreshing sleep that may result in negative daytime symptoms. In combination with the present findings, this suggests pre-sleep alcohol consumption is a disruptive stimulus that may lead to non-restorative alpha-delta sleep.

It is critical to note that negative daytime symptoms also follow acute alcohol consumption i.e., the alcohol hangover. Researchers have hypothesised that the alcohol hangover may partially result from alcohol-related sleep disturbances, including alpha-delta sleep (Chan et al., 2015; McKinney & Coyle, 2006; Swift & Davidson, 1998). Several hangover symptoms overlap with those reported in both clinical and experimental examples of alpha-delta sleep, including fatigue, musculoskeletal pain, negative mood, and memory and cognitive impairments (Prat, et al., 2008, 2009; Swift & Davidson, 1998; Tipple et al., 2016; van Schrojenstein Lantman et al., 2017; Wiese et al., 2000). For example, an investigation conducted on 27 men, aged 20 to 40 years, found that acute alcohol intoxication during learning (peak BrAC .069%) impaired next-day episodic memory recall during the hangover period (BrAC .00%), potentially reflecting compromised encoding (Soderlund et al., 2007). A study by Van Der Werf and colleagues (2009) induced alpha-delta sleep using auditory stimulation in 13 (9 female) healthy older adults aged 60.1 ± 8.3 years. They reported that visual memory encoding was notably impaired following one night of alpha-delta sleep (6.6 ± 0.26 hours) in these individuals. These next-day memory impairments may reflect disruptions to long-term potentiation, a neurophysiological process that is essential for memory consolidation or encoding (Cirelli, 2013). Long-term potentiation is thought to be characteristic of SWS due to its highly synchronous pattern of EEG activation (Tononi & Cirelli, 2003, 2006,

2014). The current study provides further evidence that this pattern may be disrupted by dyssynchronous alpha EEG activity following alcohol consumption (Chan et al., 2015). It is possible that alcohol-induced alpha-delta sleep may contribute to next-day impairments in learning and memory following pre-sleep alcohol consumption in young people. However, further research in this age group is required to verify this possibility.

The detection of alpha-delta sleep in late adolescence is particularly concerning as development is still ongoing, and because heavy alcohol use is common, during this time period (AIHW, 2017; WHO, 2018). Further to this, there is evidence that young people experience more frequent and severe alcohol hangovers than older age groups (Tolstrup et al., 2014). This likely reflects notably higher single-occasion alcohol use in this population and may also indicate young people experience alpha-delta sleep more frequently than older populations (AIHW, 2017; Tolstrup et al., 2014; WHO, 2018). Indeed, the current investigation provides evidence that alpha-delta sleep is also present in heavy-drinking late adolescents who already regularly engage in high levels of acute alcohol use. This suggests that tolerance to this EEG abnormality may not develop. This is supported by preliminary findings in six adult men diagnosed with an alcohol use disorder, aged approximately 35.5 years (Wagman & Allen, 1975). After one week of total abstinence, acute alcohol was administered daily in increasing doses over approximately two weeks. Wagman and Allen (1975) reported that alpha-delta sleep was still evident following ten days of repeated alcohol administration. Further to this, compared to abstinence, alpha power remained elevated for the first three hours of the sleep period, whereas delta power was only elevated for the first hour, closely mirroring the findings of the current investigation, and Chan and colleagues (2015). These findings collectively

provide evidence that high doses of alcohol reliably elicit alpha-delta sleep, regardless of age or habitual alcohol use.

There are currently two alternative theories that explain the presence of alpha-delta sleep; firstly, alpha EEG activity during SWS may play a functional role in sleep maintenance, or alternatively, it may represent an endogenous cortical arousal (Moldofsky, 2001; Pivik & Harman, 1995; Roizenblatt et al., 2001). Some researchers have theorised that higher alpha spectral power during SWS sleep may represent an internal sleep regulatory process i.e., maintaining sleep continuity in the presence of a disruptive stimulus, such as acute alcohol (Pivik & Harman, 1995; Van Reen et al., 2006). The timing of elevated alpha power following alcohol consumption may support this theory, as alpha power appears highest in the first half of the sleep period when BAC would be highest, and diminishes across the sleep period as BAC would be declining and returning to zero (Chan et al., 2015; Van Reen et al., 2006). This sleep regulatory mechanism may be related to enhanced sleep continuity in the first half of the sleep period following pre-sleep alcohol consumption, and impaired sleep quality in the second half of the sleep period, when alpha power is no longer elevated.

Researchers have alternatively theorised that alpha-delta sleep represents an endogenous arousal occurring during SWS, as alpha EEG activity is typically associated with wakefulness (Carskadon & Dement, 2017; Chan et al., 2015; Moldofsky, 2001; Roizenblatt et al., 2001). According to this hypothesis, the increase in alpha power reported in the current study, and previous literature, may indicate that alcohol consumption prior to sleep leads to an endogenous cortical arousal in the first half of the sleep period (Chan et al., 2015; Van Reen et al., 2006). This would mean that despite any initial sedative effects of alcohol consumption, the

micro-quality of sleep may still be disrupted and less restorative during this time. Critically, further research is required to clarify these opposing theories. Regardless of its mechanism or function, there is considerable evidence that the presence of alpha-delta sleep indicates that sleep is substantially disrupted, and subsequent daytime functioning may be impaired (Guilleminault et al., 2006; Hauri & Hawkins, 1973; Moldofsky, 2001). Thus, alpha-delta sleep is one mechanism through which acute alcohol consumption may impede the restorative properties of sleep in young people.

In the second half of the sleep period, during the acute alcohol withdrawal period, the present study reported major sleep disturbances that aligned closely with the wider literature. Research in late adolescents has reported more arousals, more wake after sleep onset, lower sleep efficiency (Chan et al., 2013); and more stage N1 sleep and less SWS (Chan et al., 2013; Williams et al., 1983), in the second half of the sleep period following pre-sleep alcohol ingestion. This research has also shown that although REM sleep was suppressed in the first half of the sleep period, there was no increase or rebound in the second half of the sleep period (Chan et al., 2013; Williams et al., 1983). Each of these findings were replicated by the current investigation. Whilst some studies in mature adults have reported a REM sleep rebound in the second half of the sleep period (MacLean & Cairns, 1982; Roehrs & Roth, 2001a; Sagawa et al., 2011), more evidence has been presented to the contrary (Arnedt et al., 2011; Colrain et al., 2014; Koob & Colrain, 2019; Roehrs, 1999, 1991; Rundell et al., 1972). The current investigation reported less all-night REM sleep percentage following pre-sleep alcohol consumption, which has been consistently reported in late adolescents (Chan et al., 2013; Williams et al., 1983) and adults (Arnedt et al., 2011; Landolt et al., 1996; Miyata et al., 2004; Roehrs, 1999, 1991;

Rouhani et al., 1989; Van Reen et al., 2006). These findings suggest that a high dose of alcohol prior to sleep results in major REM sleep suppression in both late adolescents and adults. Finally, the current investigation reported no alterations in EEG power spectra in any sleep stage in the second half of the sleep period following pre-sleep alcohol consumption. Chan and colleagues (2015) reported that non-REM alpha and delta power was marginally but significantly lower in the fourth sleep cycle following alcohol consumption prior to sleep. As the current study compared the first and second half of the sleep period, rather than sleep cycle, it is possible that the concluding reduction in alpha and delta power reported by Chan and colleagues (2015) may have been undetected by this analysis. Taken together, these findings provide further evidence that acute alcohol consumption prior to sleep leads to notable sleep quality and architecture disturbances in late adolescents.

Objective sleep disruption in the second half of the sleep period, as BAC declines and return to zero, may reflect the discontinuation of alcohol's acute GABAergic facilitation and glutaminergic inhibition during the acute alcohol withdrawal period. A homeostatic rebound or augmentation of glutaminergic excitation, and suppression of GABAergic inhibition, may explain higher wake after sleep onset, lower sleep efficiency, and less SWS reported in the current investigation and previous research (Chan et al., 2015; Chan, 2013; Roehrs & Roth, 2001a; Williams et al., 1983). Objective sleep disruption in the second half of the sleep period may also make it more difficult to enter SWS or elicit delta EEG activity, however, the current study did not report significantly lower delta spectral power. This secondary sleep disturbance may also be related to the accumulation of toxic metabolites as alcohol is metabolised and eliminated from the body (Feige et al., 2006; Roehrs & Roth, 2001a). All-night REM sleep suppression following acute

alcohol consumption may primarily reflect the inhibition of melatonin release, delaying the onset and intensity of this circadian-controlled substance (Lee et al., 2009; Wurts & Edgar, 2000). Together with previous research, the findings of the current investigation provide strong evidence that a high dose of alcohol prior to sleep results in subtle EEG abnormalities in the first half of the sleep period, followed by major sleep disruption, in late adolescents (Chan et al., 2015; Chan et al., 2013; Williams et al., 1983). Although most findings in this age group were consistent with the adult literature, there were some fundamental differences that are worth exploring further.

Research in mature adults commonly shows no overall differences in wake after sleep onset or sleep efficiency following acute alcohol consumption compared to placebo (Feige et al., 2006; MacLean & Cairns, 1982; Miyata et al., 2004; Roehrs, 1991; Sagawa et al., 2011; Van Reen et al., 2006). This is likely due to the initial sedative effects of acute alcohol consumption (i.e., less wake after sleep onset and higher sleep efficiency in the first half of the sleep period) counterbalancing its secondary disruptive effects (i.e., more wake after sleep onset and lower sleep efficiency in the second half of the sleep period). The current study showed that late adolescents had higher overall wake after sleep onset, and lower overall sleep efficiency, following pre-sleep alcohol consumption, compared to placebo. This finding is consistent with previous research in this age group (Chan et al., 2013; Williams et al., 1983). This discrepancy suggests that, unlike mature adults, the initial sedative effects of pre-sleep alcohol are insufficient to offset the secondary sleep disturbances in late adolescents. Research in rats has directly compared the impact of acute alcohol administration (1.5 – 5.0 g/kg) on sleep in adolescent versus adult rats (Pian et al., 2008; Silveri & Spear, 1998). This research showed that,

following the same dose of pre-sleep alcohol, adolescent rats had shorter total sleep times than adult rats. As previously described, reduced sensitivity to the acute sedative effects of alcohol may reflect the immaturity of inhibitory neurotransmitter systems during adolescence (Chugani et al., 2001; Fung et al., 2010; Moy et al., 1998; Silveri, 2014; Silveri et al., 2013; Spear, 2014; Yu et al., 2006). Unfortunately, researchers have not yet directly compared the sedative effects of acute alcohol on objective sleep in human adolescents as compared to adults.

Higher overall wake after sleep onset, and lower overall sleep efficiency, following alcohol consumption in late adolescents, may also be attributable to greater alcohol-related sleep disturbance in the second half of the sleep period. Potentially supporting this theory, the detrimental impacts of acute alcohol consumption on objective sleep quality in late adolescents appeared to be larger in magnitude than those reported in the adult literature. For example, in the second half of the sleep period, the current study reported an average of 39.1 minutes of wake after sleep onset following alcohol consumption, in 46 late adolescents aged 19.61 ± 1.0 years. Consistent with this, Chan and colleagues (2013), reported an average of 38.4 minutes of wake after sleep onset in the second half of the sleep period in 24 late adolescents aged 19.1 ± 1.0 years. In contrast, following the same peak dose of pre-sleep alcohol, Arnedt and colleagues (2011) reported 17.5 minutes average wake after sleep onset in the second half of the sleep period in 93 adults aged 24.3 ± 2.7 years. Furthermore, MacLean and colleagues (1982) reported an average of 17.8 minutes wake after sleep onset in the second half of the sleep period, in 10 men aged approximately 23.6 years. Greater alcohol-related sleep disturbances in late adolescence may result from the heightened sensitivity of excitatory neurotransmitter systems at this age, signified by a developmental peak in NMDA-glutamate receptors

(Arain et al., 2013; Doremus-Fitzwater et al., 2010; Insel, Miller, & Gelhard, 1990; Petit et al., 2013; Saransaari & Oja, 1995; Spear, 2011). In combination with immature GABAergic systems, amplified glutaminergic systems during late adolescence may potentially result in greater sleep disruption during the acute alcohol withdrawal period. This is because glutaminergic excitation is further enhanced, and GABAergic inhibition further suppressed, during acute alcohol withdrawal, potentially leading to more wakefulness than mature adults. These findings provide some preliminary evidence that acute alcohol consumption may lead to clinically relevant, greater sleep disturbances in young people, however, a direct adult comparison group would be needed to confirm this.

The increase in wake after sleep onset following pre-sleep alcohol consumption reported overall in the current investigation was 25.4 minutes on average, compared to placebo. The magnitude of this difference may be clinically relevant. An epidemiological study in 22,281 adults (51.95% female) aged 47.49 ± 16.60 (mean $\pm$ standard deviation) reported that just 30 minutes less sleep on average negatively impacted well-being (Cepeda et al., 2016). This included increased odds of poor health, depression, higher BMI, and cardiovascular disease (Cepeda et al., 2016). A study by Winsler and colleagues in 27,939 adolescents (51.2% female) reported that one less hour of sleep was associated with greater odds of reporting hopelessness, substance use, and suicidality (Winsler et al., 2015). Furthermore, research in 383 adolescents (53.7% female) aged 11 to 16 years suggested an 80 percent increase in risk of obesity for each hour of sleep lost. If experienced frequently, acute alcohol-related sleep loss of approximately 25.4 minutes could negatively impact psychological and physiological health. However, further research is needed to investigate this.

As previously discussed, it is likely that acute alcohol-related sleep disturbances contribute to the next-day alcohol hangover (Chan et al., 2015; McKinney & Coyle, 2006; Swift & Davidson, 1998). The most commonly reported hangover symptoms include fatigue (McKinney & Coyle, 2006; Swift & Davidson, 1998; Wiese et al., 2000), cognitive and memory impairments (Karadayian & Cutrera, 2013; Prat et al., 2008; Stephens et al.; van Schrojenstein Lantman et al., 2017; Verster et al., 2003), and low mood (McKinney & Coyle, 2006; van Schrojenstein Lantman et al., 2017). In combination with alpha-delta sleep, it is likely that partial sleep restriction, signified by higher wake after sleep onset and lower sleep efficiency, following pre-sleep alcohol consumption, contributes to next-day experiences of fatigue. There is also substantial evidence that sleep restriction leads to notable cognitive and memory impairments (Banks & Dinges, 2007; Killgore, 2010; Lo, Ong, Leong, Gooley, & Chee, 2016; Lowe, Safati, & Hall, 2017; Lundahl, Kidwell, Van Dyk, & Nelson, 2015; McCoy & Strecker, 2011; Medic et al., 2017; Walker, 2008). A meta-analysis by Lowe and colleagues (2017) including 61 human studies in children, adolescents, and adults, showed that short-term sleep restriction was associated with impairments in long-term memory. Research in animals suggests that partial sleep loss may impair long-term potentiation, a neurophysiological process that is fundamental to memory consolidation and synaptic homeostasis (Cirelli, 2013). This has been demonstrated by in vivo and in vitro studies in rodents that showed impaired long-term potentiation in the hippocampus following short-term sleep deprivation or fragmentation (Kopp, Longordo, Nicholson, & Luthi, 2006; McDermott et al., 2003; Tartar et al., 2006; Vecsey et al., 2009). There is also evidence from animal studies that acute ethanol exposure may directly impair long-term potentiation (Blitzer et al., 1990; Givens &

McMahon, 1995), and this impairment may be augmented in adolescence (Pyapali et al., 1999; White & Swartzwelder, 2005). This is supported by findings that ethanol exposure to a slice of vivisected adolescent rat hippocampal tissue prevented long-term potentiation at notably lower alcohol doses than adult hippocampal tissue (Pyapali et al., 1999). Research has also shown that selective REM sleep deprivation leads to greater next-day emotional reactivity to threatening stimuli, suggesting that REM sleep may be important for emotional regulation and processing (Rosales-Lagarde et al., 2012; Tempesta et al., 2018; Vandekerckhove & Wang, 2017). Together with previous literature, the current study found that REM sleep is grossly suppressed following pre-sleep alcohol consumption, which may potentially contribute to the experience of low mood during the alcohol hangover. In summary, this research suggests that the objective sleep disturbances observed in the current study, such as alpha-delta sleep and sleep restriction, may contribute to alcohol hangover symptoms. However, as the current investigation did not assess next-day hangover symptoms further research is required to confirm this.

7.1.1 Sex differences

There were no differences in BrAC between males and females at lights out. There was a main effect of sex on SWS percentage, which was driven by an interaction between sex and acute alcohol consumption. Females had approximately 4.6 percent more SWS overall in the placebo condition, compared to males, however, there were no differences in SWS percentage in the alcohol condition. Unsurprisingly, this interaction was mirrored for delta EEG spectral power. Furthermore, there was a main effect of sex on stage N2 sleep, indicating that regardless of experimental condition, females had less stage N2 sleep percentage

than males. Ultimately, the present findings provide evidence that acute alcohol ingestion appears to impact objective sleep in a similar manner between heavy- and light-drinking female and male late adolescents.

These findings are consistent with the normal sleep literature, which has consistently reported that females have more SWS percentage, and less stage N2 sleep, than males across the lifespan (Baker & O'Brien, 2017; Carskadon & Dement, 2017; Dijk et al., 1989; Ehlers & Kupfer, 1997; Mourtazaev et al., 1995; Walsleben et al., 2004). However, sex differences in objective sleep are generally subtle in young people, and are not always detected (Baker & O'Brien, 2017; Carskadon & Dement, 2017). For example, Chan and colleagues (2013) did not report any differences in stage N2 sleep or SWS percentage between their male (n=12) and female (n=12) light-drinking participants aged 18 to 21 years old. An investigation by Ehlers and colleagues (1997) suggested that sex differences in visually scored SWS percentage generally emerge between 30 to 40 years of age (n=61; 28 women). It has been suggested that sex differences in sleep become more apparent when there is a challenge or injury to the sleep system, such as disease or normal aging (Baker & O'Brien, 2017; Carskadon & Dement, 2017). There is considerable evidence that chronic alcohol consumption, such as that observed in long-term alcohol use disorders, presents a substantial challenge to the sleep system (Colrain et al., 2014; Colrain et al., 2009b). It is possible that the inclusion of heavy-drinking participants in the current investigation may have contributed to the detection of sex differences in this younger age group. Although no two-way interaction between sex and habitual alcohol use was detected for delta spectral power, there was a three-way interaction between sex, acute alcohol consumption, and habitual alcohol use for SWS percentage. Potentially supporting the system challenge hypothesis, in the

placebo condition, light-drinking females had 3.6 percent more overall SWS than heavy-drinking females, 5.1 percent more SWS than light-drinking males, and finally, 7.4 percent more SWS than heavy-drinking males. Notably, the differences in SWS percentage were largest between light-drinking female and heavy-drinking male late adolescents. This could suggest that habitual alcohol use does amplify sex differences in SWS percentage. It is important to note the present study may not have been powered to accurately detect three-way interactions. Therefore, future research is required to replicate and interpret these findings. This interaction is discussed in further detail in Section 7.3.1.

Male participants in the current study were marginally but significantly older than female participants by approximately 9.4 months. This could indicate that male participants were further advanced in their neural development than females, resulting in lower SWS and higher stage N2 sleep percentage, during normal sleep (Campbell & Feinberg, 2009; Courchesne et al., 2000; Feinberg & Campbell, 2010; Feinberg et al., 1990; Lebel & Beaulieu, 2011; Sheldon, 2014). However, there is substantial evidence that females commence and complete these sleep and neural changes earlier than males, which may make this explanation less likely (Baker et al., 2012; Baker et al., 2016; Campbell et al., 2005; Feinberg & Campbell, 2010). Although it is less common to observe sex differences in SWS and stage N2 sleep in this younger age group, this pattern of results is still typical of the normal sleep literature (Baker & O'Brien, 2017; Dijk et al., 1989; Ehlers & Kupfer, 1997; Mourtazaev et al., 1995; Walsleben et al., 2004).

Finally, it should be noted that females generally had higher spectral power across all frequency bands than males, in all sleep stages. This sex difference is highly typical of the normal sleep literature, and reflects underlying neuro- and

electro-physiological differences between men and women (Achermann & Borbély, 2017; Baker & O'Brien, 2017; Bersagliere et al., 2018; Carrier et al., 2001; Carskadon & Dement, 2017; Dijk et al., 1989; Latta et al., 2005; Mourtazaev et al., 1995; Nir et al., 2011). In addition to this, the current study identified several unexpected interactions between sex and acute alcohol consumption for EEG power spectra. These findings were complex and difficult to interpret. Unfortunately, research in adults investigating the acute effects of alcohol on nocturnal spectral power has been undertaken exclusively in either male (Dijk et al., 1992; Landolt et al., 1996) or female (Van Reen et al., 2006) samples. Chan and colleagues' (2015) investigation in same-aged male and female light-drinking late adolescents did not report sex differences in EEG spectral power following alcohol consumption. It is possible that the detection of sex differences in the current study may be due to the inclusion of heavy-drinking participants, however, no three-way interaction between sex, acute alcohol consumption, and habitual alcohol use was reported. Furthermore, the present study may not have been powered to three- and four-way interactions, and may be the result of type 1 error. Additionally, as outlined in the methodology (section 5.4.2.4), this study was not powered to detect sex differences so findings related to sex must be interpreted cautiously. In summary, the current study provides evidence that acute alcohol consumption appears to impact sleep in both female and male heavy- and light-drinking late adolescents in a similar manner. However, further research is required to replicate and interpret potential sex differences in sleep EEG power spectra.

7.2 Habitual effects of alcohol on sleep in young people

The findings of the present study contribute substantial objective evidence to the limited literature currently available on the impacts of habitual alcohol use on sleep in young people. The current study provides some support for previous findings in this age group, and the adult literature (Angarita, Emadi, Hodges, & Morgan, 2016; Brower et al., 2001; Chakravorty, Chaudhary, & Brower, 2016; Cohen-Zion et al., 2001; Colrain et al., 2014; Criado et al., 2008; Ehlers et al., 2018a; Ehlers & Slawecki, 2000; Koob & Colrain, 2019; Nicholas et al., 2011; Roehrs & Roth, 2001b). Notably, the current investigation indicates that heavy-drinking late adolescents have less overall visually scored SWS percentage, and higher overall stage N2 sleep, following a minimum of 48 hours of abstinence (i.e., no acute alcohol consumption), compared to same-aged light drinkers. This finding supports preliminary research by Nicholas and colleagues (2011) that investigated the effects of habitual alcohol use on evoked K-complex incidence and amplitude in 13 males aged 18 to 21 years. Nicholas and colleagues (2011) found that, compared to same-aged light drinkers, heavy-drinking late adolescents had lower evoked K-complex incidence, but not lower amplitude, following a minimum of 48 hours of abstinence. It has been theorised that K-complexes are a functional measure of the brain's ability to synchronise and produce a single delta EEG waveform, the EEG frequency characteristic of SWS (Colrain, 2005; Nicholas et al., 2002b). A reduction in evoked K-complex incidence may suggest an impairment or alteration in the brain's ability to synchronise and elicit slow wave or delta EEG activity, a deficit that has consistently been reported in mature adults with long-term alcohol use disorders (Colrain et al., 2009a; Colrain et al., 2011; Nicholas et al., 2011). As SWS is produced via the same neural mechanisms as K-complexes, although on a larger

scale, this may also explain the decline in SWS, and augmented stage N2 sleep, reported in the current study. For example, SWS is visually scored when 20 percent or more of a 30-second EEG recording is composed of high amplitude ($>75 \mu\text{V}$) slow wave activity ($>0.5 - 2 \text{ Hz}$; AASM, 2007; Carskadon & Dement, 2017; Dijk et al., 1993). If heavy-drinking young people have a lower capacity to elicit slow wave or delta EEG activity, this 20 percent threshold may be reached less often, leading to less visually scored SWS, and more stage N2 sleep.

The current finding also supports research in animals which has consistently reported lasting reductions in SWS percentage following heavy ethanol exposure during adolescence (Criado et al., 2008; Ehlers et al., 2018a; Ehlers & Slawecki, 2000). Two studies using identical procedures exposed adolescent rats ($n=40$; $n=29$) to intermittent ethanol vapour (95% EtOH) for 12 hours a day for five weeks across adolescence and early adulthood (post-natal days 22 – 60), and reported long-lasting reductions in SWS percentage in mature adulthood following five weeks of abstinence, compared to age-matched controls (Criado et al., 2008; Ehlers et al., 2018a). These findings appear to be unique to this age group, as research has shown that heavy alcohol exposure using identical procedures in mature adult rats did not result in lasting deficits in SWS (Ehlers & Slawecki, 2000). The age-matched control groups in these studies were treated identically to the experimental group in all ways except ethanol exposure, suggesting that SWS degradations may be a direct result of heavy habitual alcohol use in adolescence (Criado et al., 2008; Ehlers et al., 2018a; Ehlers & Slawecki, 2000). This could suggest that the SWS deficits observed in heavy drinkers in the current study may be the result of habitual alcohol use, and not due to a pre-existing condition. The current study also reported that previous 30-day alcohol consumption was weakly negatively correlated with SWS percentage, and

moderately positively correlated with stage N2 sleep percentage. This may provide evidence that the effects of habitual alcohol use on these sleep measures are dose dependent. It is worth noting that Cohen-Zion (2009) reported that previous 30-day alcohol consumption did not predict SWS percentage (a minimum of 24 hours since last alcoholic beverage) in 49 young people aged 16.3 to 21.4 years, however, the primary independent variable of their study was habitual marijuana use. The well-established impacts of marijuana on sleep architecture may have confounded this finding (Garcia & Salloum, 2015). In the current investigation, participants who used medications or drugs known to affect sleep, including marijuana, were excluded. Taken together, these findings suggest that heavy alcohol use during the final stages of brain development may be related to impairments in the onset, and/or continuation, of SWS.

In the current study, heavy drinking late adolescents had 3.3 percent less SWS overall than light drinkers, in the placebo condition. Due to limited research in this age group, it is unclear whether the magnitude of this SWS deficit would be clinically significant. However, the magnitude of the statistical effect was large (Cohen, 1988; Richardson, 2011). It is well-established that SWS is functionally important for physiological and neurological restoration and repair, as well as learning and memory (Huber et al., 2004; Mendelsohn & Larrick, 2013; Tononi & Cirelli, 2006; Van Cauter, 2000; Wang, Grone, Colas, Appelbaum, & Mourrain, 2011). It is possible that lower baseline SWS in heavy-drinking young people could negatively impact these critical functions, potentially affecting health, development, and daytime functioning. Supporting this theory, research has demonstrated that heavy alcohol use in young people is associated with poorer physical health and development, including delayed pubertal onset (Dees et al., 2017), lower bone

mineral density (LaBrie et al., 2018; Lucas et al., 2012), poor general health (Clark et al., 2001; Oesterle et al., 2004; Okoro et al., 2004), and increased risk of obesity and hypertension (Brown & Tapert, 2004b; Oesterle et al., 2004). There is also substantial evidence that young people who engage in heavy alcohol use, or binge drinking, demonstrate notable degradations in brain structure and function, compared to same-aged light drinkers (Cservenka & Brumback, 2017; Ewing et al., 2014; Jones et al., 2018; Lees et al., 2018; Lisdahl et al., 2013a; Lisdahl et al., 2013b; Luciana et al., 2013; McQueeney et al., 2009; Petit et al., 2014; Pfefferbaum et al., 2018; Silveri et al., 2016; Squeglia et al., 2009; Squeglia et al., 2012; Squeglia et al., 2015; Wilson et al., 2015). Furthermore, there is considerable evidence that heavy alcohol use in young people is associated with impairments in learning and memory (Crego et al., 2009; Heffernan et al., 2009; Heffernan & O'Neill, 2012; Mota et al., 2013; Nguyen-Louie et al., 2016; Parada et al., 2011). A longitudinal study by Nguyen-Louie and colleagues (2016) investigated verbal learning and memory in 112 early adolescents (12 to 16 years old) prior to the onset of alcohol use, and then repeated these measures six years later in late adolescence (18 to 22 years old). They reported that the initiation of binge drinking resulted in dose-dependent impairments in verbal learning and memory, most notably the acquisition of new verbal information, despite no differences in ability prior to the onset of alcohol use. Finally, a large study in 2,590 young adults aged 18 to 29 demonstrated that binge drinking predicted lower quality of life (Mohamed & Ajmal, 2015). It is possible that lower baseline SWS percentage in heavy-drinking late adolescents could contribute to alcohol-related impairments in physiological and neurological health, learning and memory, and quality of life.

Of concern, the sleep architecture alterations reported in the current investigation are largely consistent with findings reported in mature adults diagnosed with long-term alcohol use disorders, although the effects are less pronounced (Angarita et al., 2016; Brower et al., 2001; Chakravorty et al., 2016; Colrain et al., 2014; Koob & Colrain, 2019; Roehrs & Roth, 2001b). As well as less SWS and more stage N2 sleep percentage, the current study reported that heavy-drinking late adolescents had shorter REM sleep onset latencies, irrespective of pre-sleep alcohol or placebo consumption, compared to same-aged light drinkers. In adults recovering from long-term alcohol use disorders, research has consistently reported more stage N2 sleep, less SWS percentage (Brower, 2003; Gross et al., 1973; Gross & Hastey, 1975; Johnson et al., 1970; Wagman & Allen, 1975; Williams & Rundell, 1981), and shorter REM sleep onset latencies (Gillin et al., 1990a; Gillin et al., 1990b; Snyder & Karacan, 1985; Williams & Rundell, 1981) following approximately one to eight weeks of abstinence. For example, Williams and Rundell (1981) reported more stage N2 sleep, less SWS, and shorter REM sleep onset latencies, in 48 men recovering from an alcohol use disorder, aged 23 to 63 years. These patients were abstinent for approximately 35.3 days, following an average of 16.6 years of heavy alcohol use, compared to 20 age-matched healthy control participants. The replication of this general pattern of findings by the current investigation suggests that heavy-drinking late adolescents may already be showing signs of the protracted sleep disturbances reported in adults recovering from long-term alcohol use disorders. This would be particularly concerning given that heavy-drinking participants in the current study had substantially shorter drinking histories on average (approximately 3.3 ± 1.5 years, with a median of 2.8 years), consumed less alcohol in their lifetime, and were not currently diagnosed with an alcohol use disorder. Further to this, the final stages

of human neural development are still ongoing during this critical time period (Johnson et al., 2009; Sowell et al., 1999; Sowell et al., 2004; Tarokh et al., 2011). Williams and Rundell (1981) also reported that the degree of SWS deficits, and REM sleep onset latency decline, was predictive of relapse in abstinent adults with long-term alcohol use disorders. This finding has been consistently replicated (Adamson & Burdick, 1973; Brower et al., 1998; Clark et al., 1998; Drummond et al., 1998; Gillin et al., 1994) and could suggest the sleep architecture deficits identified in the current investigation may contribute to ongoing alcohol consumption in heavy-drinking young people. It is worth noting that although there appears to be some improvement in sleep architecture following recovery from an alcohol use disorder, some deficits appear to be long-lasting. Notably, higher stage N2 sleep, lower SWS (Adamson & Burdick, 1973; Allen et al., 1980; Brower et al., 1998; Colrain et al., 2009b; Drummond et al., 1998; Imatoh et al., 1986; Williams & Rundell, 1981), and reduced REM sleep onset latency (Benca et al., 1992; Brower et al., 2011; Clark et al., 1998; Colrain et al., 2009b; Drummond et al., 1998; Gillin et al., 1994; Imatoh et al., 1986; Williams & Rundell, 1981) have been detected following one to two years of extended abstinence. The persistence of these sleep deficits following the cessation of problematic alcohol use in mature adults suggests that the deficits observed in the current investigation could also be enduring, however, longitudinal research is required to verify this.

Although the findings of the current investigation were largely consistent with the adolescent and adult literature, there were some notable discrepancies. Firstly, the current study reported that heavy-drinking late adolescents did not have higher overall REM sleep percentage than same-aged light drinkers, a finding that is commonly reported in adults with alcohol use disorders during both short- (Gillin et

al., 1990a; Gillin et al., 1990b; Snyder & Karacan, 1985; Williams & Rundell, 1981) and long-term abstinence (Benca et al., 1992; Brower et al., 2011; Clark et al., 1998; Colrain et al., 2009b; Drummond et al., 1998; Gillin et al., 1994; Imatoh et al., 1986; Williams & Rundell, 1981). Despite this discrepancy, the current study did find that the distribution of visually scored REM sleep across the sleep period differed between heavy- and light-drinking late adolescents. This was such that heavy-drinking late adolescents had less REM sleep percentage in the second half of the sleep period compared to same-aged light drinkers, irrespective of experimental condition. This finding may be due to heavy drinkers commencing REM sleep earlier in the sleep period, signified by their shortened REM sleep onset latencies, leading to less REM sleep percentage in the second half of the sleep period. Consistent with the current findings, Cohen-Zion and colleagues (2009) reported that higher previous 30-day alcohol consumption predicted shorter REM sleep onset latencies, but not REM sleep percentage, in a sample of adolescents who engaged in both habitual alcohol and marijuana consumption. Taken together, these findings may suggest that heavy alcohol use in young people does not augment REM sleep to the same degree as adults recovering from long-term alcohol use disorders. This may be due to their shorter and less intense periods of heavy alcohol use, and/or their continuing neurological development. For example, augmented glutaminergic neurotransmission in late adolescence, the neurotransmitter system primarily responsible for REM sleep onset and continuation, may make habitual alcohol-related REM sleep changes less apparent or likely (Arain et al., 2013; Datta et al., 2001; Doremus-Fitzwater et al., 2010; Gonzales & Jaworski, 1997; Insel et al., 1990; Knowles et al., 1968; Kodama et al., 1998; Petit et al., 2013; Saransaari & Oja, 1995; Spear, 2011). Further research is required to elucidate the impact of habitual alcohol use on REM sleep in young

people. However, these preliminary findings suggest that REM sleep is impacted by habitual alcohol use in a similar pattern to mature adults, though to a lesser degree. Finally, there was an unexpected moderate positive correlation suggesting that higher habitual alcohol use in light-drinking late adolescents was associated with longer REM sleep onset latencies in the placebo condition. This finding was surprising given heavy alcohol use, such as that observed in the current study and the general literature, is consistently associated with shorter REM sleep onset latencies (Benca et al., 1992; Brower et al., 2011; Clark et al., 1998; Cohen-Zion et al., 2009; Colrain et al., 2009b; Drummond et al., 1998; Gillin et al., 1994; Imatoh et al., 1986; Williams & Rundell, 1981). The underlying mechanism driving this unexpected finding is unclear and further research is required to confirm and comprehend this unusual finding.

The current study reported no differences in objective sleep quality between heavy- and light-drinking late adolescents. These findings were in contrast to the notable degradations in sleep quality reported in mature adults with long-term alcohol use disorders, including longer sleep onset latencies, more arousals, more wake after sleep onset, and lower sleep efficiency, compared to age-matched healthy control participants (Angarita et al., 2016; Brower, 2003; Brower et al., 2001; Chakravorty et al., 2016; Colrain et al., 2014; Conroy, Arnedt, & Brower, 2011; Roehrs & Roth, 2001b; Stein & Friedmann, 2005). Furthermore, Cohen-Zion and colleagues (2009) reported that previous 30-day alcohol consumption predicted longer sleep onset latencies in young people (16.3 – 21.4 years) who habitually consumed alcohol and marijuana (Cohen-Zion et al., 2009). However, this previous finding was not supported by the current investigation and may have been confounded by polysubstance use in the earlier study (Cohen-Zion et al., 2009).

Despite these discrepancies, the current investigation found that habitual alcohol use (i.e., number of years drinking, previous 30-day alcohol consumption, and lifetime history of alcohol consumption) was positively correlated with wake after sleep onset, and negatively correlated with sleep efficiency, in the placebo condition. The strength of these relationships ranged from weak to moderate and became notably stronger when examining only heavy-drinking late adolescents. These findings are in line with the adult literature that has consistently reported more wake after sleep onset, and lower sleep efficiency, during both acute and protracted alcohol withdrawal syndrome in adults recovering from long-term alcohol use disorder (Aldrich et al., 1999; Brower, 2001; Drummond et al., 1998; Gillin et al., 1990a; Gross et al., 1973; Gross & Hastey, 1975; Le Bon et al., 1997; Moeller et al., 1993; Snyder & Karacan, 1985; Wagman & Allen, 1975; Williams & Rundell, 1981). There is evidence that most deficits in sleep quality, including shorter total sleep time, normalise following approximately one to two years of extended abstinence in adults recovering from alcohol use disorders (Adamson & Burdick, 1973; Colrain et al., 2009b; Drummond et al., 1998; Williams & Rundell, 1981). Furthermore, the magnitude of decline in total sleep time during early abstinence is predictive of relapse (Brower et al., 1998; Clark et al., 1998; Drummond et al., 1998; Gillin et al., 1994). This could suggest that alcohol-related impairments in objective sleep quality may contribute to ongoing alcohol use in young people, and/or potentially show recovery following an extended period of abstinence. However, longitudinal research is needed to verify this. There is substantial evidence that heavy-drinking young people self-report notable impairments in subjective sleep quality (Bartel et al., 2015; Ehlers et al., 2018b; Johnson & Breslau, 2001; Kenney et al., 2012; Kenney et al., 2014; Marmorstein, 2017; Miller et al., 2016; Morioka et al., 2013; Nguyen-Louie et

al., 2018; Pieters et al., 2010; Popovici & French, 2013; Sivertsen et al., 2015; Warren et al., 2017; Wong et al., 2004; Wong et al., 2015; Zhabenko et al., 2016). To illustrate, a large population study by Morioka and colleagues (2013) in 98,967 Japanese adolescents reported a dose-dependent relationship between habitual alcohol use and subjective sleep disturbances. The current study adds critical objective evidence to this literature. Taken together, these findings suggest that heavy alcohol use in late adolescence may impair objective sleep quality in a dose-dependent manner, however, these effects were not as large as those reported in adults diagnosed with long-term alcohol use disorders.

In contrast with the general literature, the current study did not report differences in delta EEG spectral power in any sleep stage between heavy- and light-drinking late adolescents. Previous research has consistently reported lower non-REM delta power in mature adults recovering from alcohol use disorders (Colrain et al., 2009b; Irwin, Miller, Gillin, DeModena, & Ehlers, 2000; Wagman & Allen, 1975). For example, Colrain and colleagues (2009b) reported that 42 men and women diagnosed with an alcohol use disorder, aged 51.1 ± 9.7 years, had shorter REM sleep onset latencies, less SWS percentage, and lower non-REM delta power following approximately six months of abstinence, compared to 40 age- and sex-matched control participants. Although the current investigation also reported that heavy-drinking late adolescents had less SWS percentage, and shorter REM sleep onset latencies, compared to same-aged light drinkers, no differences were detected in delta power in any sleep stage. This was also discrepant with findings in adolescent animal models. Research in rats has consistently demonstrated that, following heavy ethanol exposure in adolescence, there are long-lasting reductions in delta power detected in mature adulthood, compared to age-matched controls (Criado

et al., 2008; Ehlers et al., 2018a; Ehlers & Slawecki, 2000). The current study's divergent findings suggest that heavy alcohol use in young humans may not impact delta power in the same way as animals or human adults with long-term alcohol use disorders. However, it is worth noting that the animal research was undertaken longitudinally, and the adult participants in the human studies were markedly older than the current investigation. It is possible that deficits in delta spectral power related to heavy alcohol exposure in adolescence may not become apparent until later in the lifespan. Longitudinal research is required to investigate this possibility.

Although there were no differences in delta spectral power, the current study reported that heavy-drinking late adolescents had higher overall sigma spectral power in both stage N2 sleep and SWS, compared to same-aged light drinkers, irrespective of pre-sleep alcohol or placebo consumption. As sigma EEG activity is the electrophysiological state that precedes the onset of delta EEG activity, an increase in sigma power may also reflect changes in the same neurological processes that elicit and maintain SWS and delta EEG activity (Dossi et al., 1992; Steriade et al., 1991). Research undertaken in cats has demonstrated that the hyperpolarisation of cortical and thalamocortical cell membranes initially leads to production of sigma EEG activity, however, further hyperpolarisation of these cells leads to slow wave or delta EEG activity (Dossi et al., 1992; Steriade et al., 1991; Volgushev et al., 2006). The unique pattern of findings in the current study suggest that heavy-drinking late adolescents are not meeting the hyperpolarisation threshold required to elicit slow wave activity as often as same-aged light drinkers, leading to more stage N2 sleep, lower SWS percentage, and higher sigma EEG power within these sleep stages. Potentially supporting these novel findings, Nicholas and colleagues (2011) reported a lower evoked K-complex incidence, but not amplitude, in six heavy-drinking late

adolescent males, compared to seven light drinkers, a finding that was inconsistent with the adult literature (Colrain et al., 2011). This suggests that although heavy-drinking late adolescents may experience fewer evoked K-complexes, and less visually scored SWS, than same-aged light drinkers, when they do successfully elicit a K-complex, or enter SWS, there are no deficits in the intensity or amplitude of delta EEG activity.

Higher sigma power in heavy-drinking late adolescents during SWS may also suggest there is an electrophysiological irregularity within the deepest and most restorative stage of non-REM sleep. It is possible that sigma EEG activity could disrupt the highly synchronous EEG pattern of SWS required for long-term potentiation, fundamental to learning and memory (Tononi & Cirelli, 2003, 2006, 2014). Although this is purely speculative, substantial learning and memory deficits have been reported in heavy-drinking young people (Crego et al., 2009; Heffernan et al., 2009; Heffernan & O'Neill, 2012; Mota et al., 2013; Nguyen-Louie et al., 2016; Parada et al., 2011). Higher sigma power may be unique to habitual alcohol use in this developing age group, as it has not previously been reported in mature adults (Colrain et al., 2009b; Irwin et al., 2000; Wagman & Allen, 1975). Although further research is needed to confirm and understand these findings, the current study provides novel evidence that habitual alcohol exposure in late adolescence may be related to deficits in the elicitation and continuation of SWS, and although delta EEG activity appears to be unaffected, electrophysiological abnormalities in sigma EEG activity may be present.

It has been theorised that elevated sigma power during non-REM sleep, as identified in heavy-drinking late adolescents in the current investigation, may represent a neurophysiological protective mechanism that counteracts sleep

disturbance (Dang-Vu, McKinney, Buxton, Solet, & Ellenbogen, 2010; Spiegelhalder et al., 2012). Evidence for this theory has been provided by Dang-Vu and colleagues (2010) who examined the relationship between sleep spindles, or sigma spectral power, and noise-related sleep disruption in 12 healthy participants aged 26.3 ± 7.5 years. They identified that higher baseline sigma power in stage N2 sleep and SWS was associated with fewer arousals following the presentation of 40 decibel or louder noise stimuli across two consecutive nights of sleep. Dang-Vu and colleagues (2010) concluded that individuals with higher sigma power were better able to maintain sleep continuity in the presence of a disruptive stimulus, such as noise. Further supporting this theory, research has shown that patients with primary insomnia demonstrate higher non-REM sigma power during sleep (Krystal, Edinger, Wohlgemuth, & Marsh, 2002; Spiegelhalder et al., 2012). It is possible that elevated sigma power in heavy-drinking late adolescents may represent a sleep protective mechanism. For example, heavy alcohol use may be considered a disruptive sleep stimulus, and increased sigma power in stage N2 sleep and SWS, irrespective of pre-sleep alcohol or placebo consumption, may improve sleep continuity in these individuals. This could potentially explain why there were no gross differences in objective sleep quality between heavy- and light-drinking late adolescents in the current investigation, as augmented sigma power in heavy-drinking young people may enhance sleep continuity. This could be one potential mechanism that uniquely protects young people from alcohol-related objective sleep disturbances. However, this theory requires further research evidence to be substantiated, including the replication of this novel finding of higher sigma power in heavy-drinking young people.

There are several mechanisms that may underly the objective sleep differences between heavy- and light-drinking late adolescents detected in the current investigation and previous literature. Firstly, it is possible that some sleep deficits observed in the current study may represent alcohol-related changes in neural integrity and connectivity. For example, it has been hypothesised that degradations in K-complexes, SWS, non-REM delta EEG activity, and objective sleep quality, observed in adults with a current or previous alcohol use disorder may reflect underlying alcohol-related brain damage, including neural grey and white matter atrophy (Colrain et al., 2009a; Colrain et al., 2014; Colrain et al., 2011; Colrain et al., 2009b; Fortier et al., 2011; Harper et al., 2003; Harper & Kril, 1989; Koob & Colrain, 2019; Nicholas et al., 2002a; Pfefferbaum et al., 2001b). Exemplifying this, Colrain and colleagues (2011) demonstrated that 40 abstinent older adults (14 women) with long-term alcohol use disorders, following approximately 25 years of heavy alcohol use, had a reduced incidence and amplitude of evoked K-complexes (i.e., a discrete instance of delta EEG activity) compared to 40 healthy age-matched control participants. Furthermore, MRI scans revealed that these patients had smaller cortical grey matter volumes compared to controls, and this volume predicted K-complex amplitude (Colrain et al., 2011). Thus, alcohol-related neural damage results in fewer neurons, and poorer connections between these neurons, leading to a reduced ability to synchronise and produce the burst firing required to elicit K-complexes or delta EEG activity, and hence SWS. Critically, alcohol-related neurodegeneration is most prominent in frontal brain regions, where these measures are known to be preferentially generated (Harper, 2009; Harper & Matsumoto, 2005; Heikkinen et al., 2017; Kril et al., 1997; Silveri et al., 2016). Although findings in heavy-drinking late adolescents suggest that degradations in K-complex amplitude

and delta EEG activity are not yet present, the deficits detected in visually scored SWS could potentially reflect underlying alcohol-related neural damage (Nicholas et al., 2011).

Alcohol is a well-established teratogen, and as adolescents and young adults are still undergoing the final stages of neural development, it has been theorised that the neurodegenerative impact of habitual alcohol use may be heightened (Arain et al., 2013; Gogtay et al., 2004; Guerri & Pascual, 2010; Hames, 2012; Lubman et al., 2007; Miller, 2006; Phillips, 2014; Sadrian et al., 2013). Highlighting this, animal models have provided evidence that ethanol exposure during adolescence results in unique patterns of neural damage (Crews, Braun, Hoplight, Switzer, & Knapp, 2000; Crews et al., 2006). For example, Crews and colleagues (2000) exposed adolescent (post-natal days 35) and adult (post-natal days 80 to 90) rats to ethanol intragastrically for four consecutive days, mirroring a binge-drinking pattern. Following this procedure, alcohol-related neural damage was detected in both adolescent and adult rats, however, this damage was significantly more extensive in adolescents, particularly in frontal brain regions. As in mature adults, adolescents diagnosed with alcohol use disorders demonstrate long-lasting changes in structural and functional grey and white matter, with changes being most prominent in frontal brain regions (De Bellis et al., 2000; De Bellis et al., 2005; De Bellis et al., 2008; Fein et al., 2013; Medina et al., 2008; Medina et al., 2007; Nagel, Schweinsburg et al., 2005; Welch et al., 2013). Further to this, there is evidence that binge drinking in adolescence leads to lasting deficits in neural integrity and connectivity, also greatest in frontal areas (Cservenka & Brumback, 2017; Ewing et al., 2014; Hanson et al., 2011; Heikkinen et al., 2017; Jones et al., 2018; Lees et al., 2018; Lisdahl et al., 2013a; McQueeney et al., 2009; Petit et al., 2014; Pfefferbaum et al., 2018; Silveri et

al., 2016; Squeglia et al., 2009; Squeglia et al., 2012; Squeglia et al., 2015; Wilson et al., 2015). Demonstrating this, Heikkinen and colleagues (2017) investigated 35 (20 female) binge-drinking adolescents who were not diagnosed with an alcohol use disorder, and 27 age- and sex-matched light drinkers, over a 10-year period. At approximately 25 years of age, all participants underwent an MRI scan that revealed participants who participated in binge drinking during adolescence had smaller grey matter volumes than light drinkers, particularly in frontal brain regions. Structural and functional neural deficits related to heavy alcohol use in young people could contribute to the sleep deficits observed in the current study. Again, fewer neurons and/or poorer connections between neurons may impede the production of slow wave or delta EEG activity required to meet the criteria for visually scored SWS, which could result in less SWS, more stage N2 sleep percentage, and higher sigma power within these sleep stages, as identified in the current investigation (AASM, 2007).

Less SWS percentage in heavy-drinking late adolescents, compared to same-aged light drinkers, may also reflect a decline in homeostatic sleep drive. There is substantial evidence that adults diagnosed with alcohol use disorders have a reduced homeostatic sleep drive (Armitage et al., 2012; Brower et al., 2011; Colrain et al., 2014; Irwin et al., 2002; Thakkar et al., 2015). Research has shown that abstinent men and women diagnosed with an alcohol use disorder experience a blunted homeostatic response to acute sleep deprivation (i.e., a three hour delay in bedtime), as indicated by lower SWS percentage and delta spectral power, compared to healthy age-matched control participants (Armitage et al., 2012; Brower et al., 2011). This represents reduced sleep drive, or pressure, and may contribute to impairments in sleep onset and continuity in these individuals (Angarita et al., 2016; Brower et al., 2001; Colrain et al., 2014; Conroy et al., 2011; Thakkar et al., 2015). Although the

present study did not report any gross differences in objective sleep quality between heavy- and light- drinking late adolescents, higher habitual alcohol use was associated with higher wake after sleep onset, and lower sleep efficiency, in the placebo condition. Further to this, higher sigma power in heavy drinkers could potentially represent an electrophysiological process that promotes sleep continuity, despite a lowered homeostatic sleep drive (Dang-Vu et al., 2010, Krystal et al., 2002; Spiegelhalder et al., 2012). However, it is critical to note that the current investigation did not report lower delta power in heavy-drinking late adolescents, compared to same-aged light drinkers. This may suggest that heavy alcohol use in young people may not impact homeostatic sleep drive to the same degree as adults with long-term alcohol use disorders. Furthermore, this finding suggests that alcohol-related neural damage in young people may not be sufficient to impact delta power. This may be due to late adolescents' age, developing sleep and neural systems, and shorter, less-intense periods of heavy drinking, compared to mature adults diagnosed with alcohol use disorders. Further, alterations in REM sleep are unlikely to reflect alcohol-related structural brain changes, as this measure does not reflect structural neural integrity in the same functional manner as SWS. Taken together, these findings suggest that alcohol-related neural damage may explain some, but not all, objective sleep differences related to habitual alcohol use in this age group. Future research is required to investigate the impact of habitual alcohol use on sleep homeostasis in young people.

It is also possible that the pattern of results observed in the current investigation may reflect the adaptation of neurotransmitter systems to heavy alcohol exposure. It has been suggested that chronic alcohol consumption, such as that observed in long-term alcohol use disorders, results in the homeostatic

downregulation of inhibitory GABAergic neurotransmission, and upregulation of excitatory glutaminergic neurotransmission (Gonzales & Jaworski, 1997; Koob & Colrain, 2019; Kumar et al., 2009; Most et al., 2014; Roberto & Varodayan, 2017). This adaptation occurs in response to prolonged alcohol exposure in order to maintain neurochemical homeostasis in the brain and sleep systems. This adaptation may involve the modulation of pre-synaptic neurotransmitter release and the number of post-synaptic neurotransmitter receptors (Koob & Colrain, 2019; Kumar et al., 2009; Most et al., 2014). As previously highlighted, GABAergic neurotransmission facilitates sleep onset and continuation, and promotes SWS (Feld et al., 2013; Gottesmann, 2002; Siegel, 2004; Walsh, 2009). In contrast, glutaminergic neurotransmission stimulates wakefulness, and supports REM sleep onset and continuation (Datta et al., 2001; Fraigne et al., 2015; Kodama et al., 1998; Lu et al., 2006). In combination, these systems control sleep onset, continuity, and sleep stage distribution, so their adaptation results in alterations to sleep quality and architecture (Colrain et al., 2014; Datta et al., 2001; Fraigne et al., 2015; Gonzales & Jaworski, 1997; Kodama et al., 1998; Koob & Colrain, 2019; Kumar et al., 2009; Loving, 1997; Walsh, 2009). The downregulation of the GABAergic neurotransmitter system could potentially explain less SWS, more stage N2 sleep, and higher sigma power, reported in heavy-drinking late adolescents in the current investigation (Colrain et al., 2014; Gonzales & Jaworski, 1997; Koob & Colrain, 2019; Kumar et al., 2009; Walsh, 2009). The upregulation of the glutaminergic system could contribute to shorter REM sleep onset latencies in heavy-drinking late adolescents, as well as more wakefulness with increasing habitual alcohol consumption (Colrain et al., 2014; Datta et al., 2001; Fraigne et al., 2015; Kodama et al., 1998; Koob & Colrain, 2019; Kumar et al., 2009).

In heavy-drinking late adolescents, augmented stage N2 sleep and diminished SWS, compared to same-aged light drinkers, was only evident in the placebo condition of the current study (i.e., 48 hours or more of abstinence). Further to this, habitual alcohol use was positively correlated with wake after sleep onset and stage N2 sleep, and negatively correlated with sleep efficiency and SWS, in the placebo condition only. These findings may reflect neurochemical adaptation, as these relationships were no longer present following acute alcohol consumption. For instance, these sleep measures may normalise, or return to baseline levels, following pre-sleep alcohol ingestion in this age group. Supporting this theory, Silveri and colleagues (2014) showed that 23 binge-drinking young people (11 female), aged 18 to 24 years, had less intracellular GABA in the frontal lobe and anterior cingulate cortex, compared to 31 same-aged light drinkers. Lower intracellular GABA levels in heavy-drinking late adolescents could directly contribute to less SWS percentage, more stage N2 sleep, and higher sigma power, reported in the current investigation. Again, the hyperpolarisation of cortical and thalamocortical cell membrane potentials initially leads to sigma EEG activity, however further hyperpolarisation results in delta EEG activity, and eventually visually scored SWS (Dijk, 1995; Dossi et al., 1992; Steriade et al., 1991; Steriade et al., 1993). If the threshold for hyperpolarisation of cell membrane potentials is less likely to be reached due to a downregulation in intracellular GABAergic neurotransmission, this may result in higher sigma power, more stage N2 sleep, and less SWS, reported in the current study. As alcohol consumption prior to sleep acutely facilitates GABAergic neurotransmission, this may explain why SWS percentage returns to baseline, or the same level as light drinkers, following pre-sleep alcohol consumption in heavy-drinking late adolescents (Kumar et al., 2009; Lovinger, 1997). Supporting this

theory, acute alcohol administration in abstinent men recovering from an alcohol use disorder results in notable increases in SWS (Allen et al., 1977; Allen et al., 1980; Brower, 2001; Gross et al., 1973; Gross & Hastey, 1975; Wagman & Allen, 1975; Zarcone, 1978). Wagman and Allen (1975) administered varying doses of alcohol over multiple nights to six men diagnosed with an alcohol use disorder (mean age 35.5 years) who were abstinent for one week, following approximately eight years of problem drinking. They reported dose-dependent increases in SWS percentage following acute alcohol consumption, however, tolerance to this response developed within four nights of repeated administration (Wagman & Allen, 1975). As in mature adults with alcohol use disorders, acute alcohol consumption in heavy-drinking late adolescents may normalise sleep, potentially indicating some neurochemical adaptation to heavy alcohol use.

Unlike the GABAergic neurotransmitter system, the glutaminergic system is fully developed at birth, and augmented during adolescence and young adulthood (Arain et al., 2013; Doremus-Fitzwater et al., 2010; Insel et al., 1990; Petit et al., 2013; Saransaari & Oja, 1995; Spear, 2011). This is due to a developmental climax in the sensitivity of the brain's reward system, hypothesised to be evolutionarily advantageous at this age (Arain et al., 2013; Casey et al., 2011; Ellis et al., 2012; Spear, 2011). Indeed, the enhanced plasticity of the glutaminergic neurotransmitter system during adolescence and young adulthood may be one potential mechanism driving the increased incidence of alcohol use disorders in young people (Carpenter-Hyland & Chandler, 2007). Further to this, there is some evidence in animal models that heavy alcohol exposure during adolescence is related to enhanced glutaminergic neurotransmission in mature adulthood (Pascual, Boix, Felipo, & Guerri, 2009; Swartzwelder, Park, & Acheson, 2017). For example, an animal study by Pascual

and colleagues (2009) demonstrated that intermittent ethanol exposure (3.0 g/kg) in adolescent rats (postnatal day 25) over 14 days resulted in the higher baseline glutamate levels in adulthood. The upregulation of glutaminergic neurotransmitter systems in heavy-drinking late adolescents may explain shortened REM sleep onset latencies reported in the current study, regardless of experimental condition. The general augmentation of excitatory neurotransmission in young people may also explain why fewer REM sleep differences related to habitual alcohol use were reported in this age group, compared to mature adults. For example, there were no differences in overall REM sleep percentage between heavy and light drinkers, which may reflect the global augmentation of the glutaminergic system at this age. In summary, habitual alcohol use may impact sleep in young people via the adaptation of neurotransmitter systems. These effects may be unique to this developing age group due to the immaturity of the inhibitory neurotransmitter system and augmentation of the excitatory system.

The protracted development of the GABAergic neurotransmitter system, and augmented glutaminergic neurotransmission, has been related to increased impulsivity, reward seeking, and reduced cognitive control in young people (Gleich et al., 2015; Pascual et al., 2009; Silveri et al., 2013). A study by Silveri and colleagues (2013) demonstrated that lower levels of GABA in the anterior cingulate cortex, measured using proton magnetic resonance spectroscopy, was associated with poorer response inhibition and higher impulsivity, in 50 (25 female) young people, aged 12 to 24 years. A study by Gleich and colleagues (2015) reported that higher levels of glutamate in the anterior cingulate cortex, measured using functional and spectroscopy MRI, was associated with activation of the ventral striatum (i.e., the brain's reward centre) and increased impulsivity, when completing a gambling task,

in 28 early adolescents (13 female; 14.4 ± 0.6 years), compared to 26 adults (14 female; 26.1 ± 4.4 years). Deficits in these critical executive functions have also been implicated in the onset and acceleration of heavy alcohol use in this age group (Hermens et al., 2013; Nixon, 2013; Peeters et al., 2015; Peeters et al., 2014; Tarter et al., 2003). If the GABA system is then further downregulated, and the glutaminergic system further upregulated, as a result of heavy alcohol use, this could potentially lead to further degradations in these critical executive functions and promote ongoing alcohol use in young people. There is substantial evidence that heavy alcohol use during adolescence and young adulthood leads to notable changes in executive function (Gil-Hernandez & Garcia-Moreno, 2016; Lannoy et al., 2017; Lees et al., 2019; Parada et al., 2011; Peeters et al., 2014; Scaife & Duka, 2009). Gil-Hernandez and colleagues (2016) investigated executive function in 223 male and female adolescents aged 12 to 18 years and found that binge drinking was associated with greater disinhibition, executive dysfunction, and poorer working memory. A study by Lannoy and colleagues (2017) showed that 40 binge-drinking university students (19 female; 20.6 ± 1.7 years) demonstrated poorer executive control than age- and sex-matched controls. A meta-analysis of 21 neuropsychological studies showed that binge drinking in young people aged 10 to 24 years was associated with general neurocognitive impairment, and specific deficits in decision-making and inhibition (Lees et al., 2018; Lees et al., 2019). If the objective sleep deficits observed in the present study signify the adaptation of the excitatory and inhibitory neurotransmitter systems, this may reflect, or even result in, the cognitive and behavioural deficits associated with heavy alcohol use in this age group. This is one mechanism through which heavy alcohol use, and the associated sleep changes observed in the current investigation, may contribute to cognitive dysfunction and

ongoing alcohol use in young people. Future research is needed to explore this possibility.

Circadian alterations may also drive some of the objective sleep differences reported in the current study, particularly those regarding REM sleep timing. Circadian dysregulation has been identified in abstinent adults recovering from alcohol use disorders (Danel et al., 2009; Kuhlwein et al., 2003). Although circadian phase was not measured in the current study, it is possible that a circadian advancement could lead to earlier REM sleep timing in heavy-drinking late adolescents. However, research in adults suggests that alcohol use disorders are associated with a circadian phase delay, rather than advancement (Danel et al., 2009; Kuhlwein et al., 2003). This could suggest that the REM sleep advancement reported in the current investigation and general adult literature (Benca et al., 1992; Brower et al., 2011; Clark et al., 1998; Colrain et al., 2009b; Drummond et al., 1998; Gillin et al., 1994; Imatoh et al., 1986; Williams & Rundell, 1981) may primarily reflect neurochemical adaptation, or augmented glutaminergic neurotransmission, following recurrent heavy alcohol exposure, rather than a circadian disruption (Koob & Colrain, 2019). Further, a developmental peak in circadian phase delay occurs between approximately 15 and 21 years old, which may also influence the effects of habitual alcohol use on the circadian system in this age group (Hagenauer & Lee, 2013; Hagenauer et al., 2009; Roenneberg et al., 2004). It has been hypothesised that the circadian delay observed during adolescence and young adulthood may contribute to heavy alcohol use in this population (Hasler et al., 2015; Wong, 2010). Researchers have theorised that this relationship may be driven by sleep restriction resulting from circadian misalignment, leading to behavioural dysregulation, as well as circadian alterations in reward processing (Hasler et al., 2015). Thus, the potential

impact of habitual alcohol use on the circadian system in this age group warrants further investigation.

Heavy-drinking participants in the current study commenced habitual alcohol consumption earlier in their lifespan than same-aged light-drinking participants, by approximately one year. Further, heavy-drinking late adolescents had been consuming alcohol for approximately one year longer than light drinkers, likely reflecting their earlier age of drinking onset. It is possible that this may have contributed to the detection of objective sleep differences between heavy- and light-drinking late adolescents in the current investigation. There is substantial research evidence that younger age of drinking onset is associated with higher risk of developing an alcohol use disorder (Grant & Dawson, 1997; Grant, Stinson, & Harford, 2001; Hingson et al., 2006a, 2006b; Hingson & Zha, 2009; McGorry et al., 2011). This may be due to a pre-existing vulnerability to heavy alcohol consumption, and/or the promotion of future alcohol use, in these individuals. The risk is greatest with a drinking onset prior to 14 years of age (Grant & Dawson, 1997; Hingson et al., 2006a). On average, heavy-drinking participants in the current study commenced drinking at approximately 16.7 years old. This was older than the mean age of drinking onset in Australia, which was 16.1 years in 2016 (AIHW, 2017). Further to this, no participants in the current study commenced alcohol consumption prior to 14 years of age. However, earlier alcohol consumption is still associated with an increased likelihood of developing an alcohol use disorder, increased risk of experiencing alcohol-related harm, and higher single-occasion alcohol use (Grant et al., 2001; Hingson & Zha, 2009). It is possible that earlier and longer periods of habitual alcohol exposure may have contributed to the habitual alcohol-related objective sleep differences observed in present study. However, both heavy- and

light-drinking participants in the current study had comparatively short drinking histories, approximately 3.3 ± 1.5 years (median 2.8 years), and 2.4 ± 1.5 years (median 2.3 years), respectively. Nevertheless, it is possible that these demographic differences between heavy- and light-drinking late adolescents contributed to the objective sleep differences observed in the current investigation. This may be due to earlier and longer periods of exposure, and/or a pre-existing vulnerability to heavy alcohol use, however, longitudinal research is required to clarify this.

Although there is evidence that objective sleep differences related to habitual alcohol consumption in young people may represent underlying alcohol-related changes to the brain and sleep systems, it is also possible that some deficits may be pre-existing. There is currently no evidence of pre-existing deficits in visually scored sleep, such as the deficits reported in the current investigation (Tarokh & Carskadon, 2010; Tarokh et al., 2012). However, there is evidence that both children and adolescents with a family history of alcohol use disorders, a well-established risk factor for developing an alcohol use disorder, demonstrate EEG power spectra abnormalities prior to the onset of alcohol consumption (Tarokh & Carskadon, 2010; Tarokh et al., 2012). Tarokh and colleagues (2012) longitudinally assessed sleep PSG in 10 (4 female) children, aged 9 to 13 years, and 10 (5 female) adolescents, aged 15 to 19 years, with family histories of alcohol use disorders, compared to age-matched control participants (14 children; 15 adolescents) with no family history. They reported that alcohol-naïve children and adolescents with family histories of alcohol use disorders had lower non-REM delta power than control participants. Furthermore, deficits in non-REM delta power became more notable with increasing age. This finding likely reflects the underlying structural and functional neural deficits identified in alcohol-naïve children and adolescents with a family history of

alcohol use disorders, resulting in an impaired capacity to synchronise and elicit high amplitude delta EEG activity (Acheson et al., 2014; Benegal et al., 2007; Cservenka, 2016; Henderson et al., 2018; Herting et al., 2011; Spadoni et al., 2013; Squeglia et al., 2014; Venkatasubramanian et al., 2007). These sleep and neural changes are accompanied by cognitive deficits, most notably in executive functioning, which have been hypothesised to contribute to the onset and acceleration of alcohol use in young people with a family history of alcohol use disorders (Nigg et al., 2004). However, it is important to note that the current study did not report lower delta power in heavy-drinking late adolescents, compared to light drinkers. Further to this, there is no evidence that children and adolescents with a family history of alcohol use disorders have augmented sigma power, suggesting this EEG abnormality detected in the present investigation may not be pre-existing. As previously suggested, the use of experimental control groups in animal studies may provide evidence that binge ethanol exposure in adolescence causes objective sleep disturbances (Criado et al., 2008; Ehlers et al., 2018a; Ehlers & Slawecki, 2000). Furthermore, as both heavy- and light-drinking participants in the current study did not have a family history of alcohol use disorders (this was an exclusion criterion), and were closely matched in age and demographics, the objective sleep differences detected may primarily be a consequence of their habitual alcohol use, rather than a pre-existing condition. However, longitudinal research in young people with no family history of alcohol use disorders commencing prior to the onset of alcohol consumption, is needed to determine causation.

Lastly, it is possible that the positive relationship between high habitual alcohol use and objective sleep disturbances identified in the current study, could be bi-directional. There is a well-established bi-directional relationship between sleep

disturbance and heavy alcohol use in mature adults (Brower, 2003; Brower et al., 2001; Roehrs & Roth, 2001b, 2018). For example, adults diagnosed with insomnia are more likely to develop an alcohol use disorder than the general population (Brower, 2003; Weissman et al., 1997). A large epidemiological investigation in 14,485 adults aged over 18 years showed that individuals diagnosed with uncomplicated insomnia were at higher risk of developing an alcohol use disorder one year later, compared to individuals without insomnia (Weissman et al., 1997). Further to this, objective sleep disturbances, including shorter total sleep time, less SWS, and shorter REM sleep onset latencies, are predictive of relapse during abstinence or recovery from a long-term alcohol use disorder (Brower et al., 1998; Clark et al., 1998; Drummond et al., 1998; Gillin et al., 1994). There are several prospective studies that suggest poor sleep precedes, or even predicts, the onset of alcohol use and alcohol-related problems in young people (Bartel et al., 2015; Miller, Janssen, & Jackson, 2017; Nguyen-Louie et al., 2018; Pasch et al., 2012; Sivertsen et al., 2015; Wong & Brower, 2012; Wong et al., 2004; Wong et al., 2010; Wong et al., 2015). For instance, a prospective study in 6,504 adolescents showed that self-report sleeping difficulties, and shorter sleep duration, in adolescence predicated problematic alcohol-use in young adulthood (Wong et al., 2015). Although further evidence is needed, young people may be less likely to consume alcohol to self-medicate sleeping difficulties, a prospective pathway that is commonly cited in the adult literature (Brower, 2003; Brower et al., 2001; Roehrs & Roth, 2001b, 2018). This theory is supported by growing evidence that young people may be less susceptible to the sedative actions of acute alcohol consumption, discussed in the previous section (Chan et al., 2013; Linsenbardt et al., 2009; Little et al., 1996; Moy

et al., 1998; Pian et al., 2008; Quoilin et al., 2010; Silveri & Spear, 1998; White et al., 2002; York & Chan, 1993).

The prospective relationship between sleep disturbance and heavy alcohol use in young people may be mediated by impairments in executive functioning. Indeed, chronic sleep restriction in both adolescence and mature adulthood has been associated with notable impairments in executive functioning and increased risk-taking behaviour, including heavy alcohol use (Carskadon, 2011; Casey & Jones, 2010; Cohen-Zion, Shabi, Levy, Glasner, & Wiener, 2016; Hasler et al., 2015; Lo et al., 2016; Lowe et al., 2017; Lundahl et al., 2015; Van Dongen & Dinges, 2005; Van Dongen et al., 2003; Wittmann et al., 2006; Wolfson & Carskadon, 1998). A meta-analysis involving 61 experimental studies revealed that short-term sleep restriction was associated with impairments in executive functioning across all ages (Lowe et al., 2017). Further to this, immature executive functioning in young people, due to the protracted development of frontal and prefrontal brain regions, and neurotransmitter systems, has been hypothesised to contribute to higher habitual alcohol use in this age group, as well as increased risk of developing an alcohol use disorder (Arain et al., 2013; Bava & Tapert, 2010; Brown & Tapert, 2004a; Carskadon, 2011; Dahl & Lewin, 2002; Matthews, 2010; Monti et al., 2005; Nixon & McClain, 2010). Taken together, these findings suggest that the relationship between heavy alcohol consumption and sleep disturbance in young people may be bi-directional. However, longitudinal research is required to elucidate this possibility.

7.2.1 Sex differences

A unique strength of the current investigation is that it included both male and female participants when investigating the impacts of habitual alcohol use on sleep, as few studies have done this, particularly in young people (Colrain et al., 2014). It is again worth noting that, irrespective of acute or habitual alcohol consumption, late adolescent females had less stage N2 sleep than same-aged males. This finding was consistent with the normal sleep literature which indicates that females have higher SWS percentage, and lower stage N2 sleep, than males across the lifespan (Baker & O'Brien, 2017; Carskadon & Dement, 2017; Dijk et al., 1989; Ehlers & Kupfer, 1997; Mourtazaev et al., 1995; Walsleben et al., 2004). The current study also reported an interaction between sex and habitual alcohol use for stage N2 sleep percent. This interaction demonstrated that heavy-drinking females had higher stage N2 sleep than light-drinking females, irrespective of pre-sleep alcohol or placebo consumption. In contrast, there were no overall differences in stage N2 sleep percentage between heavy- and light-drinking males. As previously described, research in adults has consistently reported that both men and women diagnosed with alcohol use disorders have higher stage N2 sleep percentage than healthy age-matched controls (Adamson & Burdick, 1973; Allen et al., 1980; Brower, 2003; Brower et al., 1998; Colrain et al., 2009b; Drummond et al., 1998; Gross et al., 1973; Gross & Hastey, 1975; Imatoh et al., 1986; Johnson et al., 1970; Wagman & Allen, 1975; Williams & Rundell, 1981). Interestingly, the majority of this research was undertaken in men only (Adamson & Burdick, 1973; Allen et al., 1980; Brower et al., 1998; Drummond et al., 1998; Gross et al., 1973; Gross & Hastey, 1975; Imatoh et al., 1986; Johnson et al., 1970; Wagman & Allen, 1975; Williams & Rundell, 1981), so it is surprising that this effect was not detected in males in the present

study. It is possible that this null finding may be due to a ceiling effect, as stage N2 sleep was already higher in male participants. This finding may suggest that habitual alcohol use in young females impacts sleep architecture more than same-aged males. However, research in mature adults has reported that sleep architecture is impacted in a similar manner in both men and women diagnosed with alcohol use disorders (Colrain et al., 2009b). It is possible that this finding may be unique to late adolescents, however, further research is required to elucidate this unexpected finding.

There was a surprising three-way interaction between sex, habitual alcohol use, and electrode site for beta EEG spectral power in stage N1 sleep. This indicated that heavy-drinking males had lower overall beta power in stage N1 sleep, at frontal and central electrode sites, but not occipital, compared to light-drinking males. In contrast, there were no differences in beta power during stage N1 sleep between heavy- and light-drinking females at any electrode site. This observation is difficult to interpret as there is currently no research evidence that heavy alcohol consumption is associated with lower beta power (Colrain et al., 2014; Feige, Scaal, Hornyak, Gann, & Riemann, 2007; Irwin et al., 2002). This unexpected and discrepant finding may potentially be explained by the age of this developing cohort. It is well established that stage N1 sleep increases linearly with normal aging (Bliwise & Scullin, 2017; Carskadon et al., 1982; Ohayon et al., 2004). As late adolescents have less stage N1 sleep than older age groups, small changes in EEG activity within this sleep stage may be more easily detected, potentially leading to a type 1 statistical error. Furthermore, the current study may not have been powered to detect three-way interactions, so future research is required to replicate this unexpected finding in a larger sample.

Lastly, in both stage N1 and REM sleep, there were two unexpected four-way interactions between sex, habitual alcohol use, half night, and electrode site for theta EEG spectral power. These interactions indicated that heavy-drinking males had higher overall theta power in the first half of the sleep period compared to light-drinking males, but the magnitude of this difference was largest at central electrode sites, where theta EEG activity is known to be preferentially generated (Groppe et al., 2013). There were no differences in the second half of the sleep period, and this interaction was not detected in females. There is evidence that binge-drinking young adults, and adults with long-term alcohol use disorders, have higher theta power than healthy age-matched controls during wakefulness (Lopez-Caneda et al., 2017; Rangaswamy et al., 2003). Interestingly, EEG spectral power during stage N1 and REM sleep is most similar to wake, which may explain these similar findings. Higher theta power in stage N1 and REM sleep could represent an electrophysiological dysfunction related to heavy alcohol use. However, it is currently unclear why these differences were reported in male but not female late adolescents. Again, it is possible that these unexpected findings may be type 1 errors as the current investigation was not powered to detect four-way interactions. Additionally, as outlined in the methodology (section 5.4.2.4), this study was not powered to detect sex differences and so findings related to sex should be interpreted cautiously. Therefore, adequately powered research is required to draw definitive conclusions. Altogether, the preliminary findings of the current investigation suggest that habitual alcohol use largely impacts sleep in a similar manner in male and female late adolescents, however, there may be some critical differences that warrant further investigation.

7.3 Acute and habitual alcohol use interactions

There are very few studies that have simultaneously investigated the effects of both acute and habitual alcohol consumption on objective measures of sleep (Allen et al., 1977; Brower, 2001, 2003; Gross & Hastey, 1975; Wagman & Allen, 1975). Indeed, this is the first study to investigate acute and habitual alcohol use concurrently in a late adolescent population. The current study reported a negative correlation between previous 30-day alcohol consumption, and REM sleep onset latency, following acute pre-sleep alcohol ingestion. This weak but significant relationship suggested that higher levels of habitual alcohol consumption in late adolescents was related to shorter REM sleep onset latencies following acute pre-sleep alcohol consumption. This may potentially reflect an interaction between acute and habitual alcohol use, and REM sleep onset latency, in this cohort. However, the reason for this relationship is currently unclear. It is well-established that acute pre-sleep alcohol consumption lengthens REM sleep onset latency, and suppresses REM sleep percentage, in both late adolescents and mature adults (Aldrich, 1998; Chan et al., 2013; Feige et al., 2006; MacLean & Cairns, 1982; Miyata et al., 2004; Prinz et al., 1980; Roehrs et al., 1989; Rundell et al., 1972; Sagawa et al., 2011; Van Reen et al., 2006; Williams et al., 1983; Yules et al., 1967). Furthermore, acute alcohol administration in abstinent adults undergoing treatment for long-term alcohol use disorders also leads to longer REM sleep onset latencies, and REM sleep suppression (Allen et al., 1977; Allen et al., 1980; Brower, 2001; Gross et al., 1973; Gross & Hastey, 1975; Wagman & Allen, 1975; Zarcone, 1978). However, unlike the current investigation, none of these studies included a light- and heavy-drinking comparison group. It is possible that acute and habitual alcohol use may interact to impact REM

sleep uniquely in young people, however, additional research is required to replicate and interpret this unexpected finding.

Finally, when considering light-drinking late adolescents only, REM sleep percentage was positively associated with previous 30-day alcohol use, number of years drinking, and lifetime history of alcohol consumption, following acute pre-sleep alcohol ingestion. In other words, higher levels of light habitual alcohol use in late adolescents, who did not participate in binge drinking, was moderately associated with higher REM sleep percentage following acute alcohol consumption. This finding was unexpected, difficult to interpret, and was not evident when investigating heavy-drinking participants only. It is currently unclear why higher levels of light habitual alcohol use, but not heavy alcohol use, is associated with higher REM sleep percentage following alcohol consumption. Unfortunately, there are currently no other studies investigating REM sleep differences in light- and heavy-drinking late adolescents or adults. Speculatively, this finding could suggest that even low levels of habitual alcohol exposure during late adolescence, without binge drinking, may modify the effects of acute alcohol consumption on REM sleep. As previously suggested, differences in REM sleep architecture in late adolescents may reflect underlying neurochemical adaptation to habitual alcohol consumption. However, further research in this cohort is needed to confirm and comprehend these novel findings.

7.3.1 Sex differences

The limited studies that have investigated the interaction between acute and habitual alcohol use have been exclusively undertaken in male adults undergoing treatment for alcohol use disorders (Allen et al., 1977; Brower, 2001, 2003; Gross &

Hastey, 1975; Wagman & Allen, 1975). This highlights one novel aspect of the current investigation as it included both female and male heavy-drinking late adolescents. The current study revealed an interaction between sex, acute alcohol consumption, and habitual alcohol use for all-night SWS percentage. Firstly, in heavy-drinking males, all-night SWS percentage was higher following acute pre-sleep alcohol consumption, compared to placebo. In contrast, heavy-drinking females had lower all-night SWS percentage following alcohol consumption, compared to placebo. There were no differences in all-night SWS percentage between the alcohol and placebo condition in light-drinking males or females. This interaction also indicated that heavy-drinking females had less all-night SWS than same-aged light-drinking females, in both the alcohol and placebo condition. Conversely, compared to light-drinking males, heavy-drinking males had higher all-night SWS following acute alcohol consumption, with no differences in the placebo condition. Finally, there were no differences in SWS percentage between heavy-drinking males and females in the placebo condition.

This non-significant interaction effect suggests that acute alcohol ingestion impacts SWS in a similar manner in male and female light-drinking late adolescents. This supports research in both late adolescents, and mature adults, that has consistently reported an absence of differences in all-night SWS percentage following pre-sleep alcohol or placebo consumption in habitual light drinkers (Chan et al., 2013; Feige et al., 2006; Pressman, 2012; Rundell et al., 1972; Williams et al., 1983). This likely reflects alcohol's well-established biphasic effects on SWS, in which the initial SWS enhancement is offset by the secondary suppression, resulting in no all-night differences. However, this three-way interaction also suggests that acute pre-sleep alcohol consumption may uniquely impact all-night SWS in heavy-

drinking late adolescents. Specifically, acute pre-sleep alcohol appears to increase SWS in heavy-drinking males but suppress SWS in heavy-drinking females.

This finding in heavy-drinking males supports the adult literature which has consistently reported higher all-night SWS percentage following pre-sleep alcohol consumption in men diagnosed with long-term alcohol use disorders (Allen et al., 1977; Allen et al., 1980; Brower, 2001; Gross et al., 1973; Gross & Hastey, 1975; Wagman & Allen, 1975; Zarcone, 1978). It is critical to note that no previous research has included female participants, or a healthy age-matched control group, for comparison. Gross and Hastey (1975) compared baseline SWS percentage following approximately 3.5 weeks of abstinence (i.e., no acute alcohol) to four consecutive days of drinking (alcohol dose 1.6 – 3.2 g/kg) in 12 men aged 26 to 48 years diagnosed with alcohol use disorders. They reported that participants whose baseline SWS percentage was greater than 20 percent of total sleep time showed higher SWS percentage following acute alcohol consumption. However, participants who had less than 20 percent baseline SWS demonstrated no changes in SWS percentage following alcohol consumption. Gross and Hastey (1975) theorised that SWS enhancement following alcohol consumption in men experiencing alcohol use disorders can only occur if the brain and sleep systems are structurally and functionally capable of eliciting slow wave activity. Supporting their finding, heavy-drinking late-adolescent males in the current study had approximately 21.4 percent baseline SWS in the placebo condition, which increased by approximately 7.8 percent following alcohol consumption. Higher SWS percentage following alcohol consumption in heavy-drinking late-adolescent males may indicate that the brain and sleep systems are structurally and functionally capable of eliciting high amplitude slow wave activity. This SWS response to acute alcohol may reflect the adaptation of

neurotransmitter systems to high habitual alcohol use, in particular the downregulation of the GABAergic inhibitory system, critical for the onset and continuation of SWS (Chastain, 2006; Feld et al., 2013; Harrison et al., 2017; Saper et al., 2005; Sommer & Spanagel, 2013; Svanberg & Beaunieux, 2015; Walsh, 2009). As alcohol acutely enhances GABAergic neurotransmission, this may explain the increase or normalisation of SWS following alcohol consumption, and lower SWS in the placebo condition (Chastain, 2006; Harrison et al., 2017; Roehrs & Roth, 2001a; Sommer & Spanagel, 2013; Svanberg & Beaunieux, 2015).

It is currently unclear why heavy-drinking late-adolescent females experienced a small but significant decrease in all-night SWS percentage following acute alcohol consumption, compared to placebo. It is possible that this discrepant finding may be related to sex-specific differences in the interaction between acute and habitual alcohol use. This finding may indicate that heavy-drinking late-adolescent females experience greater SWS disturbances following pre-sleep alcohol consumption, compared to heavy-drinking late-adolescent males. Considering the current findings, all-night SWS increased by 7.8 percent in heavy-drinking males, however, heavy-drinking females showed a 1.4 percent decrease in SWS.

Examining the results more closely, in the first half of the sleep period, heavy-drinking males had a 12.6 percent more SWS, compared to placebo, whereas heavy-drinking females showed only a 0.1 percent difference. Furthermore, in the second half of the sleep period, heavy-drinking males had 0.8 percent less SWS following pre-sleep alcohol, however, heavy-drinking women had a larger 2.8 percent deficit in SWS, compared to placebo. This may suggest that acute alcohol consumption does not facilitate SWS in young heavy-drinking females in the same manner as heavy-drinking males and may lead to amplified secondary SWS disruption. This seems

consistent with a large body of literature which shows that women diagnosed with alcohol use disorders experience poorer physiological and psychological health outcomes, compared to men, despite having shorter drinking histories, less overall alcohol consumption, and longer periods of abstinence following recovery (Ashley et al., 1977; Ceylan-Isik et al., 2010; Colrain et al., 2011; Pfefferbaum et al., 2001a; SAMHSA/CSAT, 2009). This phenomenon has primarily been attributed to women's physiological sensitivity to acute alcohol intoxication (Brady & Randall, 1999; Ceylan-Isik et al., 2010; Greenfield et al., 2007; SAMHSA/CSAT, 2009). Specifically, after consuming the same alcohol dose per unit weight, women attain 20 to 25 percent higher BACs than men with the same body mass, due to their smaller pharmacological volume of distribution (Cavacuiti & Woodward, 2011; Goist & Sutker, 1985). This physiological vulnerability to acute alcohol may interact with habitual alcohol use to impact SWS in heavy-drinking late-adolescent females. While, possibly not powered to detect three-way interactions, the present study may provide some preliminary evidence that heavy alcohol use leads to poorer SWS outcomes in young females, compared to males. These preliminary findings require replication and further investigation to interpret.

Finally, the current study reported two complex interactions between sex, half night, acute, and habitual alcohol use, for both wake after sleep onset and sleep efficiency. These interactions suggest that late-adolescent heavy-drinking males, and light-drinking females, had less wake after sleep onset, and higher sleep efficiency, in the first half of the sleep period following acute alcohol consumption compared to placebo. These effects were not present in light-drinking males or heavy-drinking females. The reason for these effects is unclear. Due to the small samples in these comparisons the current investigation was not powered to detect four-way

interactions. It is therefore possible that these interactions may be the result of type 1 error. Additionally, as outlined in the methodology (section 5.4.2.4), this study was not powered to detect sex differences and so findings related to sex should be interpreted cautiously. Even so, these preliminary findings suggest that further investigation is warranted in this novel research area. In summary, the current study provides preliminary evidence that sex may interact with both the acute and habitual effects of alcohol on sleep in young people, although further research with larger sample sizes would be needed to elucidate such effects.

7.4 Broader implications and integration of findings

Together with previous research, the findings of the current investigation provide key evidence that both acute and habitual alcohol use in young people is associated with notable disturbances in objective sleep (Chan et al., 2015; Chan et al., 2013; Cohen-Zion et al., 2009; Nicholas et al., 2011; Williams et al., 1983). The integration of the current findings poses several critical implications concerning the impacts of alcohol use on sleep during the final stages of human neural development. The collective findings of the current study suggest that heavy-drinking young people are subject to ongoing sleep disturbances, present during both normal sleep and following an acute alcohol binge. Perhaps most notable were the enduring degradations in the amount and quality of SWS, detected following both alcohol and placebo consumption. SWS is the deepest, and arguably most functionally important, state of sleep, as demonstrated by its homeostatic regulation and precedence (Achermann & Borbely, 2017; Bonnet, 2011; Borbely et al., 1981; Dijk et al., 1990; Dijk et al., 1993; Moses et al., 1975). Long-term inadequate or low quality SWS could contribute to negative physical and mental health outcomes in heavy-drinking

young people. For example, persistent EEG abnormalities in SWS, such as alpha-delta sleep, following acute pre-sleep alcohol consumption, and augmented sigma spectral power, irrespective of pre-sleep alcohol consumption, may interfere with SWS's highly synchronous pattern of EEG activation. This may disturb fundamental SWS learning and memory processes, such as synaptic homeostasis and long-term potentiation (Huber et al., 2004; Tononi & Cirelli, 2006; Wang et al., 2011). This may also contribute to the robust impairments in long-term memory reported in heavy-drinking young people (Crego et al., 2009; Heffernan et al., 2009; Heffernan & O'Neill, 2012; Lees et al., 2019; Mota et al., 2013; Nguyen-Louie et al., 2016; Parada et al., 2011; Peeters et al., 2014). There is also substantial evidence that SWS is fundamental to neural and physiological restoration and growth (Horne, 1992; Krueger et al., 2016; Mendelsohn & Larrick, 2013; Van Cauter, 2000). This includes the clearance of neural waste via the brain's glymphatic system (Hablitz et al., 2019; Mendelsohn & Larrick, 2013; Xie et al., 2013), and the release of critical growth hormones (Feinberg, 2000; Sassin et al., 1969; Van Cauter, 2000) during SWS. Ongoing alcohol-related SWS deficits, and EEG irregularities, could also impact these critical functions, contributing to worse physiological health outcomes (Brown & Tapert, 2004b; Clark et al., 2001; LaBrie et al., 2018; Oesterle et al., 2004; Okoro et al., 2004), and lasting degradations in neural integrity and connectivity in heavy-drinking young people (Cservenka & Brumback, 2017; Ewing et al., 2014; Hanson et al., 2011; Heikkinen et al., 2017; Jones et al., 2018; Lees et al., 2018; Lisdahl et al., 2013a; McQueeney et al., 2009; Petit et al., 2014; Pfefferbaum et al., 2018; Silveri et al., 2016; Squeglia et al., 2009; Squeglia et al., 2012; Squeglia et al., 2015; Wilson et al., 2015). Although further research in this age group is needed, it is possible that the extent of SWS deficits, and the consequences of this, may contribute to ongoing

heavy alcohol consumption in young people (Adamson & Burdick, 1973; Brower et al., 1998; Clark et al., 1998; Drummond et al., 1998; Gillin et al., 1994). The findings of the current study suggest that acute and habitual SWS disturbances may be more prominent in young females who engage in heavy alcohol use; however, further research is required to confirm this. The accumulative effects of SWS sleep deficits in heavy-drinking young people may negatively impact development, functioning, and well-being.

There is substantial evidence that objective sleep disruption is a direct consequence of pre-sleep alcohol consumption due to its acute pharmacological effects on the brain and sleep systems (Chan et al., 2015; Chan et al., 2013; Chastain, 2006; Feige et al., 2006; Harrison et al., 2017; Roehrs & Roth, 2001a; Sommer & Spanagel, 2013; Svanberg & Beaunieux, 2015). However, it is still uncertain whether habitual alcohol-related sleep disturbance, in the absence of pre-sleep alcohol consumption, represents a pre-existing vulnerability to heavy alcohol use, alcohol-related changes to the brain and sleep systems, or both. Longitudinal research commencing prior to the onset of alcohol use is required to elucidate this. Pre-existing sleep disturbances may reflect neurophysiological and/or cognitive differences that promote heavy alcohol use in young people. For example, ongoing sleep disturbances or chronic sleep restriction in young people, prior to the onset of alcohol use, may lead to degradations in critical executive function that regulate the onset and acceleration of alcohol use (Carskadon, 2011; Casey & Jones, 2010; Cohen-Zion et al., 2016; Hasler et al., 2015; Lo et al., 2016; Lowe et al., 2017; Lundahl et al., 2015; Van Dongen & Dinges, 2005; Van Dongen et al., 2003; Wittmann et al., 2006; Wolfson & Carskadon, 1998). This is supported by evidence that sleep restriction in young people is associated with increased risk-taking

behaviours, including sexual activity, physical altercations, suicide, and drug and alcohol use (McKnight-Eily et al., 2011; O'Brien & Mindell, 2005; Wolfson & Carskadon, 1998). Pre-existing sleep disturbances may also reflect neurological abnormalities that impair executive function and promote alcohol use. For example, children and adolescents with a family history of alcohol use disorders demonstrate sleep and neurological deficits prior to the onset of alcohol use (Acheson et al., 2014; Benegal et al., 2007; Cservenka, 2016; Henderson et al., 2018; Herting et al., 2011; Spadoni et al., 2013; Squeglia et al., 2014; Tarokh & Carskadon, 2010; Tarokh et al., 2012; Venkatasubramanian et al., 2007). These deficits are accompanied by impairments in executive function, inhibitory control, and increased risk-taking (Dougherty et al., 2015; Kamarajan et al., 2015; Nigg et al., 2004). Critically, none of the objective sleep deficits observed in heavy-drinking late adolescents in the current study have been reported in alcohol naïve children or adolescents with a family history of alcohol use disorders (Tarokh & Carskadon, 2010; Tarokh et al., 2012). This may indicate that these sleep deficits are not pre-existing. However, there is still substantial subjective evidence that sleep deficits precede, or even predict, the onset of heavy alcohol use in young people (Bartel et al., 2015; Miller et al., 2017; Nguyen-Louie et al., 2018; Pasch et al., 2012; Sivertsen et al., 2015; Wong & Brower, 2012; Wong et al., 2004; Wong et al., 2010; Wong et al., 2015). Therefore, an investigation of objective sleep prior to the onset of alcohol use in the general population, not only young people at-risk of problematic alcohol use, is warranted. If some, or all, of the objective sleep deficits observed in the current study are pre-existing, this could be utilised as a potential biomarker to identify young people who are at risk for heavy alcohol use. This would allow for the implementation of early interventions to improve sleep and delay the onset of alcohol use in these individuals.

If the pattern of sleep deficits identified in the current investigation are not pre-existing, their presence may signify underlying neurological changes that are a direct consequence of heavy alcohol use in late adolescence. Concerningly, this would also indicate that habitual alcohol-related sleep and neural deficits develop relatively quickly in this population. This is because young people exhibit notably shorter and less intense periods of heavy drinking than adults with long-term alcohol use disorders. As previously highlighted, there is substantial neurophysiological evidence that heavy-drinking young people experience structural, functional, and neurochemical brain changes (Cservenka & Brumback, 2017; Ewing et al., 2014; Jones et al., 2018; Lees et al., 2018; Lisdahl et al., 2013a; Luciana et al., 2013; McQueeney et al., 2009; Petit et al., 2014; Pfefferbaum et al., 2018; Silveri et al., 2014; Silveri et al., 2016; Squeglia et al., 2009; Squeglia et al., 2012; Squeglia et al., 2015; Wilson et al., 2015). These changes are mirrored by impairments in critical executive functions that are essential for regulating alcohol use, such as inhibitory control (Gil-Hernandez & Garcia-Moreno, 2016; Lannoy et al., 2017; Peeters et al., 2014; Scaife & Duka, 2009). The degree to which these sleep and neural changes recover following the cessation of alcohol use is still uncertain, given that development is still ongoing at this time. Research in humans and animal models suggest that alcohol-related sleep, neural, and cognitive changes in young people may be long-lasting (Criado et al., 2008; Cservenka & Brumback, 2017; Ehlers et al., 2018a; Hanson et al., 2011; Heikkinen et al., 2017; Squeglia et al., 2015; Tapert et al., 2002). Although further research is needed, the combination of neural, cognitive, and sleep disturbances in heavy-drinking young people could perpetuate alcohol use (Adamson & Burdick, 1973; Brower et al., 1998; Clark et al., 1998; Drummond et al., 1998; Gillin et al., 1994). Sleep PSG could potentially be utilised as a non-

invasive tool to detect alcohol-related changes to the brain and sleep systems in young people. This could provide an estimation of the type (neurochemical, structural and/or functional) and severity of alcohol-related neural and sleep changes. The identification of these changes could aid in the implementation of interventions targeting alcohol consumption and sleep in heavy-drinking young people and prevent the onset of alcohol use disorders. Sleep PSG could also be utilised to assess neural and sleep recovery following a discontinuation or reduction of alcohol use in these individuals.

The established bi-directional relationship between heavy alcohol use and sleep disturbance suggests that the pattern of results observed in the current study may reflect a combination of both pre-existing and consequential sleep deficits (Brower, 2003; Brower et al., 2001; Roehrs & Roth, 2001b, 2018). Although longitudinal research is required to verify this possibility, this relationship may be mediated by underlying neurological changes and/or cognitive impairments in young people, as depicted in Figure 7.1. This growing body of evidence suggests there may be a complex, vicious cycle impacting the brain, cognition, sleep, and alcohol use in this developing age group. For instance, cognitive differences related to protracted neural development, and chronic sleep restriction, experienced globally in adolescence and young adulthood, may contribute to the onset and acceleration of acute alcohol use in this population (Carskadon, 2011; Dahl & Lewin, 2002; Hagenauer et al., 2009; Leger et al., 2012; Spear, 2000). As previously discussed, the findings of the current study, and previous research, suggest that objective sleep promotion is unlikely to motivate acute alcohol use in young people (Crews et al., 2007; Spear, 2014). Instead, the prospective relationship between sleep restriction and alcohol consumption is more likely to be mediated by impairments in executive

function, and increased risk-taking behaviour (Carskadon, 2011; Casey & Jones, 2010; Cohen-Zion et al., 2016; Hasler et al., 2015; Lo et al., 2016; Lowe et al., 2017; Lundahl et al., 2015; Van Dongen & Dinges, 2005; Van Dongen et al., 2003; Wittmann et al., 2006; Wolfson & Carskadon, 1998). Concerningly, this age group is already at heightened risk of chronic sleep restriction due to their unique developmental sleep changes, including a circadian phase delay, decline in homeostatic sleep drive, and socio-environmental factors, such as early-morning wake times and social prioritisation (Carskadon, 2011; Hagenauer et al., 2009; Wittmann et al., 2006). Acute and habitual alcohol-related sleep disturbances may further exacerbate chronic sleep restriction in this vulnerable population (Dahl & Lewin, 2002; Hagenauer et al., 2009; Spear, 2000). Although additional evidence is required, the current findings suggest that acute alcohol-related sleep disturbance, or restriction, could be exaggerated in young people, due to less initial sedation, and more secondary sleep disruption. Sleep disruption following acute alcohol ingestion may contribute to chronic sleep restriction, and impair next-day functioning, in young people. This could in-turn facilitate ongoing alcohol consumption by further exacerbating executive dysfunction and risk-taking behaviours. Habitual alcohol use may subsequently lead to the adaptation of the developing brain and sleep systems to heavy alcohol exposure, as indicated by the pattern of objective sleep deficits observed in the current study. For example, less SWS, more stage N2 sleep, and higher sigma power in heavy drinkers, compared to light drinkers, may signal the downregulation of the inhibitory GABAergic neurotransmitter system, and/or underlying changes in neural density and/or connectivity. Furthermore, shortened REM sleep onset latencies in heavy drinkers may signify an upregulation in excitatory glutaminergic neurotransmission. These sleep and neural changes could

further exacerbate cognitive and behavioural deficits, such as executive dysfunction and sensation seeking, that perpetuate ongoing alcohol consumption. Although longitudinal research is required to understand and substantiate this cycle, the integration of the present findings with previous literature provides some preliminary support. This complex cycle may contribute to higher single-occasion alcohol use, as well as heightened risk of developing an alcohol use disorder, in young people (AIHW, 2017; Arain et al., 2013; Crews et al., 2007; Marmorstein, 2017; Nixon & McClain, 2010; Pascual et al., 2009; Petit et al., 2013; WHO, 2018).

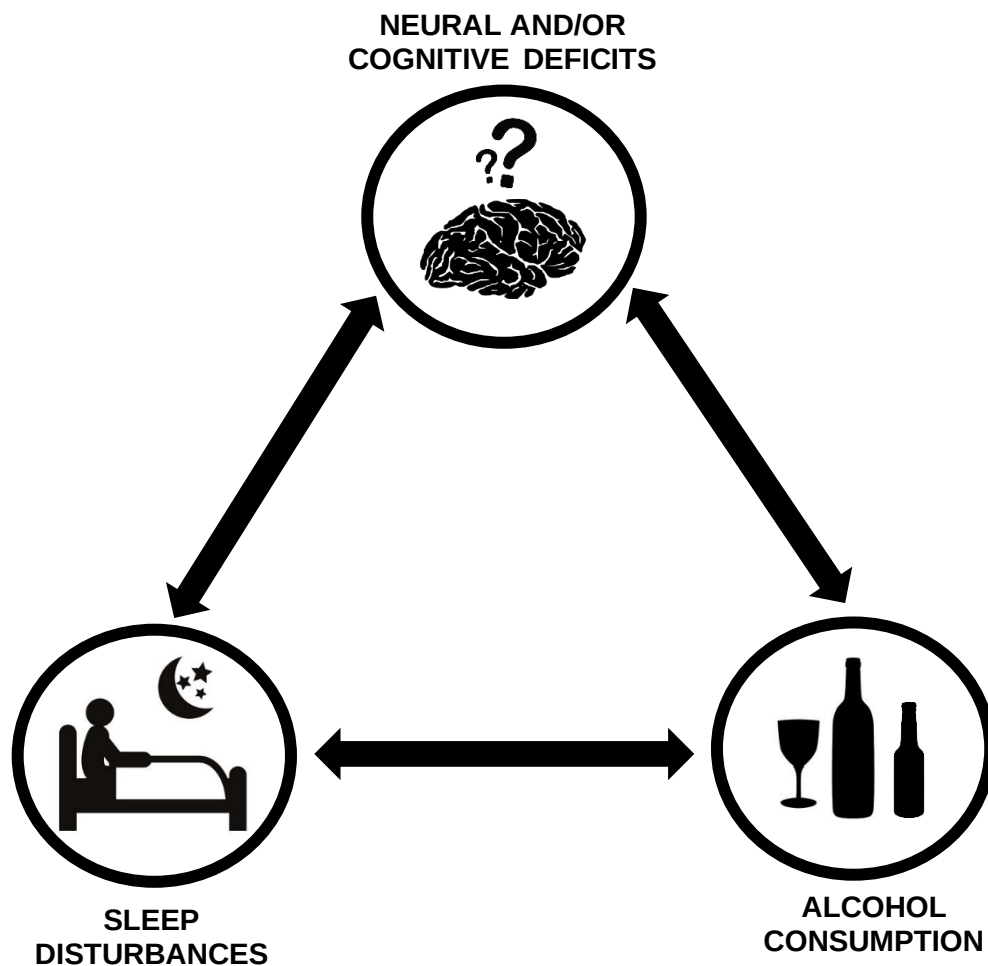


Figure 7.1. A visual representation of the theoretical vicious cycle, or bi-directional relationships, uniting alcohol consumption, sleep disturbances, and neural and/or cognitive deficits in young people.

The current findings provide evidence that the robust alcohol-related subjective sleep disturbances reported in young people may represent underlying objective sleep disturbances (Bartel et al., 2015; Ehlers et al., 2018b; Johnson & Breslau, 2001; Kenney et al., 2012; Kenney et al., 2014; Marmorstein, 2017; Miller et al., 2016; Morioka et al., 2013; Patrick, Griffin, Huntley, & Maggs, 2018; Pieters et al., 2010; Popovici & French, 2013; Sivertsen et al., 2015; Warren et al., 2017; Wong et al., 2015; Zhabenko et al., 2016). As adolescents and young adults consume the highest amounts of alcohol per single occasion worldwide, this growing literature suggests that young people are experiencing alcohol-related objective sleep disruption on a global scale (AIHW, 2017; WHO, 2018). Sleep disturbance may be particularly detrimental in this age group due to their continuing neural development, and high reliance on cognitive processes, during this unique time period (Brown & Tapert, 2004a). Adolescence and young adulthood are commonly associated with the greatest academic load in the lifespan due to the completion of secondary education, commencement of tertiary education and, commonly, entry into the workforce (Brown & Tapert, 2004a). Widespread alcohol use, and hence alcohol-related sleep disruption, during this crucial time period could have negative consequences for productivity and functioning in this population, which may impact quality of life. Indeed, there is evidence that both heavy alcohol use (Mohamed & Ajmal, 2015), and shorter sleep durations (Chen, Gelaye, & Williams, 2014), are independently associated with lower quality of life in young people. An investigation by Singleton and colleagues (2009) assessed self-report sleep, alcohol use, and academic performance in 236 (124 female) 18- to 22-year-old university students. They reported that higher levels of habitual alcohol consumption, shorter sleep durations, and more daytime sleepiness, directly predicted poorer academic performance.

Further to this, the relationship between higher levels of alcohol consumption and poorer academic performance, was mediated by self-report of sleep disturbances. Research has also demonstrated that higher levels of acute and habitual alcohol use throughout university is directly associated with lower academic grades and income potential (Wolaver, 2002). A large cross-sectional study in 14,138 (8,667 female) university students showed that 62.5 percent of frequent binge drinkers ($n=3,135$), 30.9 percent of occasional binge drinkers ($n=2,962$), and only 8.8 percent of non-binge drinkers ($n=5,063$), missed academic classes (Wechsler, Lee, Kuo, & Lee, 2000). Furthermore, 46.3 percent of frequent binge drinkers, 26.0 percent of occasional binge drinkers, and 9.8 percent in non-binge drinkers, reported falling behind in coursework. Although sleep was not assessed in these studies, it is possible these findings may also have been mediated by alcohol-related sleep disturbance (Zeigler et al., 2005). There is extensive evidence that sleep restriction is associated with impaired academic performance during primary, secondary, and tertiary education (see Curcio, 2006 for review). An investigation by Howell and colleagues (2004) in 246 (77 men) full-time university students (mean age 20.1 ± 3.8 years), demonstrated that poor self-report sleep quality was associated with poorer academic performance. As habitual alcohol consumption is common in both young people (AIHW, 2017; WHO, 2018) and university students (Dantzer, Wardle, Fuller, Pampalone, & Steptoe, 2006), alcohol-related sleep disruption may also mediate this relationship. Finally, the substantial global economic cost of workplace absenteeism, and decreased productivity, attributed to alcohol use, may be partially driven by alcohol-related sleep disturbances and its negative daytime consequences (Pidd, Berry, Roche, & Harrison, 2006; Roche, Pidd, & Kostadinov, 2016; Roche, Pidd, Berry, & Harrison, 2008; Thavorncharoensap, Teerawattananon, Yothasamut,

Lertpitakpong, & Chaikledkaew, 2009; WHO, 2018). In summary, acute, and habitual, alcohol-related sleep disturbances may contribute to poorer quality of life, academic performance and financial outcomes in young people.

Together with previous literature, the results of the current study provide critical evidence that it is important to prevent and/or counteract alcohol-related objective sleep disturbances in young people. Although further research is needed, the theoretical cycle involving the brain, cognition, sleep, and alcohol use, suggests there are several pathways through which this can occur, as summarised below in Figure 7.2. Interventions aiming to reduce alcohol-related sleep disturbances in young people could target alcohol use, sleep, and neural and/or cognitive function. The broader literature suggests that each of these potential targets are interdependent, meaning an improvement in one area may lead to improvement in other areas. As depicted in Figure 7.2, reducing alcohol use may improve both sleep and cognitive function, or alternatively, improving sleep may reduce alcohol consumption and improve cognitive function, and finally, enhancing cognitive function may reduce alcohol use and improve sleep. Ideally, interventions should aim to target each of these critical domains for maximum impact and effectiveness. Prevention programmes should be implemented towards the end of primary education and/or commencement of secondary education before the onset of alcohol use. Treatment programmes, targeting young people already experiencing alcohol-related sleep disturbances, may be more pertinent later in secondary education, throughout tertiary education, and beyond. These programmes should aim to educate young people about their continuing neural and physical development, and how this can impact their sleep, cognitive function, and behaviour, including alcohol use. They should emphasise the importance of sleep for performance and well-being, and explore the

unique negative consequences of inadequate sleep, and heavy alcohol use, in this age group. Furthermore, interventions should emphasise that alcohol is an extremely disruptive stimulus for sleep. In terms of practical skills, these programs should aim to develop excellent sleep hygiene, improve sleep duration and quality, enhance executive function, delay the onset of alcohol use, and reduce alcohol consumption. Interventions could be implemented utilising multiple formats, including mass media campaigns, school and university curriculums, or family-based, group-based, one-on-one, and/or online interventions (Das, Salam, Arshad, Finkelstein, & Bhutta, 2016).

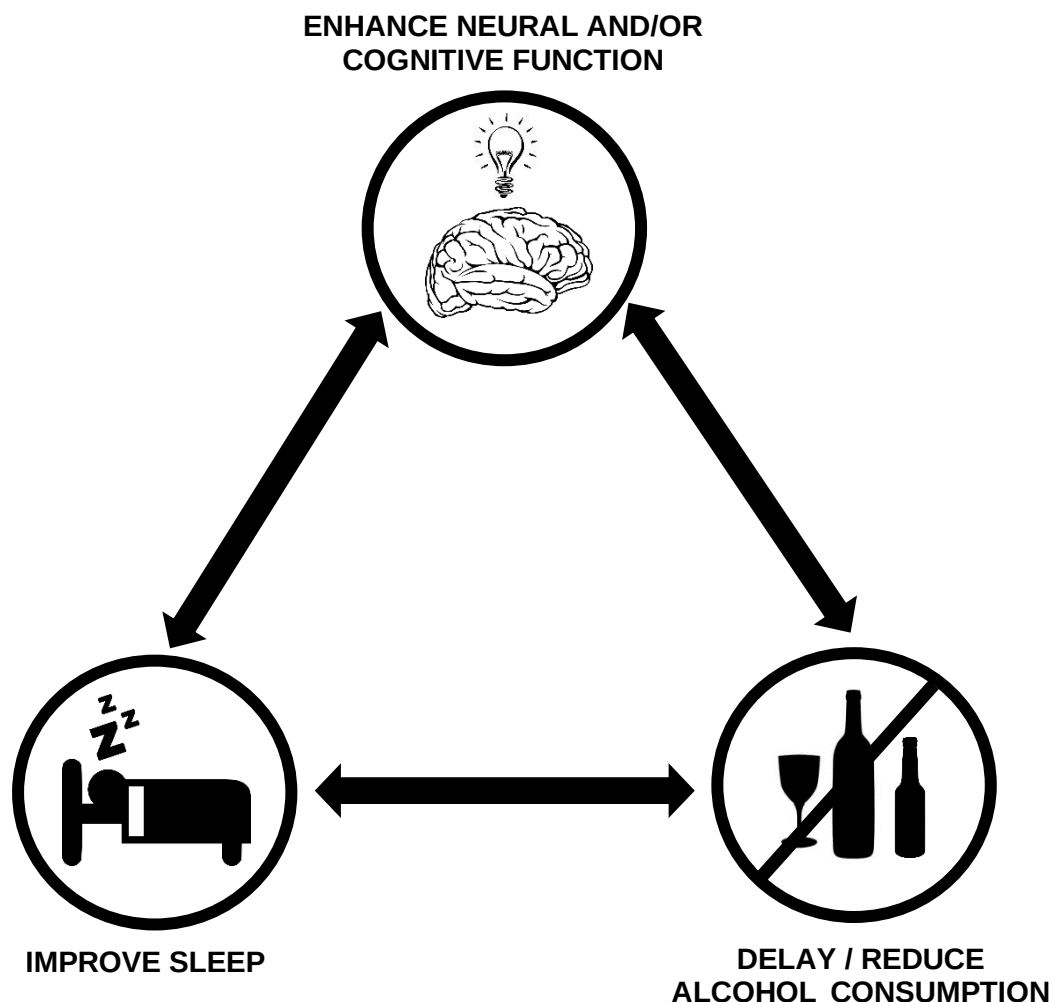


Figure 7.2. Potential intervention pathways to delay and/or reduce alcohol consumption, improve sleep disturbances, and enhance neural and/or cognitive function in young people.

Research has demonstrated that harm minimisation is the most effective approach to reduce alcohol consumption, and alcohol-related harm (e.g., sleep disturbances) in young people (Midford et al., 2017; Midford et al., 2014; Newton, Andrews, Teesson, & Vogl, 2009; Newton, Teesson, Vogl, & Andrews, 2010; Newton, Vogl, Teesson, & Andrews, 2009; Vogl et al., 2009; Vogl, Newton, Champion, & Teesson, 2014). Harm minimisation programmes aim to reduce alcohol-related harm to the individual and society, rather than stop alcohol consumption entirely (Adolescent Health Committee, 2008). A cluster-randomised controlled trial by Midford and colleagues (2017) compared a harm minimisation drug and alcohol programme, involving psychoeducation and cognitive skills development, embedded in early secondary school curriculums over two years (n=1,163), compared to business as usual (n=589). One year after the completion of the program (approximately 15 – 16 years old), participants in the programme had a lower trajectory to alcohol use, and experienced less alcohol-related harm, compared to controls. Furthermore, alcohol consumption, and alcohol-related harm, decreased in heavy-drinking participants. Although it was not assessed, these findings may also indicate that heavy-drinking participants were experiencing less acute alcohol-related sleep disturbance, as acute alcohol consumption decreased. A study by Bootzin and colleagues (2005) used an insomnia intervention to treat 55 (35 female) young people (aged 13 to 19 years) diagnosed with a substance use disorder and who were experiencing sleeping difficulties. In this sample, 50.9 percent selected marijuana as their substance of choice, 18.2 percent selected cocaine, 16.4 percent selected hallucinogens, and 14.6 percent selected speed, heroin, or alcohol. The 23 (10 female) patients who completed the treatment program showed improvements in both subjective and objective sleep quality, measured using sleep diaries and

actigraphy respectively, and lower substance use at a 12-month follow up, compared to 33 (11 female) participants who did not complete the intervention. Although this study did not exclusively investigate alcohol use, it may provide some preliminary evidence that improvements in objective sleep could reduce alcohol consumption in heavy-drinking young people.

The following interventions have each been independently shown to reduce alcohol use, improve sleep, and enhance executive function, in adolescents and/or young adults: Psychoeducation (Bootzin & Stevens, 2005; Carey, Scott-Sheldon, Carey, & DeMartini, 2007; Cortesi, Giannotti, Sebastiani, Bruni, & Ottaviano, 2004; Das-Friebel et al., 2019; de Sousa, AraÚJo, & de Azevedo, 2007; Fucito et al., 2017; Gipson, Chilton, Dickerson, Alfred, & Haas, 2019; Leeman, Perez, Nogueira, & DeMartini, 2015; Quek et al., 2012; Quinn et al., 2019; Tomaka, Palacios, Morales-Monks, & Davis, 2012), cognitive behavioural therapy (Bailey, Baker, Webster, & Lewin, 2004; Blake et al., 2017a; Blake et al., 2016; Blake et al., 2018; Blake et al., 2017b; Bootzin & Stevens, 2005; Carey et al., 2007; Carr & Stewart, 2019; Hides et al., 2010; Kay-Lambkin, Baker, Lewin, & Carr, 2009; Moseley & Gradisar, 2009), mindfulness (Blake et al., 2017a; Blake et al., 2016; Blake et al., 2018; Blake et al., 2017b; Bootzin & Stevens, 2005; Dunning et al., 2019; Dvorakova et al., 2017; Jaiswal, Tsai, Juan, Liang, & Muggleton, 2018; Mak, Whittingham, Cunningham, & Boyd, 2017; Park, Russell, & Fendrich, 2018; Russell, Hutchison, & Fusco, 2019), and exercise (Baldursdottir, Taehtinen, Sigfusdottir, Krettek, & Valdimarsdottir, 2017; Brand et al., 2010; Gatz, Kelly, & Clark, 2018; Gerber et al., 2014; Ludyga, Gerber, Brand, Puhse, & Colledge, 2018; Mendelson et al., 2016; Murphy, Pagano, & Marlatt, 1986; Park & Etner, 2019; Simonton, Young, & Johnson, 2018; Wu et al., 2019). The versatility of these interventions again highlights the interdependent

nature of these targets and suggests that programs should take advantage of this in their design (see Figure 7.2). For example, Fucito and colleagues (2017) implemented a brief four-week web-based psychoeducation programme in 42 heavy-drinking young adults (20 women), incorporating both evidence-based sleep hygiene and alcohol harm minimisation content. Post-intervention, all participants reported less weekly alcohol consumption, less alcohol-related harm, and better sleep quality. Interestingly, these effects were larger than similar interventions that addressed alcohol use only (Carey et al., 2007; Leeman et al., 2015). This suggests that targeting multiple domains simultaneously, including sleep disruption, may be more effective at improving overall outcomes in young people. Future research is required to determine the utility and outcomes of interventions that specifically aim to delay or reduce alcohol-related sleep disturbances in young people.

7.5 Strengths, limitations, and future directions

The design of the current study had several critical strengths that contributed uniquely to the growing body of research investigating the effects of alcohol use on sleep in young people. Firstly, the current study utilised the gold standard of objective sleep measurement, PSG (AASM, 2007). It also completed a spectral analysis of the EEG that detected subtle sleep differences related to alcohol use that would not have been easily quantified using traditional measures of visual sleep scoring (AASM, 2007; Colrain et al., 2009b). To encapsulate the final stages of human neural development, and encompass the population most likely to experience alcohol-related sleep disturbance globally, the current study was carried out exclusively in participants aged between 18 to 21 years old (AIHW, 2017; Feinberg et al., 1990; Lebel & Beaulieu, 2011; WHO, 2018). Few studies have investigated

the effects of alcohol consumption on sleep in this population due to the constraints of legal drinking age in countries such as the USA. The current study included a closely equal distribution of female and male late adolescents (AIHW, 2017; Johnston & White, 2004). Historically, research investigating the impacts of alcohol on sleep has focussed primarily on men, and the limited studies undertaken in women generally have not accounted for menstrual cycle phase (Arnedt et al., 2011; Cohen-Zion et al., 2009; Van Reen et al., 2006; Williams et al., 1983). As the menstrual cycle impacts sleep, the current study carefully scheduled female participant's sleep studies during the appropriate menstrual phase (Baker & Driver, 2004, 2007; Baker et al., 2001; Romans et al., 2015). Finally, this was the first study of its kind to concurrently examine the effects of both acute and habitual alcohol consumption on sleep in young people. The utilisation of a mixed-model design allowed for a unique comparison between heavy- and light-drinking, male and female late adolescents in their response to pre-sleep alcohol consumption, and their normal baseline sleep. This had not been investigated previously and the unique findings related to habitual alcohol use in the present study supported the theoretical reasoning underpinning the inclusion of this cohort.

No research investigation, however, is without its limitations. The primary limitation of the current study was its cross-sectional design. There is substantial interindividual variability in the distribution of visually scored sleep stages across the night, and EEG spectral power (Davies, 1976; De Gennaro, Ferrara, Vecchio, Curcio, & Bertini, 2005; Finelli, Achermann, & Borbely, 2001; Tucker, Dinges, & Van Dongen, 2007). Interindividual variability may have reduced the likelihood of detecting objective sleep differences between heavy- and light-drinking young people, however, as differences were detected this was not likely an issue. These

differences were more difficult to interpret as it was not possible to determine whether differences were pre-existing, and/or the result of habitual alcohol use, using this cross-sectional design. To address this, future research could utilise a longitudinal design to investigate objective sleep prior to, and after, the onset of heavy alcohol use in young people. As previously mentioned, the current study may have not been powered to accurately detect three- or four-way interactions, as this was outside the scope of the current investigation. It is currently unclear whether the three- and four-way interactions identified in the current study were meaningful. Research with larger sample sizes would be needed to verify or dismiss these preliminary findings. It is worth noting that a major longitudinal study is currently being undertaken in the USA called the National Consortium on Alcohol and Neurodevelopment in Adolescence (NCANDA) which may address some of the limitations of the current study (Baker et al., 2016; Goldstone et al., 2018; Pfefferbaum et al., 2016).

The current study utilised a timeline follow-back procedure to measure habitual alcohol consumption. Although this procedure can reliably distinguish light and heavy drinkers, there is evidence that it can lead to an underestimation of alcohol use, particularly at higher levels (Dulin, Alvarado, Fitterling, & Gonzalez, 2017; Monk, Heim, Qureshi, & Price, 2015; Poikolainen, 1985). This suggests that participants in the current study may have underestimated their previous 30-day alcohol intake, particularly heavy drinkers. Although this is not a major limitation of the current study, as categorising light and heavy drinkers was the primary function of this tool, it may be useful for future research to utilise a more accurate alcohol consumption measurement. For example, daily smartphone alcohol diaries have been shown to provide a more accurate measure of habitual alcohol consumption than a

timeline follow-back procedure (Dulin et al., 2017; Monk et al., 2015). This would allow for more accurate correlations between objective sleep measures and habitual alcohol use, than those reported in the current study.

There was substantial variability in the amount of alcohol consumed in the previous 30 days, and across the lifetime, particularly amongst heavy-drinking participants in the current study. It is possible that different levels of habitual alcohol use may have differential effects on sleep, which were not elucidated by the current investigation. For example, in adults experiencing long-term alcohol use disorders, the relationship between chronic alcohol use and objective sleep disturbances appears to be dose dependent (Brower, 2003; Brower et al., 2001; Feige et al., 2006; Roehrs & Roth, 2001b). It is possible this dose-dependent relationship may also be present in heavy-drinking young people. Indeed, the correlations identified in the current study between objective sleep disturbances, and habitual alcohol use, provide preliminary evidence for this. Future research could take this into account by utilising more accurate measures of habitual alcohol consumption and selecting and/or grouping participants that closely match each other in habitual alcohol use.

The blinding procedures undertaken in the current study may not have succeeded. As the total volume of the alcohol and placebo beverage were matched to control for the impacts of liquid volume, the alcohol beverage contained a considerable proportion of vodka. This distinct flavour may have been easily recognised by participants. Furthermore, as there was only one experimenter, the experimental condition was not double blinded. Although it is unlikely that expectancy effects or experimenter bias would impact objective sleep, it is possible that some measures may have been influenced, such as sleep onset latency. Future studies could counteract these limitations by utilising a non-alcoholic beverage that

effectively masks the flavour of alcohol, measuring participant blinding success, administering alcohol intravenously, and/or employing two experimenters for double blinding. In addition, a subjective measurement could be used to assess subjective sleep and next-day effects, such as hangover symptoms, following pre-sleep alcohol consumption.

The current study measured only one night of objective sleep following acute alcohol consumption. Limited research in adults suggests that sleep disturbances following acute alcohol consumption may persist for multiple nights (Ebrahim et al., 2013; Feige et al., 2006; Stein & Friedmann, 2005). Furthermore, research in animals suggests that acute alcohol administration (dose 1.5 – 3 g/kg) in adolescent rats leads to larger reductions in delta EEG spectral power in the second sleep period, compared to adults (Ehlers, Desikan, & Wills, 2013). Given that a binge pattern of alcohol consumption is typical in young people, it would be worthwhile investigating whether acute alcohol ingestion continues to negatively impact sleep over multiple nights (AIHW, 2017; WHO, 2018). If sleep continues to be disrupted over multiple nights, in the absence of acute alcohol consumption, this could contribute to the development of chronic sleep restriction in young people, and potentially perpetuate ongoing alcohol use.

Finally, together with previous research, the findings of the current study suggest that young people may experience less sensitivity to the initial sedative effects of acute pre-sleep alcohol, and more secondary sleep disruption, compared to mature adults. However, this interpretation is purely speculative as there was no adult comparison group in the current investigation. It would be useful for future studies to include an older comparison to elucidate whether young people respond

differently to pre-sleep alcohol consumption compared to mature adults, as this may have important implications.

7.6 Conclusions

The current study added to the substantial body of evidence that acute alcohol consumption prior to sleep leads to major objective sleep disturbances in both late adolescents and mature adults, including the elicitation of alpha-delta sleep (Aldrich, 1998; Arnedt et al., 2011; Chan et al., 2015; Chan et al., 2013; Colrain et al., 2014; Dijk et al., 1992; Ebrahim et al., 2013; Feige et al., 2006; Landolt et al., 1996; MacLean & Cairns, 1982; Roehrs & Roth, 2001a; Stein & Friedmann, 2005; Van Reen et al., 2006; Williams et al., 1983). This pattern of sleep disruption may compromise the restorative properties of sleep in young people, and contribute to the next-day alcohol hangover and chronic sleep restriction. The current study provided novel evidence that acute alcohol ingestion disrupts sleep in heavy-drinking late adolescents, a population regularly consuming high doses of alcohol (AIHW, 2017; WHO, 2018). Preliminary findings indicated SWS disruption following pre-sleep alcohol may be amplified in heavy-drinking young women, however, further research is required to confirm this. Finally, this study uniquely demonstrated that habitual alcohol use in young people is associated with disturbances to normal sleep, irrespective of pre-sleep alcohol consumption. Concerningly, despite their relatively short drinking histories, this pattern of deficits largely mirrored those reported in adults with long-term alcohol use disorders, including lower baseline levels of SWS (Angarita et al., 2016; Brower et al., 2001; Chakravorty et al., 2016; Colrain et al., 2014; Koob & Colrain, 2019; Roehrs & Roth, 2001b). In addition, some sleep disturbances appeared to be unique to this developing age group, such as augmented

sigma power during SWS. Given its functional importance, enduring degradations in SWS may be particularly detrimental in young people. Although longitudinal research is required, the sleep degradations observed in the current investigation may reflect a pre-existing vulnerability to heavy alcohol use, and/or alcohol-related changes to the brain and sleep systems. Taken together, the findings of the current investigation show that both acute and habitual alcohol use disturbs objective sleep in late adolescence.

In summary, the current investigation provides critical objective evidence that alcohol is an extremely disruptive stimulus to sleep in young people. The current findings also suggest that acute and habitual alcohol-related sleep deficits do not occur in isolation, indicating that heavy-drinking young people may suffer enduring sleep deficits. The costs of alcohol-related sleep disturbances may be particularly high in young people, due to their ongoing neural development and high reliance on cognitive processes during this crucial time period. It is imperative that action is taken to reduce the burden of alcohol-related sleep disturbances in young people to the individual and society. The bi-directional relationships uniting alcohol use, sleep, neural and cognitive function suggest that each of these critical areas could be targeted in young people for maximum impact and benefit. The prevention or successful treatment of alcohol-related sleep disturbances may improve sleep, reduce alcohol consumption, and/or improve neural and cognitive function. This would greatly enhance the quality of life, and protect the cognitive capacities, of young people in future generations.

REFERENCES

- AASM. (2007). *The AASM manual for the scoring of sleep and associated events: Rules, terminology and technical specifications*. Westchester, NY: American Academy of Sleep Medicine.
- ABS. (2018). *Apparent consumption of alcohol, Australia, 2016 - 2017*. Canberra: Australian Government.
- Achermann, P., & Borbely, A. A. (2017). Sleep homeostasis and models of sleep regulation. In M. H. Kryger, T. Roth, & W. C. Dement (Eds.), *Principles and Practice of Sleep Medicine* (6th ed., pp. 377-387). Philadelphia, PA: Elsevier.
- Achermann, P., Dijk, D.-J., Brunner, D. P., & Borbély, A. A. (1993). A model of human sleep homeostasis based on EEG slow-wave activity: Quantitative comparison of data and simulations. *Brain Research Bulletin*, 31(1-2), 97-113. doi:10.1016/0361-9230(93)90016-5
- Achermann, P., Dijk, D. J., Brunner, D. P., & Borbely, A. A. (1993). A model of human sleep homeostasis based on EEG slow-wave activity: Quantitative comparison of data and simulations. *Brain Research Bulletin*, 31(1-2), 97-113. doi:10.1016/0361-9230(93)90016-5
- Acheson, A., Wijtenburg, S. A., Rowland, L. M., Winkler, A. M., Gaston, F., Mathias, C. W., . . . Kochunov, P. (2014). Assessment of whole brain white matter integrity in youths and young adults with a family history of substance-use disorders. *Human Brain Mapping*, 35(11), 5401-5413. doi:10.1002/hbm.22559
- Acheson, S. K., Richardson, R., & Swartzwelder, H. S. (1999). Developmental changes in seizure susceptibility during ethanol withdrawal. *Alcohol*, 18(1), 23-26. doi:10.1016/S0741-8329(98)00063-9
- Acheson, S. K., Stein, R. M., & Swartzwelder, H. S. (1998). Impairment of semantic and figural memory by acute ethanol: Age-dependent effects. *Alcoholism: Clinical and Experimental Research*, 22(7), 1437-1442. doi:10.1111/j.1530-0277.1998.tb03932.x

- Adamson, J., & Burdick, J. A. (1973). Sleep of dry alcoholics. *Archives of General Psychiatry*, 28(1), 146-149. doi:10.1001/archpsyc.1973.01750310116019
- Adan, A., Benaiges, I., & Forero, D. A. (2016). Heavy episodic drinking or binge drinking: a booming consumption pattern. In V. R. Preedy (Ed.), *Neuropathology of drug addictions and substance misuse. Foundations of understanding, tobacco, alcohol, cannabinoids and opioids* (Vol. 1, pp. 389-397). London: Academic Press.
- Adolescent Health Committee. (2008). Harm reduction: An approach to reducing risky health behaviours in adolescents. *Paediatrics and Child Health*, 13(1), 53-60. doi:10.1093/pch/13.1.53
- Agargun, M. Y., Kara, H., & Solmaz, M. (1997). Sleep disturbances and suicidal behavior in patients with major depression. *The Journal of Clinical Psychiatry*, 58(6), 249-251. doi:10.4088/jcp.v58n0602
- AGDH. (2010). *Standard drinks guide*. Canberra, ACT: Australian Government Department of Health.
- AGDH. (2012). *Alcohol- the Australian standard drink*. Canberra, ACT: Australian Government Department of Health.
- AIHW. (2017). *National Drug Strategy Household Survey 2016. Detailed Findings*. Canberra, ACT: Australian Institute of Health and Welfare.
- AIHW. (2018). *Impact of alcohol and illicit drug use on the burden of disease and injury in Australia: Australian Burden of Disease Study 2011*. Canberra, ACT: Australian Institute of Health and Welfare.
- Alba-Ferrara, L. M., & de Erausquin, G. A. (2013). What does anisotropy measure? Insights from increased and decreased anisotropy in selective fiber tracts in schizophrenia. *Frontiers in Integrative Neuroscience*, 7, 9. doi:10.3389/fnint.2013.00009

- Aldrich, M. S. (1998). Effects of alcohol on sleep. In E. L. Gombert, A. M. Hegedus, & R. A. Zucker (Eds.), *Alcohol Problems and Aging* (pp. 281- 300). Bethesda, MD: National Institute of Health.
- Aldrich, M. S., Brower, K. J., & Hall, J. M. (1999). Sleep-disordered breathing in alcoholics. *Alcoholism: Clinical and Experimental Research*, 23(1), 134-140. doi:10.1111/j.1530-0277.1999.tb04034.x
- Alexander, A. L., Lee, J. E., Lazar, M., & Field, A. S. (2007). Diffusion tensor imaging of the brain. *Neurotherapeutics*, 4(3), 316-329. doi:10.1016/j.nurt.2007.05.011
- Allen, R. P., Wagman, A. M., & Funderburk, F. R. (1977). Slow wave sleep changes: Alcohol tolerance and treatment implications. *Advances in Experimental Medicine and Biology*, 85A, 629-640. doi:10.1007/978-1-4899-5181-6_40
- Allen, R. P., Wagman, A. M., Funderburk, F. R., & Wells, D. T. (1980). Slow wave sleep: A predictor of individual differences in response to drinking? *Biological Psychiatry*, 15(2), 345-348.
- American Psychiatric Association (APA). (2013). Diagnostic and statistical manual of mental disorders (5th ed.). Arlington, VA: American Psychiatric Publishing.
- Amzica, F., & Steriade, M. (1998). Electrophysiological correlates of sleep delta waves. *Electroencephalography and Clinical Neurophysiology*, 107(2), 69-83. doi:10.1016/S0013-4694(98)00051-0
- ANCD. (2013). *Alcohol Action Plan*. Canberra, ACT: Australian National Council on Drugs.
- Anderson, B. M., Stevens, M. C., Meda, S. A., Jordan, K., Calhoun, V. D., & Pearlson, G. D. (2011). Functional imaging of cognitive control during acute alcohol intoxication. *Alcoholism: Clinical and Experimental Research*, 35(1), 156-165. doi:10.1111/j.1530-0277.2010.01332.x

- Andrillon, T., Nir, Y., Staba, R. J., Ferrarelli, F., Cirelli, C., Tononi, G., & Fried, I. (2011). Sleep spindles in humans: Insights from intracranial EEG and unit recordings. *The Journal of Neuroscience*, 31(49), 17821-17834. doi:10.1523/JNEUROSCI.2604-11.2011
- Angarita, G. A., Emadi, N., Hodges, S., & Morgan, P. T. (2016). Sleep abnormalities associated with alcohol, cannabis, cocaine, and opiate use: A comprehensive review. *Addiction Science and Clinical Practice*, 11(1), 9. doi:10.1186/s13722-016-0056-7
- Arain, M., Haque, M., Johal, L., Mathur, P., Nel, W., Rais, A., . . . Sharma, S. (2013). Maturation of the adolescent brain. *Neuropsychiatric Disease and Treatment*, 9, 449-461. doi:10.2147/NDT.S39776
- Ariwodola, O. J., Crowder, T. L., Grant, K. A., Daunais, J. B., Friedman, D. P., & Weiner, J. L. (2003). Ethanol modulation of excitatory and inhibitory synaptic transmission in rat and monkey dentate granule neurons. *Alcoholism: Clinical and Experimental Research*, 27(10), 1632-1639. doi:10.1097/01.ALC.0000089956.43262.17
- Armitage, R. (1995). Microarchitectural findings in sleep EEG in depression: Diagnostic implications. *Biological Psychiatry*, 37(2), 72-84. doi:10.1016/0006-3223(94)00082-E
- Armitage, R., Hoffmann, R., Conroy, D. A., Arnedt, J. T., & Brower, K. J. (2012). Effects of a 3-hour sleep delay on sleep homeostasis in alcohol dependent adults. *Sleep*, 35(2), 273-278. doi:10.5665/sleep.1638
- Arnedt, J. T., Rohsenow, D. J., Almeida, A. B., Hunt, S. K., Gokhale, M., Gottlieb, D. J., & Howland, J. (2011). Sleep following alcohol intoxication in healthy, young adults: Effects of sex and family history of alcoholism. *Alcoholism: Clinical and Experimental Research*, 35(5), 870-878. doi:10.1111/j.1530-0277.2010.01417.x

- Arria, A. M., Dohey, M. A., Mezzich, A. C., Bukstein, O. G., & Van Thiel, D. H. (1995). Self-reported health problems and physical symptomatology in adolescent alcohol abusers. *Journal of Adolescent Health, 16*(3), 226-231. doi:10.1016/1054-139X(94)00066-N
- Ashley, M. J., Olin, J. S., le Riche, W. H., Kornaczewski, A., Schmidt, W., & Rankin, J. G. (1977). Morbidity in alcoholics. Evidence for accelerated development of physical disease in women. *Archives of Internal Medicine, 137*(7), 883-887. doi:10.1001/archinte.137.7.883
- Baglioni, C., Regen, W., Teghen, A., Spiegelhalder, K., Feige, B., Nissen, C., & Riemann, D. (2014). Sleep changes in the disorder of insomnia: A meta-analysis of polysomnographic studies. *Sleep Medicine Reviews, 18*(3), 195-213. doi:10.1016/j.smrv.2013.04.001
- Bailey, K. A., Baker, A. L., Webster, R. A., & Lewin, T. J. (2004). Pilot randomized controlled trial of a brief alcohol intervention group for adolescents. *Drug and Alcohol Review, 23*(2), 157-166. doi:10.1080/09595230410001704136
- Baker, F. C., & Driver, H. S. (2004). Self-reported sleep across the menstrual cycle in young, healthy women. *Journal of Psychosomatic Research, 56*(2), 239-243. doi:10.1016/S0022-3999(03)00067-9S0022399903000679 [pii]
- Baker, F. C., & Driver, H. S. (2007). Circadian rhythms, sleep, and the menstrual cycle. *Sleep Medicine, 8*(6), 613-622. doi:10.1016/j.sleep.2006.09.011
- Baker, F. C., Mitchell, D., & Driver, H. S. (2001). Oral contraceptives alter sleep and raise body temperature in young women. *Pflügers Archiv: European Journal of Physiology, 442*(5), 729-737. doi:10.1007/s004240100582
- Baker, F. C., & O'Brien, L. M. (2017). Sex differences and menstrual related changes in sleep and circadian rhythms. In M. Kryger, T. Roth, & W. C. Dement (Eds.), *Principles and Practice of Sleep Medicine* (6th ed., pp. 1556-1524). Philadelphia, PA: Elsevier.

- Baker, F. C., Turlington, S. R., & Colrain, I. (2012). Developmental changes in the sleep electroencephalogram of adolescent boys and girls. *Journal of Sleep Research, 21*(1), 59-67. doi:10.1111/j.1365-2869.2011.00930.x
- Baker, F. C., Willoughby, A. R., de Zambotti, M., Franzen, P. L., Prouty, D., Javitz, H., . . . Colrain, I. M. (2016). Age-Related Differences in Sleep Architecture and Electroencephalogram in Adolescents in the National Consortium on Alcohol and Neurodevelopment in Adolescence Sample. *Sleep, 39*(7), 1429-1439. doi:10.5665/sleep.5978
- Baldursdottir, B., Taehtinen, R. E., Sigfusdottir, I. D., Krettek, A., & Valdimarsdottir, H. B. (2017). Impact of a physical activity intervention on adolescents' subjective sleep quality: A pilot study. *Global Health Promotion, 24*(4), 14-22. doi:10.1177/1757975915626112
- Banerjee, N. (2014). Neurotransmitters in alcoholism: A review of neurobiological and genetic studies. *Indian Journal Human Genetics, 20*(1), 20-31. doi:10.4103/0971-6866.132750
- Banks, S., & Dinges, D. F. (2007). Behavioral and physiological consequences of sleep restriction. *Journal of Clinical Sleep Medicine, 3*(5), 519-528. doi:10.5664/jcsm.26918
- Bar, K. J., Boettger, M. K., Boettger, S., Groteluschen, M., Neubauer, R., Jochum, T., . . . Voss, A. (2006). Reduced baroreflex sensitivity in acute alcohol withdrawal syndrome and in abstained alcoholics. *Drug and Alcohol Dependence, 85*(1), 66-74. doi:10.1016/j.drugalcdep.2006.03.014
- Barnow, S., Schuckit, M. A., Lucht, M., John, U., & Freyberger, H. J. (2002). The importance of a positive family history of alcoholism, parental rejection and emotional warmth, behavioral problems and peer substance use for alcohol problems in teenagers: A path analysis. *Journal of Studies on Alcohol, 63*(3), 305-315. doi:10.15288/jsa.2002.63.305

- Bartel, K. A., Gradisar, M., & Williamson, P. (2015). Protective and risk factors for adolescent sleep: A meta-analytic review. *Sleep Medicine Reviews*, 21, 72-85. doi:10.1016/j.smrv.2014.08.002
- Bartsch, A. J., Homola, G., Biller, A., Smith, S. M., Weijers, H. G., Wiesbeck, G. A., . . . Bendszus, M. (2007). Manifestations of early brain recovery associated with abstinence from alcoholism. *Brain*, 130(Pt 1), 36-47. doi:10.1093/brain/awl303
- Baumberg, B. (2006). The global economic burden of alcohol: A review and some suggestions. *Drug and Alcohol Review*, 25(6), 537-551. doi:10.1080/09595230600944479
- Bava, S., & Tapert, S. F. (2010). Adolescent brain development and the risk for alcohol and other drug problems. *Neuropsychology Review*, 20(4), 398-413. doi:10.1007/s11065-010-9146-6
- Bayard, M., McIntyre, J., Hill, K. R., & Woodside, J., Jr. (2004). Alcohol withdrawal syndrome. *American Family Physician*, 69(6), 1443-1450.
- Bazov, I., Kononenko, O., Watanabe, H., Kuntic, V., Sarkisyan, D., Taqi, M. M., . . . Bakalkin, G. (2013). The endogenous opioid system in human alcoholics: Molecular adaptations in brain areas involved in cognitive control of addiction. *Addiction Biology*, 18(1), 161-169. doi:10.1111/j.1369-1600.2011.00366.x
- Bechler, M. E., Byrne, L., & Ffrench-Constant, C. (2015). CNS myelin sheath lengths are an intrinsic property of oligodendrocytes. *Current Biology*, 25(18), 2411-2416. doi:10.1016/j.cub.2015.07.056
- Becker, H. C., & Ron, D. (2014). Animal models of excessive alcohol consumption: Recent advances and future challenges. *Alcohol*, 48(3), 205-208. doi:10.1016/j.alcohol.2014.04.001

- Beersma, D. G., Dijk, D. J., Blok, C. G., & Everhardus, I. (1990). REM sleep deprivation during 5 hours leads to an immediate REM sleep rebound and to suppression of non-REM sleep intensity. *Electroencephalography and Clinical Neurophysiology*, 76(2), 114-122.
doi:10.1016/0013-4694(90)90209-3
- Bell, S. H., Stade, B., Reynolds, J. N., Rasmussen, C., Andrew, G., Hwang, P. A., & Carlen, P. L. (2010). The remarkably high prevalence of epilepsy and seizure history in fetal alcohol spectrum disorders. *Alcoholism: Clinical and Experimental Research*, 34(6), 1084-1089. doi:10.1111/j.1530-0277.2010.01184.x
- Benca, R. M., Obermeyer, W. H., Thisted, R. A., & Gillin, J. C. (1992). Sleep and psychiatric disorders. A meta-analysis. *Archives of General Psychiatry*, 49(8), 651-668; discussion 669-670. doi:10.1001/archpsyc.1992.01820080059010
- Benegal, V., Antony, G., Venkatasubramanian, G., & Jayakumar, P. N. (2007). Gray matter volume abnormalities and externalizing symptoms in subjects at high risk for alcohol dependence. *Addiction Biology*, 12(1), 122-132.
doi:10.1111/j.1369-1600.2006.00043.x
- Benham, G. (2010). Sleep: An important factor in stress-health models. *Stress and Health*, 26(3), 204-214. doi:10.1002/smi.1304
- Benoit, O., Foret, J., Bouard, G., Merle, B., Landau, J., & Marc, M. E. (1980). Habitual sleep length and patterns of recovery sleep after 24 hour and 36 hour sleep deprivation. *Electroencephalography and Clinical Neurophysiology*, 50(5-6), 477-485. doi:10.1016/0013-4694(80)90014-0
- Bersagliere, A., Pascual-Marqui, R. D., Tarokh, L., & Achermann, P. (2018). Mapping slow waves by eeg topography and source localization: Effects of sleep deprivation. *Brain Topography*, 31(2), 257-269. doi:10.1007/s10548-017-0595-6

- Best, J. R., & Miller, P. H. (2010). A developmental perspective on executive function. *Child Development*, 81(6), 1641-1660. doi:10.1111/j.1467-8624.2010.01499.x
- Bishara, A. J., & Hittner, J. B. (2012). Testing the significance of a correlation with nonnormal data: Comparison of Pearson, Spearman, transformation, and resampling approaches. *Psychological Methods*, 17(3), 399-417. doi:10.1037/a0028087
- Bishara, A. J., & Hittner, J. B. (2015). Reducing bias and error in the correlation coefficient due to nonnormality. *Educational and Psychological Measurement*, 75(5), 785-804. doi:10.1177/0013164414557639
- Bishop, N. A., Lu, T., & Yankner, B. A. (2010). Neural mechanisms of ageing and cognitive decline. *Nature*, 464(7288), 529-535. doi:10.1038/nature08983
- Bixler, E. O., Papaliaga, M. N., Vgontzas, A. N., Lin, H. M., Pejovic, S., Karataraki, M., . . . Chrousos, G. P. (2009). Women sleep objectively better than men and the sleep of young women is more resilient to external stressors: Effects of age and menopause. *Journal of Sleep Research*, 18(2), 221-228. doi:10.1111/j.1365-2869.2008.00713.x
- Blake, M., Schwartz, O., Waloszek, J. M., Raniti, M., Simmons, J. G., Murray, G., . . . Allen, N. B. (2017a). The sense study: Treatment mechanisms of a cognitive behavioral and mindfulness-based group sleep improvement intervention for at-risk adolescents. *Sleep*, 40(6), zsx061. doi:10.1093/sleep/zsx061
- Blake, M., Waloszek, J. M., Schwartz, O., Raniti, M., Simmons, J. G., Blake, L., . . . Allen, N. B. (2016). The SENSE study: Post intervention effects of a randomized controlled trial of a cognitive-behavioral and mindfulness-based group sleep improvement intervention among at-risk adolescents. *Journal of Consulting and Clinical Psychology*, 84(12), 1039-1051. doi:10.1037/ccp0000142

- Blake, M. J., Blake, L. M., Schwartz, O., Raniti, M., Waloszek, J. M., Murray, G., . . . Allen, N. B. (2018). Who benefits from adolescent sleep interventions? Moderators of treatment efficacy in a randomized controlled trial of a cognitive-behavioral and mindfulness-based group sleep intervention for at-risk adolescents. *Journal of Child Psychology and Psychiatry*, 59(6), 637-649. doi:10.1111/jcpp.12842
- Blake, M. J., Snoep, L., Raniti, M., Schwartz, O., Waloszek, J. M., Simmons, J. G., . . . Allen, N. B. (2017b). A cognitive-behavioral and mindfulness-based group sleep intervention improves behavior problems in at-risk adolescents by improving perceived sleep quality. *Behaviour Research and Therapy*, 99, 147-156. doi:10.1016/j.brat.2017.10.006
- Blitzer, R. D., Gil, O., & Landau, E. M. (1990). Long-term potentiation in rat hippocampus is inhibited by low concentrations of ethanol. *Brain Research*, 537(1-2), 203-208. doi:10.1016/0006-8993(90)90359-J
- Bliwise, D. L. (1993). Sleep in normal aging and dementia. *Sleep*, 16(1), 40-81. doi:10.1093/sleep/16.1.40
- Bliwise, D. L., & Scullin, M. K. (2017). Normal Aging. In M. H. Kryger, T. Roth, & W. C. Dement (Eds.), *Principles and Practice of Sleep Medicine* (6th ed., pp. 25-38). Philadelphia, PA: Elsevier.
- Blume, S. B. (1986). Women and alcohol. A review. *The Journal of the American Medical Association*, 256(11), 1467-1470. doi:10.1001/jama.1986.03380110073029
- Bode, C., & Bode, J. C. (1997). Alcohol's role in gastrointestinal tract disorders. *Alcohol Health and Research World*, 21(1), 76-83.
- Boivin, D. B., & Boudreau, P. (2014). Impacts of shift work on sleep and circadian rhythms. *Pathologie Biologie*, 62(5), 292-301. doi:10.1016/j.patbio.2014.08.001

- Bonnet, M. H. (2011). Acute sleep deprivation. In M. H. Kryger, T. Roth, & W. C. Dement (Eds.), *Principles and Practice of Sleep Medicine* (5th ed., pp. 27-42). Philadelphia, PA: Elsevier Saunders.
- Bootzin, R. R., & Stevens, S. J. (2005). Adolescents, substance abuse, and the treatment of insomnia and daytime sleepiness. *Clinical Psychology Review*, 25(5), 629-644. doi:10.1016/j.cpr.2005.04.007
- Borbely, A. A. (1982a). Sleep regulation. Introduction. *Human Neurobiology*, 1(3), 161-162.
- Borbely, A. A. (1982b). A two process model of sleep regulation. *Human Neurobiology*, 1(3), 195-204.
- Borbely, A. A. (2001). From slow waves to sleep homeostasis: New perspectives. *Archives Italiennes de Biologie*, 139(1-2), 53-61.
- Borbely, A. A., & Achermann, P. (1999). Sleep homeostasis and models of sleep regulation. *Journal of Biological Rhythms*, 14(6), 557-568. doi:10.1177/074873099129000894
- Borbely, A. A., Baumann, F., Brandeis, D., Strauch, I., & Lehmann, D. (1981). Sleep deprivation: Effect on sleep stages and EEG power density in man. *Electroencephalography and Clinical Neurophysiology*, 51(5), 483-495. doi:10.1016/0013-4694(81)90225-x
- Boyd, S. J., Corbin, W. R., Morean, M. E., & Martin, C. S. (2017). Alcohol stimulation and sedation: A critical review of the biphasic alcohol effects scale. *Current Addiction Reports*, 4(2), 209-220. doi:10.1007/s40429-017-0150-2
- Boyle, P. (2013). *Alcohol: Science, policy and public health*. Oxford: Oxford University Press.
- Brady, K. T., & Randall, C. L. (1999). Gender differences in substance use disorders. *Psychiatric Clinics of North America*, 22(2), 241-252. doi:10.1016/j.cpr.2017.10.012

- Brand, S., Gerber, M., Beck, J., Hatzinger, M., Puhse, U., & Holsboer-Trachsler, E. (2010). High exercise levels are related to favorable sleep patterns and psychological functioning in adolescents: A comparison of athletes and controls. *Journal of Adolescent Health, 46*(2), 133-141. doi:10.1016/j.jadohealth.2009.06.018
- Brand, S., & Kirov, R. (2011). Sleep and its importance in adolescence and in common adolescent somatic and psychiatric conditions. *International Journal of General Medicine, 4*, 425-442. doi:10.2147/IJGM.S11557
- Brasser, S. M., & Spear, N. E. (2002). Physiological and behavioral effects of acute ethanol hangover in juvenile, adolescent, and adult rats. *Behavioral Neuroscience, 116*(2), 305-320. doi:10.1037/0735-7044.116.2.305
- Brower, K. J. (2001). Alcohol's effects on sleep in alcoholics. *Alcohol Research and Health, 25*(2), 110-125.
- Brower, K. J. (2003). Insomnia, alcoholism and relapse. *Sleep Medicine Reviews, 7*(6), 523-539. doi:10.1016/S1087-0792(03)90005-0
- Brower, K. J., Aldrich, M. S., & Hall, J. M. (1998). Polysomnographic and subjective sleep predictors of alcoholic relapse. *Alcoholism: Clinical and Experimental Research, 22*(8), 1864-1871. doi:10.1111/j.1530-0277.1998.tb03995.x
- Brower, K. J., Aldrich, M. S., Robinson, E. A. R., Zucker, R. A., & Greden, J. F. (2001). Insomnia, self-medication and relapse to alcoholism. *American Journal of Psychiatry, 158*(3), 399-404. doi:10.1176/appi.ajp.158.3.399
- Brower, K. J., Krentzman, A., & Robinson, E. A. (2011). Persistent insomnia, abstinence, and moderate drinking in alcohol-dependent individuals. *The American Journal on Addictions, 20*(5), 435-440. doi:10.1111/j.1521-0391.2011.00152.x
- Brown, S. A., & Tapert, S. F. (2004). Adolescence and the trajectory of alcohol use: Basic to clinical studies. *Annals of the New York Academy of Sciences, 1021*, 234-244. doi:10.1196/annals.1308.028

- Brown, S.A., & Tapert, S.F. (2004b). Health consequences of adolescent alcohol involvement. In R. Bonnie, & M. O'Connell (Eds.), *Reducing underage drinking: A collective responsibility* (pp. 383–401). Washington, DC: The National Academies Press.
- Brown, S. A., Tapert, S. F., Granholm, E., & Delis, D. C. (2000). Neurocognitive functioning of adolescents: Effects of protracted alcohol use. *Alcoholism: Clinical and Experimental Research*, 24(2), 164-171. doi:10.1111/j.1530-0277.2000.tb04586.x
- Brunelle, C., Barrett, S. P., & Pihl, R. O. (2007). Relationship between the cardiac response to acute intoxication and alcohol-induced subjective effects throughout the blood alcohol concentration curve. *Human Psychopharmacology: Clinical and Experimental*, 22(7), 437-443. doi:10.1002/hup.866
- Brunner, D. P., Dijk, D. J., & Borbely, A. A. (1993). Repeated partial sleep deprivation progressively changes in EEG during sleep and wakefulness. *Sleep*, 16(2), 100-113. doi:10.1093/sleep/16.2.100
- Brunner, D. P., Dijk, D. J., Tobler, I., & Borbely, A. A. (1990). Effect of partial sleep deprivation on sleep stages and EEG power spectra: Evidence for non-REM and REM sleep homeostasis. *Electroencephalography and Clinical Neurophysiology*, 75(6), 492-499. doi:10.1016/0013-4694(90)90136-8
- Buchmann, A., Ringli, M., Kurth, S., Schaerer, M., Geiger, A., Jenni, O. G., & Huber, R. (2011). EEG sleep slow-wave activity as a mirror of cortical maturation. *Cerebral Cortex*, 21(3), 607-615. doi:10.1093/cercor/bhq129
- Buckman, J. F., Eddie, D., Vaschillo, E. G., Vaschillo, B., Garcia, A., & Bates, M. E. (2015). Immediate and complex cardiovascular adaptation to an acute alcohol dose. *Alcoholism: Clinical and Experimental Research*, 39(12), 2334-2344. doi:10.1111/acer.12912

- Bushey, D., Tononi, G., & Cirelli, C. (2011). Sleep and synaptic homeostasis: Structural evidence in *Drosophila*. *Science*, 332(6037), 1576-1581. doi:10.1126/science.1202839
- Butterworth, R. F. (1995). Pathophysiology of alcoholic brain damage: Synergistic effects of ethanol, thiamine deficiency and alcoholic liver disease. *Metabolic Brain Disease*, 10(1), 1-8. doi:10.1007/BF01991777
- Butterworth, R. F. (2003). Hepatic encephalopathy- A serious complication of alcoholic liver disease. *Alcohol Research and Health*, 27(2), 143-145.
- Buyse, D. J., Grunstein, R., Horne, J., & Lavie, P. (2010). Can an improvement in sleep positively impact on health? *Sleep Medicine Reviews*, 14(6), 405-410. doi:10.1016/j.smr.2010.02.001
- Campbell, I. G., Darchia, N., Higgins, L. M., Dykan, I. V., Davis, N. M., de Bie, E., & Feinberg, I. (2011). Adolescent changes in homeostatic regulation of EEG activity in the delta and theta frequency bands during NREM sleep. *Sleep*, 34(1), 83-91. doi:10.1093/sleep/34.1.83
- Campbell, I. G., Darchia, N., Khaw, W. Y., Higgins, L. M., & Feinberg, I. (2005). Sleep EEG evidence of sex differences in adolescent brain maturation. *Sleep*, 28(5), 637-643. doi:10.1093/sleep/28.5.637
- Campbell, I. G., & Feinberg, I. (2009). Longitudinal trajectories of non-rapid eye movement delta and theta EEG as indicators of adolescent brain maturation. *Proceedings of the National Academy of Sciences of the United States of America*, 106(13), 5177-5180. doi:10.1073/pnas.0812947106
- Capellini, I., Nunn, C. L., McNamara, P., Preston, B. T., & Barton, R. A. (2008). Energetic constraints, not predation, influence the evolution of sleep patterning in mammals. *Functional Ecology*, 22(5), 847-853. doi:10.1111/j.1365-2435.2008.01449.x

- Cardenas, V. A., Greenstein, D., Fouche, J. P., Ferrett, H., Cuzen, N., Stein, D. J., & Fein, G. (2013). Not lesser but greater fractional anisotropy in adolescents with alcohol use disorders. *NeuroImage: Clinical*, 2, 804-809. doi:10.1016/j.nicl.2013.06.002
- Carey, K. B., Scott-Sheldon, L. A., Carey, M. P., & DeMartini, K. S. (2007). Individual-level interventions to reduce college student drinking: A meta-analytic review. *Addictive Behaviors*, 32(11), 2469-2494. doi:10.1016/j.addbeh.2007.05.004
- Carpenter-Hyland, E. P., & Chandler, L. J. (2007). Adaptive plasticity of NMDA receptors and dendritic spines: Implications for enhanced vulnerability of the adolescent brain to alcohol addiction. *Pharmacology Biochemistry and Behavior*, 86(2), 200-208. doi:10.1016/j.pbb.2007.01.016
- Carr, K. L., & Stewart, M. W. (2019). Effectiveness of school-based health center delivery of a cognitive skills building intervention in young, rural adolescents: Potential applications for addiction and mood. *Journal of Pediatric Nursing*, 47, 23-29. doi:10.1016/j.pedn.2019.04.013
- Carrier, J., Land, S., Buysse, D. J., Kupfer, D. J., & Monk, T. H. (2001). The effects of age and gender on sleep EEG power spectral density in the middle years of life (ages 20-60 years old). *Psychophysiology*, 38(2), 232-242. doi:10.1111/1469-8986.3820232
- Carskadon, M. A. (2004). Sleep deprivation: Health consequences and societal impact. *Medical Clinics of North America*, 88(3), 767-776. doi:10.1016/j.mcna.2004.03.001
- Carskadon, M. A. (2011). Sleep in adolescents: The perfect storm. *Pediatric Clinics of North America*, 58(3), 637-647. doi:10.1016/j.pcl.2011.03.003
- Carskadon, M. A., Acebo, C., & Jenni, O. G. (2004). Regulation of adolescent sleep: Implications for behavior. *Annals of the New York Academy of Sciences*, 1021, 276-291. doi:10.1196/annals.1308.032

- Carskadon, M. A., Brown, E. D., & Dement, W. C. (1982). Sleep fragmentation in the elderly: Relationship to daytime sleep tendency. *Neurobiology of Aging*, 3(4), 321-327. doi:10.1016/0197-4580(82)90020-3
- Carskadon, M. A., & Dement, W. C. (2017). Normal human sleep: An overview. In M. H. Kryger, T. Roth, & W. C. Dement (Eds.), *Principles and Practice of Sleep Medicine* (6th ed., pp. 15-24). Philadelphia, PA: Elsevier.
- Carta, M., Mameli, M., & Valenzuela, C. F. (2004). Alcohol enhances GABAergic transmission to cerebellar granule cells via an increase in Golgi cell excitability. *The Journal of Neuroscience*, 24(15), 3746-3751. doi:10.1523/JNEUROSCI.0067-04.2004
- Casey, B., Jones, R. M., & Somerville, L. H. (2011). Braking and accelerating of the adolescent brain. *Journal of Adolescent Research*, 21(1), 21-33. doi:10.1111/j.1532-7795.2010.00712.x
- Casey, B. J., & Jones, R. M. (2010). Neurobiology of the adolescent brain and behavior: Implications for substance use disorders. *Journal of the American Academy of Child and Adolescent Psychiatry*, 49(12), 1189-1201; quiz 1285. doi:10.1016/j.jaac.2010.08.017
- Cavacuiti, C. A., & Woodward, J. J. (2011). The pharmacology of alcohol. In C. Cavacuiti (Ed.), *Principles of addiction medicine: The essentials* (pp. 32-36). Philadelphia, PA: Lippincott Williams & Wilkins.
- Cederbaum, A. I. (2012). Alcohol metabolism. *Clinical Liver Disease*, 16(4), 667-685. doi:10.1016/j.cld.2012.08.002
- Cepeda, M. S., Stang, P., Blacketer, C., Kent, J. M., & Wittenberg, G. M. (2016). Clinical relevance of sleep duration: Results from a cross-sectional analysis using NHANES. *Journal of Clinical Sleep Medicine*, 12(6), 813-9. doi:10.5664/jcsm.5876.
- Ceylan-Isik, A. F., McBride, S. M., & Ren, J. (2010). Sex difference in alcoholism: Who is at a greater risk for development of alcoholic complication? *Life Sciences*, 87(5-6), 133-138. doi:10.1016/j.lfs.2010.06.002

- Chakravorty, S., Chaudhary, N. S., & Brower, K. J. (2016). Alcohol dependence and its relationship with insomnia and other sleep disorders. *Alcoholism: Clinical and Experimental Research*, 40(11), 2271-2282. doi:10.1111/acer.13217
- Chan, J. K., Trinder, J., Colrain, I. M., & Nicholas, C. L. (2015). The acute effects of alcohol on sleep electroencephalogram power spectra in late adolescence. *Alcoholism: Clinical and Experimental Research*, 39(2), 291-299. doi:10.1111/acer.12621
- Chan, J. K. M. (2013). *The effects of acute alcohol consumption on sleep and memory in young adults (PhD)*. University of Melbourne, Melbourne.
- Chan, J. K. M., Trinder, J., Andrewes, H. E., Colrain, I. M., & Nicholas, C. L. (2013). The acute effects of alcohol on sleep architecture in late adolescence. *Alcoholism: Clinical and Experimental Research*, 37(10), 1720-1728. doi:10.1111/acer.12141
- Chang, J. S., Hsiao, J. R., & Chen, C. H. (2017). ALDH2 polymorphism and alcohol-related cancers in Asians: A public health perspective. *Journal of Biomedical Science*, 24(1), 19. doi:10.1186/s12929-017-0327-y
- Chastain, G. (2006). Alcohol, neurotransmitter systems, and behavior. *Journal of Experimental Psychology: General*, 133(4), 329-335. doi:10.3200/GENP.133.4.329-335
- Chen, X., Gelaye, B., & Williams, M. A. (2014). Sleep characteristics and health-related quality of life among a national sample of American young adults: Assessment of possible health disparities. *Quality of Life Research*, 23(2), 613-625. doi:10.1007/s11136-013-0475-9
- Chevalier, N., Kurth, S., Doucette, M. R., Wiseheart, M., Deoni, S. C., Dean, D. C., 3rd, . . . LeBourgeois, M. K. (2015). Myelination is associated with processing speed in early childhood: Preliminary insights. *PLoS One*, 10(10), e0139897. doi:10.1371/journal.pone.0139897

- Chin, V. S., Van Skike, C. E., Berry, R. B., Kirk, R. E., Diaz-Granados, J., & Matthews, D. B. (2011). Effect of acute ethanol and acute allopregnanolone on spatial memory in adolescent and adult rats. *Alcohol*, 45(5), 473-483. doi:10.1016/j.alcohol.2011.03.001
- Choi, J. W., Song, J. S., Lee, Y. J., & Jeong, D. U. (2017). Periodic limb movements in sleep is associated with increased mortality. *Psychiatry Investigation*, 14(5), 669-673. doi:10.4306/pi.2017.14.5.669
- Chugani, D. C., Muzik, O., Juhász, C., Janisse, J. J., Ager, J., & Chugani, H. T. (2001). Postnatal maturation of human GABA_A receptors measured with positron emission tomography. *Annals of Neurology*, 49(5), 618-626. doi:10.1002/ana.1003
- Chumin, E. J., Goni, J., Halcomb, M. E., Durazzo, T. C., Dziedzic, M., & Yoder, K. K. (2018). Differences in white matter microstructure and connectivity in nontreatment-seeking individuals with alcohol use disorder. *Alcoholism: Clinical and Experimental Research*, 42(5), 889-896. doi:10.1111/acer.13629
- Churchwell, J. C., & Yurgelun-Todd, D. A. (2011). Neuroimaging, adolescence and risky behaviour. In M. T. Bardo, D. H. Fishbein, & R. Milich (Eds.), *Inhibitory control and drug abuse prevention* (pp. 101-124). New York, NY: Springer.
- Cingi, C., Emre, I. E., & Muluk, N. B. (2018). Jetlag related sleep problems and their management: A review. *Travel Medicine and Infectious Disease*, 24, 59-64. doi:10.1016/j.tmaid.2018.05.008
- Cirelli, C. (2013). Sleep and synaptic changes. *Current Opinion in Neurobiology*, 23(5), 841-846. doi:10.1016/j.conb.2013.04.001
- Clark, C. P., Gillin, J. C., Golshan, S., Demodena, A., Smith, T. L., Danowski, S., . . . Schuckit, M. (1998). Increased REM sleep density at admission predicts relapse by three months in primary alcoholics with a lifetime diagnosis of secondary depression. *Biological Psychiatry*, 43(8), 601-607. doi:10.1016/S0006-3223(97)00457-5

- Clark, D. B., Lynch, K. G., Donovan, J. E., & Block, G. D. (2001). Health problems in adolescents with alcohol use disorders: Self-report, liver injury, and physical examination findings and correlates. *Alcoholism: Clinical and Experimental Research*, 25(9), 1350-1359. doi:10.1111/j.1530-0277.2001.tb02358.x
- Clark, D. B., Thatcher, D. L., & Tapert, S. F. (2008). Alcohol, psychological dysregulation, and adolescent brain development. *Alcoholism: Clinical and Experimental Research*, 32(3), 375-385. doi:10.1111/j.1530-0277.2007.00601.x
- Clark, I., & Landolt, H. P. (2017). Coffee, caffeine, and sleep: A systematic review of epidemiological studies and randomized controlled trials. *Sleep Medicine Reviews*, 31, 70-78. doi:10.1016/j.smr.2016.01.006
- Clarke, M. E., & Gibbard, W. B. (2003). Overview of fetal alcohol spectrum disorders for mental health professionals. *The Canadian Child and Adolescent Psychiatry Review*, 12(3), 57-63.
- Clement, O., Sapin, E., Berod, A., Fort, P., & Luppi, P. H. (2011). Evidence that neurons of the sublaterodorsal tegmental nucleus triggering paradoxical (REM) sleep are glutamatergic. *Sleep*, 34(4), 419-423. doi:10.1093/sleep/34.4.419
- Cogliano, V. J., Baan, R., Straif, K., Grosse, Y., Lauby-Secretan, B., El Ghissassi, F., . . . Wild, C. P. (2011). Preventable exposures associated with human cancers. *Journal of the National Cancer Institute*, 103(24), 1827-1839. doi:10.1093/jnci/djr483
- Cohen-Zion, M., Drummond, S. P., Padula, C. B., Winward, J., Kanady, J., Medina, K. L., & Tapert, S. F. (2009). Sleep architecture in adolescent marijuana and alcohol users during acute and extended abstinence. *Addictive Behaviors*, 34(11), 976-979. doi:10.1016/j.addbeh.2009.05.011

- Cohen-Zion, M., Shabi, A., Levy, S., Glasner, L., & Wiener, A. (2016). Effects of partial sleep deprivation on information processing speed in adolescence. *Journal of the International Neuropsychological Society*, 22(4), 388-398. doi:10.1017/S1355617716000072
- Cohen-Zion, M., Stepnowsky, C., Marler, Shochat, T., Kripke, D. F., & Ancoli-Israel, S. (2001). Changes in cognitive function associated with sleep disordered breathing in older people. *Journal of the American Geriatrics Society*, 49(12), 1622-1627. doi:10.1111/j.1532-5415.2001.49270.x
- Cohen, J. (1988). *Statistical Power Analysis for the Behavioural Sciences* (Vol. 2). New York, NY: Lawrence Erlbaum Associates.
- Cohen, J. (1992). A power primer. *Psychological Bulletin*, 112(1), 155-159. doi:10.1037/0033-2909.112.1.155
- Cohn, T. J., Foster, J. H., & Peters, T. J. (2003). Sequential studies of sleep disturbance and quality of life in abstaining alcoholics. *Addiction Biology*, 8(4), 455-462. doi:10.1080/13556210310001646439
- Collet, T. H., van der Klaauw, A. A., Henning, E., Keogh, J. M., Suddaby, D., Dachi, S. V., . . . Schmid, S. M. (2016). The sleep/wake cycle is directly modulated by changes in energy balance. *Sleep*, 39(9), 1691-1700. doi:10.5665/sleep.6094
- Collin, G., & van den Heuvel, M. P. (2013). The ontogeny of the human connectome: Development and dynamic changes of brain connectivity across the life span. *Neuroscientist*, 19(6), 616-628. doi:10.1177/1073858413503712
- Collins, D. J., & Lapsley, H. M. (2008a). *The costs of tobacco, alcohol and illicit drug abuse to Australian society in 2004/05*. Canberra, ACT: Australian Government: Department of Health and Aging.
- Collins, D. J., & Lapsley, H. M. (2008b). *The avoidable costs of alcohol abuse in Australia and the potential benefits of effective policies to reduce the social costs of alcohol*. Canberra, ACT: Australian Government: Department of Health and Aging.

- Colrain, I. M. (2005). The K-complex: A 7-decade history. *Sleep*, 28(2), 255-273. doi:10.1093/sleep/28.2.255
- Colrain, I. M., & Baker, F. C. (2011). Changes in sleep as a function of adolescent development. *Neuropsychology Review*, 21(1), 5-21. doi:10.1007/s11065-010-9155-5
- Colrain, I. M., Crowley, K. E., Nicholas, C. L., Afifi, L., Baker, F. C., Padilla, M., . . . Trinder, J. (2010). Sleep evoked delta frequency responses show a linear decline in amplitude across the adult lifespan. *Neurobiology of Aging*, 31(5), 874-883. doi:10.1016/j.neurobiolaging.2008.06.003
- Colrain, I. M., Crowley, K. E., Nicholas, C. L., Padilla, M., & Baker, F. C. (2009a). The impact of alcoholism on sleep evoked delta frequency responses. *Biological Psychiatry*, 66, 177-184. doi:10.1016/j.biopsych.2008.10.010
- Colrain, I. M., Nicholas, C. L., & Baker, F. C. (2014). Alcohol and the sleeping brain. In M. J. Aminoff, F. Boller, & D. F. Swaab (Eds.), *Handbook of Clinical Neurology* (Vol. 125., pp. 415-431). Amsterdam: Elsevier. doi:10.1016/B978-0-444-62619-6.00024-0
- Colrain, I. M., Sullivan, E. V., Rohlfing, T., Baker, F. C., Nicholas, C. L., Padilla, M. L., . . . Pfefferbaum, A. (2011). Independent contributions of cortical gray matter, aging, sex and alcoholism to K-complex amplitude evoked during sleep. *Sleep*, 34(6), 787-795. doi:10.5665/SLEEP.1050
- Colrain, I. M., Turlington, S., & Baker, F. C. (2009b). Impact of alcoholism on sleep architecture and EEG power spectra in men and women. *Sleep*, 32(10), 1341-1352. doi:10.1093/sleep/32.10.1341
- Connor, J. P., Haber, P. S., & Hall, W. D. (2016). Alcohol use disorders. *Lancet*, 387(10022), 988-998. doi:10.1016/S0140-6736(15)00122-1
- Conroy, D. A., Arnedt, J. T., & Brower, K. J. (2011). Sleep in substance use disorders. In J. Winkelman & D. Plante (Eds.), *Foundations of Psychiatric Sleep Medicine* (pp. 314-329). New York, NY: Cambridge University Press.

- Coons, S., & Guilleminault, C. (1982). Development of sleep-wake patterns and non-rapid eye movement sleep stages during the first six months of life in normal infants. *Pediatrics*, 69(6), 793-798.
- Coren, S. (2009). The prevalence of self-reported sleep disturbances in young adults. *International Journal of Neuroscience*, 79(1-2), 67-73.
doi:10.3109/00207459408986068
- Cortesi, F., Giannotti, F., Sebastiani, T., Bruni, O., & Ottaviano, S. (2004). Knowledge of sleep in Italian high school students: Pilot-test of a school-based sleep educational program. *Journal of Adolescent Health*, 34(4), 344-351. doi:10.1016/j.jadohealth.2003.07.003
- Cosgrove, K. P., Krantzler, E., Frohlich, E. B., Stiklus, S., Pittman, B., Tamagnan, G. D., . . . Staley, J. K. (2009). Dopamine and serotonin transporter availability during acute alcohol withdrawal: Effects of comorbid tobacco smoking. *Neuropsychopharmacology*, 34(10), 2218-2226. doi:10.1038/npp.2009.49
- Courchesne, E., Chisum, H. J., Townsend, J., Cowles, A., Covington, J., Egaas, B., . . . Press, G. A. (2000). Normal brain development and aging: Quantitative analysis at in vivo MR imaging in healthy volunteers. *Radiology*, 216(3), 672-682. doi:10.1148/radiology.216.3.r00au37672
- Crego, A., Holguin, S. R., Parada, M., Mota, N., Corral, M., & Cadaveira, F. (2009). Binge drinking affects attentional and visual working memory processing in young university students. *Alcoholism: Clinical and Experimental Research*, 33(11), 1870-1879. doi:10.1111/j.1530-0277.2009.01025.x
- Crews, F., He, J., & Hodge, C. (2007). Adolescent cortical development: A critical period of vulnerability for addiction. *Pharmacology Biochemistry and Behavior*, 86(2), 189-199. doi:10.1016/j.pbb.2006.12.001
- Crews, F. T., & Boettiger, C. A. (2009). Impulsivity, frontal lobes and risk for addiction. *Pharmacology Biochemistry and Behavior*, 93(3), 237-247. doi:10.1016/j.pbb.2009.04.018

- Crews, F. T., Braun, C. J., Hoplight, B., Switzer, R. C., 3rd, & Knapp, D. J. (2000). Binge ethanol consumption causes differential brain damage in young adolescent rats compared with adult rats. *Alcoholism: Clinical and Experimental Research*, 24(11), 1712-1723. doi:10.1111/j.1530-0277.2000.tb01973.x
- Crews, F. T., Mdzinarishvili, A., Kim, D., He, J., & Nixon, K. (2006). Neurogenesis in adolescent brain is potently inhibited by ethanol. *Neuroscience*, 137(2), 437-445. doi:10.1016/j.neuroscience.2005.08.090
- Crews, F. T., & Nixon, K. (2009). Mechanisms of neurodegeneration and regeneration in alcoholism. *Alcohol and Alcoholism*, 44(2), 115-127. doi:10.1093/alcalc/agn079
- Crews, F. T., Vetreno, R. P., Broadwater, M. A., & Robinson, D. L. (2016). Adolescent alcohol exposure persistently impacts adult neurobiology and behavior. *Pharmacological Reviews*, 68(4), 1074-1109. doi:10.1124/pr.115.012138
- Criado, J. R., Wills, D. N., Walker, B. M., & Ehlers, C. L. (2008). Effects of adolescent ethanol exposure on sleep in adult rats. *Alcohol*, 42(8), 631-639. doi:10.1016/j.alcohol.2008.08.001
- Crowley, K., Sullivan, E. V., Adalsteinsson, E., Pfefferbaum, A., & Colrain, I. M. (2005). Differentiating pathologic delta from healthy physiologic delta in patients with Alzheimer disease. *Sleep*, 28(7), 865-870. doi:10.1093/sleep/28.7.865
- Crowley, K. E., Trinder, J., & Colrain, I. M. (2002). An examination of evoked K-complex amplitude and frequency of occurrence in the elderly. *Journal of Sleep Research*, 11, 129-140. doi:10.1046/j.1365-2869.2002.00293.x
- Crowley, S. J., Acebo, C., & Carskadon, M. A. (2007). Sleep, circadian rhythms, and delayed phase in adolescence. *Sleep Medicine*, 8(6), 602-612. doi:10.1016/j.sleep.2006.12.002

- Crowley, S. J., Van Reen, E., LeBourgeois, M. K., Acebo, C., Tarokh, L., Seifer, R., . . . Carskadon, M. A. (2014). A longitudinal assessment of sleep timing, circadian phase, and phase angle of entrainment across human adolescence. *PLoS One*, 9(11), e112199. doi:10.1371/journal.pone.0112199
- Cservenka, A. (2016). Neurobiological phenotypes associated with a family history of alcoholism. *Drug and Alcohol Dependence*, 158, 8-21. doi:10.1016/j.drugalcdep.2015.10.021
- Cservenka, A., & Brumback, T. (2017). The burden of binge and heavy drinking on the brain: effects on adolescent and young adult neural structure and function. *Frontiers in Psychology*, 8, 1111. doi:10.3389/fpsyg.2017.01111
- Cservenka, A., Herting, M. M., & Nagel, B. J. (2012). Atypical frontal lobe activity during verbal working memory in youth with a family history of alcoholism. *Drug and Alcohol Dependence*, 123(1-3), 98-104. doi:10.1016/j.drugalcdep.2011.10.021
- Cunningham, T., Pardilla-Delgado, E., Alger, S., & Payne, J. (2014). The role of rem sleep in emotional memory and affective reactivity in humans. In C. L. Saylor (Ed.), *REM Sleep: Characteristics, Disorders and Physiological Effects* (pp. 1-28). New York, NY: Nova Science Publishers.
- Curcio, G., Ferrara, M., & De Gennaro, L. (2006). Sleep loss, learning capacity and academic performance. *Sleep Medicine Reviews*, 10(5), 323-337. doi:10.1016/j.smrv.2005.11.001
- Curtin, J. J., & Fairchild, B. A. (2003). Alcohol and cognitive control: Implications for regulation of behavior during response conflict. *Journal of Abnormal Psychology*, 112(3), 424-436. doi:10.1037/0021-843x.112.3.424
- Czeisler, C. A., & Klerman, E. B. (1999). Circadian and sleep-dependent regulation of hormone release in humans. *Recent Progress in Hormone Research*, 54, 97-130; discussion 130-132.

- Czeisler, C. A., Kronauer, R. E., Allan, J. S., Duffy, J. F., Jewett, M. E., Brown, E. N., & Ronda, J. M. (1989). Bright light induction of strong (type 0) resetting of the human circadian pacemaker. *Science*, 244(4910), 1328-1333. doi:10.1126/science.2734611
- Dahl, R. E., & Lewin, D. S. (2002a). Pathways to adolescent health sleep regulation and behavior. *Journal of Adolescent Health*, 31(6), 175-184. doi:10.1016/s1054-139x(02)00506-2
- Dahl, R. E., & Lewin, D. S. (2002b). Pathways to adolescent health sleep regulation and behavior. *Journal of Adolescent Health*, 31(6 Suppl), 175-184. doi:10.1016/S1054-139X(02)00506-2
- Dahl, R. E., Williamson, D. E., Bertocci, M. A., Stolz, M. V., Ryan, N. D., & Ehlers, C. L. (2003). Spectral analyses of sleep EEG in depressed offspring of fathers with or without a positive history of alcohol abuse or dependence: A pilot study. *Alcohol*, 30(3), 193-200. doi:10.1016/j.alcohol.2003.06.001
- Danel, T., Cottencin, O., Tisserand, L., & Touitou, Y. (2009). Inversion of melatonin circadian rhythm in chronic alcoholic patients during withdrawal: Preliminary study on seven patients. *Alcohol and Alcoholism*, 44(1), 42-45. doi:10.1093/alcalc/agn091
- Dang-Vu, T. T., Desseilles, M., Laureys, S., Degueldre, C., Perrin, F., Phillips, C., . . . Peigneux, P. (2005). Cerebral correlates of delta waves during non-REM sleep revisited. *Neuroimage*, 28, 14-21. doi:10.1016/j.neuroimage.2005.05.028
- Dang-Vu, T. T., McKinney, S. M., Buxton, O. M., Solet, J. M., & Ellenbogen, J. M. (2010). Spontaneous brain rhythms predict sleep stability in the face of noise. *Current Biology*, 20(15), R626-627. doi:10.1016/j.cub.2010.06.032
- Dang-Vu, T. T., Schabus, M., Desseilles, M., Albouy, G., Boly, M., Darsaud, A., . . . Maquet, P. (2008). Spontaneous neural activity during human slow wave sleep. *Proceedings of the National Academy of Sciences of the United States of America*, 105(39), 15160-15165. doi:10.1073/pnas.0801819105

- Dantzer, C., Wardle, J., Fuller, R., Pampalone, S. Z., & Steptoe, A. (2006). International study of heavy drinking: attitudes and sociodemographic factors in university students. *Journal of American College Health*, 55(2), 83-89. doi:10.3200/JACH.55.2.83-90
- Das-Friebel, A., Perkinson-Gloor, N., Brand, S., Dewald-Kaufmann, J. F., Grob, A., Wolke, D., & Lemola, S. (2019). A pilot cluster-randomised study to increase sleep duration by decreasing electronic media use at night and caffeine consumption in adolescents. *Sleep Medicine*, 60, 109-115. doi:10.1016/j.sleep.2018.11.010
- Das, J. K., Salam, R. A., Arshad, A., Finkelstein, Y., & Bhutta, Z. A. (2016). Interventions for adolescent substance abuse: An overview of systematic reviews. *Journal of Adolescent Health*, 59(4S), S61-S75. doi:10.1016/j.jadohealth.2016.06.021
- Datta, S., & Maclean, R. R. (2007). Neurobiological mechanisms for the regulation of mammalian sleep-wake behavior: Reinterpretation of historical evidence and inclusion of contemporary cellular and molecular evidence. *Neuroscience and Biobehavioral Reviews*, 31(5), 775-824. doi:10.1016/j.neubiorev.2007.02.004
- Datta, S., Spoley, E. E., & Patterson, E. H. (2001). Microinjection of glutamate into the pedunculopontine tegmentum induces REM sleep and wakefulness in the rat. *American Journal of Physiology Regulatory, Integrative and Comparative Physiology*, 280(3), R752-759. doi:10.1152/ajpregu.2001.280.3.R752
- Davies, D. R. (1976). Individual differences in sleep patterns. *Postgraduate Medical Journal*, 52(603), 10-14. doi:10.1136/pgmj.52.603.10
- Davies, M. (2003). The role of GABA_A receptors in mediating the effects of alcohol in the central nervous system. *Journal of Psychiatry and Neuroscience*, 28(4), 263-274.

- De Bellis, M. D., Clark, D. B., Beers, S. R., Soloff, P. H., Boring, A. M., Hall, J., . . . Keshavan, M. S. (2000). Hippocampal volume in adolescent-onset alcohol use disorders. *American Journal of Psychiatry*, 157(5), 737-744. doi:10.1176/appi.ajp.157.5.737
- De Bellis, M. D., Narasimhan, A., Thatcher, D. L., Keshavan, M. S., Soloff, P., & Clark, D. B. (2005). Prefrontal cortex, thalamus, and cerebellar volumes in adolescents and young adults with adolescent-onset alcohol use disorders and comorbid mental disorders. *Alcoholism: Clinical and Experimental Research*, 29(9), 1590-1600. doi:10.1097/01.alc.0000179368.87886.76
- De Bellis, M. D., Van Voorhees, E., Hooper, S. R., Gibler, N., Nelson, L., Hege, S. G., . . . MacFall, J. (2008). Diffusion tensor measures of the corpus callosum in adolescents with adolescent onset alcohol use disorders. *Alcoholism: Clinical and Experimental Research*, 32(3), 395-404. doi:10.1111/j.1530-0277.2007.00603.x
- De Gennaro, L., Ferrara, M., Vecchio, F., Curcio, G., & Bertini, M. (2005). An electroencephalographic fingerprint of human sleep. *Neuroimage*, 26(1), 114-122. doi:10.1016/j.neuroimage.2005.01.020
- de Silva, P. N. (2018). Do patterns of synaptic pruning underlie psychoses, autism and ADHD? *British Journal of Psychiatry Advances*, 24(03), 212-217. doi:10.1192/bja.2017.27
- de Sousa, I. C., Araújo, J. F., & de Azevedo, C. V. M. (2007). The effect of a sleep hygiene education program on the sleep? Wake cycle of Brazilian adolescent students. *Sleep and Biological Rhythms*, 5(4), 251-258. doi:10.1111/j.1479-8425.2007.00318.x
- Dees, W. L., Dissen, G. A., Hiney, J. K., Lara, F., & Ojeda, S. R. (2000). Alcohol ingestion inhibits the increased secretion of puberty-related hormones in the developing female rhesus monkey. *Endocrinology*, 141(4), 1325-1331. doi:10.1210/endo.141.4.7413

- Dees, W. L., Hiney, J. K., & Srivastava, V. K. (2017). Alcohol and Puberty: Mechanisms of Delayed Development. *Alcohol Research: Current Reviews*, 38(2), 277-282.
- Degenhardt, L., Hall, W., Teesson, M., & Lynskey, M. (2000). *Alcohol use disorders in Australia: Findings from the National Survey of Mental Health and Well-Being*. Sydney, NSW: National Drug and Alcohol Research Centre.
- Degenhardt, L., O'Loughlin, C., Swift, W., Romaniuk, H., Carlin, J., Coffey, C., . . . Patton, G. (2013). The persistence of adolescent binge drinking into adulthood: Findings from a 15-year prospective cohort study. *The British Medical Journal Open*, 3(8), e003015. doi:10.1136/bmjopen-2013-003015
- Del Boca, F. K., Darkes, J., Greenbaum, P. E., & Goldman, M. S. (2004). Up close and personal: Temporal variability in the drinking of individual college students during their first year. *Journal of Consulting and Clinical Psychology*, 72(2), 155-164. doi:10.1037/0022-006X.72.2.155
- Dement, W. (1960). The effect of dream deprivation. *Science*, 131(3415), 1705-1707. doi:10.1126/science.131.3415.1705
- Dement, W., & Kleitman, N. (1957). The relation of eye movements during sleep to dream activity: An objective measure for the study of dreaming. *Journal of Experimental Psychology*, 53, 339-346. doi:10.1037/h0048189
- Deoni, S. C., O'Muircheartaigh, J., Elison, J. T., Walker, L., Doernberg, E., Waskiewicz, N., . . . Jernis, N. L. (2016). White matter maturation profiles through early childhood predict general cognitive ability. *Brain Structure and Function*, 221(2), 1189-1203. doi:10.1007/s00429-014-0947-x
- Dijk, D. J. (1995). EEG slow waves and sleep spindles: Windows on the sleeping brain. *Behavioural Brain Research*, 69(1-2), 109-116. doi:10.1016/0166-4328(95)00007-g
- Dijk, D. J. (2009). Regulation and functional correlates of slow wave sleep. *Journal of Clinical Sleep Medicine*, 5(2 Suppl), S6-15. doi:10.5664/jcsm.5.2S.S6

- Dijk, D. J., Beersma, D. G., & Bloem, G. M. (1989). Sex differences in the sleep EEG of young adults: Visual scoring and spectral analysis. *Sleep*, 12(6), 500-507. doi:10.1093/sleep/12.6.500
- Dijk, D. J., Beersma, D. G., Daan, S., Bloem, G. M., & Van den Hoofdakker, R. H. (1987). Quantitative analysis of the effects of slow wave sleep deprivation during the first 3 h of sleep on subsequent EEG power density. *European Archives of Psychiatry and Clinical Neuroscience*, 236(6), 323-328. doi:10.1007/BF00377420
- Dijk, D. J., Brunner, D. P., Aeschbach, D., Tobler, I., & Borbely, A. A. (1992). The effects of ethanol on human sleep EEG power spectra differ from those of benzodiazepine receptor agonists. *Neuropsychopharmacology*, 7(3), 225-232.
- Dijk, D. J., Brunner, D. P., Beersma, D. G., & Borbely, A. A. (1990). Electroencephalogram power density and slow wave sleep as a function of prior waking and circadian phase. *Sleep*, 13(5), 430-440. doi:10.1093/sleep/13.5.430
- Dijk, D. J., Cajochen, C., Tobler, I., & Borbely, A. A. (1991). Sleep extension in humans: Sleep stages, EEG power spectra and body temperature. *Sleep*, 14(4), 294-306. doi:10.1093/sleep/14.4.294
- Dijk, D. J., Hayes, B., & Czeisler, C. A. (1993). Dynamics of electroencephalographic sleep spindles and slow wave activity in men: Effect of sleep deprivation. *Brain Research*, 626(1-2), 190-199. doi: 10.1016/0006-8993(93)90579-C
- Dolsen, M. R., Cheng, P., Arnedt, J. T., Swanson, L., Casement, M. D., Kim, H. S., .. Deldin, P. J. (2017). Neurophysiological correlates of suicidal ideation in major depressive disorder: Hyperarousal during sleep. *Journal of Affective Disorders*, 212, 160-166. doi:10.1016/j.jad.2017.01.025
- Doremus-Fitzwater, T. L., & Spear, L. P. (2007). Developmental differences in acute ethanol withdrawal in adolescent and adult rats. *Alcoholism: Clinical and Experimental Research*, 31(9), 1516-1527. doi:10.1111/j.1530-0277.2007.00457.x

- Doremus-Fitzwater, T. L., Varlinskaya, E. I., & Spear, L. P. (2010). Motivational systems in adolescence: Possible implications for age differences in substance abuse and other risk-taking behaviors. *Brain and Cognition*, 72(1), 114-123. doi:10.1016/j.bandc.2009.08.008
- Doremus, T. L., Brunell, S. C., Varlinskaya, E. I., & Spear, L. P. (2003). Anxiogenic effects during withdrawal from acute ethanol in adolescent and adult rats. *Pharmacology Biochemistry and Behavior*, 75(2), 411-418. doi:10.1016/S0091-3057(03)00134-5
- Dossi, R. C., Nunez, A., & Steriade, M. (1992). Electrophysiology of a slow (0.5-4 Hz) intrinsic oscillation of cat thalamocortical neurones in vivo. *The Journal of Physiology*, 447, 215-234. doi:10.1113/jphysiol.1992.sp018999
- Dougherty, D. M., Lake, S. L., Mathias, C. W., Ryan, S. R., Bray, B. C., Charles, N. E., & Acheson, A. (2015). Behavioral impulsivity and risk-taking trajectories across early adolescence in youths with and without family histories of alcohol and other drug use disorders. *Alcoholism: Clinical and Experimental Research*, 39(8), 1501-1509. doi:10.1111/acer.12787
- Dragan, M. (2015). Difficulties in emotion regulation and problem drinking in young women: The mediating effect of metacognitions about alcohol use. *Addictive Behaviors*, 48, 30-35. doi:10.1016/j.addbeh.2015.04.008
- Drake, C. L., Roehrs, T., & Roth, T. (2003). Insomnia causes, consequences, and therapeutics: An overview. *Depression and Anxiety*, 18(4), 163-176. doi:10.1002/da.10151
- Drewes, A. M., Nielsen, K. D., Arendt-Nielsen, L., Birket-Smith, L., & Hansen, L. M. (1997). The effect of cutaneous and deep pain on the electroencephalogram during sleep- An experimental study. *Sleep*, 20(8), 632-640. doi:10.1093/sleep/20.8.632

- Drummond, S. P. A., Gillin, J. C., Smith, T. L., & DeModena, A. (1998). The sleep of abstinent pure primary alcoholic patients: Natural course and relationship to relapse. *Alcoholism: Clinical and Experimental Research*, 22(8), 1796-1802. doi:10.1111/j.1530-0277.1998.tb03983.x
- Dry, M. J., Burns, N. R., Nettelbeck, T., Farquharson, A. L., & White, J. M. (2012). Dose-related effects of alcohol on cognitive functioning. *PLoS One*, 7(11), e50977. doi:10.1371/journal.pone.0050977
- Dube, J., Lafortune, M., Bedetti, C., Bouchard, M., Gagnon, J. F., Doyon, J., . . . Carrier, J. (2015). Cortical thinning explains changes in sleep slow waves during adulthood. *The Journal of Neuroscience*, 35(20), 7795-7807. doi:10.1523/JNEUROSCI.3956-14.2015
- Duffy, J. F., & Wright, K. P., Jr. (2005). Entrainment of the human circadian system by light. *Journal of Biological Rhythms*, 20(4), 326-338. doi:10.1177/0748730405277983
- Dulin, P. L., Alvarado, C. E., Fitterling, J. M., & Gonzalez, V. M. (2017). Comparisons of alcohol consumption by time-line follow back vs. Smartphone-based daily interviews. *Addiction Research and Theory*, 25(3), 195-200. doi:10.1080/16066359.2016.1239081
- Dunning, D. L., Griffiths, K., Kuyken, W., Crane, C., Foulkes, L., Parker, J., & Dalgleish, T. (2019). Research Review: The effects of mindfulness-based interventions on cognition and mental health in children and adolescents - a meta-analysis of randomized controlled trials. *Journal of Child Psychology and Psychiatry*, 60(3), 244-258. doi:10.1111/jcpp.12980
- Dvorakova, K., Kishida, M., Li, J., Elavsky, S., Broderick, P. C., Agrusti, M. R., & Greenberg, M. T. (2017). Promoting healthy transition to college through mindfulness training with first-year college students: Pilot randomized controlled trial. *Journal of American College Health*, 65(4), 259-267. doi:10.1080/07448481.2017.1278605

- Ebrahim, I. O., Shapiro, C. M., Williams, A. J., & Fenwick, P. B. (2013). Alcohol and sleep I: Effects on normal sleep. *Alcoholism: Clinical and Experimental Research*, 37(4), 539- 549. doi:10.1111/acer.12006
- Eckardt, M. J., File, S. E., Gessa, G. L., Grant, K. A., Guerri, C., Hoffman, P. L., . . . Tabakoff, B. (1998). Effects of moderate alcohol consumption on the central nervous system. *Alcoholism: Clinical and Experimental Research*, 22(5), 998-1040. doi:10.1111/j.1530-0277.1998.tb03695.x.
- Eckel-Mahan, K., & Sassone-Corsi, P. (2013). Metabolism and the circadian clock converge. *Physiological Reviews*, 93(1), 107-135. doi:10.1152/physrev.00016.2012
- Edenberg, H. J. (2007). The genetics of alcohol metabolism: Role of alcohol dehydrogenase and aldehyde dehydrogenase variants. *Alcohol Research and Health*, 30(1), 5-13.
- Ehlers, C. L., & Criado, J. R. (2010). Adolescent ethanol exposure: Does it produce long-lasting electrophysiological effects? *Alcohol*, 44(1), 27-37. doi:10.1016/j.alcohol.2009.09.033
- Ehlers, C. L., Desikan, A., & Wills, D. N. (2013a). Developmental differences in EEG and sleep responses to acute ethanol administration and its withdrawal (hangover) in adolescent and adult Wistar rats. *Alcohol*, 47(8), 601-610. doi:10.1016/j.alcohol.2013.09.040
- Ehlers, C. L., & Kupfer, D. J. (1997). Slow-wave sleep: Do young adult men and women age differently? *Journal of Sleep Research*, 6(3), 211-215. doi:10.1046/j.1365-2869.1997.00041.x
- Ehlers, C. L., Liu, W., Wills, D. N., & Crews, F. T. (2013b). Periadolescent ethanol vapor exposure persistently reduces measures of hippocampal neurogenesis that are associated with behavioral outcomes in adulthood. *Neuroscience*, 244, 1-15. doi:10.1016/j.neuroscience.2013.03.058

- Ehlers, C. L., & Phillips, E. (2003). EEG low-voltage alpha and alpha power in African American young adults: Relation to family history of alcoholism. *Alcoholism: Clinical and Experimental Research*, 27(5), 765-772. doi:10.1097/01.ALC.0000065439.09492.67
- Ehlers, C. L., Phillips, E., Finnerman, G., Gilder, D., Lau, P., & Criado, J. (2007). P3 components and adolescent binge drinking in Southwest California Indians. *Neurotoxicology and Teratology*, 29(1), 153-163. doi:10.1016/j.ntt.2006.11.013
- Ehlers, C. L., Sanchez-Alavez, M., & Wills, D. (2018a). Effect of gabapentin on sleep and delta and theta EEG power in adult rats exposed to chronic intermittent ethanol vapor and protracted withdrawal during adolescence. *Psychopharmacology (Berl)*, 235(6), 1783-1791. doi:10.1007/s00213-018-4888-6
- Ehlers, C. L., & Slawecki, C. J. (2000). Effects of chronic ethanol exposure on sleep in rats. *Alcohol*, 20, 173-179. doi:10.1016/S0741-8329(99)00077-4
- Ehlers, C. L., Wills, D., & Gilder, D. A. (2018b). A history of binge drinking during adolescence is associated with poorer sleep quality in young adult Mexican Americans and American Indians. *Psychopharmacology (Berl)*, 235(6), 1775-1782. doi:10.1007/s00213-018-4889-5
- Eisermann, M., Kaminska, A., Moutard, M. L., Soufflet, C., & Plouin, P. (2013). Normal EEG in childhood: From neonates to adolescents. *Clinical Neurophysiology*, 43(1), 35-65. doi:10.1016/j.neucli.2012.09.091
- Ejaz, S. M., Khawaja, I. S., Bhatia, S., & Hurwitz, T. D. (2011). Obstructive sleep apnea and depression: A review. *Innovations in Clinical Neuroscience*, 8(8), 17-25.
- Elliott, J. C., Carey, K. B., & Bonafide, K. E. (2012). Does family history of alcohol problems influence college and university drinking or substance use? A meta-analytical review. *Addiction*, 107(10), 1774-1785. doi:10.1111/j.1360-0443.2012.03903.x

- Ellis, B. J., Del Giudice, M., Dishion, T. J., Figueredo, A. J., Gray, P., Griskevicius, V., . . . Wilson, D. S. (2012). The evolutionary basis of risky adolescent behavior: Implications for science, policy, and practice. *Developmental Psychology Journal*, 48(3), 598-623. doi:10.1037/a0026220
- Elston, G. N. (2000). Pyramidal cells of the frontal lobe: All the more spinous to think with. *The Journal of Neuroscience*, 20(18), RC95. doi:10.1523/JNEUROSCI.20-18-j0002.2000.
- Eng, M. Y., Luczak, S. E., & Wall, T. L. (2007). ALDH2, ADH1B, and ADH1C genotypes in Asians: A literature review. *Alcohol Research and Health*, 30(1), 22-27.
- Eriksson, C. J. (2001). The role of acetaldehyde in the actions of alcohol (update 2000). *Alcoholism: Clinical and Experimental Research*, 25(5 Suppl ISBRA), 15S-32S. doi:10.1097/00000374-200105051-00005
- Ewing, S. W., Sakhardande, A., & Blakemore, S. J. (2014). The effect of alcohol consumption on the adolescent brain: A systematic review of MRI and fMRI studies of alcohol-using youth. *NeuroImage: Clinical*, 5, 420-437. doi:10.1016/j.nicl.2014.06.011
- Fatima, Y., Doi, S. A., Najman, J. M., & Mamun, A. A. (2016). Exploring gender difference in sleep quality of young adults: Findings from a large population study. *Clinical Medicine and Research*, 14(3-4), 138-144. doi:10.3121/cmr.2016.1338
- Feige, B., Gann, H., Brueck, R., Hornyak, M., Litsch, S., Hohagen, F., & Riemann, D. (2006). Effects of alcohol on polysomnographically recorded sleep in healthy subjects. *Alcoholism: Clinical and Experimental Research*, 30(9), 1527-1537. doi:10.1111/j.1530-0277.2006.00184.x
- Feige, B., Scaal, S., Hornyak, M., Gann, H., & Riemann, D. (2007). Sleep electroencephalographic spectral power after withdrawal from alcohol in alcohol-dependent patients. *Alcoholism: Clinical and Experimental Research*, 31(1), 19-27. doi:10.1111/j.1530-0277.2006.00260.x

- Fein, G., Bachman, L., Fisher, S., & Davenport, L. (1990). Cognitive impairments in abstinent alcoholics. *Western Journal of Medicine*, 152(5), 531-537.
- Fein, G., Di Sclafani, V., Cardenas, A., Goldmann, H., Tolou-Shams, M., & Meyerhoff, D. J. (2002). Cortical gray matter loss in treatment-naive alcohol dependent individuals. *Alcoholism: Clinical and Experimental Research*, 26(4), 558-564. doi:10.1111/j.1530-0277.2002.tb02574.x
- Fein, G., Greenstein, D., Cardenas, V. A., Cuzen, N. L., Fouche, J. P., Ferrett, H., . . . Stein, D. J. (2013). Cortical and subcortical volumes in adolescents with alcohol dependence but without substance or psychiatric comorbidities. *Psychiatry Research*, 214(1), 1-8. doi:10.1016/j.psychresns.2013.06.001
- Fein, G., Landman, B., Tran, H., McGillivray, S., Finn, P., Barakos, J., & Moon, K. (2006a). Brain atrophy in long-term abstinent alcoholics who demonstrate impairment on a simulated gambling task. *Neuroimage*, 32(3), 1465-1471. doi:10.1016/j.neuroimage.2006.06.013
- Fein, G., Shimotsu, R., Chu, R., & Barakos, J. (2009). Parietal gray matter volume loss is related to spatial processing deficits in long-term abstinent alcoholic men. *Alcoholism: Clinical and Experimental Research*, 33(10), 1806-1814. doi:10.1111/j.1530-0277.2009.01019.x
- Fein, G., Torres, J., Price, L. J., & Di Sclafani, V. (2006b). Cognitive performance in long-term abstinent alcoholic individuals. *Alcoholism: Clinical and Experimental Research*, 30(9), 1538-1544. doi:10.1111/j.1530-0277.2006.00185.x
- Feinberg, I. (2000). Slow wave sleep and release of growth hormone. *The Journal of the American Medical Association*, 284(21), 2717-2718. doi:10.1172/JCI119587
- Feinberg, I., & Campbell, I. G. (2010). Sleep EEG changes during adolescence: an index of a fundamental brain reorganization. *Brain and Cognition*, 72(1), 56-65. doi:10.1016/j.bandc.2009.09.008

- Feinberg, I., de Bie, E., Davis, N. M., & Campbell, I. G. (2011). Topographic differences in the adolescent maturation of the slow wave EEG during NREM sleep. *Sleep*, 34(3), 325-333. doi:10.1093/sleep/34.3.325
- Feinberg, I., Thode, H. C., Jr., Chugani, H. T., & March, J. D. (1990). Gamma distribution model describes maturational curves for delta wave amplitude, cortical metabolic rate and synaptic density. *Journal of Theoretical Biology*, 142(2), 149-161. doi:10.1016/S0022-5193(05)80218-8
- Feld, G. B., Wilhelm, I., Ma, Y., Groch, S., Binkofski, F., Molle, M., & Born, J. (2013). Slow wave sleep induced by GABA agonist tiagabine fails to benefit memory consolidation. *Sleep*, 36(9), 1317-1326. doi:10.5665/sleep.2954
- Field, A. (2009). *Discovering statistics using SPSS third edition*. London: SAGE Publications LTD.
- Fields, R. D. (2008a). White matter in learning, cognition and psychiatric disorders. *Trends in Neurosciences*, 31(7), 361-370. doi:10.1016/j.tins.2008.04.001
- Fields, R. D. (2008b). White matter matters. *Scientific American*, 298(3), 42-49.
- Fillmore, M. T., Ostling, E. W., Martin, C. A., & Kelly, T. H. (2009). Acute effects of alcohol on inhibitory control and information processing in high and low sensation-seekers. *Drug and Alcohol Dependence*, 100(1-2), 91-99. doi:10.1016/j.drugalcdep.2008.09.007
- Finelli, L. A., Achermann, P., & Borbely, A. A. (2001). Individual 'fingerprints' in human sleep EEG topography. *Neuropsychopharmacology*, 25(5 Suppl), S57-62. doi:10.1016/S0893-133X(01)00320-7
- Finelli, L. A., Borbely, A. A., & Achermann, P. (2001). Functional topography of the human nonREM sleep electroencephalogram. *European Journal of Neuroscience*, 13, 2282-2290. doi:10.1046/j.0953-816x.2001.01597.x
- Finnigan, F., Hammersley, R., & Millar, K. (1998). Effects of meal composition on blood alcohol level, psychomotor performance and subjective state after ingestion of alcohol. *Appetite*, 31(3), 361-375. doi:10.1006/appe.1998.0168

- Floyd, J. A., Janisse, J. J., Jenuwine, E. S., & Ager, J. W. (2007). Changes in REM-sleep percentage over the adult lifespan. *Sleep*, 30(7), 829-836. doi:10.1093/sleep/30.7.829
- Foley, D., Ancoli-Israel, S., Britz, P., & Walsh, J. (2004). Sleep disturbances and chronic disease in older adults: Results of the 2003 National Sleep Foundation Sleep in America Survey. *Journal of Psychosomatic Research*, 56(5), 497-502. doi:10.1016/j.jpsychores.2004.02.010
- Fortier-Brochu, E., & Morin, C. M. (2014). Cognitive impairment in individuals with insomnia: Clinical significance and correlates. *Sleep*, 37(11), 1787-1798. doi:10.5665/sleep.4172
- Fortier, C. B., Leritz, E. C., Salat, D. H., Venne, J. R., Maksimovskiy, A. L., Williams, V., . . . McGlinchey, R. E. (2011). Reduced cortical thickness in abstinent alcoholics and association with alcoholic behavior. *Alcoholism: Clinical and Experimental Research*, 35(12), 2193-2201. doi:10.1111/j.1530-0277.2011.01576.x
- Fox, H. C., Hong, K. A., & Sinha, R. (2008). Difficulties in emotion regulation and impulse control in recently abstinent alcoholics compared with social drinkers. *Addictive Behaviors*, 33(2), 388-394. doi:10.1016/j.addbeh.2007.10.002
- Fraigne, J. J., Torontali, Z. A., Snow, M. B., & Peever, J. H. (2015). REM sleep at its core - circuits, neurotransmitters, and pathophysiology. *Frontiers in Neurology*, 6, 123. doi:10.3389/fneur.2015.00123
- Freyer, C. H., Morley, K. C., & Haber, P. S. (2016). Alcohol use disorders in Australia. *Internal Medicine Journal*, 46(11), 1259-1268. doi:10.1111/imj.13237
- Fucito, L. M., DeMartini, K. S., Hanrahan, T. H., Yaggi, H. K., Heffern, C., & Redeker, N. S. (2017). Using sleep interventions to engage and treat heavy-drinking college students: A randomized pilot study. *Alcoholism: Clinical and Experimental Research*, 41(4), 798-809. doi:10.1111/acer.13342

- Fung, S. J., Webster, M. J., Sivagnanasundaram, S., Duncan, C., Elashoff, M., & Weickert, C. S. (2010). Expression of interneuron markers in the dorsolateral prefrontal cortex of the developing human and in schizophrenia. *American Journal of Psychiatry*, 167(12), 1479-1488.
doi:10.1176/appi.ajp.2010.09060784
- Garcia, A. N., & Salloum, I. M. (2015). Polysomnographic sleep disturbances in nicotine, caffeine, alcohol, cocaine, opioid, and cannabis use: A focused review. *The American Journal on Addictions*, 24(7), 590-598.
doi:10.1111/ajad.12291
- Gatz, J., Kelly, A. M., & Clark, S. L. (2018). Improved executive function and science achievement for at-risk middle school girls in an aerobic fitness program. *The Journal of Early Adolescence*, 39(3), 453-469.
doi:10.1177/0272431618770786
- Gauthier, P., Arnaud, C., Gandolfo, G., & Gottesmann, C. (1997). Influence of a GABA_B receptor antagonist on the sleep-waking cycle in the rat. *Brain Research*, 773(1-2), 8-14. doi:10.1016/S0006-8993(97)00643-4
- Gazdzinski, S., Durazzo, T. C., Mon, A., Yeh, P. H., & Meyerhoff, D. J. (2010). Cerebral white matter recovery in abstinent alcoholics- A multimodality magnetic resonance study. *Brain*, 133(Pt 4), 1043-1053.
doi:10.1093/brain/awp343
- Geiger, B. B., & MacKerron, G. (2016). Can alcohol make you happy? A subjective wellbeing approach. *Social Science and Medicine*, 156, 184-191.
doi:10.1016/j.socscimed.2016.03.034
- Geiker, N. R. W., Astrup, A., Hjorth, M. F., Sjodin, A., Pijls, L., & Markus, C. R. (2018). Does stress influence sleep patterns, food intake, weight gain, abdominal obesity and weight loss interventions and vice versa? *Obesity Reviews*, 19(1), 81-97. doi:10.1111/obr.12603

- Gentry, R. T. (2000). Effect of food on the pharmacokinetics of alcohol absorption. *Alcoholism: Clinical and Experimental Research*, 24(4), 403-404.
doi:10.1097/00000374-200004000-00003
- Gerber, M., Brand, S., Herrmann, C., Colledge, F., Holsboer-Trachsler, E., & Puhse, U. (2014). Increased objectively assessed vigorous-intensity exercise is associated with reduced stress, increased mental health and good objective and subjective sleep in young adults. *Physiology and Behavior*, 135, 17-24.
doi:10.1016/j.physbeh.2014.05.047
- Giedd, J. N., Blumenthal, J., Jeffries, N. O., Castellanos, F. X., Liu, H., Zijdenbos, A., . . . Rapoport, J. L. (1999). Brain development during childhood and adolescence: A longitudinal MRI study. *Nature Neuroscience*, 2(10), 861-863.
doi:10.1038/13158
- Gil-Hernandez, S., & Garcia-Moreno, L. M. (2016). Executive performance and dysexecutive symptoms in binge drinking adolescents. *Alcohol*, 51, 79-87.
doi:10.1016/j.alcohol.2016.01.003
- Gillberg, M., Anderzen, I., & Akerstedt, T. (1991). Recovery within day-time sleep after slow wave sleep suppression. *Electroencephalography and Clinical Neurophysiology*, 78(4), 267-273. doi:10.1016/0013-4694(91)90180-C
- Gillin, J. C., Smith, T. L., Irwin, M., Butters, N., Demodena, A., & Schuckit, M. (1994). Increased pressure for rapid eye movement sleep at time of hospital admission predicts relapse in nondepressed patients with primary alcoholism at 3-month follow-up. *Archives of General Psychiatry*, 51(3), 189-197.
doi:10.1001/archpsyc.1994.03950030025003
- Gillin, J. C., Smith, T. L., Irwin, M., Kripke, D. F., Brown, S., & Schuckit, M. (1990a). Short REM latency in primary alcoholic patients with secondary depression. *American Journal of Psychiatry*, 147(1), 106-109.
doi:10.1176/ajp.147.1.106

- Gillin, J. C., Smith, T. L., Irwin, M., Kripke, D. F., & Schuckit, M. (1990b). EEG sleep studies in "pure" primary alcoholism during subacute withdrawal: Relationships to normal controls, age, and other clinical variables. *Biological Psychiatry*, 27(5), 477-488. doi:10.1016/0006-3223(90)90439-9
- Gipson, C. S., Chilton, J. M., Dickerson, S. S., Alfred, D., & Haas, B. K. (2019). Effects of a sleep hygiene text message intervention on sleep in college students. *Journal of American College Health*, 67(1), 32-41. doi:10.1080/07448481.2018.1462816
- Givens, B., & McMahon, K. (1995). Ethanol suppresses the induction of long-term potentiation in vivo. *Brain Research*, 688(1-2), 27-33. doi:10.1016/0006-8993(95)00499-G
- Glatter, K. A., Myers, R., & Chiamvimonvat, N. (2012). Recommendations regarding dietary intake and caffeine and alcohol consumption in patients with cardiac arrhythmias: What do you tell your patients to do or not to do? *Current Treatment Options in Cardiovascular Medicine*, 14(5), 529-535. doi:10.1007/s11936-012-0193-6
- Gleich, T., Lorenz, R. C., Pohland, L., Raufelder, D., Deserno, L., Beck, A., . . . Gallinat, J. (2015). Frontal glutamate and reward processing in adolescence and adulthood. *Brain Structure and Function*, 220(6), 3087-3099. doi:10.1007/s00429-014-0844-3
- Gogtay, N., Giedd, J. N., Lusk, L., Hayashi, K. M., Greenstein, D., Vaituzis, A. C., . . . Thompson, P. M. (2004). Dynamic mapping of human cortical development during childhood through early adulthood. *Proceedings of the National Academy of Sciences of the United States of America*, 101(21), 8174-8179. doi:10.1073/pnas.0402680101
- Goist, K. C., Jr., & Sutker, P. B. (1985). Acute alcohol intoxication and body composition in women and men. *Pharmacology Biochemistry and Behavior*, 22(5), 811-814. doi:10.1016/0091-3057(85)90532-5

- Goldstein, D., Hahn, C. S., Hasher, L., Wiprzycka, U. J., & Zelazo, P. D. (2007). Time of day, intellectual performance, and behavioral problems in morning versus evening type adolescents: Is there a synchrony effect? *Personality and Individual Differences*, 42(3), 431-440. doi:10.1016/j.paid.2006.07.008
- Goldstone, A., Willoughby, A. R., de Zambotti, M., Franzen, P. L., Kwon, D., Pohl, K. M., . . . Baker, F. C. (2018). The mediating role of cortical thickness and gray matter volume on sleep slow-wave activity during adolescence. *Brain Structure and Function*, 223(2), 669-685. doi:10.1007/s00429-017-1509-9
- Gonzales, R. A., & Jaworski, J. N. (1997). Alcohol and glutamate. *Alcohol Health and Research World*, 21(2), 120-127.
- Gorg, B., Qvartrskhava, N., Bidmon, H. J., Palomero-Gallagher, N., Kircheis, G., Zilles, K., & Haussinger, D. (2010). Oxidative stress markers in the brain of patients with cirrhosis and hepatic encephalopathy. *Hepatology*, 52(1), 256-265. doi:10.1002/hep.23656
- Goril, S., Zalai, D., Scott, L., & Shapiro, C. M. (2016). Sleep and melatonin secretion abnormalities in children and adolescents with fetal alcohol spectrum disorders. *Sleep Medicine*, 23, 59-64. doi:10.1016/j.sleep.2016.06.002
- Gottesmann, C. (2002). GABA mechanisms and sleep. *Neuroscience*, 111(2), 231-239. doi:10.1016/s0306-4522(02)00034-9
- Grant, B. F., & Dawson, D. A. (1997). Age at onset of alcohol use and its association with DSM-IV alcohol abuse and dependence: Results from the National Longitudinal Alcohol Epidemiologic Survey. *Journal of Substance Abuse Treatment*, 9, 103-110. doi:10.1016/S0899-3289(97)90009-2
- Grant, B. F., Stinson, F. S., & Harford, T. C. (2001). Age at onset of alcohol use and DSM-IV alcohol abuse and dependence: A 12-year follow-up. *Journal of Substance Abuse Treatment*, 13(4), 493-504. doi:10.1016/S0899-3289(01)00096-7

- Greenfield, S. F., Brooks, A. J., Gordon, S. M., Green, C. A., Kropp, F., McHugh, R. K., . . . Miele, G. M. (2007). Substance abuse treatment entry, retention, and outcome in women: a review of the literature. *Drug and Alcohol Dependence*, 86(1), 1-21. doi:10.1016/j.drugalcdep.2006.05.012
- Groppe, D. M., Bickel, S., Keller, C. J., Jain, S. K., Hwang, S. T., Harden, C., & Mehta, A. D. (2013). Dominant frequencies of resting human brain activity as measured by the electrocorticogram. *Neuroimage*, 79, 223-233. doi:10.1016/j.neuroimage.2013.04.044
- Gross, M. M., Goodenough, D. R., Hasty, J., & Lewis, E. (1973). Experimental study of sleep in chronic alcoholics before, during, and after four days of heavy drinking with a nondrinking comparison. *Annals of the New York Academy of Sciences*, 215, 254-265. doi:10.1111/j.1749-6632.1973.tb28281.x
- Gross, M. M., & Hasty, J. M. (1975). The relation between baseline slow wave sleep and the slow wave sleep response to alcohol in alcoholics. In M. M. Gross (Ed.), *Alcohol Intoxication and Withdrawal* (Vol. 59, pp. 467-475). New York, NY: Plenum.
- Grucza, R. A., Norberg, K., Bucholz, K. K., & Bierut, L. J. (2008). Correspondence between secular changes in alcohol dependence and age of drinking onset among women in the United States. *Alcoholism: Clinical and Experimental Research*, 32(8), 1493-1501. doi:10.1111/j.1530-0277.2008.00719.x
- Guerri, C., & Pascual, M. (2010). Mechanisms involved in the neurotoxic, cognitive, and neurobehavioral effects of alcohol consumption during adolescence. *Alcohol*, 44(1), 15-26. doi:10.1016/j.alcohol.2009.10.003
- Guilleminault, C. (1994). *Fatal familial insomnia: Inherited prion diseases, sleep, and the thalamus*. New York, NY: Raven Press.
- Guilleminault, C., Poyares, D., Rosa, A., Kirisoglu, C., Almeida, T., & Lopes, M. C. (2006). Chronic fatigue, unrefreshing sleep and nocturnal polysomnography. *Sleep Medicine*, 7(6), 513-520. doi:10.1016/j.sleep.2006.03.016

- Gupta, K. K., Gupta, V. K., & Shirasaka, T. (2016). An update on fetal alcohol syndrome-pathogenesis, risks, and treatment. *Alcoholism: Clinical and Experimental Research*, 40(8), 1594-1602. doi:10.1111/acer.13135
- Gupta, N. K., Mueller, W. H., Chan, W., & Meininger, J. C. (2002). Is obesity associated with poor sleep quality in adolescents? *American Journal of Human Biology*, 14(6), 762–768. doi:10.1002/ajhb.10093
- Gur, R. C., Turetsky, B. I., Matsui, M., Yan, M., Bilker, W., Huggett, P., & Gur, R. E. (1999). Sex differences in brain gray and white matter in healthy young adults: Correlations with cognitive performance. *The Journal of Neuroscience*, 19(10), 4065-4072. doi:10.1523/JNEUROSCI
- Hablitz, L. M., Vinitsky, H. S., Sun, Q., Staeger, F. F., Sigurdsson, B., Mortensen, K. N., . . . Nedergaard, M. (2019). Increased glymphatic influx is correlated with high EEG delta power and low heart rate in mice under anesthesia. *Science Advances*, 5(2), eaav5447. doi:10.1126/sciadv.aav5447
- Hagen, E., Erga, A. H., Hagen, K. P., Nesvag, S. M., McKay, J. R., Lundervold, A. J., & Walderhaug, E. (2016). Assessment of executive function in patients with substance use disorder: A comparison of inventory- and performance-based assessment. *Journal of Substance Abuse Treatment*, 66, 1-8. doi:10.1016/j.jsat.2016.02.010
- Hagenauer, M. H., & Lee, T. M. (2013). Adolescent sleep patterns in humans and laboratory animals. *Hormones and Behavior*, 64(2), 270-279. doi:10.1016/j.yhbeh.2013.01.013
- Hagenauer, M. H., Perryman, J. I., Lee, T. M., & Carskadon, M. A. (2009). Adolescent changes in the homeostatic and circadian regulation of sleep. *International Journal of Developmental Neuroscience*, 31(4), 276-284. doi:10.1159/000216538
- Hames, G. (2012). *Alcohol in world history*. New York, NY: Routledge.
- Hansel, C. (2019). Deregulation of synaptic plasticity in autism. *Neuroscience Letters*, 688, 58-61. doi:10.1016/j.neulet.2018.02.003

- Hanson, K. L., Cummins, K., Tapert, S. F., & Brown, S. A. (2011). Changes in neuropsychological functioning over 10 years following adolescent substance abuse treatment. *Psychology of Addictive Behaviors*, 25(1), 127-142. doi:10.1037/a0022350
- Haorah, J., Ramirez, S. H., Floreani, N., Gorantla, S., Morsey, B., & Persidsky, Y. (2008). Mechanism of alcohol-induced oxidative stress and neuronal injury. *Free Radical Biology and Medicine*, 45(11), 1542-1550. doi:10.1016/j.freeradbiomed.2008.08.030
- Harding, A. J., Halliday, G. M., Ng, J. L., Harper, C. G., & Kril, J. J. (1996). Loss of vasopressin-immunoreactive neurons in alcoholics is dose-related and time-dependent. *Neuroscience*, 72(3), 699-708. doi:10.1016/0306-4522(95)00577-3
- Harding, F. M., Hingson, R. W., Klitzner, M., Mosher, J. F., Brown, J., Vincent, R. M., . . . Cannon, C. L. (2016). Underage drinking: A review of trends and prevention strategies. *American Journal of Preventive Medicine*, 51(4 Suppl 2), S148-157. doi:10.1016/j.amepre.2016.05.020
- Harford, T. C., Yi, H. Y., Faden, V. B., & Chen, C. M. (2009). The dimensionality of DSM-IV alcohol use disorders among adolescent and adult drinkers and symptom patterns by age, gender, and race/ethnicity. *Alcoholism: Clinical and Experimental Research*, 33(5), 868-878. doi:10.1111/j.1530-0277.2009.00910.x
- Harper, C. (2009). The neuropathology of alcohol-related brain damage. *Alcohol and Alcoholism*, 44(2), 136-40. 136-140. doi:10.1093/alcalc/agn102
- Harper, C., Dixon, G., Sheedy, D., & Garrick, T. (2003a). Neuropathological alterations in alcoholic brains. Studies arising from the New South Wales tissue resource centre. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, 27, 951-961. doi:10.1016/S0278-5846(03)00155-6

- Harper, C., Dixon, G., Sheedy, D., & Garrick, T. (2003b). Neuropathological alterations in alcoholic brains. Studies arising from the New South Wales Tissue Resource Centre. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, 27(6), 951-961. doi:10.1016/s0278-5846(03)00155-6
- Harper, C., & Kril, J. (1989). Patterns of neuronal loss in the cerebral cortex in chronic alcoholic patients. *Journal of the Neurological Sciences*, 92(1), 81-89. doi:10.1016/0022-510X(89)90177-9
- Harper, C., & Matsumoto, I. (2005). Ethanol and brain damage. *Current Opinion in Pharmacology*, 5(1), 73-78. doi:10.1016/j.coph.2004.06.011
- Harper, C. G., & Kril, J. J. (1988). Corpus callosal thickness in alcoholics. *British Journal of Addiction*, 83(5), 577-580. doi:10.1111/j.1360-0443.1988.tb02577.x
- Harper, C. G., Smith, N. A., & Kril, J. J. (1990). The effects of alcohol on the female brain: A neuropathological study. *Alcohol and Alcoholism*, 25(5), 445-448. doi:10.1093/oxfordjournals.alcalc.a045035
- Harrison, L., Kelly, P., Lindsay, J., Advocat, J., & Hickey, C. (2011). 'I don't know anyone that has two drinks a day': Young people, alcohol and the government of pleasure. *Health, Risk and Society*, 13(5), 469-486. doi:10.1080/13698575.2011.596190
- Harrison, N. L., Skelly, M. J., Grosserode, E. K., Lowes, D. C., Zeric, T., Phister, S., & Salling, M. C. (2017). Effects of acute alcohol on excitability in the CNS. *Neuropharmacology*, 122, 36-45. doi:10.1016/j.neuropharm.2017.04.007
- Hart, C. L., & Ksir, C. (2011). *Drugs, society and human behaviour* (Vol. 14). New York, NY: McGraw-Hill.
- Hartse, K. M. (2011). The phylogeny of sleep. In M. J. Aminoff, F. Boller, & D. F. Swaab (Eds.), *Handbook of Clinical Neurology* (Vol. 98., pp. 97-109). Amsterdam: Elsevier. doi:10.1016/B978-0-444-52006-7.00007-1

- Hartwell, E. E., Bujarski, S., Glasner-Edwards, S., & Ray, L. A. (2015). The association of alcohol severity and sleep quality in problem drinkers. *Alcohol and Alcoholism*, 50(5), 536-541. doi:10.1093/alcalc/agt046
- Hasler, B. P., Soehner, A. M., & Clark, D. B. (2015). Sleep and circadian contributions to adolescent alcohol use disorder. *Alcohol*, 49(4), 377-387. doi:10.1016/j.alcohol.2014.06.010
- Hasselmo, M. E. (1999). Neuromodulation: Acetylcholine and memory consolidation. *Trends in Cognitive Sciences*, 3(9), 351-359. doi:10.1016/S1364-6613(99)01365-0
- Hauke, J., & Kossowski, T. (2011). Comparison of values of pearson's and spearman's Correlation coefficients on the same sets of data. *Quaestiones Geographicae*, 3(2), 87-93. doi:10.2478/v10117-011-0021-1
- Hauri, P., & Hawkins, D. R. (1973). Alpha-delta sleep. *Electroencephalography and Clinical Neurophysiology*, 34(3), 233-237. doi:10.1016/0013-4694(73)90250-2
- Haus, E. L., & Smolensky, M. H. (2013). Shift work and cancer risk: Potential mechanistic roles of circadian disruption, light at night, and sleep deprivation. *Sleep Medicine Reviews*, 17(4), 273-284. doi:10.1016/j.smr.2012.08.003
- Heeb, J. L., Gmel, G., Rehm, J., & Mohler-Kuo, M. (2008). Exploring daily variations of drinking in the Swiss general population. A growth curve analysis. *International Journal of Methods in Psychiatric Research*, 17(1), 1-11. doi:10.1002/mpr.238
- Heffernan, T., Clark, R., Bartholomew, J., Ling, J., & Stephens, S. (2009). Does binge drinking in teenagers affect their everyday prospective memory? *Drug and Alcohol Dependence*. doi:10.1016/j.drugalcdep.2009.12.013

- Heffernan, T., & O'Neill, T. (2012). Time based prospective memory deficits associated with binge drinking: Evidence from the Cambridge Prospective Memory Test (CAMPROMPT). *Drug and Alcohol Dependence*, 123(1-3), 207-212. doi:10.1016/j.drugalcdep.2011.11.014
- Heikkinen, N., Niskanen, E., Kononen, M., Tolmunen, T., Kekkonen, V., Kivimäki, P., . . . Vanninen, R. (2017). Alcohol consumption during adolescence is associated with reduced grey matter volumes. *Addiction*, 112(4), 604-613. doi:10.1111/add.13697
- Hemphill, J. F. (2003). Interpreting the magnitudes of correlation coefficients. *American Psychologist*, 58(1), 78-79. doi:10.1037/0003-066X.58.1.78
- Henderson, K. E., Vaidya, J. G., Kramer, J. R., Kuperman, S., Langbehn, D. R., & O'Leary, D. S. (2018). Cortical thickness in adolescents with a family history of alcohol use disorder. *Alcoholism: Clinical and Experimental Research*, 42(1), 89-99. doi:10.1111/acer.13543
- Hermens, D. F., Lagopoulos, J., Tobias-Webb, J., De Regt, T., Dore, G., Juckes, L., . . . Hickie, I. B. (2013). Pathways to alcohol-induced brain impairment in young people: A review. *Cortex*, 49(1), 3-17. doi:10.1016/j.cortex.2012.05.021
- Herting, M. M., Fair, D., & Nagel, B. J. (2011). Altered fronto-cerebellar connectivity in alcohol-naïve youth with a family history of alcoholism. *Neuroimage*, 54(4), 2582-2589. doi:10.1016/j.neuroimage.2010.10.030
- Herz, A. (1997). Endogenous opioid systems and alcohol addiction. *Psychopharmacology (Berl)*, 129(2), 99-111. doi:10.1007/s002130050169.
- Hides, L., Carroll, S., Catania, L., Cotton, S. M., Baker, A., Scaffidi, A., & Lubman, D. I. (2010). Outcomes of an integrated cognitive behaviour therapy (CBT) treatment program for co-occurring depression and substance misuse in young people. *Journal of Affective Disorders*, 121(1-2), 169-174. doi:10.1016/j.jad.2009.06.002

- Hingson, R. W., Heeren, T., & Winter, M. R. (2006a). Age at drinking onset and alcohol dependence: Age at onset, duration, and severity. *Archives of Pediatrics and Adolescent Medicine*, 160(7), 739-746. doi:10.1001/archpedi.160.7.739
- Hingson, R. W., Heeren, T., & Winter, M. R. (2006b). Age of alcohol-dependence onset: Associations with severity of dependence and seeking treatment. *Pediatrics*, 118(3), e755-763. doi:10.1542/peds.2006-0223
- Hingson, R. W., & Zha, W. (2009). Age of drinking onset, alcohol use disorders, frequent heavy drinking, and unintentionally injuring oneself and others after drinking. *Pediatrics*, 123(6), 1477-1484. doi:10.1542/peds.2008-2176
- Hirshkowitz, M., Whiton, K., Albert, S. M., Alessi, C., Bruni, O., DonCarlos, L., . . . Adams Hillard, P. J. (2015). National Sleep Foundation's sleep time duration recommendations: Methodology and results summary. *Sleep Health*, 1(1), 40-43. doi:10.1016/j.sleh.2014.12.010
- Hoffman, P. L., Rabe, C. S., Moses, F., & Tabakoff, B. (1989). N-methyl-D-aspartate receptors and ethanol: Inhibition of calcium flux and cyclic GMP production. *Journal of Neurochemistry*, 52(6), 1937-1940. doi:10.1111/j.1471-4159.1989.tb07280.x
- Hogan, H. A., Sampson, H. W., Cashier, E., & Ledoux, N. (1997). Alcohol consumption by young actively growing rats: A study of cortical bone histomorphometry and mechanical properties. *Alcoholism: Clinical and Experimental Research*, 21(5), 809-816. doi:10.1111/j.1530-0277.1997.tb03844.x
- Hollingshead, A. B. (1957). *Two factor index of social position*. New Haven, CT: Yale University.
- Hollingshead, A. B. (1971). Commentary on the indiscriminate state of social class measurement. *Social Forces*, 49(4), 563-567. doi:10.2307/2576737
- Holshoe, J. M. (2009). Antidepressants and sleep: A review. *Perspectives in Psychiatric Care*, 45(3), 191-197. doi:10.1111/j.1744-6163.2009.00221.x

- Holt, S. (1981). Observations on the relation between alcohol absorption and the rate of gastric emptying. *Canadian Medical Association Journal*, 124(3), 267-277, 297.
- Holz, J., Piosczyk, H., Feige, B., Spiegelhalder, K., Baglioni, C., Riemann, D., & Nissen, C. (2012). EEG sigma and slow-wave activity during NREM sleep correlate with overnight declarative and procedural memory consolidation. *Journal of Sleep Research*, 21(6), 612–619. doi:10.1111/j.1365-2869.2012.01017.x
- Hong, M., & Krauss, R. S. (2017). Ethanol itself is a holoprosencephaly-inducing teratogen. *PLoS One*, 12(4): e0176440. doi:10.1371/journal.pone.0176440
- Horne, J. (1992). Human slow wave sleep: A review and appraisal of recent findings, with implications for sleep functions, and psychiatric illness. *Experientia*, 48(10), 941-954. doi:10.1007/BF01919141.
- Horne, J. A., & Ostberg, O. (1976). A self-assessment questionnaire to determine morningness-eveningness in human circadian rhythms. *Chronobiology International*, 4(2), 97-110. doi:10.3109/07420529709001458
- Horne, J. A., & Shackell, B. S. (1991). Alpha-like EEG activity in non-REM sleep and the fibromyalgia (fibrositis) syndrome. *Electroencephalography and Clinical Neurophysiology*, 79(4), 271-276.
doi:10.1016/0013-4694(91)90122-K
- Horowitz, M., Maddox, A., Bochner, M., Wishart, J., Bratasiuk, R., Collins, P., & Shearman, D. (1989). Relationships between gastric emptying of solid and caloric liquid meals and alcohol absorption. *American Journal of Physiology*, 257(2 Pt 1), G291-298. doi:10.1152/ajpgi.1989.257.2.G291
- Howell, A. J., Jahrig, J. C., & Powell, R. A. (2004). Sleep quality, sleep propensity and academic performance. *Perceptual and Motor Skills*, 99(2), 525-535. doi:10.2466/pms.99.2.525-535

- Hu, X., Oroszi, G., Chun, J., Smith, T. L., Goldman, D., & Schuckit, M. A. (2005). An expanded evaluation of the relationship of four alleles to the level of response to alcohol and the alcoholism risk. *Alcoholism: Clinical & Experimental Research*, 29(1), 8-16.
doi:10.1097/01.Alc.0000150008.68473.62
- Huber, R., Ghilardi, M. F., Massimini, M., & Tononi, G. (2004). Local sleep and learning. *Nature*, 430(6995), 78-81. doi:10.1038/nature02663
- Hughes, J. R. (2009). Alcohol withdrawal seizures. *Epilepsy and Behavior*, 15(2), 92-97. doi:10.1016/j.yebeh.2009.02.037
- Hung, C. S., Sarasso, S., Ferrarelli, F., Riedner, B., Ghilardi, M. F., Cirelli, C., & Tononi, G. (2013). Local experience-dependent changes in the wake EEG after prolonged wakefulness. *Sleep*, 36(1), 59-72. doi:10.5665/sleep.2302
- Huttenlocher, P. R. (1979). Synaptic density in human frontal cortex - Developmental changes and effects of aging. *Brain Research*, 163(2), 195-205.
doi:10.1016/0006-8993(79)90349-4.
- Ikeda-Sagara, M., Ozaki, T., Shahid, M., Morioka, E., Wada, K., Honda, K., . . . Ikeda, M. (2012). Induction of prolonged, continuous slow-wave sleep by blocking cerebral H₁ histamine receptors in rats. *British Journal of Pharmacology*, 165(1), 167-182. doi:10.1111/j.1476-5381.2011.01547.x
- Imatoh, N., Nakazawa, Y., Ohshima, H., Ishibashi, M., & Yokoyama, T. (1986). Circadian rhythm of REM sleep of chronic alcoholics during alcohol withdrawal. *Drug and Alcohol Dependence*, 18(1), 77-85. doi:10.1016/0376-8716(86)90116-X
- Insel, T. R., Miller, L. P., & Gelhard, R. E. (1990). The ontogeny of excitatory amino acid receptors in rat forebrain-I. N-methyl-D-aspartate and quisqualate receptors. *Neuroscience*, 35(1), 31-43. doi: 10.1016/0306-4522(90)90117-M
- Iorio, K. R., Reinlib, L., Tabakoff, B., & Hoffman, P. L. (1992). Chronic exposure of cerebellar granule cells to ethanol results in increased N-methyl-D-aspartate receptor function. *Molecular Pharmacology*, 41(6), 1142-1148.

- Irwin, M., Gillin, J. C., Dang, J., Weissman, J., Phillips, E., & Ehlers, C. L. (2002). Sleep deprivation as a probe of homeostatic sleep regulation in primary alcoholics. *Biological Psychiatry*, 51(8), 632-641. doi:10.1016/S0006-3223(01)01304-X
- Irwin, M., Miller, C., Gillin, J. C., DeModena, A., & Ehlers, C. L. (2000). Polysomnographic and spectral sleep EEG in primary alcoholics: An interaction between alcohol dependence and African-American ethnicity. *Alcoholism: Clinical and Experimental Research*, 24(9), 1376-1384. doi:10.1111/j.1530-0277.2000.tb02106.x
- Jackson, M. L., Howard, M. E., & Barnes, M. (2011). Cognition and daytime functioning in sleep-related breathing disorders. *Progress in Brain Research*, 190, 53-68. doi:10.1016/B978-0-444-53817-8.00003-7
- Jacobus, J., & Tapert, S. F. (2013). Neurotoxic effects of alcohol in adolescence. *Annual Review of Clinical Psychology*, 9, 703-721. doi:10.1146/annurev-clinpsy-050212-185610
- Jaimcharyatam, N., Rodriguez, C. L., & Budur, K. (2011). Prevalence and correlates of alpha-delta sleep in major depressive disorders. *Innovations in Clinical Neuroscience*, 8(7), 35-49.
- Jaiswal, S., Tsai, S. Y., Juan, C. H., Liang, W. K., & Muggleton, N. G. (2018). Better cognitive performance is associated with the combination of high trait mindfulness and low trait anxiety. *Frontiers in Psychology*, 9, 627. doi:10.3389/fpsyg.2018.00627
- Jasper, H. (1958). Report of committee on methods of clinical exam in EEG. *Electroencephalography and Clinical Neurophysiology*, 10, 370-375. doi:10.1016/0013-4694(58)90053-1.
- Jasper, H. H., & Tessier, J. (1971). Acetylcholine liberation from cerebral cortex during paradoxical (REM) sleep. *Science*, 172(3983), 601-602. doi:10.1126/science.172.3983.601

- Jesse, S., Brathen, G., Ferrara, M., Keindl, M., Ben-Menachem, E., Tanasescu, R., . . . Ludolph, A. C. (2017). Alcohol withdrawal syndrome: Mechanisms, manifestations, and management. *Acta Neurologica Scandinavica*, 135(1), 4-16. doi:10.1111/ane.12671
- Johansen-Berg, H. (2010). Behavioural relevance of variation in white matter microstructure. *Current Opinion in Neurology*, 23(4), 351-358. doi:10.1097/WCO.0b013e32833b7631
- Johnson, E. O., & Breslau, N. (2001). Sleep problems and substance use in adolescence. *Drug and Alcohol Dependence*, 64(1), 1-7. doi:10.1016/s0376-8716(00)00222-2
- Johnson, E. O., Roth, T., Schultz, L., & Breslau, N. (2006). Epidemiology of DSM-IV insomnia in adolescence: lifetime prevalence, chronicity, and an emergent gender difference. *Pediatrics*, 117(2), e247-256. doi:10.1542/peds.2004-2629
- Johnson, L. C., Burdick, J. A., & Smith, J. (1970). Sleep during alcohol intake and withdrawal in the chronic alcoholic. *Archives of General Psychiatry*, 22(5), 406-418. doi:10.1001/archpsyc.1970.01740290022004
- Johnson, S. B., Blum, R. W., & Giedd, J. N. (2009). Adolescent maturity and the brain: the promise and pitfalls of neuroscience research in adolescent health policy. *Journal of Adolescent Health*, 45(3), 216-221. doi:10.1016/j.jadohealth.2009.05.016
- Johnston, K. L., & White, K. M. (2004). Binge-drinking in female university students: A theory of planned behaviour perspective. *Youth Studies Australia*, 32(2), 22-30.
- Jones, A. W., & Holmgren, P. (2003). Comparison of blood-ethanol concentration in deaths attributed to acute alcohol poisoning and chronic alcoholism. *Journal of Forensic Sciences*, 48(4), 874-879. doi:10.1520/JFS2002420
- Jones, S. A., Lueras, J. M., & Nagel, B. J. (2018). Effects of binge drinking on the developing brain. *Alcohol Research: Current Reviews*, 39(1), 87-96.

- Kaczurkin, A. N., Raznahan, A., & Satterthwaite, T. D. (2019). Sex differences in the developing brain: insights from multimodal neuroimaging. *Neuropsychopharmacology*, 44(1), 71-85. doi:10.1038/s41386-018-0111-z
- Kahkonen, S. (2004). Mechanisms of cardiovascular dysregulation during alcohol withdrawal. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, 28(6), 937-941. doi:10.1016/j.pnpbp.2004.05.039
- Kalant, H. (1977). Alcohol withdrawal syndromes in the human: Comparison with animal models. *Advances in Experimental Medicine and Biology*, 85B, 57-64. doi:10.1007/978-1-4615-9038-5_5
- Kamarajan, C., Pandey, A. K., Chorlian, D. B., Manz, N., Stimus, A. T., Anokhin, A. P., . . . Porjesz, B. (2015). Deficient event-related theta oscillations in individuals at risk for alcoholism: A study of reward processing and impulsivity features. *PLoS One*, 10(11), e0142659. doi:10.1371/journal.pone.0142659
- Kang, M., Spigelman, I., Sapp, D. W., & Olsen, R. W. (1996). Persistent reduction of GABA(A) receptor-mediated inhibition in rat hippocampus after chronic intermittent ethanol treatment. *Brain Research*, 709(2), 221-228. doi:10.1016/0006-8993(95)01274-5
- Karadayian, A. G., & Cutrera, R. A. (2013). Alcohol hangover: Type and time-extension of motor function impairments. *Behavioural Brain Research*, 247, 165-173. doi:10.1016/j.bbr.2013.03.037
- Katz, R. J., & Liebler, L. (1978). GABA involvement in memory consolidation: Evidence from posttrial amino-oxyacetic acid. *Psychopharmacology (Berl)*, 56(2), 191-193. doi:10.1007/bf00431848
- Kay-Lambkin, F. J., Baker, A. L., Lewin, T. J., & Carr, V. J. (2009). Computer-based psychological treatment for comorbid depression and problematic alcohol and/or cannabis use: A randomized controlled trial of clinical efficacy. *Addiction*, 104(3), 378-388. doi:10.1111/j.1360-0443.2008.02444.x

- Kemple, M., O'Toole, S., & O'Toole, C. (2016). Sleep quality in patients with chronic illness. *Journal of Clinical Nursing*, 25(21-22), 3363-3372.
doi:10.1111/jocn.13462
- Kenney, S. R., LaBrie, J. W., Hummer, J. F., & Pham, A. T. (2012). Global sleep quality as a moderator of alcohol consumption and consequences in college students. *Addictive Behaviors*, 37(4), 507-512.
doi:10.1016/j.addbeh.2012.01.006
- Kenney, S. R., Paves, A. P., Grimaldi, E. M., & LaBrie, J. W. (2014). Sleep quality and alcohol risk in college students: Examining the moderating effects of drinking motives. *Journal of American College Health*, 62(5), 301-308.
doi:10.1080/07448481.2014.897953
- Keppel, G. (1982). *Design and analysis: A researchers handbook* (Vol. 2). New Jersey: Prentice Hall.
- Kessler, R. C., McGonagle, K. A., Zhao, S., Nelson, C. B., Hughes, M., Eshleman, S., . . . Kendler, K. S. (1994). Lifetime and 12-month prevalence of DSM-III-R psychiatric disorders in the United States. Results from the National Comorbidity Survey. *Archives of General Psychiatry*, 51(1), 8-19.
doi:10.1001/archpsyc.1994.03950010008002.
- Keyes, K. M., Grant, B. F., & Hasin, D. S. (2008). Evidence for a closing gender gap in alcohol use, abuse, and dependence in the United States population. *Drug and Alcohol Dependence*, 93(1-2), 21-29.
doi:10.1016/j.drugalcdep.2007.08.017
- Khan, S., Okuda, M., Hasin, D. S., Secades-Villa, R., Keyes, K., Lin, K. H., . . . Blanco, C. (2013). Gender differences in lifetime alcohol dependence: Results from the national epidemiologic survey on alcohol and related conditions. *Alcoholism: Clinical and Experimental Research*, 37(10), 1696-1705.
doi:10.1111/acer.12158
- Killgore, W. D. (2010). Effects of sleep deprivation on cognition. *Progress in Brain Research*, 185, 105-129. doi:10.1016/B978-0-444-53702-7.00007-5

- Kim, S. J., Lee, Y. J., Cho, S. J., Cho, I. H., Lim, W., & Lim, W. (2011). Relationship between weekend catch-up sleep and poor performance on attention tasks in Korean adolescents. *Archives of Pediatrics and Adolescent Medicine*, 165(9), 806-812. doi:10.1001/archpediatrics.2011.128
- King, M. A., Hunter, B. E., & Walker, D. W. (1988). Alterations and recovery of dendritic spine density in rat hippocampus following long-term ethanol ingestion. *Brain Research*, 459(2), 381-385. doi:10.1016/0006-8993(88)90656-7
- Klemm, W. R. (2011). Why does rem sleep occur? A wake-up hypothesis. *Frontiers in Systems Neuroscience*, 5, 73. doi:10.3389/fnsys.2011.00073
- Knauert, M., Naik, S., Gillespie, M. B., & Kryger, M. (2015). Clinical consequences and economic costs of untreated obstructive sleep apnea syndrome. *World Journal of Otorhinolaryngology - Head and Neck Surgery*, 1(1), 17-27. doi:10.1016/j.wjorl.2015.08.001
- Knowles, J. B., Laverty, S. G., & Kuechler, H. A. (1968). Effects on REM sleep. *Journal of Studies on Alcohol and Drugs*, 29(2), 342-349.
- Kodama, T., Lai, Y. Y., & Siegel, J. M. (1998). Enhanced glutamate release during REM sleep in the rostromedial medulla as measured by in vivo microdialysis. *Brain Research*, 780(1), 178-181. doi:10.1016/s0006-8993(97)01308-5
- Kolla, B. P., Schneekloth, T., Biernacka, J., Mansukhani, M., Geske, J., Karpyak, V., . . . Frye, M. A. (2014). The course of sleep disturbances in early alcohol recovery: an observational cohort study. *The American Journal on Addictions*, 23(1), 21-26. doi:10.1111/j.1521-0391.2013.12056.x
- Koo, B. B., Blackwell, T., Lee, H. B., Stone, K. L., Louis, E. D., & Redline, S. (2016). Restless legs syndrome and depression: Effect mediation by disturbed sleep and periodic limb movements. *The American Journal of Geriatric Psychiatry*, 24(11), 1105-1116. doi:10.1016/j.jagp.2016.04.003

- Koob, G. F., & Colrain, I. M. (2019). Alcohol use disorder and sleep disturbances: A feed-forward allostatic framework. *Neuropsychopharmacology*. doi:10.1038/s41386-019-0446-0
- Kopp, C., Longordo, F., Nicholson, J. R., & Luthi, A. (2006). Insufficient sleep reversibly alters bidirectional synaptic plasticity and NMDA receptor function. *The Journal of Neuroscience*, 26(48), 12456-12465. doi:10.1523/JNEUROSCI.2702-06.2006
- Krause, A. J., Simon, E. B., Mander, B. A., Greer, S. M., Saletin, J. M., Goldstein-Piekarski, A. N., & Walker, M. P. (2017). The sleep-deprived human brain. *Nature Reviews Neuroscience*, 18(7), 404-418. doi:10.1038/nrn.2017.55
- Kril, J. J., Halliday, G. M., Svoboda, M. D., & Cartwright, H. (1997). The cerebral cortex is damaged in chronic alcoholics. *Neuroscience*, 79(4), 983-998. doi:10.1016/S0306-4522(97)00083-3
- Kroener, S., Mulholland, P. J., New, N. N., Gass, J. T., Becker, H. C., & Chandler, L. J. (2012). Chronic alcohol exposure alters behavioral and synaptic plasticity of the rodent prefrontal cortex. *PLoS One*, 7(5), e37541. doi:10.1371/journal.pone.0037541
- Krueger, J. M., Frank, M. G., Wisor, J. P., & Roy, S. (2016). Sleep function: Toward elucidating an enigma. *Sleep Medicine Reviews*, 28, 46-54. doi:10.1016/j.smrv.2015.08.005
- Kryger, M., Roth, T., & Dement, W. C. (2017). *Principles and practice of sleep medicine* (6th ed.). Philadelphia, PA: Elsevier.
- Krystal, A. D. (2012). Psychiatric disorders and sleep. *Neurologic Clinics*, 30(4), 1389-1413. doi:10.1016/j.ncl.2012.08.018
- Krystal, A. D., Edinger, J. D., Wohlgemuth, W. K., & Marsh, G. R. (2002). NREM sleep EEG frequency spectral correlates of sleep complaints in primary insomnia subtypes. *Sleep*, 25(6), 630-640. doi:10.1093/sleep/25.6.626

- Kuhlwein, E., Hauger, R. L., & Irwin, M. R. (2003). Abnormal nocturnal melatonin secretion and disordered sleep in abstinent alcoholics. *Biological Psychiatry*, 54(12), 1437-1443. doi:10.1016/S0006-3223(03)00005-2
- Kumar, S., Porcu, P., Werner, D. F., Matthews, D. B., Diaz-Granados, J. L., Helfand, R. S., & Morrow, A. L. (2009). The role of GABA_A receptors in the acute and chronic effects of ethanol: a decade of progress. *Psychopharmacology (Berl)*, 205(4), 529-564. doi:10.1007/s00213-009-1562-z
- Kuntsche, E., & Gmel, G. (2013). Alcohol consumption in late adolescence and early adulthood- Where is the problem? *Swiss Medical Weekly*, 143, w13826. doi:10.4414/smw.2013.13826
- Kuntsche, E., Knibbe, R., Gmel, G., & Engels, R. (2005). Why do young people drink? A review of drinking motives. *Clinical Psychology Review*, 25(7), 841-861. doi:10.1016/j.cpr.2005.06.002
- Kuntsche, E., & Labhart, F. (2012). Investigating the drinking patterns of young people over the course of the evening at weekends. *Drug and Alcohol Dependence*, 124(3), 319-324. doi:10.1016/j.drugalcdep.2012.02.001
- Kupfer, D. J., Reynolds, C. F., 3rd, & Ehlers, C. L. (1989). Comparison of EEG sleep measures among depressive subtypes and controls in older individuals. *Psychiatry Research*, 27(1), 13-21. doi:10.1016/0165-1781(89)90004-8
- Kurth, S., Jenni, O. G., Riedner, B. A., Tononi, G., Carskadon, M. A., & Huber, R. (2010). Characteristics of sleep slow waves in children and adolescents. *Sleep*, 33(4), 475-480. doi:10.1093/sleep/33.4.475
- Kushida, C. A., Littner, M. R., Morgenthaler, T., Alessi, C. A., Bailey, D., Coleman, J., . . . Wise, M. (2005). Practice parameters for the indications for polysomnography and related procedures: An update for 2005. *Sleep*, 28(4), 499-523. doi:10.1093/sleep/28.4.499
- Kwasnicka, A., & Auerbach, S. (2011). Sleep disorders related to alcohol and other drug use. . In C. Cavacuiti (Ed.), *Principles of addiction medicine: The essentials* (pp. 32-36). Philadelphia: Lippincott Williams & Wilkins. .

- Kwo, P. Y., Ramchandani, V. A., O'Connor, S., Amann, D., Carr, L. G., Sandrasegaran, K., . . . Li, T. K. (1998). Gender differences in alcohol metabolism: relationship to liver volume and effect of adjusting for body mass. *Gastroenterology*, 115(6), 1552-1557. doi:10.1016/S0016-5085(98)70035-6
- LaBrie, J. W., Boyle, S., Earle, A., & Almstedt, H. C. (2018). Heavy episodic drinking is associated with poorer bone health in adolescent and young adult women. *Journal of Studies on Alcohol and Drugs*, 79(3), 391-398. doi:10.15288/jsad.2018.79.391
- Landolt, H.-P., & Borbély, A. A. (2001). Age-dependent changes in sleep EEG topography. *Clinical Neurophysiology*, 112(2), 369-377. doi:10.1016/s1388-2457(00)00542-3
- Landolt, H.-P., Roth, C., Dijk, D.-J., & Borbely, A. A. (1996). Late-afternoon ethanol intake affects nocturnal sleep and the sleep EEG in middle-aged men. *Journal of Clinical Psychopharmacology*, 16(6), 428-436. doi:10.1097/00004714-199612000-00004
- Lannoy, S., Heeren, A., Moyaerts, N., Bruneau, N., Evrard, S., Billieux, J., & Maurage, P. (2017). Differential impairments across attentional networks in binge drinking. *Psychopharmacology (Berl)*, 234(7), 1059-1068. doi:10.1007/s00213-017-4538-4
- Larner, A. J. (2014). Effect size (Cohen's d) of cognitive screening instruments examined in pragmatic diagnostic accuracy studies. *Dementia and Geriatric Cognitive Disorders*, 4(2), 236-241. doi:10.1159/000363735
- Latta, F., Leproult, R., Tasali, E., Hofmann, E., & Van Cauter, E. (2005). Sex differences in delta and alpha EEG activities in healthy older adults. *Sleep*, 28(12), 1525-1534. doi:10.1093/sleep/28.12.1525

- Le Bon, O., Verbanck, P., Hoffmann, G., Murphy, J. R., Staner, L., De Groote, D., . . . Pelc, I. (1997). Sleep in detoxified alcoholics: Impairment of most standard sleep parameters and increased risk for sleep apnea, but not for myoclonias--A controlled study. *Journal of Studies on Alcohol*, 58, 30-36.
doi:10.15288/jsa.1997.58.30
- Lebel, C., & Beaulieu, C. (2011). Longitudinal development of human brain wiring continues from childhood into adulthood. *The Journal of Neuroscience*, 31(30), 10937-10947. doi:10.1523/JNEUROSCI.5302-10.2011
- Lebel, C., Walker, L., Leemans, A., Phillips, L., & Beaulieu, C. (2008). Microstructural maturation of the human brain from childhood to adulthood. *Neuroimage*, 40(3), 1044-1055. doi:10.1016/j.neuroimage.2007.12.053
- Lechin, F., Pardey-Maldonado, B., van der Dijs, B., Benaim, M., Baez, S., Orozco, B., & Lechin, A. E. (2004). Circulating neurotransmitters during the different wake-sleep stages in normal subjects. *Psychoneuroendocrinology*, 29(5), 669-685. doi:10.1016/s0306-4530(03)00095-7
- Lee, H., Roh, S., & Kim, D. J. (2009a). Alcohol-induced blackout. *International Journal of Environmental Research and Public Health*, 6(11), 2783-2792. doi:10.3390/ijerph6112783
- Lee, M. L., Swanson, B. E., & de la Iglesia, H. O. (2009b). Circadian timing of REM sleep is coupled to an oscillator within the dorsomedial suprachiasmatic nucleus. *Current Biology*, 19(10), 848-852. doi:10.1016/j.cub.2009.03.051
- Leeman, R. F., Perez, E., Nogueira, C., & DeMartini, K. S. (2015). Very-brief, web-based interventions for reducing alcohol use and related problems among college students: A review. *Frontiers in Psychiatry*, 6, 129. doi:10.3389/fpsy.2015.00129
- Lees, B., Mewton, L., Stapinski, L., Squeglia, L. M., Rae, C., & Teesson, M. (2018). Binge drinking in young people: Protocol for a systematic review of neuropsychological, neurophysiological and neuroimaging studies. *The British Medical Journal Open*, 8(7), e023629. doi:10.1136/bmjopen-2018-023629

- Lees, B., Mewton, L., Stapinski, L. A., Squeglia, L. M., Rae, C. D., & Teesson, M. (2019). Neurobiological and cognitive profile of young binge drinkers: A systematic review and meta-analysis. *Neuropsychology Review*, 29(3), 357-385. doi:10.1007/s11065-019-09411-w
- Leger, D., Beck, F., Richard, J. B., & Godeau, E. (2012). Total sleep time severely drops during adolescence. *PLoS One*, 7(10), e45204. doi:10.1371/journal.pone.0045204
- Leng, Y., Blackwell, T., Stone, K. L., Hoang, T. D., Redline, S., & Yaffe, K. (2016). Periodic limb movements in sleep are associated with greater cognitive decline in older men without dementia. *Sleep*, 39(10), 1807-1810. doi:10.5665/sleep.6158
- Lenroot, R. K., & Giedd, J. N. (2006). Brain development in children and adolescents: Insights from anatomical magnetic resonance imaging. *Neuroscience and Biobehavioral Reviews*, 30(6), 718-729. doi:10.1016/j.neubiorev.2006.06.001
- Lenroot, R. K., & Giedd, J. N. (2010). Sex differences in the adolescent brain. *Brain and Cognition*, 72(1), 46-55. doi:10.1016/j.bandc.2009.10.008
- Lenroot, R. K., Gogtay, N., Greenstein, D. K., Wells, E. M., Wallace, G. L., Clasen, L. S., . . . Giedd, J. N. (2007). Sexual dimorphism of brain developmental trajectories during childhood and adolescence. *Neuroimage*, 36(4), 1065-1073. doi:10.1016/j.neuroimage.2007.03.053
- Leproult, R., Copinschi, G., Buxton, O., & Van Cauter, E. (1997). Sleep loss results in an elevation of cortisol levels the next evening. *Sleep*, 20(10), 865-870. doi:10.1093/sleep/20.10.865
- Levenson, R. W., Sher, K. J., Grossman, L. M., Newman, J., & Newlin, D. B. (1980). Alcohol and stress response dampening: Pharmacological effects, expectancy, and tension reduction. *Journal of Abnormal Psychology*, 89(4), 528-538. doi:10.1037//0021-843X.89.4.528

- Li, Y., Zhang, X., Winkelman, J. W., Redline, S., Hu, F. B., Stampfer, M., . . . Gao, X. (2014). Association between insomnia symptoms and mortality: a prospective study of U.S. men. *Circulation*, 129(7), 737-746.
doi:10.1161/CIRCULATIONAHA.113.004500
- Lieb, R., Merikangas, K. R., Hofler, M., Pfister, H., Isensee, B., & Wittchen, H. U. (2002). Parental alcohol use disorders and alcohol use and disorders in offspring: A community study. *Psychological Medicine*, 32(1), 63-78.
doi:10.1017/S0033291701004883
- Lieber, C. S. (1998). Hepatic and other medical disorders of alcoholism: From pathogenesis to treatment. *Journal of Studies on Alcohol*, 59(1), 9-25.
doi:10.15288/jsa.1998.59.9
- Lieberman, O. J., McGuirt, A. F., Tang, G., & Sulzer, D. (2018). Roles for neuronal and glial autophagy in synaptic pruning during development. *Neurobiology of Disease*, 122, 49-63. doi:10.1016/j.nbd.2018.04.017
- Light, J. M., Irvine, K. M., & Kjerulf, L. (1996). Estimating genetic and environmental effects of alcohol use and dependence from a national survey: A "quasi-adoption" study. *Journal of Studies on Alcohol*, 57(5), 507-520.
doi:10.15288/jsa.1996.57.507
- Lim, J., & Dinges, D. F. (2010). A meta-analysis of the impact of short-term sleep deprivation on cognitive variables. *Psychological Bulletin*, 136(3), 375-389.
doi:10.1037/a0018883
- Lineberger, M. D., Means, M. K., & Edinger, J. D. (2007). Sleep disturbance in fibromyalgia. *Sleep Medicine Clinics*, 2, 31-39.
doi:10.1016/j.jsmc.2006.11.006
- Linsenbardt, D. N., Moore, E. M., Gross, C. D., Goldfarb, K. J., Blackman, L. C., & Boehm, S. L., 2nd. (2009). Sensitivity and tolerance to the hypnotic and ataxic effects of ethanol in adolescent and adult C57BL/6J and DBA/2J mice. *Alcoholism: Clinical and Experimental Research*, 33(3), 464-476.
doi:10.1111/j.1530-0277.2008.00857.x

- Lisdahl, K. M., Gilbert, E. R., Wright, N. E., & Shollenbarger, S. (2013a). Dare to delay? The impacts of adolescent alcohol and marijuana use onset on cognition, brain structure, and function. *Frontiers in Psychiatry*, 4, 53. doi:10.3389/fpsyt.2013.00053
- Lisdahl, K. M., Thayer, R., Squeglia, L. M., McQueeney, T. M., & Tapert, S. F. (2013b). Recent binge drinking predicts smaller cerebellar volumes in adolescents. *Psychiatry Research*, 211(1), 17-23. doi:10.1016/j.psychresns.2012.07.009
- Liston, C., Watts, R., Tottenham, N., Davidson, M. C., Niogi, S., Ulug, A. M., & Casey, B. J. (2006). Frontostriatal microstructure modulates efficient recruitment of cognitive control. *Cerebral Cortex*, 16(4), 553-560. doi:10.1093/cercor/bhj003
- Litovitz, T. (1986). The alcohols: Ethanol, methanol, isopropanol, ethylene glycol. *Pediatric Clinics of North America*, 33(2), 311-323. doi:10.1016/s0031-3955(16)35004-0.
- Little, P. J., Kuhn, C. M., Wilson, W. A., & Swartzwelder, H. S. (1996). Differential effects of ethanol in adolescent and adult rats. *Alcoholism: Clinical and Experimental Research*, 20(8), 1346-1351. doi:10.1111/j.1530-0277.1996.tb01133.x
- Liu, L., & Ancoli-Israel, S. (2008). Sleep disturbances in cancer. *Psychiatric Annals*, 38(9), 627-634. doi:10.3928/00485713-20080901-01
- Lo, J. C., Groeger, J. A., Santhi, N., Arbon, E. L., Lazar, A. S., Hasan, S., . . . Dijk, D. J. (2012). Effects of partial and acute total sleep deprivation on performance across cognitive domains, individuals and circadian phase. *PLoS One*, 7(9), e45987. doi:10.1371/journal.pone.0045987
- Lo, J. C., Ong, J. L., Leong, R. L., Gooley, J. J., & Chee, M. W. (2016). Cognitive performance, sleepiness, and mood in partially sleep deprived adolescents: The need for sleep study. *Sleep*, 39(3), 687-698. doi:10.5665/sleep.5552

- Lobo, I. A., & Harris, R. A. (2008). GABA_A receptors and alcohol. *Pharmacology Biochemistry and Behavior*, 90(1), 90-94. doi:10.1016/j.pbb.2008.03.006
- LoConte, N. K., Brewster, A. M., Kaur, J. S., Merrill, J. K., & Alberg, A. J. (2018). Alcohol and cancer: A statement of the american society of clinical oncology. *Journal of Clinical Oncology*, 36(1), 83-93. doi:10.1200/JCO.2017.76.1155
- Lopez-Caneda, E., Cadaveira, F., Correias, A., Crego, A., Maestu, F., & Rodriguez Holguin, S. (2017). The brain of binge drinkers at rest: Alterations in theta and beta oscillations in first-year college students with a binge drinking pattern. *Frontiers in Behavioral Neuroscience*, 11, 168. doi:10.3389/fnbeh.2017.00168
- Louis, J., Zhang, J. X., Revol, M., Debilly, G., & Challamel, M. J. (1992). Ontogenesis of nocturnal organization of sleep spindles: A longitudinal study during the first 6 months of life. *Electroencephalography and Clinical Neurophysiology*, 83(5), 289-296. doi:10.1016/0013-4694(92)90088-Y
- Love, S. (2006). Demyelinating diseases. *Journal of Clinical Pathology*, 59(11), 1151-1159. doi:10.1136/jcp.2005.031195
- Lovinger, D. M. (1997). Serotonin's role in alcohol's effects on the brain. *Alcohol Health and Research World*, 21(2), 114-120.
- Lovinger, D. M., White, G., & Weight, F. F. (1989). Ethanol inhibits NMDA-activated ion current in hippocampal neurons. *Science*, 243(4899), 1721-1724. doi:10.1126/science.2467382
- Lowe, C. J., Safati, A., & Hall, P. A. (2017). The neurocognitive consequences of sleep restriction: A meta-analytic review. *Neuroscience and Biobehavioral Reviews*, 80, 586-604. doi:10.1016/j.neubiorev.2017.07.010
- Lu, J., Sherman, D., Devor, M., & Saper, C. B. (2006). A putative flip-flop switch for control of REM sleep. *Nature*, 441(7093), 589-594. doi:10.1038/nature04767
- Lu, Y., & Cederbaum, A. I. (2008). CYP2E1 and oxidative liver injury by alcohol. *Free Radical Biology and Medicine*, 44(5), 723-738. doi:10.1016/j.freeradbiomed.2007.11.004

- Lubman, D. I., Yucel, M., & Hall, W. D. (2007). Substance use and the adolescent brain: a toxic combination? *Journal of Psychopharmacology*, 21(8), 792-794. doi:10.1177/0269881107078309
- Lucas, R., Fraga, S., Ramos, E., & Barros, H. (2012). Early initiation of smoking and alcohol drinking as a predictor of lower forearm bone mineral density in late adolescence: A cohort study in girls. *PLoS One*, 7(10), e46940. doi:10.1371/journal.pone.0046940
- Luciana, M., Collins, P. F., Muetzel, R. L., & Lim, K. O. (2013). Effects of alcohol use initiation on brain structure in typically developing adolescents. *The American Journal of Drug and Alcohol Abuse*, 39(6), 345-355. doi:10.3109/00952990.2013.837057
- Luders, E., Gaser, C., Narr, K. L., & Toga, A. W. (2009). Why sex matters: Brain size independent differences in gray matter distributions between men and women. *The Journal of Neuroscience*, 29(45), 14265-14270. doi:10.1523/JNEUROSCI.2261-09.2009
- Ludyga, S., Gerber, M., Brand, S., Puhse, U., & Colledge, F. (2018). Effects of aerobic exercise on cognitive performance among young adults in a higher education setting. *Research Quarterly for Exercise and Sport*, 89(2), 164-172. doi:10.1080/02701367.2018.1438575
- Lundahl, A., Kidwell, K. M., Van Dyk, T. R., & Nelson, T. D. (2015). A meta-analysis of the effect of experimental sleep restriction on youth's attention and hyperactivity. *Developmental Neuropsychology*, 40(3), 104-121. doi:10.1080/87565641.2014.939183
- Ma, H., & Zhu, G. (2014). The dopamine system and alcohol dependence. *Shanghai Archives of Psychiatry*, 26(2), 61-68. doi:10.3969/j.issn.1002-0829.2014.02.002
- MacLean, A. W., & Cairns, J. (1982). Dose-response effects of ethanol on the sleep of young men. *Journal of Studies on Alcohol*, 43(5), 434-444. doi:10.15288/jsa.1982.43.434

- Mahowald, M. L., & Mahowald, M. W. (2000). Nighttime sleep and daytime functioning (sleepiness and fatigue) in less well-defined chronic rheumatic diseases with particular reference to the 'alpha-delta NREM sleep anomaly'. *Sleep Medicine*, 1(3), 195-207. doi:10.1016/S1389-9457(00)00028-9
- Mak, C., Whittingham, K., Cunnington, R., & Boyd, R. N. (2017). Efficacy of mindfulness-based interventions for attention and executive function in children and adolescents- A systematic review. *Mindfulness*, 9(1), 59-78. doi:10.1007/s12671-017-0770-6
- Makkar, S. R., Zhang, S. Q., & Cranney, J. (2010). Behavioral and neural analysis of GABA in the acquisition, consolidation, reconsolidation, and extinction of fear memory. *Neuropsychopharmacology: Official Publication of the American College of Neuropsychopharmacology*, 35(8), 1625-1652. doi:10.1038/npp.2010.53
- Malhotra, A., & Loscalzo, J. (2009). Sleep and cardiovascular disease: An overview. *Progress in Cardiovascular Diseases*, 51(4), 279-284. doi:10.1016/j.pcad.2008.10.004
- Mander, B. A., Rao, V., Lu, B., Saletin, J. M., Lindquist, J. R., Ancoli-Israel, S., . . . Walker, M. P. (2013). Prefrontal atrophy, disrupted NREM slow waves and impaired hippocampal-dependent memory in aging. *Nature Neuroscience*, 16(3), 357-364. doi:10.1038/nn.3324
- Mander, B. A., Winer, J. R., & Walker, M. P. (2017). Sleep and human aging. *Neuron*, 94(1), 19-36. doi:10.1016/j.neuron.2017.02.004
- Mann, R. E., Sobell, L. C., Sobell, M. B., & Pavan, D. (1985). Reliability of a family tree questionnaire for assessing family history of alcohol problems. *Drug and Alcohol Dependence*, 15(1-2), 61-67. doi:10.1016/0376-8716(85)90030-4.
- Maquet, P. (2001). The role of sleep in learning and memory. *Science*, 294(5544), 1048-1052. doi:10.1126/science.1062856

- Marmorstein, N. R. (2017). Sleep patterns and problems among early adolescents: Associations with alcohol use. *Addictive Behaviors*, 66, 13-16.
doi:10.1016/j.addbeh.2016.11.002
- Marques-Vidal, P., Arveiler, D., Evans, A., Amouyel, P., Ferrieres, J., & Ducimetiere, P. (2001). Different alcohol drinking and blood pressure relationships in France and Northern Ireland: The PRIME Study. *Hypertension*, 38(6), 1361-1366. doi:10.1161/hy1101.095328
- Marquez-Ruiz, J., & Escudero, M. (2008). Tonic and phasic phenomena underlying eye movements during sleep in the cat. *Journal of Physiology*, 586(14), 3461-3477. doi:10.1113/jphysiol.2008.153239
- Marshall, N. S., Wong, K. K., Liu, P. Y., Cullen, S. R., Knuiman, M. W., & Grunstein, R. R. (2008). Sleep apnea as an independent risk factor for all-cause mortality: The Busselton Health Study. *Sleep*, 31(8), 1079-1085.
doi:10.5665/sleep/31.8.1079
- Marshall, W. A., & Tanner, J. M. (1969). Variations in pattern of pubertal changes in girls. *Archives of Disease in Childhood*, 44(235), 291-303.
doi:10.1136/ad.44.235.291
- Marshall, W. A., & Tanner, J. M. (1970). Variations in the pattern of pubertal changes in boys. *Archives of Disease in Childhood*, 45(239), 13-23.
doi:10.1136/ad.45.239.13
- Martin, C. S., Kaczynski, N. A., Maisto, S. A., Bukstein, O. M., & Moss, H. B. (1995). Patterns of DSM-IV alcohol abuse and dependence symptoms in adolescent drinkers. *Journal of Studies on Alcohol*, 56(6), 672-680.
doi:10.15288/jsa.1995.56.672
- Martin, P. R., Singleton, C. K., & Hiller-Sturmhofel, S. (2003). The role of thiamine deficiency in alcoholic brain disease. *Alcohol Research and Health*, 27(2), 134-142. doi:10.1.1.551.9543

- Martindale, S. L., Hurley, R. A., & Taber, K. H. (2017). Chronic Alcohol Use and Sleep Homeostasis: Risk Factors and Neuroimaging of Recovery. *The Journal of Neuropsychiatry and Clinical Neurosciences*, 29(1), A6-5.
doi:10.1176/appi.neuropsych.16110307
- Matsumoto, Y., Mishima, K., Satoh, K., Tozawa, T., Mishima, Y., Shimizu, T., & Hishikawa, Y. (2001). Total sleep deprivation induces an acute and transient increase in NK cell activity in healthy young volunteers. *Sleep*, 24(7), 804-809. doi:10.1093/sleep/24.7.806
- Matthews, D. B. (2010). Adolescence and alcohol: recent advances in understanding the impact of alcohol use during a critical developmental window. *Alcohol*, 44(1), 1-2. doi:10.1016/j.alcohol.2009.10.018
- Maurage, P., de Timary, P., Billieux, J., Collignon, M., & Heeren, A. (2014). Attentional alterations in alcohol dependence are underpinned by specific executive control deficits. *Alcoholism: Clinical and Experimental Research*, 38(7), 2105-2112. doi:10.1111/acer.12444
- Mayfield, R. D., Harris, R. A., & Schuckit, M. A. (2008). Genetic factors influencing alcohol dependence. *British Journal of Pharmacology*, 154(2), 275-287.
doi:10.1038/bjp.2008.88
- McCarty, C. A., Ebel, B. E., Garrison, M. M., DiGiuseppe, D. L., Christakis, D. A., & Rivara, F. P. (2004). Continuity of binge and harmful drinking from late adolescence to early adulthood. *Pediatrics*, 114(3), 714-719.
doi:10.1542/peds.2003-0864-L
- McCoy, J. G., & Strecker, R. E. (2011). The cognitive cost of sleep lost. *Neurobiology of Learning and Memory*, 96(4), 564-582.
doi:10.1016/j.nlm.2011.07.004
- McDermott, C. M., LaHoste, G. J., Chen, C., Musto, A., Bazan, N. G., & Magee, J. C. (2003). Sleep deprivation causes behavioral, synaptic, and membrane excitability alterations in hippocampal neurons. *The Journal of Neuroscience*, 23(29), 9687-9695.

- McEwen, B. S. (2006). Sleep deprivation as a neurobiologic and physiologic stressor: Allostasis and allostatic load. *Metabolism*, 55(10 Suppl 2), S20-23.
doi:10.1016/j.metabol.2006.07.008
- McFarlane, A., Pooley, L., Welch, I. M., Rumsey, R. D., & Read, N. W. (1986). How does dietary lipid lower blood alcohol concentrations? *Gut*, 27(1), 15-18.
doi:10.1136/gut.27.1.15
- McGorry, P. D., Purcell, R., Goldstone, S., & Amminger, G. P. (2011). Age of onset and timing of treatment for mental and substance use disorders: Implications for preventive intervention strategies and models of care. *Current Opinion in Psychiatry*, 24(4), 301-306. doi:10.1097/YCO.0b013e3283477a09
- McKeon, A., Frye, M. A., & Delanty, N. (2008). The alcohol withdrawal syndrome. *Journal of Neurology, Neurosurgery, and Psychiatry*, 79(8), 854-862.
doi:10.1136/jnnp.2007.128322
- McKinney, A., & Coyle, K. (2006). Alcohol hangover effects on measures of affect the morning after a normal night's drinking. *Alcohol and Alcoholism*, 41(1), 54-60. doi:10.1093/alcalc/agh226
- McKnight-Eily, L. R., Eaton, D. K., Lowry, R., Croft, J. B., Presley-Cantrell, L., & Perry, G. S. (2011). Relationships between hours of sleep and health-risk behaviors in US adolescent students. *Preventive Medicine*, 53(4-5), 271-273.
doi:10.1016/j.ypmed.2011.06.020
- McNamara, J. P., Wang, J., Holiday, D. B., Warren, J. Y., Paradoa, M., Balkhi, A. M., . . . McCrae, C. S. (2014). Sleep disturbances associated with cigarette smoking. *Psychology, Health and Medicine*, 19(4), 410-419.
doi:10.1080/13548506.2013.832782
- McNamara, P., Barton, R. A., & Nunn, C. L. (2010). *Evolution of sleep: Phylogenetic and functional perspectives*. Cambridge, Cambs: Cambridge University Press.

- McQueeney, T., Schweinsburg, B. C., Schweinsburg, A. D., Jacobus, J., Bava, S., Frank, L. R., & Tapert, S. F. (2009). Altered white matter integrity in adolescent binge drinkers. *Alcoholism: Clinical and Experimental Research*, 33(7), 1278-1285. doi:10.1111/j.1530-0277.2009.00953.x
- Medic, G., Wille, M., & Hemels, M. E. (2017). Short- and long-term health consequences of sleep disruption. *Nature and Science of Sleep*, 9, 151-161. doi:10.2147/NSS.S134864
- Medina, K. L., McQueeney, T., Nagel, B. J., Hanson, K. L., Schweinsburg, A. D., & Tapert, S. F. (2008). Prefrontal cortex volumes in adolescents with alcohol use disorders: unique gender effects. *Alcoholism: Clinical and Experimental Research*, 32(3), 386-394. doi:10.1111/j.1530-0277.2007.00602.x
- Medina, K. L., Schweinsburg, A. D., Cohen-Zion, M., Nagel, B. J., & Tapert, S. F. (2007). Effects of alcohol and combined marijuana and alcohol use during adolescence on hippocampal volume and asymmetry. *Neurotoxicology and Teratology*, 29(1), 141-152. doi:10.1016/j.ntt.2006.10.010
- Mello, N. K., & Mendelson, J. H. (1970). Behavioral studies of sleep patterns in alcoholics during intoxication and withdrawal. *Journal of Pharmacology and Experimental Therapeutics*, 175(1), 94-112.
- Mendelsohn, A. R., & Larrick, J. W. (2013). Sleep facilitates clearance of metabolites from the brain: glymphatic function in aging and neurodegenerative diseases. *Rejuvenation Research*, 16(6), 518-523. doi:10.1089/rej.2013.1530
- Mendelson, M., Borowik, A., Michallet, A. S., Perrin, C., Monneret, D., Faure, P., . . . Flore, P. (2016). Sleep quality, sleep duration and physical activity in obese adolescents: effects of exercise training. *Pediatric Obesity*, 11(1), 26-32. doi:10.1111/ijpo.12015
- Menefee, L. A., Cohen, M. J., Anderson, W. R., Doghramji, K., Frank, E. D., & Lee, H. (2000). Sleep disturbance and nonmalignant chronic pain: A comprehensive review of the literature. *Pain Medicine*, 1(2), 156-172. doi:10.1046/j.1526-4637.2000.00022.x

- Merikangas, K. R. (1990). The genetic epidemiology of alcoholism. *Psychological Medicine*, 20(1), 11-22. doi:10.1017/s0033291700013192.
- Merikangas, K. R., & Avenevoli, S. (2000). Implications of genetic epidemiology for the prevention of substance use disorders. *Addictive Behaviors*, 25(6), 807-820. doi:10.1016/s0306-4603(00)00129-5
- Merikangas, K. R., Stolar, M., Stevens, D. E., Goulet, J., Preisig, M. A., Fenton, B., . . . Rounsaville, B. J. (1998). Familial transmission of substance use disorders. *Archives of General Psychiatry*, 55(11), 973-979. doi:10.1001/archpsyc.55.11.973
- Merrill, J. E., & Carey, C. B. (2016). Drinking over the lifespan focus on college ages. *Alcohol Research: Current Reviews*, 38(1), 103-114. doi:2016-30780-013
- Meyers, J. L., & Dick, D. M. (2010). Genetic and environmental risk factors for adolescent-onset substance use disorders. *Child and Adolescent Psychiatric Clinics of North America*, 19(3), 465-477. doi:10.1016/j.chc.2010.03.013
- Mezick, E. J., Matthews, K. A., Hall, M., Kamarck, T. W., Buysse, D. J., Owens, J. F., & Reis, S. E. (2009). Intra-individual variability in sleep duration and fragmentation: associations with stress. *Psychoneuroendocrinology*, 34(9), 1346-1354. doi:10.1016/j.psyneuen.2009.04.005
- Midford, R., Cahill, H., Lester, L., Ramsden, R., Foxcroft, D., & Venning, L. (2017). Alcohol prevention for school students: Results from a 1-year follow up of a cluster-randomised controlled trial of harm minimisation school drug education. *Drugs: Education, Prevention and Policy*, 25(1), 88-96. doi:10.1080/09687637.2017.1290788
- Midford, R., Mitchell, J., Lester, L., Cahill, H., Foxcroft, D., Ramsden, R., . . . Pose, M. (2014). Preventing alcohol harm: Early results from a cluster randomised, controlled trial in Victoria, Australia of comprehensive harm minimisation school drug education. *International Journal of Drug Policy*, 25(1), 142-150. doi:10.1016/j.drugpo.2013.05.012

- Mihic, S. J. (1999). Acute effects of ethanol on GABA_A and glycine receptor function. *Neurochemistry International*, 35(2), 115-123. doi:10.1016/S0197-0186(99)00053-4
- Miller, D. J., Duka, T., Stimpson, C. D., Schapiro, S. J., Baze, W. B., McArthur, M. J., . . . Sherwood, C. C. (2012). Prolonged myelination in human neocortical evolution. *Proceedings of the National Academy of Sciences of the United States of America*, 109(41), 16480-16485. doi:10.1073/pnas.1117943109
- Miller, M. B., DiBello, A. M., Lust, S. A., Carey, M. P., & Carey, K. B. (2016). Adequate sleep moderates the prospective association between alcohol use and consequences. *Addictive Behaviors*, 63, 23-28. doi:10.1016/j.addbeh.2016.05.005
- Miller, M. B., Janssen, T., & Jackson, K. M. (2017). The prospective association between sleep and initiation of substance use in young adolescents. *Journal of Adolescent Health*, 60(2), 154-160. doi:10.1016/j.jadohealth.2016.08.019
- Miller, M. W. (2006). *Brain development: Normal processes and the effects of alcohol and nicotine*. Oxford, Oxon: Oxford University Press.
- Mintzer, M. Z. (2007). The acute effects of alcohol on memory: A review of laboratory studies in healthy adults. *International Journal on Disability and Human Development*, 6(4), 697-403. doi:10.1515/ijdhhd.2007.6.4.397
- Mitchell, H. A., & Weinshenker, D. (2010). Good night and good luck: Norepinephrine in sleep pharmacology. *Biochemical Pharmacology*, 79(6), 801-809. doi:10.1016/j.bcp.2009.10.004
- Mitchell, M. C., Jr., Teigen, E. L., & Ramchandani, V. A. (2014). Absorption and peak blood alcohol concentration after drinking beer, wine, or spirits. *Alcoholism: Clinical and Experimental Research*, 38(5), 1200-1204. doi:10.1111/acer.12355
- Miyamoto, D., Hirai, D., & Murayama, M. (2017). The Roles of Cortical Slow Waves in Synaptic Plasticity and Memory Consolidation. *Frontiers in Neural Circuits*, 11, 92. doi:10.3389/fncir.2017.00092

- Miyata, S., Noda, A., Ito, N., Atarashi, M., Yasuma, F., Morita, S., & Koike, Y. (2004). REM sleep is impaired by a small amount of alcohol in young women sensitive to alcohol. *Internal Medicine*, 43(8), 679-684. doi:10.2169/internalmedicine.43.679.
- Moeller, F. G., Gillin, J. C., Irwin, M., Golshan, S., Kripke, D. F., & Schuckit, M. (1993). A comparison of sleep EEGs in patients with primary major depression and major depression secondary to alcoholism. *Journal of Affective Disorders*, 27(1), 39-42. doi:10.1016/0165-0327(93)90095-2
- Mohamed, S., & Ajmal, M. (2015). Multivariate analysis of binge drinking in young adult population: Data analysis of the 2007 Survey of Lifestyle, Attitude and Nutrition in Ireland. *Psychiatry and Clinical Neurosciences*, 69(8), 483-488. doi:10.1111/pcn.12284
- Mohawk, J. A., Green, C. B., & Takahashi, J. S. (2012). Central and peripheral circadian clocks in mammals. *Annual Review of Neuroscience*, 35, 445-462. doi:10.1146/annurev-neuro-060909-153128
- Moldofsky, H. (2001). Sleep and pain. *Sleep Medicine Reviews*, 5(5), 385-396. doi:10.1053/smr.2001.0179
- Moldofsky, H., & Scarisbrick, P. (1976). Induction of neurasthenic musculoskeletal pain syndrome by selective sleep stage deprivation. *Psychosomatic Medicine*, 38(1), 35-44. doi:10.1097/00006842-197601000-00006
- Moldofsky, H., Scarisbrick, P., England, R., & Smythe, H. (1975). Musculoskeletal symptoms and non-REM sleep disturbance in patients with "fibrositis syndrome" and healthy subjects. *Psychosomatic Medicine*, 37(4), 341-351. doi:10.1097/00006842-197507000-00008.
- Molina, P. E., & Nelson, S. (2018). Binge drinking's effects on the body. *Alcohol Research: Current Reviews*, 39(1), 99-109.

- Monk, R. L., Heim, D., Qureshi, A., & Price, A. (2015). "I have no clue what I drunk last night" using Smartphone technology to compare in-vivo and retrospective self-reports of alcohol consumption. *PLoS One*, 10(5), e0126209. doi:10.1371/journal.pone.0126209
- Monnig, M. A., Caprihan, A., Yeo, R. A., Gasparovic, C., Ruhl, D. A., Lysne, P., . . . Thoma, R. J. (2013a). Diffusion tensor imaging of white matter networks in individuals with current and remitted alcohol use disorders and comorbid conditions. *Psychology of Addictive Behaviors*, 27(2), 455-465. doi:10.1037/a0027168
- Monnig, M. A., Tonigan, J. S., Yeo, R. A., Thoma, R. J., & McCrady, B. S. (2013b). White matter volume in alcohol use disorders: A meta-analysis. *Addiction Biology*, 18(3), 581-592. doi:10.1111/j.1369-1600.2012.00441.x
- Monti, J. M., Jantos, H., Boussard, M., Allier, H., Orellana, C., & Olivera, S. (1991). Effects of selective activation or blockade of the histamine H₃ receptor on sleep and wakefulness. *European Journal of Pharmacology*, 205(3), 283-287. doi:10.1016/0014-2999(91)90911-9
- Monti, J. M., & Monti, D. (2005). Sleep disturbance in schizophrenia. *International Review of Psychiatry*, 17(4), 247-253. doi:10.1080/09540260500104516
- Monti, P. M., Miranda, R., Jr., Nixon, K., Sher, K. J., Swartzwelder, H. S., Tapert, S. F., . . . Crews, F. T. (2005). Adolescence: Booze, brains, and behavior. *Alcoholism: Clinical and Experimental Research*, 29(2), 207-220. doi:10.1097/01.alc.0000153551.11000.f3
- Montplaisir, J., Boucher, S., Poirier, G., Lavigne, G., Lapierre, O., & Lespérance, P. (1997). Clinical, polysomnographic, and genetic characteristics of restless legs syndrome: a study of 133 patients diagnosed with new standard criteria. *Movement Disorders: Official Journal of the Movement Disorder Society*, 12(1), 61-65. <https://doi.org/10.1002/mds.870120111>

- Morioka, H., Itani, O., Kaneita, Y., Ikeda, M., Kondo, S., Yamamoto, R., . . . Ohida, T. (2013). Associations between sleep disturbance and alcohol drinking: A large-scale epidemiological study of adolescents in Japan. *Alcohol*, 47(8), 619-628. doi:10.1016/j.alcohol.2013.09.041
- Morris, S. A., Kelso, M. L., Liput, D. J., Marshall, S. A., & Nixon, K. (2010). Similar withdrawal severity in adolescents and adults in a rat model of alcohol dependence. *Alcohol*, 44(1), 89-98. doi:10.1016/j.alcohol.2009.10.017
- Morrisett, R. A., & Swartzwelder, H. S. (1993). Attenuation of hippocampal long-term potentiation by ethanol: A patch-clamp analysis of glutamatergic and GABAergic mechanisms. *The Journal of Neuroscience*, 13(5), 2264-2272. doi:10.1073/pnas.1017856108
- Moseley, L., & Gradisar, M. (2009). Evaluation of a school-based intervention for adolescent sleep problems. *Sleep*, 32(3), 334-341. doi:10.1093/sleep/32.3.334
- Moselhy, H. F., Georgiou, G., & Kahn, A. (2001). Frontal lobe changes in alcoholism: A review of the literature. *Alcohol and Alcoholism*, 36(5), 357-368. doi:10.1093/alcalc/36.5.357
- Moses, J. M., Johnson, L. C., Naitoh, P., & Lubin, A. (1975). Sleep stage deprivation and total sleep loss: Effects on sleep behavior. *Psychophysiology*, 12(2), 141-146. doi:10.1111/j.1469-8986.1975.tb01264.x
- Moss, H. B., Kirisci, L., Gordon, H. W., & Tarter, R. E. (1994). A neuropsychologic profile of adolescent alcoholics. *Alcoholism: Clinical and Experimental Research*, 18(1), 159-163. doi:10.1111/j.1530-0277.1994.tb00897.x
- Most, D., Ferguson, L., & Harris, R. A. (2014). Molecular basis of alcoholism. In M. J. Aminoff, F. Boller, & D. F. Swaab (Eds.), *Handbook of Clinical Neurology* (Vol. 125., pp. 89-111). Amsterdam: Elsevier. doi:10.1016/B978-0-444-62619-6.00006-9

- Mota, N., Parada, M., Crego, A., Doallo, S., Caamano-Isorna, F., Rodriguez Holguin, S., . . . Corral, M. (2013). Binge drinking trajectory and neuropsychological functioning among university students: a longitudinal study. *Drug and Alcohol Dependence*, 133(1), 108-114. doi:10.1016/j.drugalcdep.2013.05.024
- Mourtazaev, M. S., Kemp, B., Zwinderman, A. H., & Kamphuisen, H. A. (1995). Age and gender affect different characteristics of slow waves in the sleep EEG. *Sleep*, 18(7), 557-564. doi:10.1093/sleep/18.7.557
- Moy, S. S., Duncan, G. E., Knapp, D. J., & Breese, G. R. (1998). Sensitivity to ethanol across development in rats: Comparison to [³H]zolpidem binding. *Alcoholism: Clinical and Experimental Research*, 22(7), 1485-1492. doi:10.1111/j.1530-0277.1998.tb03940.x
- Murphy, M., Riedner, B. A., Huber, R., Massimini, M., Ferrarelli, F., & Tononi, G. (2009). Source modeling sleep slow waves. *Proceedings of the National Academy of Sciences of the United States of America*, 106(5), 1608-1613. doi:10.1073/pnas.0807933106
- Murphy, T. J., Pagano, R. R., & Marlatt, G. A. (1986). Lifestyle modification with heavy alcohol drinkers: effects of aerobic exercise and meditation. *Addictive Behaviors*, 11(2), 175-186. doi:10.1016/0306-4603(86)90043-2
- Myhrer, T. (2003). Neurotransmitter systems involved in learning and memory in the rat: a meta-analysis based on studies of four behavioral tasks. *Brain Research Reviews*, 41(2-3), 268-287.
- Nagel, B. J., Schweinsburg, A. D., Phan, V., & Tapert, S. F. (2005). Reduced hippocampal volume among adolescents with alcohol use disorders without psychiatric comorbidity. *Psychiatry Research*, 139(3), 181-190. doi:10.1016/j.psychresns.2005.05.008
- Naimi, T. S., Nelson, D. E., & Brewer, R. D. (2010). The intensity of binge alcohol consumption among U.S. adults. *American Journal of Preventive Medicine*, 38(2), 201-207. doi:10.1016/j.amepre.2009.09.039

- Navlakha, S., Barth, A. L., & Bar-Joseph, Z. (2015). Decreasing-rate pruning optimizes the construction of efficient and robust distributed networks. *PLOS Computational Biology*, 11(7), e1004347. doi:10.1371/journal.pcbi.1004347
- Neikrug, A. B., & Ancoli-Israel, S. (2010). Sleep disorders in the older adult - A mini-review. *Gerontology*, 56(2), 181-189. doi:10.1159/000236900
- Newton, N. C., Andrews, G., Teesson, M., & Vogl, L. E. (2009). Delivering prevention for alcohol and cannabis using the Internet: A cluster randomised controlled trial. *Preventive Medicine*, 48(6), 579-584. doi:10.1016/j.ypmed.2009.04.009
- Newton, N. C., Teesson, M., Vogl, L. E., & Andrews, G. (2010). Internet-based prevention for alcohol and cannabis use: Final results of the Climate Schools course. *Addiction*, 105(4), 749-759. doi:10.1111/j.1360-0443.2009.02853.x
- Newton, N. C., Vogl, L. E., Teesson, M., & Andrews, G. (2009). CLIMATE Schools: alcohol module: Cross-validation of a school-based prevention programme for alcohol misuse. *Australian and New Zealand Journal of Psychiatry*, 43(3), 201-207. doi:10.1080/00048670802653364
- Nguyen-Louie, T. T., Brumback, T., Worley, M. J., Colrain, I. M., Matt, G. E., Squeglia, L. M., & Tapert, S. F. (2018). Effects of sleep on substance use in adolescents: A longitudinal perspective. *Addiction Biology*, 23(2), 750-760. doi:10.1111/adb.12519
- Nguyen-Louie, T. T., Tracas, A., Squeglia, L. M., Matt, G. E., Eberson-Shumate, S., & Tapert, S. F. (2016). Learning and memory in adolescent moderate, binge, and extreme-binge drinkers. *Alcoholism: Clinical and Experimental Research*, 40(9), 1895-1904. doi:10.1111/acer.13160
- NHMRC. (2009). *Australian Guidelines to reduce health risks from drinking alcohol*. Canberra, ACT: National Health and Medical Research Council of Australia.
- NHMRC. (2013). *Reduce your risk: new national guidelines for alcohol consumption*. Canberra, ACT: National Health and Medical Research Council of Australia.

- National Institute on Alcohol Abuse and Alcoholism (NIAAA). (2004). The effects of alcohol on physiological processes and biological development. *Alcohol Research and Health*, 28(3), 125–131.
- National Institute on Alcohol Abuse and Alcoholism (NIAAA). (2004/2005). *Alcohol and Development in Youth— A Multidisciplinary Overview*. Bethesda, MD: U.S. Department of Health and Human Services.
- National Institute on Alcohol Abuse and Alcoholism (NIAAA). (2007). *Alcohol Metabolism: An Update*. Bethesda, MD: U.S. Department of Health and Human Services.
- National Institute on Alcohol Abuse and Alcoholism (NIAAA). (2008). *Alcohol Alert. Alcohol and Other Drugs*. Bethesda, MD: U.S. Department of Health and Human Services.
- National Institute on Alcohol Abuse and Alcoholism (NIAAA). (2016). *Alcohol Use Disorder: A Comparison Between DSM–IV and DSM–5*. Bethesda, MD: U.S. Department of Health and Human Services.
- Nicholas, C. L., Chan, J. L. M., Alexander, M. A., Cavuoto, M. G., Trinder, J., & Colrain, I. M. (2011). Effects of acute alcohol on sleep evoked potentials in heavy drinking and light drinking male college students. *Alcoholism: Clinical and Experimental Research*, 35(s1), 127A. doi:10.1111/j.1530-0277.2011.01497.x
- Nicholas, C. L., Sullivan, E. V., Pfefferbaum, A., Trinder, J., & Colrain, I. M. (2002a). The effects of alcoholism on auditory evoked potentials. *Journal of Sleep Research*, 11, 247-253. doi:10.1046/j.1365-2869.2002.00298.x
- Nicholas, C. L., Trinder, J., & Colrain, I. M. (2002b). Increased production of evoked and spontaneous K-complexes following a night of fragmented sleep. *Sleep*, 25(8), 42-47. doi:10.1093/sleep/25.8.42
- Nickel, M., & Gu, C. (2018). Regulation of central nervous system myelination in higher brain functions. *Neural Plasticity*, 2018, 6436453. doi:10.1155/2018/6436453

- Nigg, J. T., Glass, J. M., Wong, M. M., Poon, E., Jester, J. M., Fitzgerald, H. E., . . . Zucker, R. A. (2004). Neuropsychological executive functioning in children at elevated risk for alcoholism: Findings in early adolescence. *Journal of Abnormal Psychology, 113*(2), 302-314. doi:10.1037/0021-843X.113.2.302
- Nir, Y., Staba, R. J., Andrillon, T., Vyazovskiy, V. V., Cirelli, C., Fried, I., & Tononi, G. (2011). Regional slow waves and spindles in human sleep. *Neuron, 70*(1), 153-169. doi:10.1016/j.neuron.2011.02.043
- Nixon, K., & McClain, J. A. (2010). Adolescence as a critical window for developing an alcohol use disorder: Current findings in neuroscience. *Current Opinion in Psychiatry, 23*(3), 227-232. doi:10.1097/YCO.0b013e32833864fe
- Nixon, S. J. (2013). Executive functioning among young people in relation to alcohol use. *Current Opinion in Psychiatry, 26*(4), 305-309. doi:10.1097/YCO.0b013e328361ea3c
- Nobili, L., De Gennaro, L., Proserpio, P., Moroni, F., Sarasso, S., Pigorini, A., . . . Ferrara, M. (2012). Local aspects of sleep: Observations from intracerebral recordings in humans. *Progress in Brain Research, 199*, 219-232. doi:10.1016/B978-0-444-59427-3.00013-7
- Noda, A., Okada, T., Hayashi, H., Yasuma, F., & Yokota, M. (1993). 24-hour ambulatory blood pressure variability in obstructive sleep apnea syndrome. *Chest, 103*(5), 1343-1347. doi:10.1378/chest.103.5.1343
- Nofzinger, E. A., & Maquet, P. (2017). What brain imaging reveals about sleep generation and maintenance. In M. H. Kryger, T. Roth, & W. C. Dement (Eds.), *Principles and Practice of Sleep Medicine* (6th ed., pp. 118-131). Philadelphia, PA: Elsevier.
- Novier, A., Diaz-Granados, J. L., & Matthews, D. B. (2015). Alcohol use across the lifespan: An analysis of adolescent and aged rodents and humans. *Pharmacology Biochemistry and Behavior, 133*, 65-82. doi:10.1016/j.pbb.2015.03.015

- O'Brien, E. M., & Mindell, J. A. (2005). Sleep and risk-taking behavior in adolescents. *Behavioral Sleep Medicine*, 3(3), 113-133. doi:10.1207/s15402010bsm0303_1
- O'Mara, S. (2018). The captive brain: Torture and the neuroscience of humane interrogation. *Quarterly Journal of Medicine*, 111(2), 73-78. doi:10.1093/qjmed/hcx252
- O'Shea, R. S., Dasarathy, S., McCullough, A. J., & Pack, A. I. (2010). Alcoholic liver disease. *Hepatology*, 51(1), 307-328. doi:10.1002/hep.23258
- Oesterle, S., Hill, K. G., Hawkins, J. D., Guo, J., Catalano, R. F., & Abbott, R. D. (2004). Adolescent heavy episodic drinking trajectories and health in young adulthood. *Journal of Studies on Alcohol and Drugs*, 65(2), 204-212.
- Ohayon, M. M., Carskadon, M. A., Guilleminault, C., & Vitiello, M. V. (2004). Meta-analysis of quantitative sleep parameters from childhood to old age in healthy individuals: Developing normative sleep values across the human lifespan. *Sleep*, 27(7), 1255-1273. doi:10.1093/sleep/27.7.1255.
- Okoro, C. A., Brewer, R. D., Naimi, T. S., Moriarty, D. G., Giles, W. H., & Mokdad, A. H. (2004). Binge drinking and health-related quality of life: Do popular perceptions match reality? *American Journal of Preventive Medicine*, 26(3), 230-233. doi:10.1016/j.amepre.2003.10.022
- Older, S. A., Battafarano, D. F., Danning, C. L., Ward, J. A., Grady, E. P., Derman, S., & Russell, I. J. (1998). The effects of delta wave sleep interruption on pain thresholds and fibromyalgia-like symptoms in healthy subjects; correlations with insulin-like growth factor I. *The Journal of Rheumatology*, 25(6), 1180-1186.
- Ooms, S. J., Zempel, J. M., Holtzman, D. M., & Ju, Y. S. (2017). Automated selective disruption of slow wave sleep. *The Journal of Neuroscience Methods*, 281, 33-39. doi:10.1016/j.jneumeth.2017.02.008
- Oscar-Berman, M., & Marinkovic, K. (2003). Alcoholism and the brain: An overview. *Alcohol Research and Health*, 27(2), 125-133.

- Oscar-Berman, M., & Marinkovic, K. (2007). Alcohol: Effects on neurobehavioral functions and the brain. *Neuropsychology Review*, 17(3), 239-257.
doi:10.1007/s11065-007-9038-6
- Oscar-Berman, M., Shagrin, B., Evert, D. L., & Epstein, C. (1997). Impairments of brain and behavior: The neurological effects of alcohol. *Alcohol Health and Research World*, 21(1), 65-75.
- Oscar-Berman, M., Valmas, M. M., Sawyer, K. S., Ruiz, S. M., Luhar, R. B., & Gravitz, Z. R. (2014). Profiles of impaired, spared, and recovered neuropsychologic processes in alcoholism. In M. J. Aminoff, F. Boller, & D. F. Swaab (Eds.), *Handbook of Clinical Neurology* (Vol. 125., pp. 183-210). Amsterdam: Elsevier. doi:10.1016/B978-0-444-62619-6.00012-4
- Owens, J. (2014). Insufficient sleep in adolescents and young adults: An update on causes and consequences. *Pediatrics*, 134(3), e921-932.
doi:10.1542/peds.2014-1696
- Pabst, A., Kraus, L., Piontek, D., & Baumeister, S. E. (2012). Age differences in diagnostic criteria of DSM-IV alcohol dependence among adults with similar drinking behaviour. *Addiction*, 107(2), 331-338. doi:10.1111/j.1360-0443.2011.03611.x
- Pajevic, S., Basser, P. J., & Fields, R. D. (2014). Role of myelin plasticity in oscillations and synchrony of neuronal activity. *Neuroscience*, 276, 135-147.
doi:10.1016/j.neuroscience.2013.11.007
- Pandey, A. K., Ardekani, B. A., Kamarajan, C., Zhang, J., Chorlian, D. B., Byrne, K. N., . . . Porjesz, B. (2018). Lower prefrontal and hippocampal volume and diffusion tensor imaging differences reflect structural and functional abnormalities in abstinent individuals with alcohol use disorder. *Alcoholism: Clinical and Experimental Research*, 42(10), 1883-1896.
doi:10.1111/acer.13854

- Parada, M., Corral, M., Caamano-Isorna, F., Mota, N., Crego, A., Holguin, S. R., & Cadaveira, F. (2011). Binge drinking and declarative memory in university students. *Alcoholism: Clinical and Experimental Research*, 35(8), 1475-1484. doi:10.1111/j.1530-0277.2011.01484.x
- Park, C. L., Russell, B. S., & Fendrich, M. (2018). Mind-body approaches to prevention and intervention for alcohol and other drug use/abuse in young adults. *Medicines (Basel)*, 5(3). doi:10.3390/medicines5030064
- Park, S., & Etnier, J. L. (2019). Beneficial effects of acute exercise on executive function in adolescents. *Journal of Physical Activity and Health*, 16(6), 423-429. doi:10.1123/jpah.2018-0219
- Pasch, K. E., Latimer, L. A., Cance, J. D., Moe, S. G., & Lytle, L. A. (2012). Longitudinal bi-directional relationships between sleep and youth substance use. *Journal of Youth and Adolescence*, 41(9), 1184-1196. doi:10.1007/s10964-012-9784-5
- Pascual, M., Boix, J., Felipo, V., & Guerri, C. (2009). Repeated alcohol administration during adolescence causes changes in the mesolimbic dopaminergic and glutamatergic systems and promotes alcohol intake in the adult rat. *Journal of Neurochemistry*, 108(4), 920-931. doi:10.1111/j.1471-4159.2008.05835.x
- Patenaude, C., Chapman, C. A., Bertrand, S., Congar, P., & Lacaille, J. C. (2003). GABAB receptor- and metabotropic glutamate receptor-dependent cooperative long-term potentiation of rat hippocampal GABA_A synaptic transmission. *The Journal of Physiology*, 553(1), 155-167. doi:10.1113/jphysiol.2003.049015
- Paton, A. (2005). Alcohol in the body. *The British Medical Journal*, 330(7482), 85-87. doi:10.1136/bmj.330.7482.85

- Patrick, M. E., Griffin, J., Huntley, E. D., & Maggs, J. L. (2018). Energy drinks and binge drinking predict college students' sleep quantity, quality, and tiredness. *Behavioral Sleep Medicine, 16*(1), 92-105.
doi:10.1080/15402002.2016.1173554
- Patrick, M. E., Schulenberg, J. E., Martz, M. E., Maggs, J. L., O'Malley, P. M., & Johnston, L. D. (2013). Extreme binge drinking among 12th-grade students in the United States: Prevalence and predictors. *Journal of the American Medical Association Pediatrics, 167*(11), 1019-1025.
doi:10.1001/jamapediatrics.2013.2392
- Paus, T. (2005). Mapping brain maturation and cognitive development during adolescence. *Trends in Cognitive Sciences, 9*(2), 60-68.
doi:10.1016/j.tics.2004.12.008
- Paus, T. (2010). Growth of white matter in the adolescent brain: Myelin or axon? *Brain and Cognition, 72*(1), 26-35. doi:10.1016/j.bandc.2009.06.002
- Paus, T., Keshavan, M., & Giedd, J. N. (2008). Why do many psychiatric disorders emerge during adolescence? *Nature Reviews Neuroscience, 9*(12), 947-957.
doi:10.1038/nrn2513
- Peeters, M., Janssen, T., Monshouwer, K., Boendermaker, W., Pronk, T., Wiers, R., & Vollebergh, W. (2015). Weaknesses in executive functioning predict the initiating of adolescents' alcohol use. *Developmental Cognitive Neuroscience, 16*, 139-146. doi:10.1016/j.dcn.2015.04.003
- Peeters, M., Vollebergh, W. A., Wiers, R. W., & Field, M. (2014). Psychological changes and cognitive impairments in adolescent heavy drinkers. *Alcohol and Alcoholism, 49*(2), 182-186. doi:10.1093/alcalc/agt162
- Peirano, P., Fagioli, I. I., Bes, F., & Salzarulo, P. (1993). The role of slow-wave sleep on the duration of quiet sleep in infants. *Journal of Sleep Research, 2*(3), 130-133. doi:10.1111/j.1365-2869.1993.tb00075.x

- Perry, P. J., Argo, T. R., Barnett, M. J., Liesveld, J. L., Liskow, B., Hernan, J. M., . . . Brabson, M. A. (2006). The association of alcohol-induced blackouts and grayouts to blood alcohol concentrations. *Journal of Forensic Sciences*, 51(4), 896-899. doi:10.1111/j.1556-4029.2006.00161.x
- Pessione, F., Ramond, M. J., Peters, L., Pham, B. N., Batel, P., Rueff, B., & Valla, D. C. (2003). Five-year survival predictive factors in patients with excessive alcohol intake and cirrhosis. Effect of alcoholic hepatitis, smoking and abstinence. *Liver International*, 23(1), 45-53.
- Peterson, J. B., Rothfleisch, J., Zelazo, P. D., & Pihl, R. O. (1990). Acute alcohol intoxication and cognitive functioning. *Journal of Studies on Alcohol*, 51(2), 114-122. doi:10.15288/jsa.1990.51.114
- Petit, G., Kornreich, C., Verbanck, P., Cimochovska, A., & Campanella, S. (2013). Why is adolescence a key period of alcohol initiation and who is prone to develop long-term problem use? A review of current available data. *Socioaffective Neuroscience and Psychology*, 3, 21890. doi:10.3402/snp.v3i0.21890
- Petit, G., Luminet, O., Maurage, F., Tecco, J., Lechantre, S., Ferauge, M., . . . de Timary, P. (2015). Emotion regulation in alcohol dependence. *Alcoholism: Clinical and Experimental Research*, 39(12), 2471-2479. doi:10.1111/acer.12914
- Petit, G., Maurage, P., Kornreich, C., Verbanck, P., & Campanella, S. (2014). Binge drinking in adolescents: A review of neurophysiological and neuroimaging research. *Alcohol and Alcoholism*, 49(2), 198-206. doi:10.1093/alcalc/agt172
- Pfefferbaum, A., Adalsteinsson, E., & Sullivan, E. V. (2006a). Dysmorphology and microstructural degradation of the corpus callosum: Interaction of age and alcoholism. *Neurobiology of Aging*, 27(7), 994-1009. doi:10.1016/j.neurobiolaging.2005.05.007

- Pfefferbaum, A., Adalsteinsson, E., & Sullivan, E. V. (2006b). Supratentorial profile of white matter microstructural integrity in recovering alcoholic men and women. *Biological Psychiatry*, 59(4), 364-372. doi:10.1016/j.biopsych.2005.06.025
- Pfefferbaum, A., Kwon, D., Brumback, T., Thompson, W. K., Cummins, K., Tapert, S. F., . . . Sullivan, E. V. (2018). Altered brain developmental trajectories in adolescents after initiating drinking. *American Journal of Psychiatry*, 175(4), 370-380. doi:10.1176/appi.ajp.2017.17040469
- Pfefferbaum, A., Rohlfing, T., Pohl, K. M., Lane, B., Chu, W., Kwon, D., . . . Sullivan, E. V. (2016). Adolescent development of cortical and white matter structure in the NCANDA sample: Role of sex, ethnicity, puberty, and alcohol drinking. *Cerebral Cortex*, 26(10), 4101-4121. doi:10.1093/cercor/bhv205
- Pfefferbaum, A., Rosenbloom, M., Crusan, K., & Jernigan, T. L. (1988). Brain CT changes in alcoholics: Effects of age and alcohol consumption. *Alcoholism: Clinical and Experimental Research*, 12(1), 81-87. doi:10.1111/j.1530-0277.1988.tb00137.x
- Pfefferbaum, A., Rosenbloom, M., Deshmukh, A., & Sullivan, E. (2001). Sex differences in the effects of alcohol on brain structure. *American Journal of Psychiatry*, 158(2), 188-197. doi:10.1176/appi.ajp.158.2.188
- Pfefferbaum, A., Rosenbloom, M., Serventi, K. L., & Sullivan, E. V. (2002). Corpus callosum, pons, and cortical white matter in alcoholic women. *Alcoholism: Clinical and Experimental Research*, 26(3), 400-406. doi:10.1111/j.1530-0277.2002.tb02552.x
- Pfefferbaum, A., Rosenbloom, M. J., Chu, W., Sassoon, S. A., Rohlfing, T., Pohl, K. M., . . . Sullivan, E. V. (2014). White matter microstructural recovery with abstinence and decline with relapse in alcohol dependence interacts with normal ageing: a controlled longitudinal DTI study. *Lancet Psychiatry*, 1(3), 202-212. doi:10.1016/S2215-0366(14)70301-3

- Pfefferbaum, A., & Sullivan, E. V. (2002). Microstructural but not macrostructural disruption of white matter in women with chronic alcoholism. *Neuroimage*, 15(3), 708-718. doi:10.1006/nimg.2001.1018
- Pfefferbaum, A., Sullivan, E. V., Hedehus, M., Adalsteinsson, E., Lim, K. O., & Moseley, M. (2000). In vivo detection and functional correlates of white matter microstructural disruption in chronic alcoholism. *Alcoholism: Clinical and Experimental Research*, 24(8), 1214-1221. doi:10.1111/j.1530-0277.2000.tb02086.x
- Pfefferbaum, A., Sullivan, E. V., Mathalon, D. H., & Lim, K. O. (1997). Frontal lobe volume loss observed with magnetic resonance imaging in older chronic alcoholics. *Alcoholism: Clinical and Experimental Research*, 21(3), 521-529. doi:10.1111/j.1530-0277.1997.tb03798.x
- Pfefferbaum, A., Sullivan, E. V., Mathalon, D. H., Shear, P. K., Rosenbloom, M. J., & Lim, K. O. (1995). Longitudinal changes in magnetic resonance imaging brain volumes in abstinent and relapsed alcoholics. *Alcoholism: Clinical and Experimental Research*, 19(5), 1177-1191. doi:10.1111/j.1530-0277.1995.tb01598.x.
- Pfefferbaum, A., Sullivan, E. V., Rosenbloom, M. J., Mathalon, D. H., & Lim, K. O. (1998). A controlled study of cortical gray matter and ventricular changes in alcoholic men over a 5-year interval. *Archives of General Psychiatry*, 55(10), 905-912. doi:10.1001/archpsyc.55.10.905
- Pfeiffer, A., Schmidt, T., Vidon, N., Pehl, C., & Kaess, H. (1992). Absorption of a nutrient solution in chronic alcoholics without nutrient deficiencies and liver cirrhosis. *Scandinavian Journal of Gastroenterology*, 27(12), 1023-1030.
- Phillips, R. (2014). *Alcohol: A history*. Chapel Hill, NC: The University of North Carolina Press.
- Pian, J. P., Criado, J. R., Walker, B. M., & Ehlers, C. L. (2008). Differential effects of acute alcohol on EEG and sedative responses in adolescent and adult Wistar rats. *Brain Research*, 1194, 28-36. doi:10.1016/j.brainres.2007.11.057

- Pidd, K. J., Berry, J. G., Roche, A. M., & Harrison, J. E. (2006). Estimating the cost of alcohol-related absenteeism in the Australian workforce: The importance of consumption patterns. *The Medical Journal of Australia*, 185(11-12), 637-641. doi:10.5694/j.1326-5377.2006.tb00738.x
- Pieters, S., Van Der Vorst, H., Burk, W. J., Wiers, R. W., & Engels, R. C. (2010). Puberty-dependent sleep regulation and alcohol use in early adolescents. *Alcoholism: Clinical and Experimental Research*, 34(9), 1512-1518. doi:10.1111/j.1530-0277.2010.01235.x
- Pivik, R. T., & Harman, K. (1995). A reconceptualization of EEG alpha activity as an index of arousal during sleep: All alpha activity is not equal. *Journal of Sleep Research*, 4(3), 131-137. doi:jsr004003131
- Platt, B., & Riedel, G. (2011). The cholinergic system, EEG and sleep. *Behavioural Brain Research*, 221(2), 499-504. doi:https://doi.org/10.1016/j.bbr.2011.01.017
- Pleil, K. E., Lowery-Gionta, E. G., Crowley, N. A., Li, C., Marcinkiewicz, C. A., Rose, J. H., . . . Kash, T. L. (2015). Effects of chronic ethanol exposure on neuronal function in the prefrontal cortex and extended amygdala. *Neuropharmacology*, 99, 735-749. doi:10.1016/j.neuropharm.2015.06.017
- Pohorecky, L. A. (1977). Biphasic action of ethanol. *Biobehavioral Reviews*, 1(4), 231-240. doi:10.1016/0147-7552(77)90025-0
- Poikolainen, K. (1985). Underestimation of recalled alcohol intake in relation to actual consumption. *Addiction*, 80(2), 215-216. doi:10.1111/j.1360-0443.1985.tb03276.x
- Popovici, I., & French, M. T. (2013). Binge drinking and sleep problems among young adults. *Drug and Alcohol Dependence*, 132(1-2), 207-215. doi:10.1016/j.drugalcdep.2013.02.001

- Powers, G., Berger, L., Fuhrmann, D., & Fendrich, M. (2017). Family history density of substance use problems among undergraduate college students: Associations with heavy alcohol use and alcohol use disorder. *Addictive Behaviors*, 71, 1-6. doi:10.1016/j.addbeh.2017.02.015
- Prat, G., Adan, A., Perez-Pamies, M., & Sanchez-Turet, M. (2008). Neurocognitive effects of alcohol hangover. *Addictive Behaviors*, 33(1), 15-23. doi:10.1016/j.addbeh.2007.05.002
- Prat, G., Adan, A., & Sanchez-Turet, M. (2009). Alcohol hangover: A critical review of explanatory factors. *Human Psychopharmacology: Clinical and Experimental*, 24(4), 259-267. doi:10.1002/hup.1023
- Pressman, M. R. (2012). Alcohol does not increase slow wave sleep. *Alcoholism: Clinical and Experimental Research*. doi:10.1111/j.1530-0277.2012.01746.x
- Prinz, P. N., Roehrs, T. A., Vitaliano, P. P., Linnoila, M., & Weitzman, E. D. (1980). Effect of alcohol on sleep and nighttime plasma growth hormone and cortisol concentrations. *The Journal of Clinical Endocrinology and Metabolism*, 51(4), 759-764. doi:10.1210/jcem-51-4-759
- Putnam, L. E., Johnson, R., Jr., & Roth, W. T. (1992). Guidelines for reducing the risk of disease transmission in the psychophysiology laboratory. SPR Ad Hoc Committee on the Prevention of Disease Transmission. *Psychophysiology*, 29(2), 127-141. doi:10.1111/j.1469-8986.1992.tb01676.x
- Pyapali, G. K., Turner, D. A., Wilson, W. A., & Swartzwelder, H. S. (1999). Age and dose-dependent effects of ethanol on the induction of hippocampal long-term potentiation. *Alcohol*, 19(2), 107-111. doi:10.1016/s0741-8329(99)00021-x
- Quek, L. H., White, A., Low, C., Brown, J., Dalton, N., Dow, D., & Connor, J. P. (2012). Good choices, great future: An applied theatre prevention program to reduce alcohol-related risky behaviours during Schoolies. *Drug and Alcohol Review*, 31(7), 897-902. doi:10.1111/j.1465-3362.2012.00453.x

- Quinn, C. A., Hides, L., de Andrade, D., Pocuca, N., Wilson, M., & Kavanagh, D. J. (2019). Impact of a brief psychoeducational intervention for reducing alcohol use and related harm in school leavers. *Drug and Alcohol Review*, 38(4), 339-348. doi:10.1111/dar.12920
- Quoilin, C., Didone, V., Tirelli, E., & Quertemont, E. (2010). Ontogeny of the stimulant and sedative effects of ethanol in male and female Swiss mice: Gradual changes from weaning to adulthood. *Psychopharmacology*, 212(4), 501-512. doi:10.1007/s00213-010-1971-z
- Randall, R. D., Lee, S. Y., Meyer, J. H., Wittenberg, G. F., & Gruol, D. L. (1995). Acute alcohol blocks neurosteroid modulation of synaptic transmission and long-term potentiation in the rat hippocampal slice. *Brain Research*, 701(1-2), 238-248. doi:10.1016/0006-8993(95)01007-9
- Randall, S., Roehrs, T. A., & Roth, T. (2008). Over-the-counter sleep aid medications and insomnia. *Primary Psychiatry*, 15(5), 52-60.
- Rangaswamy, M., Porjesz, B., Chorlian, D. B., Choi, K., Jones, K. A., Wang, K., . . . Begleiter, H. (2003). Theta power in the EEG of alcoholics. *Alcoholism: Clinical and Experimental Research*, 27(4), 607-615. doi:10.1097/01.ALC.0000060523.95470.8F
- Rechtschaffen, A., & Bergmann, B. M. (2002). Sleep deprivation in the rat: An update of the 1989 paper. *Sleep*, 25(1), 18-24. doi:10.1093/sleep/25.1.18
- Rechtschaffen, A., Bergmann, B. M., Everson, C. A., Kushida, C. A., & Gilliland, M. A. (2002). Sleep deprivation in the rat: X. Integration and discussion of the findings. 1989. *Sleep*, 25(1), 68-87. doi:10.1093/sleep/25.1.68
- Redline, S., Kirchner, H. L., Quan, S. F., Gottlieb, D. J., Kapur, V., & Newman, A. (2004). The effects of age, sex, ethnicity, and sleep-disordered breathing on sleep architecture. *Archives of Internal Medicine*, 164(4), 406-418. doi:10.1001/archinte.164.4.406
- Refinetti, R., & Menaker, M. (1992). The circadian rhythm of body temperature. *Physiology and Behavior*, 51(3), 613-637. doi:10.1016/0031-9384(92)90188-8

- Rehm, J. (2011). The risks associated with alcohol use and alcoholism. *Alcohol Research and Health*, 34(2), 135-143.
- Richardson, J. T. E. (2011). Eta squared and partial eta squared as measures of effect size in educational research. *Educational Research Review*, 6(2), 135-147. doi:10.1016/j.edurev.2010.12.001
- Riedel, G., Platt, B., & Micheau, J. (2003). Glutamate receptor function in learning and memory. *Behavioural Brain Research*, 140(1), 1-47. doi:10.1016/S0166-4328(02)00272-3
- Riedner, B. A., Goldstein, M. R., Plante, D. T., Rumble, M. E., Ferrarelli, F., Tononi, G., & Benca, R. M. (2016). Regional patterns of elevated alpha and high-frequency electroencephalographic activity during nonrapid eye movement sleep in chronic insomnia: A pilot study. *Sleep*, 39(4), 801-812. doi:10.5665/sleep.5632
- Riemann, D., Spiegelhalder, K., Feige, B., Voderholzer, U., Berger, M., Perlis, M., & Nissen, C. (2010). The hyperarousal model of insomnia: A review of the concept and its evidence. *Sleep Medicine Reviews*, 14(1), 19-31. doi:10.1016/j.smr.2009.04.002
- Riemann, D., & Voderholzer, U. (2003). Primary insomnia: A risk factor to develop depression? *Journal of Affective Disorders*, 76(1-3), 255-259. doi:10.1016/s0165-0327(02)00072-1
- Riley, E. P., Infante, M. A., & Warren, K. R. (2011). Fetal alcohol spectrum disorders: An overview. *Neuropsychology Review*, 21(2), 73-80. doi:10.1007/s11065-011-9166-x
- Roberto, M., & Varodayan, F. P. (2017). Synaptic targets: Chronic alcohol actions. *Neuropharmacology*, 122, 85-99. doi:10.1016/j.neuropharm.2017.01.013
- Roche, A., Pidd, K., & Kostadinov, V. (2016). Alcohol- and drug-related absenteeism: A costly problem. *Australian and New Zealand Journal of Public Health*, 40(3), 236-238. doi:10.1111/1753-6405.12414

- Roche, A. M., Pidd, K., Berry, J. G., & Harrison, J. E. (2008). Workers' drinking patterns: The impact on absenteeism in the Australian work-place. *Addiction*, 103(5), 738-748. doi:10.1111/j.1360-0443.2008.02154.x
- Rod, N. H., Vahtera, J., Westerlund, H., Kivimaki, M., Zins, M., Goldberg, M., & Lange, T. (2011). Sleep disturbances and cause-specific mortality: Results from the GAZEL cohort study. *American Journal of Epidemiology*, 173(3), 300-309. doi:10.1093/aje/kwq371
- Roehrs, T., Papineau, K., Rosenthal, L., & Roth, T. (1999). Ethanol as a hypnotic in insomniacs: Self administration and effects on sleep and mood. *Neuropsychopharmacology*, 20(3), 279-286. doi:10.1016/s0893-133x(98)00068-2
- Roehrs, T., & Roth, T. (2001a). Sleep, sleepiness and alcohol use. *Alcohol Research and Health*, 25(2), 101-109.
- Roehrs, T., & Roth, T. (2001b). Sleep, sleepiness, sleep disorders and alcohol use and abuse. *Sleep Medicine Reviews*, 5(4), 287-297. doi:10.1053/smr.2001.0162
- Roehrs, T., & Roth, T. (2018). Insomnia as a path to alcoholism: Tolerance development and dose escalation. *Sleep*, 41(8). doi:10.1093/sleep/zsy091
- Roehrs, T., Yoon, J. and Roth, T. (1991). Nocturnal and next-day effects of ethanol and basal level of sleepiness. *Human Psychopharmacology*, 6(4), 307-311. doi:10.1002/hup.470060407
- Roehrs, T., Zwyghuizen-Doorenbos, A., Timms, V., Zorick, F., & Roth, T. (1989). Sleep extension, enhanced alertness and the sedating effects of ethanol. *Pharmacology Biochemistry and Behavior*, 34(2), 321-324. doi:10.1016/0091-3057(89)90319-5
- Roenneberg, T., Kuehnle, T., Pramstaller, P. P., Ricken, J., Havel, M., Guth, A., & Mellow, M. (2004). A marker for the end of adolescence. *Current Biology*, 14(24), R1038-1039. doi:10.1016/j.cub.2004.11.039

- Roffwarg, H. P., Muzio, J. N., & Dement, W. C. (1966). Ontogenetic development of the human sleep-dream cycle. *Science*, 152(3722), 604-619.
doi:10.1126/science.152.3722.604
- Rogawski, M. A. (2005). Update on the neurobiology of alcohol withdrawal seizures. *Epilepsy Curr*, 5(6), 225-230. doi:10.1111/j.1535-7511.2005.00071.x
- Rohlfing, T., Sullivan, E. V., & Pfefferbaum, A. (2006). Deformation-based brain morphometry to track the course of alcoholism: Differences between intra-subject and inter-subject analysis. *Psychiatry Research*, 146(2), 157-170.
doi:10.1016/j.psychresns.2005.12.002
- Rohsenow, D. J., Howland, J., Arnedt, J. T., Almeida, A. B., Greece, J., Minsky, S., . . . Sales, S. (2010). Intoxication with bourbon versus vodka: Effects on hangover, sleep, and next-day neurocognitive performance in young adults. *Alcoholism: Clinical and Experimental Research*, 34(3), 509-518.
doi:10.1111/j.1530-0277.2009.01116.x
- Roizenblatt, S., Moldofsky, H., Benedito-Silva, A. A., & Tufik, S. (2001). Alpha sleep characteristics in fibromyalgia. *Arthritis and Rheumatology*, 44(1), 222-230. doi:10.1002/1529-0131
- Romans, S. E., Kreindler, D., Einstein, G., Laredo, S., Petrovic, M. J., & Stanley, J. (2015). Sleep quality and the menstrual cycle. *Sleep Medicine*, 16(4), 489-495.
doi:10.1016/j.sleep.2014.12.001
- Rosales-Lagarde, A., Armony, J. L., Del Rio-Portilla, Y., Trejo-Martinez, D., Conde, R., & Corsi-Cabrera, M. (2012). Enhanced emotional reactivity after selective REM sleep deprivation in humans: An fMRI study. *Frontiers in Behavioral Neuroscience*, 6, 25. doi:10.3389/fnbeh.2012.00025
- Rosenbloom, M., Sullivan, E. V., & Pfefferbaum, A. (2003). Using magnetic resonance imaging and diffusion tensor imaging to assess brain damage in alcoholics. *Alcohol Research and Health*, 27(2), 146-152. doi:10.1.1.587.7769
- Roth, T. (2009). Slow wave sleep: Does it matter? *Journal of Clinical Sleep Medicine*, 5(2 Suppl), S4-5. doi:10.5664/jcsm.5.2S.S4

- Rouhani, S., Tran, G., Leplaideur, F., Durlach, J., & Poenaru, S. (1989). EEG effects of a single low dose of ethanol on afternoon sleep in the nonalcohol-dependent adult. *Alcohol*, 6(1), 87-90. doi:10.1016/0741-8329(89)90078-5
- Rubinsky, A. D., Dawson, D. A., Williams, E. C., Kivlahan, D. R., & Bradley, K. A. (2013). AUDIT-C scores as a scaled marker of mean daily drinking, alcohol use disorder severity, and probability of alcohol dependence in a U.S. general population sample of drinkers. *Alcoholism: Clinical and Experimental Research*, 37(8), 1380-1390. doi:10.1111/acer.12092
- Rundell, O. H., Lester, B. K., Griffiths, W. J., & Williams, H. L. (1972). Alcohol and sleep in young adults. *Psychopharmacologia*, 26(3), 201-218. doi:10.1007/BF00422697
- Rupp, T. L., Acebo, C., & Carskadon, M. A. (2007). Evening alcohol suppresses salivary melatonin in young adults. *Chronobiology International*, 24(3), 463-470. doi:10.1080/07420520701420675
- Russell, B. S., Hutchison, M., & Fusco, A. (2019). Emotion regulation outcomes and preliminary feasibility evidence from a mindfulness intervention for adolescent substance use. *Journal of Child and Adolescent Substance Abuse*, 28(1), 21-31. doi:10.1080/1067828x.2018.1561577
- Sadrian, B., Wilson, D. A., & Saito, M. (2013). Long-lasting neural circuit dysfunction following developmental ethanol exposure. *Brain Sciences*, 3(2), 704-727. doi:10.3390/brainsci3020704
- Sagawa, Y., Kondo, H., Matsubuchi, N., Takemura, T., Kanayama, H., Kaneko, Y., . . . Shimizu, T. (2011). Alcohol has a dose-related effect on parasympathetic nerve activity during sleep. *Alcoholism: Clinical and Experimental Research*, 35(11), 2093-2100. doi:10.1111/j.1530-0277.2011.01558.x
- SAMHSA. (2017). *Reports and Detailed Tables From the 2017 National Survey on Drug Use and Health (NSDUH)*. Rockville, MD: Substance Abuse and Mental Health Services Administration.

- SAMHSA/CSAT. (2009). *Substance Abuse Treatment: Addressing the Specific Needs of Women*. Rockville, MD: Substance Abuse and Mental Health Services Administration/Center for Substance Abuse Treatment.
- Sampson, H. W. (1998). Alcohol's harmful effects on bone. *Alcohol Health and Research World*, 22(3), 190-194.
- Sampson, H. W., Chaffin, C., Lange, J., & DeFee, B., 2nd. (1997). Alcohol consumption by young actively growing rats: A histomorphometric study of cancellous bone. *Alcoholism: Clinical and Experimental Research*, 21(2), 352-359. doi:10.1111/j.1530-0277.1997.tb03772.x
- Saper, C. B., Scammell, T. E., & Lu, J. (2005). Hypothalamic regulation of sleep and circadian rhythms. *Nature*, 437(7063), 1257-1263. doi:10.1038/nature04284
- Saransaari, P., & Oja, S. S. (1995). Dizocilpine binding to cerebral cortical membranes from developing and ageing mice. *Mechanisms of Ageing and Development*, 85(2-3), 171-181. doi:10.1016/0047-6374(95)01665-1
- Sassin, J. F., Parker, D. C., Mace, J. W., Gotlin, R. W., Johnson, L. C., & Rossman, L. G. (1969). Human growth hormone release: relation to slow-wave sleep and sleep-walking cycles. *Science*, 165(3892), 513-515. doi:10.1172/JCI119587
- Sayette, M. A. (1999). Does drinking reduce stress? *Alcohol Research and Health*, 23(4), 250-255.
- Scaife, J. C., & Duka, T. (2009). Behavioural measures of frontal lobe function in a population of young social drinkers with binge drinking pattern. *Pharmacology Biochemistry and Behavior*, 93(3), 354-362. doi:10.1016/j.pbb.2009.05.015
- Schramm-Sapyta, N. L., Walker, Q. D., Caster, J. M., Levin, E. D., & Kuhn, C. M. (2009). Are adolescents more vulnerable to drug addiction than adults? Evidence from animal models. *Psychopharmacology (Berl)*, 206(1), 1-21. doi:10.1007/s00213-009-1585-5

- Schuckit, M. A. (1994). Low level of response to alcohol as a predictor of future alcoholism. *American Journal of Psychiatry*, 151(2), 184-189. doi:10.1176/ajp.151.2.184
- Schuckit, M. A. (1998). Biological, psychological and environmental predictors of the alcoholism risk: A longitudinal study. *Journal of Studies on Alcohol*, 59(5), 485-494. doi:10.15288/jsa.1998.59.485
- Schuckit, M. A., & Smith, T. L. (2000). The relationships of a family history of alcohol dependence, a low level of response to alcohol and six domains of life functioning to the development of alcohol use disorders. *Journal of Studies on Alcohol*, 61(6), 827-835. doi:10.15288/jsa.2000.61.827
- Schuckit, M. A., Smith, T. L., Anderson, K. G., & Brown, S. A. (2004). Testing the level of response to alcohol: Social information processing model of alcoholism risk: A 20-year prospective study. *Alcoholism: Clinical and Experimental Research*, 28(12), 1881-1889. doi:10.1097/01.ALC.0000148111.43332.A5
- Schulte, M. T., Ramo, D., & Brown, S. A. (2009). Gender differences in factors influencing alcohol use and drinking progression among adolescents. *Clinical Psychology Review*, 29(6), 535-547. doi:10.1016/j.cpr.2009.06.003
- Seibt, J., & Frank, M. G. (2019). Primed to sleep: The dynamics of synaptic plasticity across brain states. *Frontiers in Systems Neuroscience*, 13, 2. doi:10.3389/fnsys.2019.00002
- Selemon, L. D. (2013). A role for synaptic plasticity in the adolescent development of executive function. *Translational Psychiatry*, 3, e238. doi:10.1038/tp.2013.7
- Sellgren, C. M., Gracias, J., Watmuff, B., Biag, J. D., Thanos, J. M., Whittredge, P. B., . . . Perlis, R. H. (2019). Increased synapse elimination by microglia in schizophrenia patient-derived models of synaptic pruning. *Nature Neuroscience*, 22(3), 374-385. doi:10.1038/s41593-018-0334-7

- Shaw, P., Kabani, N. J., Lerch, J. P., Eckstrand, K., Lenroot, R., Gogtay, N., . . . Wise, S. P. (2008). Neurodevelopmental trajectories of the human cerebral cortex. *The Journal of Neuroscience*, 28(14), 3586-3594.
doi:10.1523/JNEUROSCI.5309-07.2008
- Sheldon, S. H. (2014). Development of Sleep in Infants and Children. In S. H. Sheldon, M. H. Kryger, R. Ferber, & D. Gozal (Eds.), *Principles and Practice of Pediatric Sleep Medicine* (2nd ed., pp. 17-23). London: Saunders.
- Sher, K. J., Walitzer, K. S., Wood, P. K., & Brent, E. E. (1991). Characteristics of children of alcoholics: Putative risk factors, substance use and abuse, and psychopathology. *Journal of Abnormal Psychology*, 100(4), 427-448.
doi:10.1037/0021-843X.100.4.427
- Shultz, J., Weiner, H., & Westcott, J. (1980). Retardation of ethanol absorption by food in the stomach. *Journal of Studies on Alcohol*, 41(9), 861-870.
doi:10.15288/jsa.1980.41.861
- Siegel, J. M. (2001). The REM sleep-memory consolidation hypothesis. *Science*, 294(5544), 1058-1063. doi:10.1126/science.1063049
- Siegel, J. M. (2003). Why we sleep. *Scientific American*, 289(5), 92-97.
doi:10.1038/scientificamerican1103-92 ·
- Siegel, J. M. (2004). The neurotransmitters of sleep. *The Journal of Clinical Psychiatry*, 65 Suppl 16, 4-7.
- Sieminski, M., Pyrzowski, J., & Partinen, M. (2017). Periodic limb movements in sleep are followed by increases in EEG activity, blood pressure, and heart rate during sleep. *Sleep and Breathing: International Journal of the Science and Practice of Sleep Medicine*, 21(2), 497. <https://doi.org/10.1007/s11325-017-1476-7>
- Silveri, M. M. (2014). GABAergic contributions to alcohol responsivity during adolescence: Insights from preclinical and clinical studies. *Pharmacology and Therapeutics*, 143(2), 197-216. doi:10.1016/j.pharmthera.2014.03.001

- Silveri, M. M., Cohen-Gilbert, J., Crowley, D. J., Rosso, I. M., Jensen, J. E., & Sneider, J. T. (2014). Altered anterior cingulate neurochemistry in emerging adult binge drinkers with a history of alcohol-induced blackouts. *Alcoholism: Clinical and Experimental Research*, 38(4), 969-979. doi:10.1111/acer.12346
- Silveri, M. M., Dager, A. D., Cohen-Gilbert, J. E., & Sneider, J. T. (2016). Neurobiological signatures associated with alcohol and drug use in the human adolescent brain. *Neuroscience and Biobehavioral Reviews*, 70, 244-259. doi:10.1016/j.neubiorev.2016.06.042
- Silveri, M. M., Sneider, J. T., Crowley, D. J., Covell, M. J., Acharya, D., Rosso, I. M., & Jensen, J. E. (2013). Frontal lobe gamma-aminobutyric acid levels during adolescence: Associations with impulsivity and response inhibition. *Biological Psychiatry*, 74(4), 296-304. doi:10.1016/j.biopsych.2013.01.033
- Silveri, M. M., & Spear, L. P. (1998). Decreased sensitivity to the hypnotic effects of ethanol early in ontogeny. *Alcoholism: Clinical and Experimental Research*, 22(3), 670-676. doi:10.1111/j.1530-0277.1998.tb04310.x
- Silveri, M. M., & Spear, L. P. (1999). Ontogeny of rapid tolerance to the hypnotic effects of ethanol. *Alcoholism: Clinical and Experimental Research*, 23(7), 1180-1184. doi:10.1111/j.1530-0277.1999.tb04275.x
- Simonton, A. J., Young, C. C., & Johnson, K. E. (2018). Physical activity interventions to decrease substance use in youth: A review of the literature. *Substance Use and Misuse*, 53(12), 2052-2068. doi:10.1080/10826084.2018.1452338
- Singleton, R. A., Jr., & Wolfson, A. R. (2009). Alcohol consumption, sleep, and academic performance among college students. *Journal of Studies on Alcohol and Drugs*, 70(3), 355-363. doi:10.15288/jsad.2009.70.355
- Sisk, C. L., & Zehr, J. L. (2005). Pubertal hormones organize the adolescent brain and behavior. *Frontiers in Neuroendocrinology*, 26(3-4), 163-174. doi:10.1016/j.yfrne.2005.10.003

- Sivertsen, B., Skogen, J. C., Jakobsen, R., & Hysing, M. (2015). Sleep and use of alcohol and drug in adolescence. A large population-based study of Norwegian adolescents aged 16 to 19 years. *Drug and Alcohol Dependence*, 149, 180-186. doi:10.1016/j.drugalcdep.2015.01.045
- Skeldon, A. C., Derks, G., & Dijk, D. J. (2016). Modelling changes in sleep timing and duration across the lifespan: Changes in circadian rhythmicity or sleep homeostasis? *Sleep Medicine Reviews*, 28, 96-107. doi:10.1016/j.smrv.2015.05.011
- Slade, T., Chapman, C., Swift, W., Keyes, K., Tonks, Z., & Teesson, M. (2016). Birth cohort trends in the global epidemiology of alcohol use and alcohol-related harms in men and women: Systematic review and metaregression. *The British Medical Journal Open*, 6(10), e011827. doi:10.1136/bmjopen-2016-011827
- Slater, I. H., Jones, G. T., & Moore, R. A. (1978). Inhibition of REM sleep by fluoxetine, a specific inhibitor of serotonin uptake. *Neuropharmacology*, 17(6), 383-389. doi:10.1016/0028-3908(78)90010-2
- Slawecki, C. J. (2002). Altered EEG responses to ethanol in adult rats exposed to ethanol during adolescence. *Alcoholism: Clinical and Experimental Research*, 26(2), 246-254. doi:10.1111/j.1530-0277.2002.tb02531.x
- Snyder, S., & Karacan, I. (1985). Sleep patterns of sober chronic alcoholics. *Neuropsychobiology*, 13(1-2), 97-100. doi:10.1159/000118169
- Sobell, L. C., & Sobell, M. B. (2008). Alcohol timeline followback (TLFB). In A. P. Association (Ed.), *Textbook of psychiatric measures*. Washington, DC: American Psychiatric Association.
- Sobell, M. B., Sobell, L. C., Klajner, F., Pavan, D., & Basian, E. (1986). The reliability of a timeline method for assessing normal drinker college students' recent drinking history: Utility for alcohol research. *Addictive Behaviors*, 11(2), 149-161. doi:10.1016/0306-4603(86)90040-7

- Soderlund, H., Grady, C. L., Easdon, C., & Tulving, E. (2007). Acute effects of alcohol on neural correlates of episodic memory encoding. *Neuroimage*, 35(2), 928-939. doi:10.1016/j.neuroimage.2006.12.024
- Soderlund, H., Parker, E. S., Schwartz, B. L., & Tulving, E. (2005). Memory encoding and retrieval on the ascending and descending limbs of the blood alcohol concentration curve. *Psychopharmacology (Berl)*, 182(2), 305-317. doi:10.1007/s00213-005-0096-2
- Soderpalm, B., Lof, E., & Ericson, M. (2009). Mechanistic studies of ethanol's interaction with the mesolimbic dopamine reward system. *Pharmacopsychiatry*, 42 Suppl 1, S87-94. doi:10.1055/s-0029-1220690
- Sommer, W. H., & Spanagel, R. (2013). *Behavioral neurobiology of alcohol addiction*. New York: Springer.
- Sowell, E. R., Peterson, B. S., Thompson, P. M., Welcome, S. E., Henkenius, A. L., & Toga, A. W. (2003). Mapping cortical change across the human life span. *Nature Neuroscience*, 6(3), 309-315. doi:10.1038/nn1008
- Sowell, E. R., Thompson, P. M., Holmes, C. J., Jernigan, T. L., & Toga, A. W. (1999). In vivo evidence for post-adolescent brain maturation in frontal and striatal regions. *Nature Neuroscience*, 2(10), 859-861. doi:10.1038/13154
- Sowell, E. R., Thompson, P. M., Tessner, K. D., & Toga, A. W. (2001). Mapping continued brain growth and gray matter density reduction in dorsal frontal cortex: Inverse relationships during postadolescent brain maturation. *The Journal of Neuroscience*, 21(22), 8819-8829. doi:10.1523/JNEUROSCI.21-22-08819.2001
- Sowell, E. R., Thompson, P. M., & Toga, A. W. (2004). Mapping changes in the human cortex throughout the span of life. *Neuroscientist*, 10(4), 372-392. doi:10.1177/1073858404263960

- Sowell, E. R., Trauner, D. A., Gamst, A., & Jernigan, T. L. (2002). Development of cortical and subcortical brain structures in childhood and adolescence: A structural MRI study. *Developmental Medicine and Child Neurology*, 44(1), 4-16. doi:10.1111/j.1469-8749.2002.tb00253.x
- Spadoni, A. D., Norman, A. L., Schweinsburg, A. D., & Tapert, S. F. (2008). Effects of family history of alcohol use disorders on spatial working memory BOLD response in adolescents. *Alcoholism: Clinical and Experimental Research*, 32(7), 1135-1145. doi:10.1111/j.1530-0277.2008.00694.x
- Spadoni, A. D., Simmons, A. N., Yang, T. T., & Tapert, S. F. (2013). Family history of alcohol use disorders and neuromaturation: A functional connectivity study with adolescents. *The American Journal of Drug and Alcohol Abuse*, 39(6), 356-364. doi:10.3109/00952990.2013.818680
- Spanagel, R. (2000). Recent animal models of alcoholism. *Alcohol Research and Health*, 24(2), 124-131.
- Spear, L. P. (2000). The adolescent brain and age-related behavioral manifestations. *Neuroscience and Biobehavioral Reviews*, 24(4), 417-463. doi:10.1016/s0149-7634(00)00014-2
- Spear, L. P. (2002a). The adolescent brain and the college drinker: Biological basis of propensity to use and misuse alcohol. *Journal of Studies on Alcohol, Suppl*(14), 71-81. doi:10.15288/jsas.2002.s14.71
- Spear, L. P. (2002b). Alcohol's effects on adolescents. *Alcohol Research and Health*, 26(4), 287-291.
- Spear, L. P. (2004). Adolescent brain development and animal models. *Annals of the New York Academy of Sciences*, 1021, 23-26. doi:10.1196/annals.1308.002
- Spear, L. P. (2011). Adolescent neurobehavioral characteristics, alcohol sensitivities, and intake: Setting the stage for alcohol use disorders? *Child Development Perspect*, 5(4), 231-238. doi:10.1111/j.1750-8606.2011.00182.x

- Spear, L. P. (2014). Adolescents and alcohol: Acute sensitivities, enhanced intake, and later consequences. *Neurotoxicology and Teratology*, 41, 51-59. doi:10.1016/j.ntt.2013.11.006
- Spear, L. P. (2016). Consequences of adolescent use of alcohol and other drugs: Studies using rodent models. *Neuroscience and Biobehavioral Reviews*, 70, 228-243. doi:10.1016/j.neubiorev.2016.07.026
- Spiegelhalter, K., Regen, W., Feige, B., Holz, J., Piosczyk, H., Baglioni, C., . . . Nissen, C. (2012). Increased EEG sigma and beta power during NREM sleep in primary insomnia. *Biological Psychology*, 91(3), 329-333. doi:10.1016/j.biopsycho.2012.08.009
- Squeglia, L. M., Jacobus, J., Brumback, T., Meloy, M. J., & Tapert, S. F. (2014). White matter integrity in alcohol-naive youth with a family history of alcohol use disorders. *Psychological Medicine*, 44(13), 2775-2786. doi:10.1017/S0033291714000609
- Squeglia, L. M., Jacobus, J., & Tapert, S. F. (2009a). The influence of substance use on adolescent brain development. *Clinical EEG and Neuroscience*, 40(1), 31-38. doi:10.1177/155005940904000110
- Squeglia, L. M., Sorg, S. F., Schweinsburg, A. D., Wetherill, R. R., Pulido, C., & Tapert, S. F. (2012). Binge drinking differentially affects adolescent male and female brain morphometry. *Psychopharmacology (Berl)*, 220(3), 529-539. doi:10.1007/s00213-011-2500-4
- Squeglia, L. M., Spadoni, A. D., Infante, M. A., Myers, M. G., & Tapert, S. F. (2009b). Initiating moderate to heavy alcohol use predicts changes in neuropsychological functioning for adolescent girls and boys. *Psychology of Addictive Behaviors*, 23(4), 715-722. doi:10.1037/a0016516
- Squeglia, L. M., Tapert, S. F., Sullivan, E. V., Jacobus, J., Meloy, M. J., Rohlfing, T., & Pfefferbaum, A. (2015). Brain development in heavy-drinking adolescents. *American Journal of Psychiatry*, 172(6), 531-542. doi:10.1176/appi.ajp.2015.14101249

- Stavro, K., Pelletier, J., & Potvin, S. (2013). Widespread and sustained cognitive deficits in alcoholism: A meta-analysis. *Addiction Biology*, 18(2), 203-213. doi:10.1111/j.1369-1600.2011.00418.x
- Steele, C. M., & Josephs, R. A. (1988). Drinking your troubles away. II: An attention-allocation model of alcohol's effect on psychological stress. *Journal of Abnormal Psychology*, 97(2), 196-205. doi:10.1037/0021-843X.97.2.196
- Stein, M. D., & Friedmann, P. D. (2005). Disturbed sleep and its relationship to alcohol use. *Substance Abuse*, 26(1), 1-13. doi:10.1300/j465v26n01_01
- Steinberg, L. (2005). Cognitive and affective development in adolescence. *Trends in Cognitive Sciences*, 9(2), 69-74. doi:10.1016/j.tics.2004.12.005
- Steinig, J., Foraita, R., Happe, S., & Heinze, M. (2011). Perception of sleep and dreams in alcohol-dependent patients during detoxication and abstinence. *Alcohol and Alcoholism*, 46(2), 143-147. doi:10.1093/alcalc/agq087
- Stephan, R. A., Alhassoon, O. M., Allen, K. E., Wollman, S. C., Hall, M., Thomas, W. J., . . . Grant, I. (2017). Meta-analyses of clinical neuropsychological tests of executive dysfunction and impulsivity in alcohol use disorder. *The American Journal of Drug and Alcohol Abuse*, 43(1), 24-43. doi:10.1080/00952990.2016.1206113
- Stephens, R., Ling, J., Heffernan, T. M., Heather, N., & Jones, K. (2008). A review of the literature on the cognitive effects of alcohol hangover. *Alcohol and Alcoholism*, 43(2), 163-170. doi:10.1093/alcalc/agm160
- Steriade, M. (2004a). Acetylcholine systems and rhythmic activities during the waking--sleep cycle. *Progress in Brain Research*, 145, 179-196. doi:10.1016/S0079-6123(03)45013-9
- Steriade, M. (2004b). Slow-wave sleep: Serotonin, neuronal plasticity, and seizures. *Archives Italiennes de Biologie*, 142(4), 359-367.

- Steriade, M., Dossi, R. C., & Nunez, A. (1991). Network modulation of a slow intrinsic oscillation of cat thalamocortical neurons implicated in sleep delta waves: Cortically induced synchronization and brainstem cholinergic suppression. *The Journal of Neuroscience*, 11(10), 3200-3217.
doi:10.1523/JNEUROSCI.11-10-03200.1991
- Steriade, M., McCormick, D. A., & Sejnowski, T. J. (1993a). Thalamocortical oscillations in the sleeping and aroused brain. *Science*, 262(5134), 679-685.
doi:10.1126/science.8235588
- Steriade, M., Nunez, A., & Amzica, F. (1993b). Intracellular analysis of relations between the slow (<1 Hz) neocortical oscillation and other sleep rhythms of the electroencephalogram. *The Journal of Neuroscience*, 13(8), 3266-3283.
doi:10.1523/JNEUROSCI.13-08-03266.1993
- Steriade, M., Nunez, A., & Amzica, F. (1993c). A novel slow (<1 Hz) oscillation of neocortical neurons in vivo: Depolarizing and hyperpolarizing components. *The Journal of Neuroscience*, 13(8), 3252-3265.
doi:10.1523/JNEUROSCI.13-08-03252.1993
- Stevenson, R. A., Besheer, J., & Hodge, C. W. (2008). Comparison of ethanol locomotor sensitization in adolescent and adult DBA/2J mice. *Psychopharmacology (Berl)*, 197(3), 361-370.
doi:10.1007/s00213-007-1038-y
- Stewart, D. G., & Brown, S. A. (1995). Withdrawal and dependency symptoms among adolescent alcohol and drug abusers. *Addiction*, 90(5), 627-635.
doi:10.1046/j.1360-0443.1995.9056274.x
- Stone, B. M. (1980). Sleep and low doses of alcohol. *Electroencephalography and Clinical Neurophysiology*, 48(6), 706-709.
doi:10.1016/0013-4694(80)90427-7
- Streissguth, A. P., Landesman-Dwyer, S., Martin, J. C., & Smith, D. W. (1980). Teratogenic effects of alcohol in humans and laboratory animals. *Science*, 209(4454), 353-361. doi:10.1126/science.6992275

- Streissguth, A. P., & O'Malley, K. (2000). Neuropsychiatric implications and long-term consequences of fetal alcohol spectrum disorders. *Seminars in Clinical Neuropsychiatry*, 5(3), 177-190. doi:10.1053/scnp.2000.6729
- Stutzmann, J. M., Lucas, M., Blanchard, J. C., & Laduron, P. M. (1988). Riluzole, a glutamate antagonist, enhances slow wave and REM sleep in rats. *Neuroscience Letters*, 88(2), 195-200. doi:10.1016/0304-3940(88)90125-5
- Suh, S., Cho, N., & Zhang, J. (2018). Sex differences in insomnia: From epidemiology and etiology to intervention. *Current Psychiatry Reports*, 20(9), 69. doi:10.1007/s11920-018-0940-9
- Sullivan, E. V. (2003). Compromised pontocerebellar and cerebellothalamocortical systems: speculations on their contributions to cognitive and motor impairment in nonamnesic alcoholism. *Alcoholism: Clinical and Experimental Research*, 27(9), 1409-1419. doi:10.1097/01.ALC.0000085586.91726.46
- Sullivan, E. V., Deshmukh, A., Desmond, J. E., Lim, K. O., & Pfefferbaum, A. (2000). Cerebellar volume decline in normal aging, alcoholism, and Korsakoff's syndrome: Relation to ataxia. *Neuropsychology*, 14(3), 341-352. doi:10.1037//0894-4105.14.3.341
- Sullivan, E. V., Harris, R. A., & Pfefferbaum, A. (2010). Alcohol's effects on brain and behavior. *Alcohol Research and Health*, 33(1-2), 127-143.
- Sullivan, E. V., & Pfefferbaum, A. (2005). Neurocircuitry in alcoholism: A substrate of disruption and repair. *Psychopharmacology*, 180, 583-594.
- Sullivan, E. V., Rosenbloom, M. J., & Pfefferbaum, A. (2000). Pattern of motor and cognitive deficits in detoxified alcoholic men. *Alcoholism: Clinical and Experimental Research*, 24(5), 611-621. doi:10.1111/j.1530-0277.2000.tb02032.x
- Sundell, L., Salomaa, V., Vartiainen, E., Poikolainen, K., & Laatikainen, T. (2008). Increased stroke risk is related to a binge-drinking habit. *Stroke*, 39(12), 3179-3184. doi:10.1161/STROKEAHA.108.520817

- Sutherland, G. T., Sheedy, D., & Kril, J. J. (2014). Using autopsy brain tissue to study alcohol-related brain damage in the genomic age. *Alcoholism: Clinical and Experimental Research*, 38(1), 1-8. doi:10.1111/acer.12243
- Suzuki, K., Miyamoto, M., & Hirata, K. (2017). Sleep disorders in the elderly: Diagnosis and management. *Journal of General and Family Medicine*, 18(2), 61-71. doi:10.1002/jgf2.27
- Svanberg, J., & Beaunieux, H. (2015). *Alcohol and the adult brain*. New York, NY: Psychology Press.
- Svensson, M. S., Nekaris, K. A. I., Bearder, S. K., Bettridge, C. M., Butynski, T. M., Cheyne, S. M., . . . Nijman, V. (2018). Sleep patterns, daytime predation, and the evolution of diurnal sleep site selection in lorisiforms. *American Journal of Physical Anthropology*, 166(3), 563-577. doi:10.1002/ajpa.23450
- Swartzwelder, H. S., Park, M.-H., & Acheson, S. (2017). Adolescent ethanol exposure enhances nmda receptor-mediated currents in hippocampal neurons: Reversal by gabapentin. *Scientific Reports*, 7(1), 13133. doi:10.1038/s41598-017-12956-6
- Swift, R., & Davidson, D. (1998). Alcohol hangover: Mechanisms and mediators. *Alcohol Health and Research World*, 22(1), 54-60.
- Tabachnick, B. G., & Fidell, L. S. (2001). *Using Multivariate Statistics*. Boston, MA: Allyn and Bacon.
- Tabachnick, B. G., & Fidell, L. S. (2007). *Experimental designs using ANOVA*. Belmont, MA: Thomson/Brooks/Cole.
- Tagawa, M., Kano, M., Okamura, N., Itoh, M., Sakurai, E., Watanabe, T., & Yanai, K. (2000). Relationship between effects of alcohol on psychomotor performances and blood alcohol concentrations. *The Japanese Journal of Pharmacology*, 83(3), 253-260. doi:10.1254/jjp.83.253

- Takei, Y., Komada, Y., Namba, K., Sasai, T., Nakamura, M., Sugiura, T., Hayashida, K., & Inoue, Y. (2012). Differences in findings of nocturnal polysomnography and multiple sleep latency test between narcolepsy and idiopathic hypersomnia. *Clinical Neurophysiology*, 123(1), 137–141.
<https://doi.org/10.1016/j.clinph.2011.05.024>
- Tan, X., Chapman, C. D., Cedernaes, J., & Benedict, C. (2018). Association between long sleep duration and increased risk of obesity and type 2 diabetes: A review of possible mechanisms. *Sleep Medicine Reviews*, 40, 127-134.
[doi:10.1016/j.smrv.2017.11.001](https://doi.org/10.1016/j.smrv.2017.11.001)
- Tapert, S. F., Brown, G. G., Kindermann, S. S., Cheung, E. H., Frank, L. R., & Brown, S. A. (2001). fMRI measurement of brain dysfunction in alcohol-dependent young women. *Alcoholism: Clinical and Experimental Research*, 25(2), 236-245. [doi:10.1111/j.1530-0277.2001.tb02204.x](https://doi.org/10.1111/j.1530-0277.2001.tb02204.x)
- Tapert, S. F., & Brown, S. A. (2000). Substance dependence, family history of alcohol dependence and neuropsychological functioning in adolescence. *Addiction*, 95(7), 1043-1053. [doi:10.1046/j.1360-0443.2000.95710436.x](https://doi.org/10.1046/j.1360-0443.2000.95710436.x)
- Tapert, S. F., Granholm, E., Leedy, N. G., & Brown, S. A. (2002). Substance use and withdrawal: Neuropsychological functioning over 8 years in youth. *Journal of the International Neuropsychological Society*, 8(7), 873-883.
[doi:10.1017/S1355617702870011](https://doi.org/10.1017/S1355617702870011)
- Tapert, S. F., Schweinsburg, A. D., Barlett, V. C., Brown, S. A., Frank, L. R., Brown, G. G., & Meloy, M. J. (2004). Blood oxygen level dependent response and spatial working memory in adolescents with alcohol use disorders. *Alcoholism: Clinical & Experimental Research*, 28(10), 1577-1586.
[doi:10.1097/01.Alc.0000141812.81234.A6](https://doi.org/10.1097/01.Alc.0000141812.81234.A6)
- Tarokh, L., & Carskadon, M. A. (2010a). Developmental changes in the human sleep EEG during early adolescence. *Sleep*, 33(6), 801-809.
[doi:10.1093/sleep/33.6.801](https://doi.org/10.1093/sleep/33.6.801)

- Tarokh, L., & Carskadon, M. A. (2010b). Sleep electroencephalogram in children with a parental history of alcohol abuse/dependence. *Journal of Sleep Research, 19*(1 Pt 2), 165-174. doi:10.1111/j.1365-2869.2009.00763.x
- Tarokh, L., Van Reen, E., Acebo, C., Lebourgeois, M., Seifer, R., Fallone, G., & Carskadon, M. A. (2012). Adolescence and parental history of alcoholism: Insights from the sleep eeg. *Alcoholism: Clinical and Experimental Research*. doi:10.1111/j.1530-0277.2012.01756.x
- Tarokh, L., Van Reen, E., LeBourgeois, M., Seifer, R., & Carskadon, M. A. (2011). Sleep EEG provides evidence that cortical changes persist into late adolescence. *Sleep, 34*(10), 1385-1393. doi:10.5665/SLEEP.1284
- Tartar, J. L., Ward, C. P., McKenna, J. T., Thakkar, M., Arrigoni, E., McCarley, R. W., . . . Strecker, R. E. (2006). Hippocampal synaptic plasticity and spatial learning are impaired in a rat model of sleep fragmentation. *European Journal of Neuroscience, 23*(10), 2739-2748. doi:10.1111/j.1460-9568.2006.04808.x
- Tarter, R. E., Kirisci, L., Mezzich, A., Cornelius, J. R., Pajer, K., Vanyukov, M., . . . Clark, D. (2003). Neurobehavioral disinhibition in childhood predicts early age at onset of substance use disorder. *American Journal of Psychiatry, 160*(6), 1078-1085. doi:10.1176/appi.ajp.160.6.1078
- Tarter, R. E., Mezzich, A. C., Hsieh, Y. C., & Parks, S. M. (1995). Cognitive capacity in female adolescent substance abusers. *Drug and Alcohol Dependence, 39*(1), 15-21. doi:10.1016/0376-8716(95)01129-M
- Tatebayashi, H., Motomura, H., & Narahashi, T. (1998). Alcohol modulation of single GABA_A receptor-channel kinetics. *Neuroreport, 9*(8), 1769-1775. doi:10.1097/00001756-199806010-00018
- Tayade, M. C. (2015). Fetal alcohol spectrum disorders (FASD) and slow wave sleep. *Pravara Medical Review, 7*(4), 4-5.

- Taylor, B., Irving, H. M., Kanteres, F., Room, R., Borges, G., Cherpitel, C., . . . Rehm, J. (2010). The more you drink, the harder you fall: A systematic review and meta-analysis of how acute alcohol consumption and injury or collision risk increase together. *Drug and Alcohol Dependence*, 110(1-2), 108-116. doi:10.1016/j.drugalcdep.2010.02.011
- Teesson, M., Hall, W., Slade, T., Mills, K., Grove, R., Mewton, L., . . . Haber, P. (2010). Prevalence and correlates of DSM-IV alcohol abuse and dependence in Australia: Findings of the 2007 National Survey of Mental Health and Wellbeing. *Addiction*, 105(12), 2085-2094. doi:10.1111/j.1360-0443.2010.03096.x
- Teffer, K., & Semendeferi, K. (2012). Human prefrontal cortex: Evolution, development, and pathology. *Progress in Brain Research*, 195, 191-218. doi:10.1016/B978-0-444-53860-4.00009-X
- Tempesta, D., Socci, V., De Gennaro, L., & Ferrara, M. (2018). Sleep and emotional processing. *Sleep Medicine Reviews*, 40, 183-195. doi:10.1016/j.smrv.2017.12.005
- Thakkar, M. M. (2011). Histamine in the regulation of wakefulness. *Sleep Medicine Reviews*, 15(1), 65-74. doi:10.1016/j.smrv.2010.06.004
- Thakkar, M. M., Sharma, R., & Sahota, P. (2015). Alcohol disrupts sleep homeostasis. *Alcohol*, 49(4), 299-310. doi:10.1016/j.alcohol.2014.07.019
- Thavorncharoensap, M., Teerawattananon, Y., Yothasamut, J., Lertpitakpong, C., & Chaikledkaew, U. (2009). The economic impact of alcohol consumption: a systematic review. *Substance Abuse Treatment, Prevention, and Policy*, 4, 20. doi:10.1186/1747-597X-4-20
- Thaxton, L., & Myers, M. A. (2002). Sleep disturbances and their management in patients with brain injury. *The Journal of Head Trauma Rehabilitation*, 17(4), 335-348. doi:10.1097/00001199-200208000-00007

- Thorleifsdottir, B., Björnsson, J. K., Benediktsdottir, B., Gislason, T., & Kristbjarnarson, H. (2002). Sleep and sleep habits from childhood to young adulthood over a 10-year period. *Journal of Psychosomatic Research*, 53(1), 529-537. doi:10.1016/s0022-3999(02)00444-0
- Tinguely, G., Finelli, L. A., Landolt, H. P., Borbely, A. A., & Achermann, P. (2006). Functional EEG topography in sleep and waking: State-dependent and state-independent features. *Neuroimage*, 32(1), 283-292. doi:10.1016/j.neuroimage.2006.03.017
- Tipple, C. T., Benson, S., & Scholey, A. (2016). A review of the physiological factors associated with alcohol hangover. *Current Drug Abuse Reviews*, 9(2), 93-98. doi:10.2174/1874473710666170207152933
- Tolstrup, J. S., Stephens, R., & Gronbaek, M. (2014). Does the severity of hangovers decline with age? Survey of the incidence of hangover in different age groups. *Alcoholism: Clinical and Experimental Research*, 38(2), 466-470. doi:10.1111/acer.12238
- Tomaka, J., Palacios, R., Morales-Monks, S., & Davis, S. E. (2012). An evaluation of the BASICS alcohol risk reduction model among predominantly Hispanic college students. *Substance Use and Misuse*, 47(12), 1260-1270. doi:10.3109/10826084.2012.692754
- Tononi, G., & Cirelli, C. (2003). Sleep and synaptic homeostasis: A hypothesis. *Brain Research Bulletin*, 62(2), 143-150. doi:10.1016/j.brainresbull.2003.09.004
- Tononi, G., & Cirelli, C. (2006). Sleep function and synaptic homeostasis. *Sleep Medicine Reviews*, 10(1), 49-62. doi:10.1016/j.smr.2005.05.002
- Tononi, G., & Cirelli, C. (2014). Sleep and the price of plasticity: From synaptic and cellular homeostasis to memory consolidation and integration. *Neuron*, 81(1), 12-34. doi:10.1016/j.neuron.2013.12.025

- Townshend, J. M., & Duka, T. (2005). Binge drinking, cognitive performance and mood in a population of young social drinkers. *Alcoholism: Clinical & Experimental Research*, 29(3), 317-325.
doi:10.1097/01.Alc.0000156453.05028.F5
- Trapp, B. D., Wujek, J. R., Criste, G. A., Jalabi, W., Yin, X., Kidd, G. J., . . . Ransohoff, R. (2007). Evidence for synaptic stripping by cortical microglia. *Glia*, 55(4), 360-368. doi:10.1002/glia.20462
- Treloar, H., Celio, M. A., Lisman, S. A., Miranda, R., Jr., & Spear, L. P. (2017). Subjective alcohol responses in a cross-sectional, field-based study of adolescents and young adults: Effects of age, drinking level, and dependence/consequences. *Drug and Alcohol Dependence*, 170, 156-163.
doi:10.1016/j.drugalcdep.2016.11.009
- Trevisan, L. A., Boutros, N., Petrakis, I. L., & Krystal, J. H. (1998). Complications of alcohol withdrawal: Pathophysiological insights. *Alcohol Health and Research World*, 22(1), 61-66.
- Trinder, J., Stevenson, J., Paxton, S. J., & Montgomery, I. (1982). Physical fitness, exercise, and REM sleep cycle length. *Psychophysiology*, 19(1), 89-93.
- Tucker, A. M., Dinges, D. F., & Van Dongen, H. P. (2007). Trait interindividual differences in the sleep physiology of healthy young adults. *Journal of Sleep Research*, 16(2), 170-180. doi:10.1111/j.1365-2869.2007.00594.x
- Turner, C., & McClure, R. (2003). Age and gender differences in risk-taking behaviour as an explanation for high incidence of motor vehicle crashes as a driver in young males. *International Journal of Injury Control and Safety Promotion*, 10(3), 123-130. doi:10.1076/icsp.10.3.123.14560
- Tzambazis, K., & Stough, C. (2000). Alcohol impairs speed of information processing and simple and choice reaction time and differentially impairs higher-order cognitive abilities. *Alcohol and Alcoholism*, 35(2), 197-201.
doi:10.1093/alcalc/35.2.197

- Ursin, R. (2002). Serotonin and sleep. *Sleep Medicine Reviews*, 6(1), 55-67.
doi:10.1053/smr.2001.0174
- Van Cauter, E. (2000). Slow wave sleep and release of growth hormone. *Journal of the American Medical Association*, 284(21), 2717-2718.
doi:10.1001/jama.284.21.2717
- Van Cauter, E., Leproult, R., & Plat, L. (2000). Age-related changes in slow wave sleep and REM sleep and relationship with growth hormone and cortisol levels in healthy men. *Journal of the American Medical Association*, 284(7), 861-868. doi:10.1001/jama.284.7.861
- Van Der Werf, Y. D., Altena, E., Schoonheim, M. M., Sanz-Arigita, E. J., Vis, J. C., De Rijke, W., & Van Someren, E. J. (2009). Sleep benefits subsequent hippocampal functioning. *Nature Neuroscience*, 12(2), 122-123.
doi:10.1038/nn.2253
- Van Dongen, H. P., & Dinges, D. F. (2005). Sleep, circadian rhythms, and psychomotor vigilance. *Clinical Journal of Sport Medicine*, 24(2), 237-249, vii-viii. doi:10.1016/j.csm.2004.12.007
- Van Dongen, H. P. A., Maislin, G., Mullington, J. M., & Dinges, D. F. (2003). The cumulative cost of additional wakefulness: Dose-response effects on neurobehavioral functions and sleep physiology from chronic sleep restriction and total sleep deprivation. *Sleep*, 26(2), 117-126. doi:10.1093/sleep/26.2.117
- van Eijk, J., Demirakca, T., Frischknecht, U., Hermann, D., Mann, K., & Ende, G. (2013). Rapid partial regeneration of brain volume during the first 14 days of abstinence from alcohol. *Alcoholism: Clinical and Experimental Research*, 37(1), 67-74. doi:10.1111/j.1530-0277.2012.01853.x
- Van Reen, E., Jenni, O. G., & Carskadon, M. A. (2006). Effects of alcohol on sleep and the sleep electroencephalogram in healthy young women. *Alcoholism: Clinical and Experimental Research*, 30(6), 974-981. doi:10.1111/j.1530-0277.2006.00111.x

- Van Reen, E., Roane, B. M., Barker, D. H., McGeary, J. E., Borsari, B., & Carskadon, M. A. (2016). Current alcohol use is associated with sleep patterns in first-year college students. *Sleep*, 39(6), 1321-1326. doi:10.5665/sleep.5862
- van Schrojenstein Lantman, M., Mackus, M., van de Loo, A., & Verster, J. C. (2017). The impact of alcohol hangover symptoms on cognitive and physical functioning, and mood. *Human Psychopharmacology: Clinical and Experimental*, 32(5). doi:10.1002/hup.2623
- Vandekerckhove, M., & Wang, Y. (2017). Emotion, emotion regulation and sleep: An intimate relationship. *Sleep Medicine Reviews*, 5(2), 1-17. doi:10.1016/j.smr.2010.01.002
- Varlinskaya, E. I., & Spear, L. P. (2006). Differences in the social consequences of ethanol emerge during the course of adolescence in rats: Social facilitation, social inhibition, and anxiolysis. *Developmental Psychobiology*, 48(2), 146-161. doi:10.1002/dev.20124
- Vassalli, A., & Dijk, D. J. (2009). Sleep function: Current questions and new approaches. *European Journal of Neuroscience*, 29(9), 1830-1841. doi:10.1111/j.1460-9568.2009.06767.x
- Vazquez, J., & Baghdoyan, H. A. (2001). Basal forebrain acetylcholine release during REM sleep is significantly greater than during waking. *American Journal of Physiology Regulatory, Integrative and Comparative Physiology*, 280(2), R598-601. doi:10.1152/ajpregu.2001.280.2.R598
- Vecsey, C. G., Baillie, G. S., Jaganath, D., Havekes, R., Daniels, A., Wimmer, M., . . . Abel, T. (2009). Sleep deprivation impairs cAMP signalling in the hippocampus. *Nature*, 461(7267), 1122-1125. doi:10.1038/nature08488
- Venkatasubramanian, G., Anthony, G., Reddy, U. S., Reddy, V. V., Jayakumar, P. N., & Benegal, V. (2007). Corpus callosum abnormalities associated with greater externalizing behaviors in subjects at high risk for alcohol dependence. *Psychiatry Research*, 156(3), 209-215. doi:10.1016/j.psychres.2006.12.010

- Verster, J. C. (2008). The alcohol hangover- A puzzling phenomenon. *Alcohol and Alcoholism*, 43(2), 124-126. doi:10.1093/alcalc/agm163
- Verster, J. C., van Duin, D., Volkerts, E. R., Schreuder, A. H., & Verbaten, M. N. (2003). Alcohol hangover effects on memory functioning and vigilance performance after an evening of binge drinking. *Neuropsychopharmacology*, 28(4), 740-746. doi:10.1038/sj.npp.1300090
- Vertes, R. P. (2004). Memory consolidation in sleep: Dream or reality. *Neuron*, 44(1), 135-148. doi:10.1016/j.neuron.2004.08.034
- Vertes, R. P., & Eastman, K. E. (2000). The case against memory consolidation in REM sleep. *Behavioral and Brain Sciences*, 23(6), 867-876; discussion 904-1121. doi: 10.1017/s0140525x00004003
- Vijayakumar, N., Op de Macks, Z., Shirtcliff, E. A., & Pfeifer, J. H. (2018). Puberty and the human brain: Insights into adolescent development. *Neuroscience and Biobehavioral Reviews*, 92, 417-436. doi:10.1016/j.neubiorev.2018.06.004
- Vogel, M., Braungardt, T., Meyer, W., & Schneider, W. (2012). The effects of shift work on physical and mental health. *Journal of Neural Transmission (Vienna)*, 119(10), 1121-1132. doi:10.1007/s00702-012-0800-4
- Vogl, L., Teesson, M., Andrews, G., Bird, K., Steadman, B., & Dillon, P. (2009). A computerized harm minimization prevention program for alcohol misuse and related harms: Randomized controlled trial. *Addiction*, 104(4), 564-575. doi:10.1111/j.1360-0443.2009.02510.x
- Vogl, L. E., Newton, N. C., Champion, K. E., & Teesson, M. (2014). A universal harm-minimisation approach to preventing psychostimulant and cannabis use in adolescents: A cluster randomised controlled trial. *Substance Abuse Treatment, Prevention, and Policy*, 9, 24. doi:10.1186/1747-597X-9-24
- Volgushev, M., Chauvette, S., Mukovski, M., & Timofeev, I. (2006). Precise long-range synchronization of activity and silence in neocortical neurons during slow-wave oscillations. *The Journal of Neuroscience*, 26(21), 5665-5672. doi:10.1523/JNEUROSCI.0279-06.2006

- Vonghia, L., Leggio, L., Ferrulli, A., Bertini, M., Gasbarrini, G., Addolorato, G., & Alcoholism Treatment Study, G. (2008). Acute alcohol intoxication. *European Journal of Internal Medicine*, 19(8), 561-567. doi:10.1016/j.ejim.2007.06.033
- Wagman, A. M., & Allen, R. P. (1975). Effects of alcohol ingestion and abstinence on slow wave sleep of alcoholics. *Advances in Experimental Medicine and Biology*, 59, 453-466. doi:10.1007/978-1-4757-0632-1_32
- Walker, M. P. (2008). Cognitive consequences of sleep and sleep loss. *Sleep Medicine*, 9 Suppl 1, S29-34. doi:10.1016/S1389-9457(08)70014-5
- Waller, P. F., Stewart, J. R., Hansen, A. R., Stutts, J. C., Popkin, C. L., & Rodgman, E. A. (1986). The potentiating effects of alcohol on driver injury. *The Journal of the American Medical Association*, 256(11), 1461-1466. doi:10.1001/jama.1986.03380110067028
- Walsh, J. K. (2009). Enhancement of slow wave sleep: Implications for insomnia. *Journal of Clinical Sleep Medicine*, 5(2 Suppl), S27-32. doi:10.3109/15622971003637645
- Walsleben, J. A., Kapur, V. K., Newman, A. B., Shahar, E., Bootzin, R. R., Rosenberg, C. E., . . . Nieto, F. J. (2004). Sleep and reported daytime sleepiness in normal subjects: The Sleep Heart Health Study. *Sleep*, 27(2), 293-298. doi:10.1093/sleep/27.2.293
- Wang, G., Grone, B., Colas, D., Appelbaum, L., & Mourrain, P. (2011). Synaptic plasticity in sleep: Learning, homeostasis and disease. *Trends in Neurosciences*, 34(9), 452-463. doi:10.1016/j.tins.2011.07.005
- Wang, Y., Adamson, C., Yuan, W., Altaye, M., Rajagopal, A., Byars, A. W., & Holland, S. K. (2012). Sex differences in white matter development during adolescence: A DTI study. *Brain Research*, 1478, 1-15. doi:10.1016/j.brainres.2012.08.038

- Ward, R. J., Lallemand, F., & de Witte, P. (2009). Biochemical and neurotransmitter changes implicated in alcohol-induced brain damage in chronic or 'binge drinking' alcohol abuse. *Alcohol and Alcoholism*, 44(2), 128-135. doi:10.1093/alcalc/agn100
- Warren, C. M., Riggs, N. R., & Pentz, M. A. (2017). Longitudinal relationships of sleep and inhibitory control deficits to early adolescent cigarette and alcohol use. *Journal of Adolescence*, 57, 31-41. doi:10.1016/j.adolescence.2017.03.003
- Watson, C. J., Baghdoyan, H. A., & Lydic, R. (2010). Neuropharmacology of sleep and wakefulness. *Sleep Medicine Clinics*, 5(4), 513-528. doi:10.1016/j.jsmc.2010.08.003
- Weaver, M. S., Lee, Y. H., Morris, J. L., Randall, P. K., Schallert, T., & Leslie, S. W. (1993). Effects of in vitro ethanol and fetal ethanol exposure on glutathione stimulation of N-methyl-D-aspartate receptor function. *Alcoholism: Clinical and Experimental Research*, 17(3), 643-650. doi:10.1111/j.1530-0277.1993.tb00812.x
- Webb, W. B., & Agnew, H. W., Jr. (1971). Stage 4 sleep: Influence of time course variables. *Science*, 174(4016), 1354-1356. doi:10.1126/science.174.4016.1354
- Webb, W. B., & Agnew, H. W., Jr. (1975). The effects on subsequent sleep of an acute restriction of sleep length. *Psychophysiology*, 12(4), 367-370. doi:10.1111/j.1469-8986.1975.tb00002.x
- Wechsler, H., Lee, J. E., Kuo, M., & Lee, H. (2000). College binge drinking in the 1990s: A continuing problem. Results of the Harvard School of Public Health 1999 College Alcohol Study. *Journal of American College Health*, 48(5), 199-210. doi:10.1080/07448480009599305
- Weiner, J. L., & Valenzuela, C. F. (2006). Ethanol modulation of GABAergic transmission: The view from the slice. *Pharmacology and Therapeutics*, 111(3), 533-554. doi:10.1016/j.pharmthera.2005.11.002

- Weissman, M. M., Greenwald, S., Nino-Murcia, G., & Dement, W. C. (1997). The morbidity of insomnia uncomplicated by psychiatric disorders. *General Hospital Psychiatry*, 19(4), 245-250. doi:10.1016/S0163-8343(97)00056-X
- Welch, K. A., Carson, A., & Lawrie, S. M. (2013). Brain structure in adolescents and young adults with alcohol problems: Systematic review of imaging studies. *Alcohol and Alcoholism*, 48(4), 433-444. doi:10.1093/alcalc/agt037
- Werth, E., Achermann, P., & Borbely, A. A. (1996). Brain topography of the human sleep EEG: Antero-posterior shifts of spectral power. *Neuroreport*, 8(1), 123-127. doi:10.1097/00001756-199612200-00025
- Werth, E., Achermann, P., & Borbely, A. A. (1997). Fronto-occipital EEG power gradients in human sleep. *Journal of Sleep Research*, 6(2), 102-112.
- Werth, E., Dijk, D. J., Achermann, P., & Borbely, A. A. (1996). Dynamics of the sleep EEG after an early evening nap: Experimental data and simulations. *American Journal of Physiology*, 271(3 Pt 2), R501-510. doi:10.1152/ajpregu.1996.271.3.R501
- White, A. M. (2003). What happened? Alcohol, memory blackouts, and the brain. *Alcohol Research and Health*, 27(2), 186-196.
- White, A. M., Matthews, D. B., & Best, P. J. (2000). Ethanol, memory, and hippocampal function: A review of recent findings. *Hippocampus*, 10(1), 88-93. doi:10.1002/(SICI)1098-1063(2000)10:1<88::AID-HIPO10>3.0.CO;2-L
- White, A. M., & Swartzwelder, H. S. (2005). Age-related effects of alcohol on memory and memory-related brain function in adolescents and adults. *Recent Developments in Alcoholism*, 17, 161-176. doi:10.1007/0-306-48626-1_8
- White, A. M., Truesdale, M. C., Bae, J. G., Ahmad, S., Wilson, W. A., Best, P. J., & Swartzwelder, H. S. (2002). Differential effects of ethanol on motor coordination in adolescent and adult rats. *Pharmacology Biochemistry and Behavior*, 73(3), 673-677. doi:10.1016/S0091-3057(02)00860-2

- White, D. P., Weil, J. V., & Zwillich, C. W. (1985). Metabolic rate and breathing during sleep. *Journal of Applied Physiology*, 59(2), 384-391.
doi:10.1152/jappl.1985.59.2.384
- Whitman, I. R., Agarwal, V., Nah, G., Dukes, J. W., Vittinghoff, E., Dewland, T. A., & Marcus, G. M. (2017). Alcohol Abuse and Cardiac Disease. *Journal of the American College of Cardiology*, 69(1), 13-24. doi:10.1016/j.jacc.2016.10.048
- WHO. (2011). *Global Status Report on Alcohol and Health*. Geneva: World Health Organisation.
- WHO. (2018). *Global status report on alcohol and health 2018*. Geneva: World Health Organisation.
- Wiese, J. G., Shlipak, M. G., & Browner, W. S. (2000). The alcohol hangover. *Annals of Internal Medicine*, 132(11), 897-902. doi: 10.7326/0003-4819-132-11-200006060-00008
- Wilkinson, P. K., Sedman, A. J., Sakmar, E., Kay, D. R., & Wagner, J. G. (1977). Pharmacokinetics of ethanol after oral administration in the fasting state. *Journal of Pharmacokinetics and Biopharmaceutics*, 5(3), 207-224.
doi:10.1007/BF01065396
- Williams, D. L., MacLean, A. W., & Cairns, J. (1983). Dose-response effects of ethanol on the sleep of young women. *Journal of Studies on Alcohol*, 44(3), 515-523. doi:10.15288/jsa.1983.44.515
- Williams, H. L., Hammack, J. T., Daly, R. L., Dement, W. C., & Lubin, A. (1964). Responses to auditory stimulation, sleep loss and the EEG stages of sleep. *Electroencephalography and Clinical Neurophysiology*, 16, 269-279.
doi:10.1016/0013-4694(64)90109-9
- Williams, H. L., & Rundell, O. H., Jr. (1981). Altered sleep physiology in chronic alcoholics: Reversal with abstinence. *Alcoholism: Clinical and Experimental Research*, 5(2), 318-325. doi:10.1111/j.1530-0277.1981.tb04905.x

- Wilsnack, R. W., Vogeltanz, N. D., Wilsnack, S. C., Harris, T. R., Ahlstrom, S., Bondy, S., . . . Weiss, S. (2000). Gender differences in alcohol consumption and adverse drinking consequences: Cross-cultural patterns. *Addiction*, 95(2), 251-265. doi:10.1046/j.1360-0443.2000.95225112.x
- Wilsnack, R. W., Wilsnack, S. C., Kristjanson, A. F., Vogeltanz-Holm, N. D., & Gmel, G. (2009). Gender and alcohol consumption: Patterns from the multinational GENACIS project. *Addiction*, 104(9), 1487-1500. doi:10.1111/j.1360-0443.2009.02696.x
- Wilsnack, S. C., Wilsnack, R. W., & Hiller-Sturmhofel, S. (1994). How women drink: Epidemiology of women's drinking and problem drinking. *Alcohol Health and Research World*, 18(3), 173.
- Wilson, D. A., Masiello, K., Lewin, M. P., Hui, M., Smiley, J. F., & Saito, M. (2016). Developmental ethanol exposure-induced sleep fragmentation predicts adult cognitive impairment. *Neuroscience*, 322, 18-27. doi:10.1016/j.neuroscience.2016.02.020
- Wilson, S., Malone, S. M., Thomas, K. M., & Iacono, W. G. (2015). Adolescent drinking and brain morphometry: A co-twin control analysis. *Developmental Cognitive Neuroscience*, 16, 130-138. doi:10.1016/j.dcn.2015.07.005
- Windle, M. (2016). Drinking Over the Lifespan Focus on Early Adolescents and Youth. *Alcohol Research*, 38(1), 95-101.
- Winsler, A., Deutsch, A., Vorona, R., Payne, P., & Szklo-Coxe, M. (2015). Sleepless in fairfax: The difference one more hour of sleep can make for teen hopelessness, suicidal ideation, and substance use. *Journal of Youth & Adolescence*, 44(2), 362-378. https://doi.org/10.1007/s10964-014-0170-3
- Winward, J. L., Hanson, K. L., Tapert, S. F., & Brown, S. A. (2014). Heavy alcohol use, marijuana use, and concomitant use by adolescents are associated with unique and shared cognitive decrements. *Journal of the International Neuropsychological Society*, 20(8), 784-795. doi:10.1017/S1355617714000666

- Witt, E. D. (2010). Research on alcohol and adolescent brain development: Opportunities and future directions. *Alcohol*, 44(1), 119-124. doi:10.1016/j.alcohol.2009.08.011
- Wittmann, M., Dinich, J., Merrow, M., & Roenneberg, T. (2006). Social jetlag: Misalignment of biological and social time. *Chronobiology International*, 23(1-2), 497-509. doi:10.1080/07420520500545979
- Wolaver, A. M. (2002). Effects of heavy drinking in college on study effort, grade point average, and major choice. *Contemporary Economic Policy*, 20(4), 415-428. doi:10.1093/cep/20.4.415
- Wolff, P. H. (1972). Ethnic differences in alcohol sensitivity. *Science*, 175(20), 449-450. doi:10.1126/science.175.4020.449
- Wolfson, A. R., & Carskadon, M. A. (1998). Sleep schedules and daytime functioning in adolescents. *Child Development*, 69(4). doi:10.2307/1132351
- Wong, M. M. (2010). Pubertal development, sleep problems, and alcohol use: A commentary. *Alcoholism: Clinical and Experimental Research*, 34(12), 2019-2021. doi:10.1111/j.1530-0277.2010.01299.x.
- Wong, M. M., & Brower, K. J. (2012). The prospective relationship between sleep problems and suicidal behavior in the National Longitudinal Study of Adolescent Health. *Journal of Psychiatric Research*, 46(7), 953-959. doi:10.1016/j.jpsychires.2012.04.008
- Wong, M. M., Brower, K. J., Fitzgerald, H. E., & Zucker, R. A. (2004). Sleep problems in early childhood and early onset of alcohol and other drug use in adolescence. *Alcoholism: Clinical and Experimental Research*, 28(4), 578-587. doi:10.1097/01.ALC.0000121651.75952.39
- Wong, M. M., Brower, K. J., Nigg, J. T., & Zucker, R. A. (2010). Childhood sleep problems, response inhibition, and alcohol and drug outcomes in adolescence and young adulthood. *Alcoholism: Clinical and Experimental Research*, 34(6), 1033-1044. doi:10.1111/j.1530-0277.2010.01178.x

- Wong, M. M., Robertson, G. C., & Dyson, R. B. (2015). Prospective relationship between poor sleep and substance-related problems in a national sample of adolescents. *Alcoholism: Clinical and Experimental Research*, 39(2), 355-362. doi:10.1111/acer.12618
- Woodward, S. H., Murburg, M. M., & Bliwise, D. L. (2000). PTSD-related hyperarousal assessed during sleep. *Physiology and Behavior*, 70(1-2), 197-203. doi:10.1016/S0031-9384(00)00271-7
- Wu, C. H., Karageorghis, C. I., Wang, C. C., Chu, C. H., Kao, S. C., Hung, T. M., & Chang, Y. K. (2019). Effects of acute aerobic and resistance exercise on executive function: An ERP study. *Journal of Science and Medicine in Sport*, 22(12), 1367-1372. doi:10.1016/j.jsams.2019.07.009
- Wurts, S. W., & Edgar, D. M. (2000). Circadian and homeostatic control of rapid eye movement (REM) sleep: Promotion of REM tendency by the suprachiasmatic nucleus. *The Journal of Neuroscience*, 20(11), 4300-4310. doi:10.1523/JNEUROSCI.20-11-04300.2000
- Xie, L., Kang, H., Xu, Q., Chen, M. J., Liao, Y., Thiyagarajan, M., . . . Nedergaard, M. (2013). Sleep drives metabolite clearance from the adult brain. *Science*, 342(6156), 373-377. doi:10.1126/science.1241224
- Yan, Q. S. (1999). Extracellular dopamine and serotonin after ethanol monitored with 5-minute microdialysis. *Alcohol*, 19(1), 1-7. doi:10.1016/S0741-8329(99)00006-3
- Yeung, M. S., Zdunek, S., Bergmann, O., Bernard, S., Salehpour, M., Alkass, K., . . . Frisen, J. (2014). Dynamics of oligodendrocyte generation and myelination in the human brain. *Cell*, 159(4), 766-774. doi:10.1016/j.cell.2014.10.011
- York, J. L., & Chan, A. W. (1993). Age-related differences in sensitivity to alcohol in the rat. *Alcoholism: Clinical and Experimental Research*, 17(4), 864-869. doi:10.1111/j.1530-0277.1993.tb00855.x

- York, J. L., & Welte, J. W. (1994). Gender comparisons of alcohol consumption in alcoholic and nonalcoholic populations. *Journal of Studies on Alcohol*, 55(6), 743-750. doi:10.15288/jsa.1994.55.743
- Yoshimoto, K., McBride, W. J., Lumeng, L., & Li, T. K. (1992). Ethanol enhances the release of dopamine and serotonin in the nucleus accumbens of HAD and LAD lines of rats. *Alcoholism: Clinical and Experimental Research*, 16(4), 781-785. doi:10.1111/j.1530-0277.1992.tb00678.x
- Yu, Z. Y., Wang, W., Fritschy, J. M., Witte, O. W., & Redecker, C. (2006). Changes in neocortical and hippocampal GABA_A receptor subunit distribution during brain maturation and aging. *Brain Research*, 1099(1), 73-81. doi:10.1016/j.brainres.2006.04.118
- Yules, R. B., Lippman, M. E., & Freedman, D. X. (1967). Alcohol administration prior to sleep. The effect on EEG sleep stages. *Archives of General Psychiatry*, 16(1), 94-97. doi:10.1001/archpsyc.1967.01730190096012
- Yurgelun-Todd, D. (2007). Emotional and cognitive changes during adolescence. *Current Opinion in Neurobiology*, 17(2), 251-257. doi:10.1016/j.conb.2007.03.009
- Zahr, N. M., & Pfefferbaum, A. (2017). Alcohol's effects on the brain: Neuroimaging results in humans and animal models. *Alcohol Research: Current Reviews*, 38(2), 183-206.
- Zahr, N. M., Pfefferbaum, A., & Sullivan, E. V. (2017). Perspectives on fronto-fugal circuitry from human imaging of alcohol use disorders. *Neuropharmacology*, 122, 189-200. doi:10.1016/j.neuropharm.2017.01.018
- Zakhari, S. (2006). Overview: How is alcohol metabolized by the body? *Alcohol Research and Health*, 29(4), 245-254.
- Zarate, S., Stevnsner, T., & Gredilla, R. (2017). Role of estrogen and other sex hormones in brain aging. Neuroprotection and DNA repair. *Frontiers in Aging Neuroscience*, 9, 430. doi:10.3389/fnagi.2017.00430

- Zarcone, V. (1978). Alcoholism and sleep. *Advances in the Biosciences*, 21, 29-38.
- Zee, P. C., & Turek, F. W. (2006). Sleep and health: Everywhere and in both directions. *Archives of Internal Medicine*, 166(16), 1686-1688. doi:10.1001/archinte.166.16.1686
- Zeigler, D. W., Wang, C. C., Yoast, R. A., Dickinson, B. D., McCaffree, M. A., Robinowitz, C. B., & Sterling, M. L. (2005). The neurocognitive effects of alcohol on adolescents and college students. *Preventive Medicine*, 40(1), 23-32. doi:10.1016/j.ypmed.2004.04.044
- Zhabenko, O., Austic, E., Conroy, D. A., Ehrlich, P., Singh, V., Epstein-Ngo, Q., . . . Walton, M. A. (2016). Substance use as a risk factor for sleep problems among adolescents presenting to the emergency department. *Journal of Addiction Medicine*, 10(5), 331-338. doi:10.1097/ADM.0000000000000243
- Zhang, B., & Wing, Y. K. (2006). Sex differences in insomnia: A meta-analysis. *Sleep*, 29(1), 85-93. doi:10.1093/sleep/29.1.85
- Zhang, Y., & Gruber, R. (2019). Can slow-wave sleep enhancement improve memory? A review of current approaches and cognitive outcomes. *Yale Journal of Biology and Medicine*, 92(1), 63-80.
- Zhang, Z., Cheng, J., Yang, W., Zou, H., Su, C., & Miao, J. (2020). Gender differences in clinical manifestations and polysomnographic findings in Chinese patients with obstructive sleep apnea. *Sleep and Breathing: International Journal of the Science and Practice of Sleep Medicine*, 24(3), 1019. <https://doi.org/10.1007/s11325-019-01943-y>
- Zhao, Y. N., Wang, F., Fan, Y. X., Ping, G. F., Yang, J. Y., & Wu, C. F. (2013). Activated microglia are implicated in cognitive deficits, neuronal death, and successful recovery following intermittent ethanol exposure. *Behavioural Brain Research*, 236(1), 270-282. doi:10.1016/j.bbr.2012.08.052

- Zhou, Z., Yuan, Q., Mash, D. C., & Goldman, D. (2011). Substance-specific and shared transcription and epigenetic changes in the human hippocampus chronically exposed to cocaine and alcohol. *Proceedings of the National Academy of Sciences of the United States of America*, 108(16), 6626-6631. doi:10.1073/pnas.1018514108
- Zimmerman, D., & Zumbo, B. D. (1993). Significance testing of correlation using scores, ranks, and modified ranks. *Educational and Psychological Measurement*, 53, 897-904. doi:10.1177/0013164493053004003
- Zoethout, R. W., Delgado, W. L., Ippel, A. E., Dahan, A., & van Gerven, J. M. (2011). Functional biomarkers for the acute effects of alcohol on the central nervous system in healthy volunteers. *British Journal of Clinical Pharmacology*, 71(3), 331-350. doi:10.1111/j.1365-2125.2010.03846.x
- Zorlu, N., Karavul Uzman, T., Gelal, F., Colak Kalayci, C., Polat, S., Saricicek, A., . . . Gulseren, S. (2014). Abnormal white matter integrity in long-term abstinent alcohol dependent patients. *Psychiatry Research*, 224(1), 42-48. doi:10.1016/j.psychres.2014.07.006
- Zorumski, C. F., Mennerick, S., & Izumi, Y. (2014). Acute and chronic effects of ethanol on learning-related synaptic plasticity. *Alcohol*, 48(1), 1-17. doi:10.1016/j.alcohol.2013.09.045
- Zou, Y., Murray, D. E., Durazzo, T. C., Schmidt, T. P., Murray, T. A., & Meyerhoff, D. J. (2017). Effects of abstinence and chronic cigarette smoking on white matter microstructure in alcohol dependence: Diffusion tensor imaging at 4T. *Drug and Alcohol Dependence*, 175, 42-50. doi:10.1016/j.drugalcdep.2017.01.032
- Zou, Y., Murray, D. E., Durazzo, T. C., Schmidt, T. P., Murray, T. A., & Meyerhoff, D. J. (2018). White matter microstructural correlates of relapse in alcohol dependence. *Psychiatry Research Neuroimaging*, 281, 92-100. doi:10.1016/j.psychres.2018.09.004

APPENDICES

APPENDIX A
Advertisement, plain language statements, and
consent forms

**MALE AND FEMALE
PARTICIPANTS WANTED**

aged 18 to 21 years

TO PARTICIPATE IN A SCREENING INTERVIEW
FOR A SUBSEQUENT STUDY INVESTIGATING
THE EFFECTS OF ALCOHOL ON SLEEP

Requires Approximately 45 minutes to Complete

PARTICIPANTS WILL BE REIMBURSED \$10 FOR
THEIR TIME

PLEASE READ THE PLAIN LANGUAGE STATEMENT. IF YOU
ARE INTERESTED, PLEASE E- MAIL THE GENERAL HEALTH
QUESTIONNAIRE TO

gourlayc@student.unimelb.edu.au

Sleep Laboratory, Melbourne School of Psychological Sciences
The University of Melbourne

Logo

To be

added

Plain language statement

Project Title: **The Acute Effects of Alcohol Consumption on Sleep and Sleep Quality of Young Adults: Screening Interview**

Location: Sleep Laboratory, Department of Psychology, The University of Melbourne.

Investigators:	Prof. John Trinder	8433 6365
	Dr Christian Nicholas	8344 4549
	Prof. Ian Colrain	1650 839 3915
	Ms. Julia Chan	8344 4549
	Ms Caitlyn Gourlay	8344 4549

Aims

The aim of this interview is to identify suitable participants for an experiment on the effect of acute alcohol consumption on sleep. Before completing the screening interview, you will be asked to complete an initial screening questionnaire. This initial screening questionnaire should take less than 10 minutes to complete. Suitable participants will be selected to complete a screening interview in the event that information from the initial screening questionnaire does not invalidate their data. The face-to-face interview should take less than 45 minutes to complete and will take place in the Sleep Laboratory. In two subsequent experiments we are interested in changes in participants' sleep quality and brain activity during sleep after the consumption of alcohol. Suitable participants will be invited to participate in one of these two experiments on the basis of their recent history of alcohol consumption and other factors influencing the effect of alcohol on sleep.

As part of the interview you will be asked if we may contact you at a later date to ask if you would like to participate in a subsequent experiment, however not all participants who complete the interview will subsequently be contacted. If we do contact you we will provide a second plain language statement that fully describes the experiment you are invited to participate in. Reimbursement for your time commitment to complete these surveys is unrelated to whether you choose to participate in the subsequent study. These projects have been approved by the University of Melbourne Human Research Ethics Committee.

What you will be required to do

If you are asked to participate in the screening interview, you will be required to complete 3 sections. First, you will be asked a series of questions on your lifetime consumption of alcohol, your family history of alcoholism, your ethnicity, your parent's ethnicity, menstrual cycle (for women) and general demographic information. Second, you will be asked to complete one diary of any alcohol consumption over the last 30 days and one diary of any medication or drug use over the last 30 days.

Reimbursement

To offset your time commitment, you will receive \$10 reimbursement for attending the screening interview. If for any reason you choose to withdraw from the experiment before its completion, you will be paid \$10 for attending.

Benefits

There are no direct benefits to participants in completing the interview.

Confidentiality

Your anonymity and the confidentiality of your responses will be protected to the fullest possible extent, within the limits of the law. If you are not selected or do not choose to participate in a subsequent study, your survey

material will be destroyed. If you do participate in a subsequent experiment, your survey material will be retained, however, your name and contact details will be kept in a separate file from any data that you supply and only be connected through a code that will be kept by the principle investigator and that can only be accessed by researchers directly involved in the project. Generally only group data will be reported in published articles based on this research, however, in the event that participants are mentioned individually, they will be referred to by code. Data relating to drug use and your family history of alcoholism will also be kept in a separate file from your name and contact details, but will not be connected through a code. No researcher will be able to connect your name and contact details to the drug and family history of alcoholism data and this data will only ever be referred to as group data. All data will be kept securely in the Department of Psychology for five years from the date of publication, before being destroyed.

Freedom to withdraw from the project

Please note that your participation in this survey is completely voluntary. Should you wish to withdraw at any stage, or to withdraw any unprocessed data you have supplied, you are free to do so without any adverse effects on your assessments or relationship with the School of Behavioural Sciences now or in the future.

Further information

Should you be interested in any further information about sleep, sleep disorders or alcohol related health issues, we have attached some additional information below. Should you require any further information, or have any concerns, please do not hesitate to contact any of the researchers on the numbers given above. Should you have any concerns about the conduct of the project, you are welcome to contact the Executive Officer, Human Research Ethics, The University of Melbourne, on ph: 8344 2073, or fax: 9347 6739.

ADDITIONAL INFORMATION

Sleep Health

Australasian Sleep Association

<http://www.sleepaus.on.net/factsheets.html>

<http://www.sleepaus.on.net/sleepserviceslists.html>

American Academy of Sleep Medicine

<http://www.sleepeducation.com/>

Alcohol Health

Australian Drug Foundation

<http://druginfo.adf.org.au/druginfo/drugs/drugfacts/alcohol.html>

http://druginfo.adf.org.au/druginfo/fact_sheets

National Health & Medical Research Council of Australia

<http://www.nhmrc.gov.au/publications/synopses/ds9syn.htm>

Turning Point Drug & Alcohol Centre

<http://www.turningpoint.org.au/>

Support for Sleep or Alcohol Concerns

Melbourne University Psychology Clinic

<http://www.psych.unimelb.edu.au/clinic/>

Ph: 03 9326-4774

Melbourne University Counselling Service

<http://www.services.unimelb.edu.au/counsel/index.html>

Ph: 03 8344-6927 or 03 8344-6928

Lifeline – 24hrs

<http://www.lifeline.org.au/>

Ph: 13 11 14

Turning Point Drug & Alcohol Centre

http://www.turningpoint.org.au/service_information/si_need_help.html

Directline – 24hrs

Ph: 1800 888-236

Youth Health & Wellbeing

<http://www.ysas.org.au/programs-and-services/programs-and-services>

YSASline (Youth Substance Abuse Service) – 24hrs

Ph: 1800 014-446

Letter Head

To be Added

Plain language statement

Project Title: The Acute Effects of Alcohol Consumption on Sleep and Sleep Quality of Young Adults: Sleep Study

Location: Sleep Laboratory, Department of Psychology,
The University of Melbourne.

Investigators:	Prof. John Trinder	8433 6365
	Dr Christian Nicholas	8344 4549
	Prof. Ian Colrain+	1650 839 3915
	Ms. Julia Chan	8344 4549
	Ms Caitlyn Gourlay	8344 4549

Aims

Sleep disruption can be caused by many different substances, this disruption can cause surges in heart rate and blood pressure and affect daytime functioning. Alcohol consumption at high levels is known to increase risk for developing cardiovascular disease later in life and it also has disruptive effects on sleep.

During sleep, the brain exhibits a characteristic pattern of activity which can be measured via electrodes placed on the surface of the skin. Alterations in this pattern of activity can indicate sleep disruption or alterations in neuronal activity. Adolescence and young adulthood is an important period of maturation of the brain and sleep is naturally altered during this time. Recent evidence also suggests that it is an important time for cardiovascular health with some individuals starting to show signs of early risk factors for the development of future cardiovascular disease. Understanding how alcohol might affect the cardiovascular system and the brain during adolescence and young adulthood is important given the unique academic demands on people of this age.

In this study we are interested in the effects of acute alcohol consumption on sleep and cardiovascular activity in young adults. We will first compare cardiovascular activity (heart rate, blood pressure and the ability of your blood vessels to dilate) before and after consumption of an alcoholic drink and before bed and then again the following morning after a night's sleep. During the night we will compare heart rate and blood pressure, sleep quality and patterns of brain activity during normal sleep with activity during sleep after consumption of alcohol. It should be noted however that only the group differences in these sleep patterns cardiovascular measures are meaningful. Individual values may be influenced by a number of factors, many of which cannot be measured. Thus the measures we will collect are not diagnostic tools and changes in cardiovascular activity or brain activity and sleep quality do not necessarily mean your daytime functioning will be altered.

This project has been approved by the University of Melbourne Human Ethics Committee. The study is being conducted as PhD project by Ms. Caitlyn Gourlay.

Procedures

If you agree to participate in this research you will be studied at the Sleep Laboratory in the Melbourne School of Psychological Sciences at the University of Melbourne on three night time experimental sessions within a two week period. Prior to coming into the laboratory and for the duration of the experimental sessions you will be required to maintain your normal sleep wake schedule and keep a "Sleep Diary" for each day / night over this period. The diary will record information about your sleep patterns and sleep quality for the two weeks prior to the three in laboratory night time studies. The first night will be an adaptation night, in which your natural sleep will be monitored so that you can get used to sleeping in the laboratory. The second and third nights will be experimental nights. On one of these experimental nights, you will receive a dose of alcohol sufficient for you to reach a blood alcohol level of .1% mixed in orange juice. The amount of alcohol that you receive will depend on your body size and gender. You will be asked to drink the mixture over half an hour beginning one hour before bedtime. This means that you will stop drinking the mixture half an hour before bedtime. On the other experimental night, this procedure will be repeated, however you will receive the equivalent volume of orange juice without the dose of alcohol. You should be aware that you will not be informed on which night you will receive the dose of alcohol and which night you will receive orange juice without alcohol. On all three nights,

there will be a maximum of two other participants and four researchers in the laboratory. Additionally, there will always be a female researcher present. If you feel at all uncomfortable with the number of people present, you should feel free to speak to one of the researchers and they will change scheduling to assure your concerns are addressed. Remaining procedures for all three nights at the laboratory are outlined below.

You will be asked to come to the laboratory approximately 5 hours before your normal bedtime so that a meal can be provided and monitoring equipment can be attached before we begin the experiment. You will be provided with a paid taxi to the Sleep Laboratory. You will be asked not to consume alcohol or drugs for 2 days before or caffeine or food after lunchtime on the days of the testing.

When you arrive at the laboratory and have completed the preliminary procedures, including a breathalyzer test, equipment necessary to record the physiological variables relevant to the study will be attached to you.

In order to tell when you are asleep and when you are awake, surface electrodes will be attached to your scalp, temple at the corner of each eye and chin so that we can measure your brain waves, eye movements and chin muscle contractions, respectively.

Your brain activity will be recorded using an electroencephalogram (EEG) from 11 locations on the scalp. The sensors (electrodes) will be attached to the scalp using a small piece of gauze and a glue that is specially designed for this purpose (Collodion). Each location will be prepared by rubbing the skin with an exfoliant, to remove oil, dirt and dead skin. The sensors will be removed in the morning by an experimenter using an appropriate glue remover (Collodion remover). This process is painless and involves only minimal discomfort.

The EEG sensors also need two extra sensors on your earlobes to work properly. The earlobes will also be prepared by gently rubbing the skin with an exfoliant followed by an alcohol swab. Again this process involves only minimal discomfort.

All sensors will be filled with conductive gel will be held in place with surgical tape.

Eye movements will be measured using two sensors, one on each of your temples beside each eye. To further assist in monitoring muscle activity and movement, and whether you are awake or asleep, two sensors will be placed over the submental muscles underneath your chin. Additionally, in order to monitor leg movements, two sensors will be attached about two centimetres apart over the anterior tibialis (on the shin) of each leg. Preparation and attachment of these electrodes will be the same as that of the ear electrodes.

All sensors (electrodes) will be gold, and connected to an 'electrode box' at the head of the bed and from there a cable takes the signals to the recording equipment. The electrode box also contains circuitry that isolates you from mains power.

In order to monitor heart rate, two sensors will be attached, with one placed over the right clavicle (high on the right breast area) and the second over the lower left ribcage. These will be attached in the same fashion as the eye movement and muscle activity sensors.

In order to monitor your breathing, a nasal cannula will be worn on the nasal opening and secured with surgical tape. In order to monitor breathing or respiratory movements, two elastic bands will be placed, one around your chest and one around your abdomen. A body position sensor will be attached to the elastic band around your chest in order to monitor body position. Additionally, a finger pulse oximeter (a small finger cuff) will be worn on an index finger to measure the amount of oxygen in your blood. A vibration sensor will also be attached to your neck in order to detect the presence and duration of snoring.

After attachment of all equipment we will do two short recordings (equipment attached to you will be plugged in and data will be recorded for approximately 30 minutes each) whilst you are awake, one before the drink is consumed and one after the drink is consumed. We will also measure how well the blood vessels in your fingers react to changes in blood flow. This involves measuring blood supply to the fingers in response to the release of an arm cuff. In other words, a clinical blood pressure cuff is inflated (for 5 minutes) and then released, a standard seated clinical blood pressure measurement will also be taken. After the second wake recording you will be allowed to prepare for bed and you will be put to bed at your normal bedtime. You will then be asked to go to sleep and the lights will be turned off and the bedroom door shut. You will be allowed to sleep until the following morning. Upon awakening, a third wake recording will be performed in the morning before being

given breakfast and breathalysed. You will be required to have two consecutive readings of .00% before you will be driven home in a paid taxi (payment of the taxi is in addition to other reimbursement).

As requirement of the experiment you are requested that you DO NOT drive to or from the laboratory on the second and third nights, taxi or other transport to and from the laboratory will be provided if required.

Reimbursement

To offset your time commitment, you will receive \$75 reimbursement for every night that you attend the Sleep Laboratory. If for any reason you choose to withdraw from the session before its completion, you will still be paid \$75 for the session.

Risks, Discomforts and Procedures to Minimize These.

While the risks involved with participation in this study are very low, you may encounter minor discomforts as outlined below.

1. Given that you will be consuming the alcohol beverage over a short period of time (30 minutes) there is a chance that you may experience a feeling of nausea and in rare cases physically ill. If you start to feel nauseous at any time at the start or throughout the night please let the experimenter know and we can discuss further options regarding continuing or stopping the study.
2. Although there should be no alcohol in your blood after you leave the sleep laboratory, alcohol can have hangover effects and your sleep may be disturbed. Therefore, you may feel dehydrated, dizzy and be more tired the following day. While there are no known adverse effects of such minor sleep disruption, precautions should be taken to keep hydrated and if any significant discomfort persists, medical advice should be sought. Additionally, you should be aware that sleep loss or dizziness can pose dangers when operating machinery or driving. Therefore adequate precautions should be taken or such activities avoided until you have had enough “catch up” sleep and you no longer feel these effects (this usually takes only one night).
3. If at any point you wish to discuss any issues or problems with a member of the senior research staff (Dr. Nicholas or Prof. Trinder) you can contact them on the numbers above during business hours, if this is after hours during one of the experimental sessions while you are in the laboratory please ask the experimenter present to contact them for you.
4. The equipment used for recording your brain waves, respiration, eye and body movements may be mildly uncomfortable, but no important risk is anticipated from use of these.
5. Removal of glued scalp electrodes requires a specialist remover to be used. Although no adverse consequences are anticipated this can cause irritation, and if you suspect any allergies or skin reaction, we will refrain from using Collodian glue on your skin.
6. You may experience some minor discomfort when the blood pressure finger or arm cuffs inflate, should this occur please speak to the experimenter and they will adjust the cuffs to make them more comfortable. Please do not try to adjust the cuffs yourself as they are delicate and may be damaged.

Benefits

Although there are no direct benefits to participants in these studies it is hoped that the results will lead to a greater understanding of the consequences of alcohol consumption in young individuals.

Confidentiality

Your anonymity and the confidentiality of your responses will be protected to the fullest possible extent, within the limits of the law. Your name and contact details will be kept in a separate file from any data that you supply. Generally only group data will be reported in published articles based on this research, however, in the event that participants are mentioned individually, they will be referred to by code. All data will be kept securely in

the Melbourne School of Psychological Sciences for five years from the date of publication, before being destroyed.

Feedback

The results of the experiment will be presented at academic conferences and published as abstracts and journal articles. These publications will be made available on the laboratories web page.

Freedom to withdraw from the project

Please note that your participation in this survey is completely voluntary. Should you wish to withdraw at any stage, or to withdraw any unprocessed data you have supplied, you are free to do so without any adverse effects on your assessments or relationship with the Melbourne School of Psychological Sciences now or in the future.

Further information

Should you be interested in any further information about sleep, sleep disorders or alcohol related health issues, we have attached some additional information below. Should you require any further information, or have any concerns, please do not hesitate to contact any of the researchers on the numbers given above. Should you have any concerns about the conduct of the project, you are welcome to contact the Executive Officer, Human Research Ethics, The University of Melbourne, on ph: 8344 2073, or fax: 9347 6739.

ADDITIONAL INFORMATION

Sleep Health

Australasian Sleep Association

<http://www.sleepaus.on.net/factsheets.html>

<http://www.sleepaus.on.net/sleepserviceslists.html>

American Academy of Sleep Medicine

<http://www.sleepeducation.com/>

Alcohol Health

Australian Drug Foundation

<http://druginfo.adf.org.au/druginfo/drugs/drugfacts/alcohol.html>

http://druginfo.adf.org.au/druginfo/fact_sheets

National Health & Medical Research Council of Australia

<http://www.nhmrc.gov.au/publications/synopses/ds9syn.htm>

Turning Point Drug & Alcohol Centre

<http://www.turningpoint.org.au/>

Support for Sleep or Alcohol Concerns

Melbourne University Psychology Clinic

<http://www.psych.unimelb.edu.au/clinic/>

Ph: 03 9326-4774

Melbourne University Counselling Service

<http://www.services.unimelb.edu.au/counsel/index.html>

Ph: 03 8344-6927 or 03 8344-6928

Lifeline – 24hrs

<http://www.lifeline.org.au/>

Ph: 13 11 14

Turning Point Drug & Alcohol Centre

http://www.turningpoint.org.au/service_information/si_need_help.html

Directline – 24hrs

Ph: 1800 888-236

Youth Health & Wellbeing

<http://www.ysas.org.au/programs-and-services/programs-and-services>

YSASline (Youth Substance Abuse Service) – 24hrs

Ph: 1800 014-446

Letter Head

To be Added

THE UNIVERSITY OF MELBOURNE

PSYCHOLOGICAL SCIENCES

Consent form for persons participating in research projects

PROJECT TITLE: The Acute Effects of Alcohol Consumption on Sleep and Sleep Quality of Young Adults – Screening Interview

Name of participant:

Name of investigator(s): Prof. John Trinder, Dr Christian Nicholas, Prof. Ian Colrain, Ms. Julia Chan, Ms Caitlyn Gourlay

-
1. I consent to participate in the project named above, the particulars of which - including details of tests or procedures - have been explained to me. A written copy of the information has been given to me to keep.
 2. I authorize the researcher or his or her assistant to administer to me the tests or procedures referred to under (1) above.
 3. I acknowledge that:
 - (a) the possible effects of the tests or procedures have been explained to me to my satisfaction;
 - (b) I have been informed that involvement in this project is voluntary and I am free to withdraw from the project at any time without explanation or prejudice and to withdraw any unprocessed data previously supplied;
 - (c) The project is for the purpose of research and not for treatment;
 - (d) I have been informed that the confidentiality of the information I provide will be safeguarded subject to any legal requirements.

Signature

Date

(Participant)

Letter Head
To be Added

THE UNIVERSITY OF MELBOURNE

PSYCHOLOGICAL SCIENCES

Consent form for persons participating in research projects

**PROJECT TITLE: The Acute Effects of Alcohol Consumption on Sleep and Sleep Quality of
Young Adults – Sleep Study**

Name of participant:

Name of investigator(s): Prof. John Trinder, Dr Christian Nicholas, Prof. Ian Colrain, Ms. Julia Chan , Ms Caitlyn Gourlay

-
1. I consent to participate in the project named above, the particulars of which - including details of tests or procedures - have been explained to me. A written copy of the information has been given to me to keep.
 2. I authorize the researcher or his or her assistant to administer to me the tests or procedures referred to under (1) above.
 3. I acknowledge that:
 - (a) the possible effects of the tests or procedures have been explained to me to my satisfaction;
 - (b) I have been informed that involvement in this project is voluntary and I am free to withdraw from the project at any time without explanation or prejudice and to withdraw any unprocessed data previously supplied;
 - (c) The project is for the purpose of research and not for treatment;
 - (d) I have been informed that the confidentiality of the information I provide will be safeguarded subject to any legal requirements.

Signature

Date

(Participant)

APPENDIX B

Participant screening tools

General Health Questionnaire

Please answer the following questions:

GENERAL

How old are you? years

What is your date of birth?

What is your gender? M/F

What is your ethnic background?

What is your body weight and height kg
.....meters

Please list the average amount of caffeine you consume per day.
(For example, how many cups of tea/coffee, cans of caffeinated
soft drink and chocolate bars).

SMOKING

Do you smoke? Y/N

If so, how much?

GENERAL HEALTH

When was the last time you had a medical check-up?.....

Have you had any serious accidents, head injuries or concussion? Y/N

Have you ever lost consciousness? Y/N

If Yes, for how long?

Are you currently on any medication, or taking any prescribed drug? Y/N
(e.g. pain killers, contraceptive pill)

Do you currently have any physical illness? Y/N

If so, what illness(es)?.....

Do you have hypertension, or other cardiovascular disorders?
(e.g. high blood pressure, chest pains, heart attacks or strokes) Y/N

If so, what disorders?.....

What exercise do you do weekly?

On average, in the last month, how much alcohol have you consumed
each week?

.....beer/cider etc.

.....spirits

In the last month have you consumed more than four standard drinks
on any one occasion? Y/N

If yes, on how many occasions?

SLEEP

What time do you normally wake up?

What time do you normally go to sleep?

Do you normally nap during the day?
(Please do not nap on the day of the study) Y/N

How well do you usually sleep?

very poorly 1 2 3 4 5 very well

Are you, or have you ever been involved in shift work? Y/N

If so, how long ago?

Do you have problems sleeping or have you ever been diagnosed
with a sleep disorder? Y/N

STRESS

Are you currently experiencing a greater than normal amount of stress?
(e.g. exams, relationship break-up) Y/N

Screening Interview General Information

This interview contains six items:

- 1. A general screening questionnaire**
 - 2. A lifetime consumption of alcohol questionnaire**
 - 3. A family history of alcohol use disorders questionnaire**
 - 4. A socio-economic status (SES) questionnaire**
 - 5. An alcohol consumption diary**
 - 6. A medication and drug consumption diary**
- It should take no more than 45 minutes to complete.**

The purpose of the interview is to provide information on which to select participants for a subsequent sleep experiment.

The aim of the subsequent experiments is to assess any changes in cardiovascular or brain activity during sleep and your quality of sleep after alcohol consumption. It will require you to sleep three nights in the Melbourne School of Psychological Science's Sleep Laboratory. We will contact you to inform you if you are eligible for the subsequent sleep study and give you further details of the experiment.

If you do not participate in subsequent sleep study, any identifying information (name, contact details etc.) collected about you will be removed from this information and will be destroyed.

Name:

Telephone:

Address:

E-mail:

Subject Interview:

GENERAL

Are you a vegetarian/vegan? Y veg vegan/ N

Do you have any food allergies?

Do you have sensitive skin?

What is the ethnic background of your parents? Mother:

Father:

After one or two standard alcoholic drinks, do you experience:

a) reddening of skin?	Y/N
b) feeling hot?	Y/N
c) feeling nauseous?	Y/N
d) headaches?	Y/N
e) increased heart rate?	Y/N

If you answered yes to any of these how often does it occur?

Very Rarely ----- All The Time
(Mark on Line)

On what date did you last finish menstruating? (*Girls only*)

Lifetime History of Alcohol Consumption

Introduction to Alcohol History

Now I'm going to ask you some questions about your drinking experiences over your entire lifetime. I want you to think back to when you first started drinking at least once a month, and think about how your drinking habits may have changed at different stages of your life since then.

People's drinking habits often change at different points in their lives, as they go through different life transitions.

For example, a person's habits might change as he or she grows up, goes through high school or college, starts a job, or loses a job. Other life transitions might include quitting a job, dropping out of high school or college, etc.

At different transition points in your life you may have increased the amount you were drinking, decreased it, or stopped altogether. Each time you had a change in amount you were drinking, we think about it as a distinct separate period of your life.

For each of these separate periods of your drinking life I'm going to ask about how many drinks you had a day and how many days in a typical month you would drink that amount. I will also ask you to tell me if there were days when you drank much more than your regular amount. You don't have to remember exact amounts, but try and give me your best estimate.

For each separate period, I'm also going to ask you about whether you ever missed meals while you were drinking. Remember, we will go through the same set of questions for each separate stage of your drinking life. Are you ready to start? Great.

LIFETIME ALCOHOL HISTORY

Date of last drink: _____

Subject _____ Group _____

Date of this history _____ DOB _____

Experimenter _____

Phase 1:

(1) How old are you now? _____

(2) What is your current weight? _____

(3) When was the last day you drank? _____

(4) How old were you when you first started drinking at least once a month? _____

(If subject claims never to have drunk once a month, (age)
(date:m/yr)
then ask, "When was your first drink?")

(Assume on b-day if not specified)

(5) About how much would you drink, on average, each day you drank (include type)? _____

(6) How many days a month would you drink this amount? * _____

(7) During this phase did you have many more drinks per day on certain days?
(e.g. weekends, parties, holidays)

Yes No

What is the most or maximum number of drinks you would have on these occasions? (Include type) _____

How many times a month (or year) would you?
drink this maximum? _____

(8) How long did you drink like this? _____

(9) During this phase, were there any periods when you were not drinking any alcohol
at all for more than 2 weeks?

Yes No

If yes, how many periods did you have when you were not drinking
and
how long was each period? (> 2 weeks) _____

(10) How much did you weigh then? _____

(11) During the phase of your life, was there ever a time during which you went without any food for ≥ 24 hours while drinking?

(a) *If yes:* How many consecutive days would you go without a proper meal while drinking? 1 ☐ 2 ☐ 3 ☐ DK ☐

(b) During this phase of your life, how many times per month did you have periods when you went ≥ 24 hours without eating any food because you were drinking? _____ x per month

(12) Have there been changes in your drinking since then?

Yes No

(13) What was the reason for the change in your alcohol consumption? ____

Phase 2 and on:

Can you tell me how old you were when your drinking pattern changed? _____

Age m/yr

(2) About how much would you drink, on average, each day you drank (include type)? _____

(3) How many days a month would you drink this amount? * _____

(4) During this phase did you have many more drinks per day on certain days?
(e.g. weekends, parties, holidays)

Yes No

What is the most or maximum number of drinks you would have on these occasions? (*Include type*) _____

How many times a month (or year) would you?
drink this maximum? _____

(5) How long did you drink like this? _____

(6) During this phase, were there any periods when you were not drinking any alcohol at all for more than 2 weeks? **Yes No**

If yes, how many periods did you have when you were not drinking and

(7) How much did you weigh then? _____

(8) During the phase of your life, was there ever a time during which you went without any food for ≥ 24 hours while drinking?

(a) *If yes:* How many consecutive days would you go without a proper meal while drinking? 1 ☐ 2 ☐ 3 ☐ DK ☐

(b) During this phase of your life, how many times per month did you have periods when you went ≥ 24 hours without eating any food because you were drinking? _____ x per month

(9) Have there been changes in your drinking since then?

Yes No

(10) What was the reason for the change in your alcohol consumption? ____

Family History of Alcohol Use Disorders

Study: _____

Group _____

Date: _____

Are you adopted? YES / NO

Have you ever had a head injury? YES / NO (Describe): _____

KEY QUESTIONS:

For each of your relatives please indicate the following:

Alcohol use: Has the relative had a problem with drinking? D = Don't Know; A = Abstinent; S = Social Drinker; P = Problem Drinker

Criteria (*for problem drinkers only*): If YES, tick box ; If NO, leave blank; If Unknown, Write "U"

Did your relative ever:

Have alcohol related arrests, or lose a drivers licence?

Have marital problems because of drinking habits?

Lose a job or have to give up some kind of work?

Experience social disapproval of drinking by friends or family?

Experience frequent blackouts?

Have alcohol withdrawal symptoms? (seizures, hallucinations, and/or delirium tremors)

Have cirrhosis of the liver?

Attend Alcoholics Anonymous meetings?

Enrol in a formal inpatient or outpatient treatment program for alcohol abuse?

Tx. (Seeking Treatment): Has the relative ever needed to see a Psychiatrist or be on a psychiatric ward?

Diagnosis: Has the relative ever been diagnosed with schizophrenia, manic (bipolar) depression, or dementia?

Age: What is the relative's current age or age at death?

Cause of Death: If deceased, what was the cause of the relative's death?

NOTE: Please DO NOT identify your relative by name.

Family History of Alcohol Use Disorders

[illegible]

Family History of Alcohol Use Disorders

[illegible]

Socio-Economic Status Questionnaire

Subject's Education

What is the highest level of education or professional training you have achieved in your lifetime?

_____ Ed.
score x 4 = ____

Subject's Occupation

What is the highest level occupation you have had in your life to date?

Describe responsibilities: _____

Occ. Score x 7 = ____
H. Score = ____

Primary Caretaker's* relation _____

Primary Caretaker's Education

What is the highest level of education or professional training that your primary caretaker received in their lifetime?

_____ Ed.
Score x4 = ____

Primary Caretaker's Occupation

What is the highest level occupation your primary caretaker had in their lifetime?

Describe responsibilities: _____

Occ. Score x 7 = ____
H. Score = ____

Secondary Caretaker's* relation _____

Secondary Caretaker's Education

What is the highest level of education or professional training that your secondary caretaker received in their lifetime?

_____ Ed.
score x 4 = ____

Secondary Caretaker's Occupation

What is the highest level occupation your secondary caretaker had in their lifetime?

Describe responsibilities: _____

Occ. Score x 7 = ____
H. Score = ____

Group Id:**Last 30 days Drinking Questionnaire**

Please think back over the past 30 days. For each day write down how many alcoholic drinks you had (One drink being: 350ml full strength beer, 150ml wine, 40ml spirits), and what sort. If you were taking medications list the type and daily dose.			
	Date	# Drinks & Type	Daily Dose
SAT			
SUN			
MON			
TUE			
WED			
THUR			
FRI			
SAT			
SUN			
MON			
TUE			
WED			
THUR			
FRI			
SAT			
SUN			
MON			
TUE			
WED			
THUR			
FRI			
SAT			
SUN			
MON			
TUE			
WED			
THUR			
FRI			
SAT			
SUN			
MON			
TUE			
WED			
THUR			
FRI			

Group Id:**Last 30 days Medication and Drugs Questionnaire**

Please think back over the past 30 days. For each day write down any medications or other drugs you were taking and how much.			
	Date	# Medications & Drugs and Type	Daily Dose
SAT			
SUN			
MON			
TUE			
WED			
THUR			
FRI			
SAT			
SUN			
MON			
TUE			
WED			
THUR			
FRI			
SAT			
SUN			
MON			
TUE			
WED			
THUR			
FRI			
SAT			
SUN			
MON			
TUE			
WED			
THUR			
FRI			
SAT			
SUN			
MON			
TUE			
WED			
THUR			
FRI			

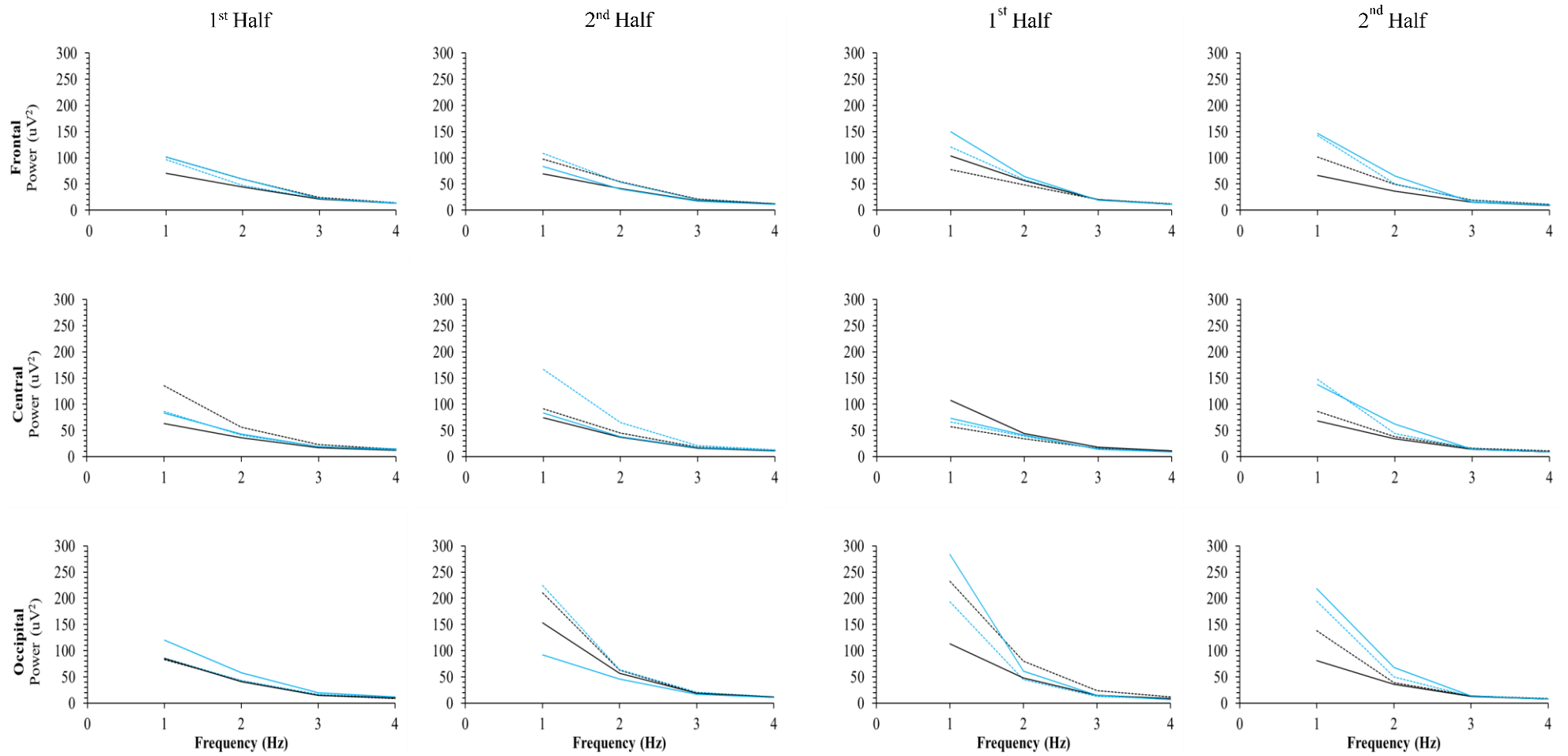
APPENDIX C

Power spectral plots

Figures C.1 to C.8 contain power spectral plots for 1 to 30 hertz (Hz) frequency EEG activity in heavy- and light-drinking females and males in the first and second halves of the sleep period, following alcohol and placebo consumption, at frontal, central and occipital EEG electrode sites for each sleep stage, stage N1 sleep, stage N2 sleep, stage N3/SWS, REM sleep. Frequency (Hz) is presented on the x-axis and power (microvolts squared; μV^2) on the y-axis. Power spectral plots were further separated into 1 to 4 Hz and 5 to 30 Hz frequency activity to allow for appropriate scaling and easier interpretation.

Figure C.1. Power (microvolts squared; μV^2) for 1 to 4 Hz frequency activity during stage N1 sleep following alcohol (dashed lines) and placebo (solid lines) at frontal (top panes), central (middle panes) and occipital (bottom panes) electrode sites in the first (1st and 3rd panes) and second (2nd and 4th panes) halves of the sleep period in heavy- (black lines) and light- (blue lines) drinking females (two left panes) and males (two right panes).

N1



Female

Male

----- Heavy Drinker - Placebo

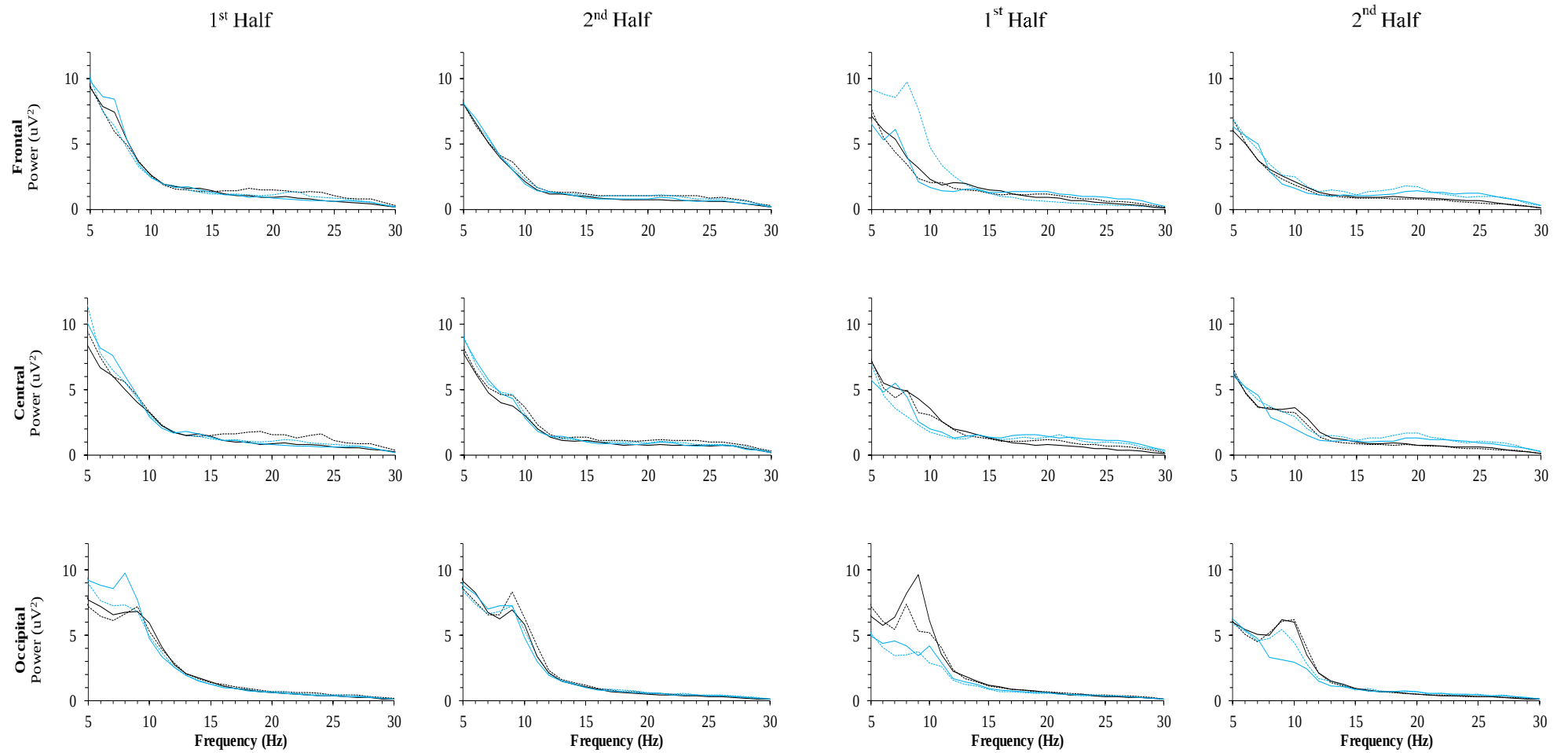
----- Light Drinker - Placebo

----- Heavy Drinker - Alcohol

----- Light Drinker - Alcohol

Figure C.2. Power (microvolts squared; μV^2) for 5 to 30 Hz frequency activity during stage N1 sleep following alcohol (dashed lines) and placebo (solid lines) at frontal (top panes), central (middle panes) and occipital (bottom panes) electrode sites in the first (1st and 3rd panes) and second (2nd and 4th panes) halves of the sleep period in heavy- (black lines) and light- (blue lines) drinking females (two left panes) and males (two right panes).

N1



Female

Male

----- Heavy Drinker - Placebo

----- Light Drinker - Placebo

— Heavy Drinker - Alcohol

— Light Drinker - Alcohol

Figure C.3. Power (microvolts squared; μV^2) for 1 to 4 Hz frequency activity during stage N2 sleep following alcohol (dashed lines) and placebo (solid lines) at frontal (top panes), central (middle panes) and occipital (bottom panes) electrode sites in the first (1st and 3rd panes) and second (2nd and 4th panes) halves of the sleep period in heavy- (black lines) and light- (blue lines) drinking females (two left panes) and males (two right panes).

N2

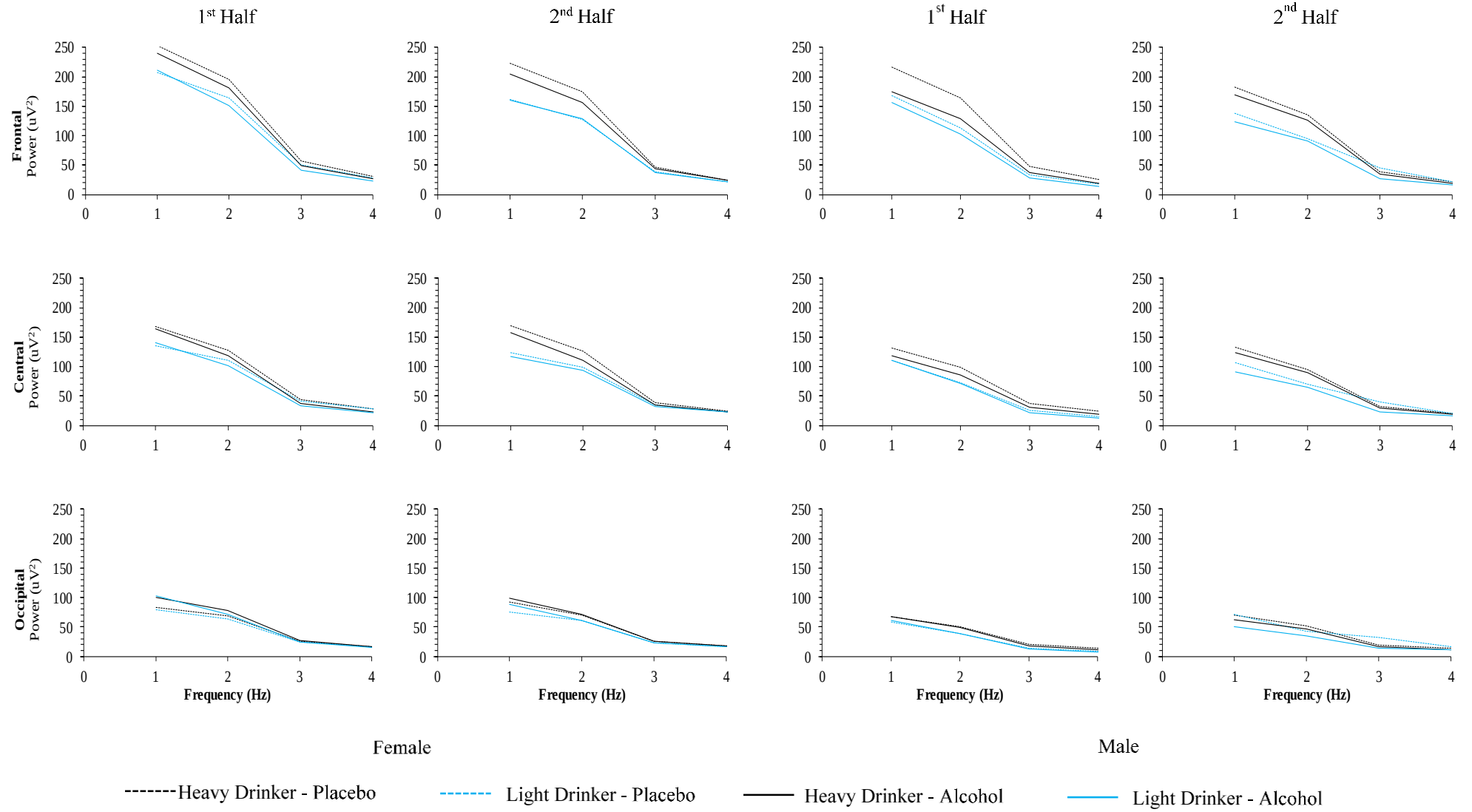


Figure C.4. Power (microvolts squared; μV^2) for 5 to 30 Hz frequency activity during stage N2 sleep following alcohol (dashed lines) and placebo (solid lines) at frontal (top panes), central (middle panes) and occipital (bottom panes) electrode sites in the first (1st and 3rd panes) and second (2nd and 4th panes) halves of the sleep period in heavy- (black lines) and light- (blue lines) drinking females (two left panes) and males (two right panes).

N2

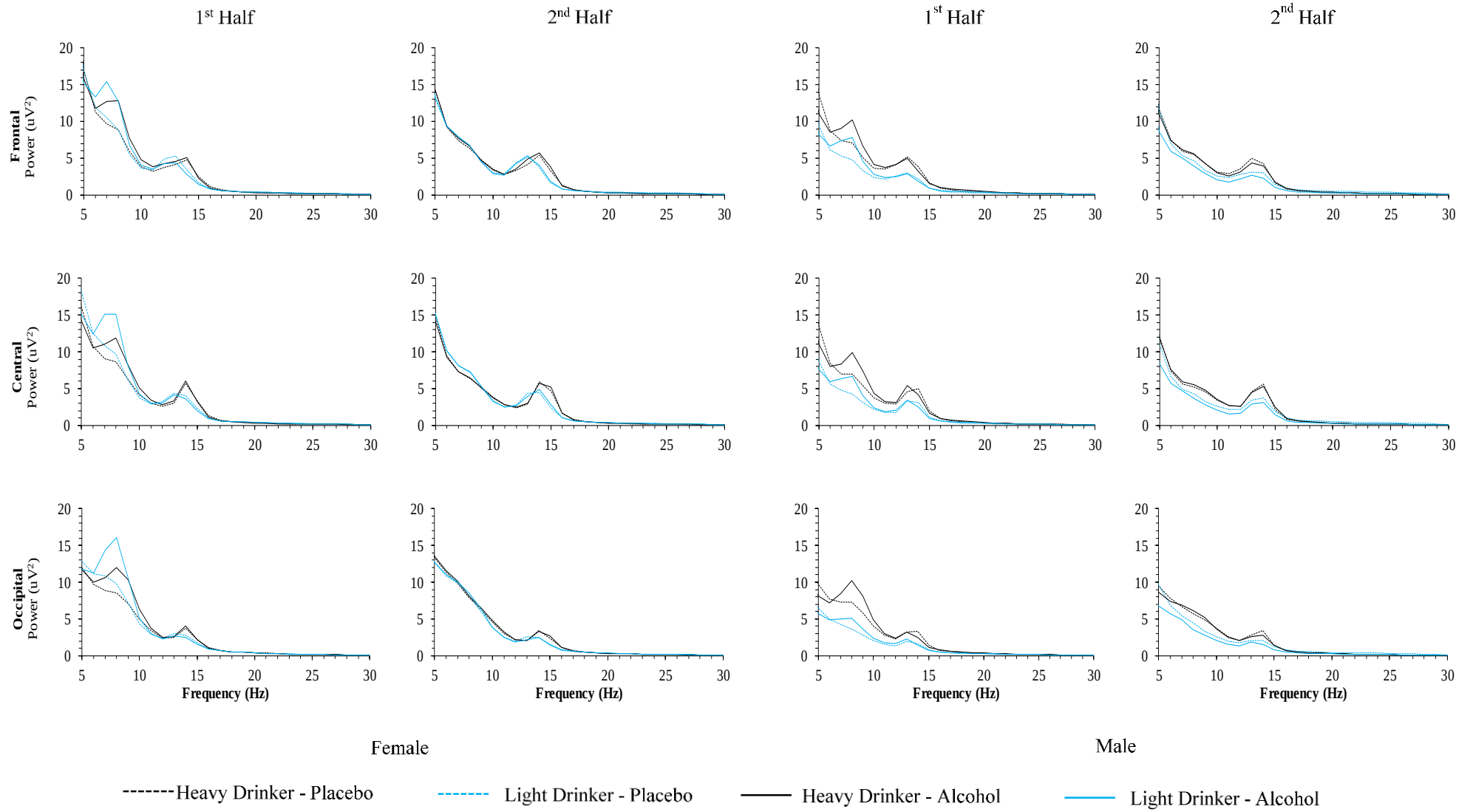
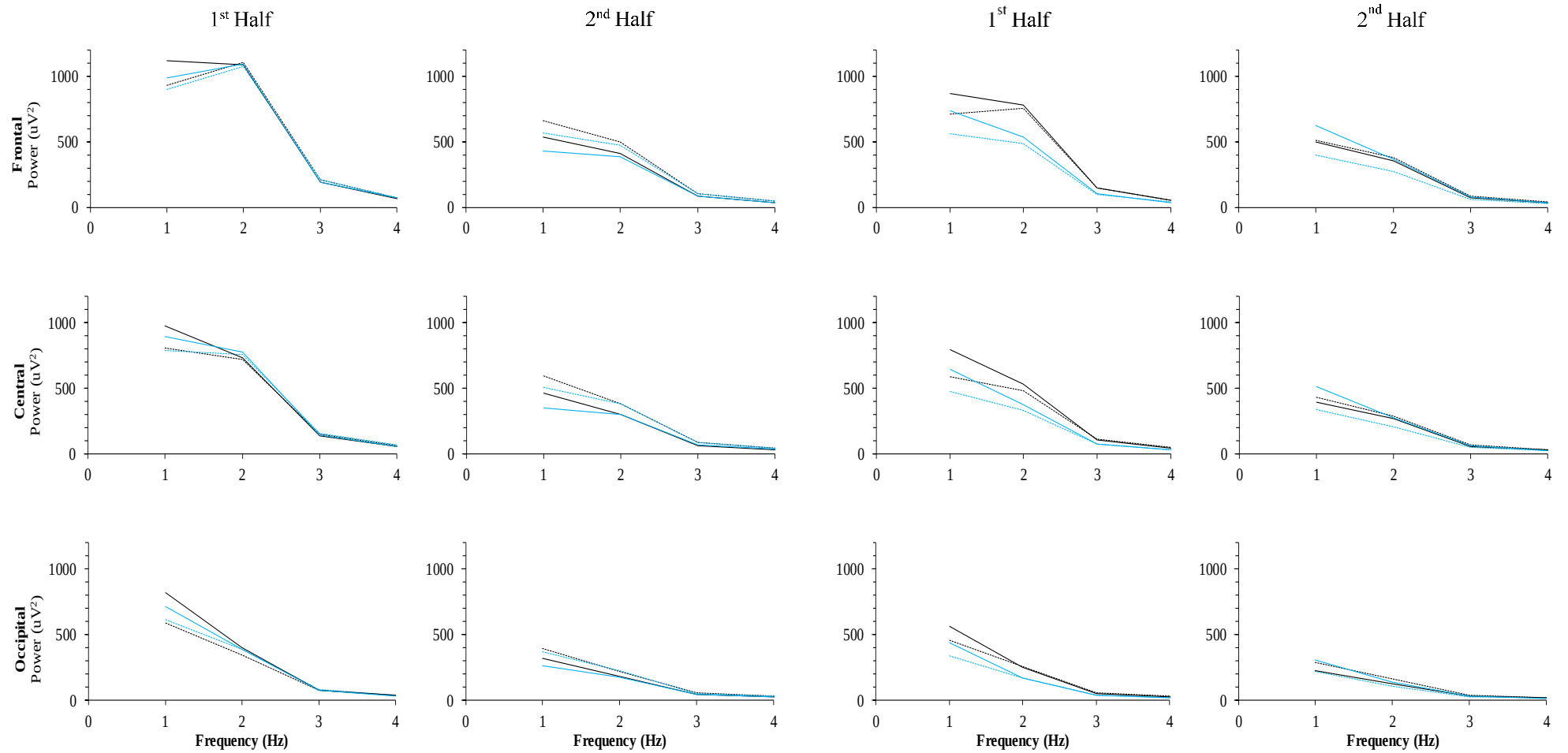


Figure C.5. Power (microvolts squared; μV^2) for 1 to 4 Hz frequency activity during slow wave sleep (SWS; N3) following alcohol (dashed lines) and placebo (solid lines) at frontal (top panes), central (middle panes) and occipital (bottom panes) electrode sites in the first (1st and 3rd panes) and second (2nd and 4th panes) halves of the sleep period in heavy- (black lines) and light- (blue lines) drinking females (two left panes) and males (two right panes).

SWS



----- Heavy Drinker - Placebo - - - - - Light Drinker - Placebo ——— Heavy Drinker - Alcohol ——— Light Drinker - Alcohol

Figure C.6. Power (microvolts squared; μV^2) for 5 to 30 Hz frequency activity during slow wave sleep (SWS; N3) following alcohol (dashed lines) and placebo (solid lines) at frontal (top panes), central (middle panes) and occipital (bottom panes) electrode sites in the first (1st and 3rd panes) and second (2nd and 4th panes) halves of the sleep period in heavy- (black lines) and light- (blue lines) drinking females (two left panes) and males (two right panes).

SWS

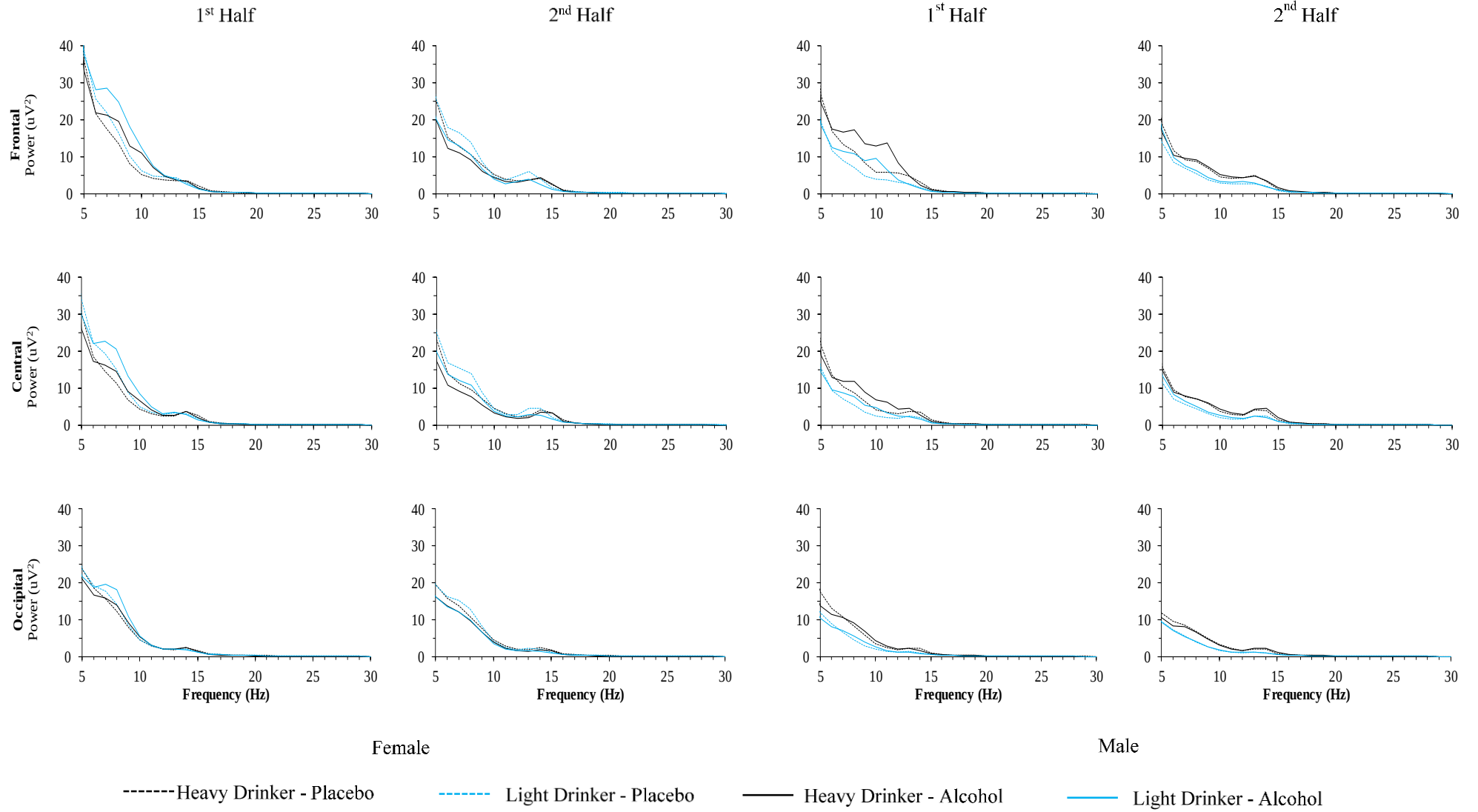


Figure C.7. Power (microvolts squared; μV^2) for 1 to 4 Hz frequency activity during rapid eye movement (REM) sleep following alcohol (dashed lines) and placebo (solid lines) at frontal (top panes), central (middle panes) and occipital (bottom panes) electrode sites in the first (1st and 3rd panes) and second (2nd and 4th panes) halves of the sleep period in heavy- (black lines) and light- (blue lines) drinking females (two left panes) and males (two right panes).

REM

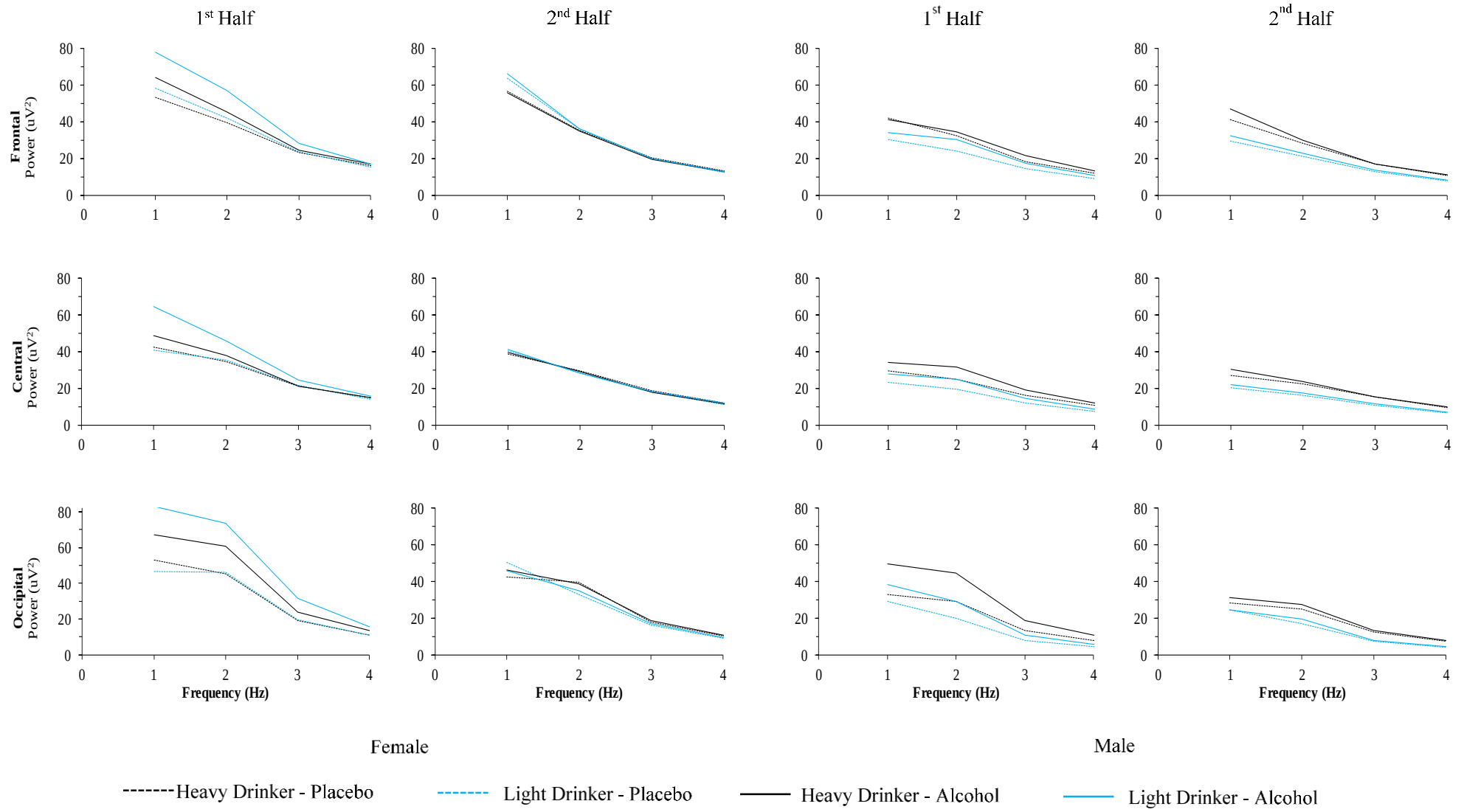
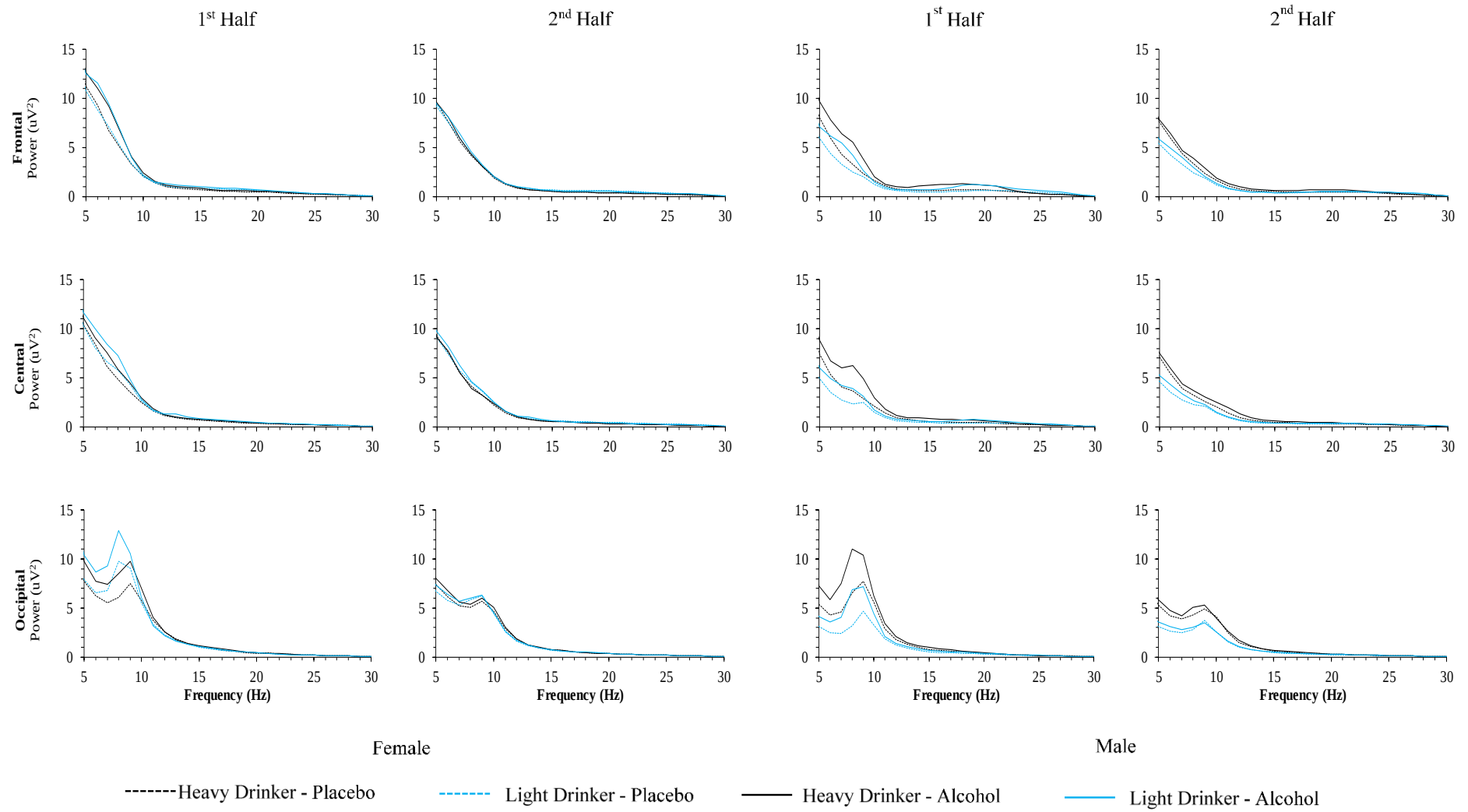


Figure C.8. Power (microvolts squared; μV^2) for 5 to 30 Hz frequency activity during rapid eye movement (REM) sleep following alcohol (dashed lines) and placebo (solid lines) at frontal (top panes), central (middle panes) and occipital (bottom panes) electrode sites in the first (1st and 3rd panes) and second (2nd and 4th panes) halves of the sleep period in heavy- (black lines) and light- (blue lines) drinking females (two left panes) and males (two right panes).

REM



APPENDIX D

Complete spectral analysis: Sleep stage

Spectral analysis for each spectral power (beta, alpha, sigma, theta and delta) and electrode site (frontal, central, occipital) by sleep stage (stage N2 sleep, stage N2 sleep, SWS, REM sleep) in both the alcohol and placebo condition separately.

Table D.1

Spectral power: *F* statistics, effect size (η^2), power, and significance levels (*p*) for each acute condition (alcohol and placebo) and electrode site; frontal, central, and occipital electrode sites across all sleep stages; stage N1, stage N2, slow wave sleep (N3), and rapid eye movement (REM) sleep, and the first and second half of the sleep period. **p* < .05 ***p* < .001

	Condition	Spectral power	Electrode site	F	df	<i>p</i>	η^2	Power
Main effect of sleep stage	Placebo	Beta	Frontal	85.92	1, 42	< .001**	.67	> .99
			Central	68.24	1, 42	< .001**	.62	> .99
			Occipital	73.88	1, 42	< .001**	.64	> .99
		Alpha	Frontal	81.56	1, 42	< .001**	.66	> .99
			Central	38.25	1, 42	< .001**	.48	> .99
			Occipital	6.59	1, 42	.001*	.14	.96
		Sigma	Frontal	79.80	1, 42	< .001**	.66	> .99
			Central	103.17	1, 42	< .001**	.71	> .99
			Occipital	45.82	1, 42	< .001**	.52	> .99
		Theta	Frontal	154.93	1, 42	< .001**	.79	> .99
			Central	114.51	1, 42	< .001**	.73	> .99
			Occipital	84.28	1, 42	< .001**	.67	> .99
		Delta	Frontal	214.84	1, 42	< .001**	.84	> .99
			Central	215.35	1, 42	< .001**	.84	> .99
			Occipital	98.52	1, 42	< .001**	.70	> .99
	Alcohol	Beta	Frontal	65.37	1, 42	< .001**	.61	> .99
			Central	56.47	1, 42	< .001**	.57	> .99
			Occipital	66.43	1, 42	< .001**	.61	> .99
		Alpha	Frontal	44.04	1, 42	< .001**	.51	> .99
			Central	28.68	1, 42	< .001**	.41	> .99
			Occipital	3.69	1, 42	.029*	.08	.66
		Sigma	Frontal	55.97	1, 42	< .001**	.57	> .99
			Central	85.99	1, 42	< .001**	.67	> .99
			Occipital	60.74	1, 42	< .001**	.59	> .99
		Theta	Frontal	54.90	1, 42	< .001**	.57	> .99
			Central	48.34	1, 42	< .001**	.54	> .99
			Occipital	36.20	1, 42	< .001**	.46	> .99
		Delta	Frontal	141.52	1, 42	< .001**	.77	> .99
			Central	166.18	1, 42	< .001**	.80	> .99
			Occipital	95.87	1, 42	< .001**	.70	> .99

APPENDIX E

Complete spectral analysis: Acute effects

Complete spectral analysis for the acute effects of alcohol on spectral power (beta, alpha, sigma, theta and delta); for each individual sleep stage (stage N2 sleep, stage N2 sleep, stage N3 sleep/SWS, REM sleep) for acute condition (alcohol vs. placebo), half (first vs. second half of the sleep period), electrode site (frontal, central and occipital), and their interactions.

Table E.1

*Spectral power: F statistics, effect size (η^2), power, and significance levels (p) across frontal, central, and occipital electrode sites for the first and second half of the sleep period in stage N1 sleep. * $p < .05$ ** $p < .001$*

Spectral power		F	df	p	η^2	Power
Beta	Condition	4.71	1, 42	.036*	.10	.56
	Half	2.97	1, 42	.092	.07	.39
	Site	42.31	1, 42	< .001**	.50	> .99
	Condition×half	0.72	1, 42	.402	.02	.13
	Condition×site	40.85	1, 42	.073	.07	.48
	Half×site	1.15	1, 42	.310	.03	.22
	Condition×half×site	0.69	1, 42	.455	.02	.14
Alpha	Condition	0.26	1, 42	.612	.01	.08
	Half	0.54	1, 42	.464	.01	.11
	Site	47.20	1, 42	< .001**	.53	> .99
	Condition×half	7.77	1, 42	.008*	.16	.77
	Condition×site	0.02	1, 42	.929	< .001	.05
	Half×site	1.54	1, 42	.224	.04	.25
	Condition×half×site	5.68	1, 42	.017*	.12	.69
Sigma	Condition	0.01	1, 42	.929	< .001	.05
	Half	16.47	1, 42	< .001**	.28	.98
	Site	0.05	1, 42	.901	.001	.06
	Condition×half	2.53	1, 42	.120	.06	.34
	Condition×site	0.20	1, 42	.816	.01	.08
	Half×site	4.80	1, 42	.013*	.10	.75
	Condition×half×site	1.87	1, 42	.172	.04	.32
Theta	Condition	0.72	1, 42	.402	.02	.13
	Half	3.07	1, 42	.087	.07	.40
	Site	1.87	1, 42	.174	.04	.31
	Condition×half	2.83	1, 42	.100	.06	.38
	Condition×site	2.55	1, 42	.089	.06	.48
	Half×site	6.97	1, 42	.006*	.14	.82
	Condition×half×site	1.41	1, 42	.250	.03	.25
Delta	Condition	0.49	1, 42	.489	.01	.12
	Half	0.21	1, 42	.652	.01	.07
	Site	8.20	1, 42	.002*	.16	.89
	Condition×half	1.09	1, 42	.302	.03	.16
	Condition×site	0.29	1, 42	.697	.01	.09
	Half×site	0.44	1, 42	.574	.01	.12
	Condition×half×site	0.10	1, 42	.844	.002	.06

Table E.2

*Spectral power: F statistics, effect size (η^2), power, and significance levels (p) across frontal, central, and occipital electrode sites for the first and second half of the sleep period in stage N2 sleep. * $p < .05$ ** $p < .001$*

Spectral power		F	df	p	η^2	Power
Beta	Condition	0.75	1, 42	.392	.02	.14
	Half	0.12	1, 42	.744	.003	.06
	Site	2.26	1, 42	.125	.05	.39
	Condition×half	1.84	1, 42	.182	.04	.26
	Condition×site	0.08	1, 42	.837	.002	.06
	Half×site	0.69	1, 42	.469	.02	.15
	Condition×half×site	3.52	1, 42	.053	.08	.53
Alpha	Condition	4.20	1, 42	.047*	.09	.52
	Half	25.30	1, 42	< .001**	.38	> .99
	Site	0.55	1, 42	.510	.01	.12
	Condition×half	16.49	1, 42	< .001**	.28	.98
	Condition×site	1.67	1, 42	.203	.04	.29
	Half×site	1.59	1, 42	.215	.04	.27
	Condition×half×site	1.39	1, 42	.253	.03	.24
Sigma	Condition	3.05	1, 42	.088	.07	.40
	Half	9.40	1, 42	.004*	.18	.85
	Site	26.53	1, 42	< .001**	.07	.39
	Condition×half	0.07	1, 42	.794	.002	.86
	Condition×site	0.02	1, 42	.975	.001	.05
	Half×site	45.89	1, 42	< .001**	.52	> .99
	Condition×half×site	2.28	1, 42	.123	.05	.39
Theta	Condition	0.99	1, 42	.326	.02	.16
	Half	11.63	1, 42	.001*	.22	.92
	Site	0.86	1, 42	.394	.02	.17
	Condition×half	7.50	1, 42	.009*	.15	.76
	Condition×site	0.39	1, 42	.639	.01	.12
	Half×site	30.54	1, 42	< .001**	.42	> .99
	Condition×half×site	2.05	1, 42	.144	.05	.37
Delta	Condition	4.84	1, 42	.033*	.10	.58
	Half	7.46	1, 42	.009*	.15	.76
	Site	118.53	1, 42	< .001**	.74	> .99
	Condition×half	0.08	1, 42	.778	.002	.06
	Condition×site	6.26	1, 42	.004*	.13	.86
	Half×site	50.97	1, 42	< .001**	.55	> .99
	Condition×half×site	6.93	1, 42	.006*	.14	.81

Table E.3

*Spectral power: F statistics, effect size (η^2), power, and significance levels (p) across frontal, central, and occipital electrode sites for the first and second half of the sleep period in stage slow wave sleep. * $p < .05$ ** $p < .001$*

Spectral power		F	df	p	η^2	Power
Beta	Condition	1.68	1, 42	.202	.04	.25
	Half	0.07	1, 42	.794	.002	.06
	Site	0.04	1, 42	.907	.001	.06
	Condition×half	0.34	1, 42	.563	.01	.09
	Condition×site	0.11	1, 42	.793	.003	.06
	Half×site	2.76	1, 42	.095	.06	.41
	Condition×half×site	0.96	1, 42	.343	.02	.17
Alpha	Condition	11.35	1, 42	.002*	.21	.91
	Half	43.44	1, 42	< .001**	.51	> .99
	Site	30.88	1, 42	< .001**	.42	> .99
	Condition×half	29.50	1, 42	< .001**	.41	> .99
	Condition×site	21.06	1, 42	< .001**	.33	.99
	Half×site	36.43	1, 42	< .001**	.46	> .99
	Condition×half×site	33.64	1, 42	< .001**	.46	> .99
Sigma	Condition	3.41	1, 42	.072	.08	.44
	Half	6.78	1, 42	.013*	.14	.72
	Site	31.09	1, 42	< .001**	.43	> .99
	Condition×half	0.02	1, 42	.882	.001	.05
	Condition×site	0.40	1, 42	.635	.01	.12
	Half×site	30.85	1, 42	< .001**	.42	> .99
	Condition×half×site	0.19	1, 42	.741	.01	.08
Theta	Condition	0.20	1, 42	.657	.01	.07
	Half	76.99	1, 42	< .001**	.65	> .99
	Site	16.21	1, 42	< .001**	.28	.99
	Condition×half	8.48	1, 42	.006*	.17	.81
	Condition×site	3.87	1, 42	.025*	.08	.67
	Half×site	35.32	1, 42	< .001**	.46	> .99
	Condition×half×site	15.20	1, 42	< .001**	.27	.99
Delta	Condition	1.01	1, 42	.321	.02	.17
	Half	136.20	1, 42	< .001**	.76	> .99
	Site	79.74	1, 42	< .001**	.66	> .99
	Condition×half	7.79	1, 42	.008*	.16	.78
	Condition×site	0.09	1, 42	.917	.002	.06
	Half×site	38.80	1, 42	< .001**	.48	> .99
	Condition×half×site	0.70	1, 42	.477	.02	.16

Table E.4

*Spectral power: F statistics, effect size (η^2), power, and significance levels (p) across frontal, central, and occipital electrode sites for the first and second half of the sleep period in stage REM sleep. * $p < .05$ ** $p < .001$*

Spectral power		F	df	p	η^2	Power
Beta	Condition	9.60	1, 42	.003*	.19	.86
	Half	37.29	1, 42	< .001**	.47	> .99
	Site	19.75	1, 42	< .001**	.32	> .99
	Condition×half	20.20	1, 42	< .001**	.33	.99
	Condition×site	6.31	1, 42	.010*	.13	.77
	Half×site	9.97	1, 42	.002*	.19	.91
	Condition×half×site	20.49	1, 42	< .001**	.33	> .99
Alpha	Condition	10.28	1, 42	.003*	.20	.88
	Half	43.51	1, 42	< .001**	.51	> .99
	Site	46.35	1, 42	< .001**	.53	> .99
	Condition×half	8.96	1, 42	.005*	.18	.83
	Condition×site	1.21	1, 42	.286	.03	.20
	Half×site	32.95	1, 42	< .001**	.44	> .99
	Condition×half×site	2.40	1, 42	.126	.05	.34
Sigma	Condition	9.140	1, 42	.004*	.18	.84
	Half	89.25	1, 42	< .001**	.68	> .99
	Site	20.75	1, 42	< .001**	.33	> .99
	Condition×half	23.40	1, 42	< .001**	.36	> .99
	Condition×site	1.10	1, 42	.315	.03	.20
	Half×site	8.20	1, 42	.003*	.16	.87
	Condition×half×site	10.67	1, 42	< .001**	.20	.97
Theta	Condition	19.92	1, 42	< .001**	.32	.99
	Half	44.24	1, 42	< .001**	.51	> .99
	Site	2.19	1, 42	.137	.05	.36
	Condition×half	34.26	1, 42	< .001**	.45	> .99
	Condition×site	1.91	1, 42	.167	.04	.33
	Half×site	3.89	1, 42	.043*	.09	.56
	Condition×half×site	5.61	1, 42	.009*	.12	.79
Delta	Condition	10.59	1, 42	.002*	.20	.89
	Half	21.14	1, 42	< .001**	.34	.99
	Site	5.83	1, 42	.012*	.12	.74
	Condition×half	7.36	1, 42	.010*	.15	.76
	Condition×site	4.03	1, 42	.042*	.09	.55
	Half×site	4.02	1, 42	.043*	.09	.55
	Condition×half×site	3.19	1, 42	.074	.07	.45

APPENDIX F

Complete spectral analysis: Habitual effects

Complete spectral analysis for the habitual effects of alcohol use on spectral power (beta, alpha, sigma, theta and delta) for each individual sleep stage (stage N1 sleep, stage N2 sleep, stage N3 sleep/SWS, REM sleep), for habitual alcohol use (habitual; heavy vs. light drinker), acute condition (alcohol vs. placebo), half (first vs. second half of the sleep period), electrode site (frontal, central and occipital), and their interactions.

Table F.1

Spectral power: F statistics, effect size (η^2), power, and significance levels (p) across frontal, central, and occipital electrode sites for the first and second half of the sleep period in stage N1 sleep.

Spectral power		F	df	p	η^2	Power
Beta	Habitual	1.65	1, 42	.205	.04	.24
	Habitual×condition	2.22	1, 42	.143	.05	.31
	Habitual×half	1.37	1, 42	.248	.03	.21
	Habitual×site	1.34	1, 42	.267	.03	.28
	Habitual×condition×half	0.42	1, 42	.523	.01	.10
	Habitual×condition×site	1.91	1, 42	.166	.04	.33
	Habitual×half×site	0.27	1, 42	.702	.01	.09
	Habitual ×condition×half×site	0.92	1, 42	.374	.02	.18
Alpha	Habitual	2.04	1, 42	.160	.05	.29
	Habitual×condition	0.89	1, 42	.352	.02	.15
	Habitual×half	0.61	1, 42	.440	.01	.12
	Habitual×site	1.41	1, 42	.247	.03	.23
	Habitual×condition×half	0.11	1, 42	.739	.003	.06
	Habitual×condition×site	0.05	1, 42	.866	.001	.06
	Habitual×half×site	0.25	1, 42	.662	.01	.08
	Habitual ×condition×half×site	0.38	1, 42	.573	.01	.10
Sigma	Habitual	0.06	1, 42	.809	.001	.06
	Habitual×condition	0.09	1, 42	.770	.002	.06
	Habitual×half	0.99	1, 42	.325	.02	.16
	Habitual×site	1.18	1, 42	.302	.03	.22
	Habitual×condition×half	0.20	1, 42	.656	.01	.07
	Habitual×condition×site	0.29	1, 42	.671	.01	.09
	Habitual×half×site	0.72	1, 42	.475	.02	.16
	Habitual ×condition×half×site	0.52	1, 42	.540	.01	.12
Theta	Habitual	0.05	1, 42	.823	.001	.06
	Habitual×condition	0.29	1, 42	.594	.01	.08
	Habitual×half	0.24	1, 42	.625	.01	.08
	Habitual×site	0.31	1, 42	.644	.01	.09
	Habitual×condition×half	0.71	1, 42	.403	.02	.13
	Habitual×condition×site	0.07	1, 42	.922	.002	.06
	Habitual×half×site	0.01	1, 42	.963	< .001	.05
	Habitual ×condition×half×site	0.36	1, 42	.623	.01	.10
Delta	Habitual	1.51	1, 42	.227	.04	.22
	Habitual×condition	0.90	1, 42	.349	.02	.15
	Habitual×half	0.55	1, 42	.462	.01	.11
	Habitual×site	0.19	1, 42	.754	.004	.07
	Habitual×condition×half	0.65	1, 42	.424	.02	.12
	Habitual×condition×site	0.97	1, 42	.364	.02	.19
	Habitual×half×site	1.06	1, 42	.333	.02	.20
	Habitual ×condition×half×site	0.65	1, 42	.478	.02	.14

Table F.2

Spectral power: F statistics, effect size (η^2), power, and significance levels (p) across frontal, central, and occipital electrode sites for the first and second half of the sleep period in stage N2 sleep.

Spectral power		F	df	p	η^2	Power
Beta	Habitual	0.14	1, 42	.713	.003	.07
	Habitual×condition	1.20	1, 42	.279	.03	.19
	Habitual×half	2.31	1, 42	.136	.05	.32
	Habitual×site	0.18	1, 42	.775	.004	.07
	Habitual×condition×half	2.64	1, 42	.112	.06	.36
	Habitual×condition×site	0.19	1, 42	.729	.01	.07
	Habitual×half×site	0.95	1, 42	.371	.02	.19
	Habitual ×condition×half×site	2.84	1, 42	.085	.06	.44
Alpha	Habitual	2.53	1, 42	.119	.06	.34
	Habitual×condition	1.44	1, 42	.237	.03	.22
	Habitual×half	2.06	1, 42	.158	.05	.29
	Habitual×site	0.43	1, 42	.572	.01	.11
	Habitual×condition×half	0.01	1, 42	.926	< .001	.05
	Habitual×condition×site	1.67	1, 42	.203	.04	.29
	Habitual×half×site	0.17	1, 42	.760	.004	.07
	Habitual ×condition×half×site	0.16	1, 42	.761	.004	.07
Sigma	Habitual	5.78	1, 42	.021*	.12	.65
	Habitual×condition	2.29	1, 42	.137	.05	.32
	Habitual×half	0.07	1, 42	.789	.002	.06
	Habitual×site	0.58	1, 42	.512	.01	.13
	Habitual×condition×half	0.13	1, 42	.724	.003	.06
	Habitual×condition×site	0.56	1, 42	.565	.01	.14
	Habitual×half×site	0.68	1, 42	.473	.02	.15
	Habitual ×condition×half×site	0.02	1, 42	.949	.001	.05
Theta	Habitual	0.24	1, 42	.630	.01	.08
	Habitual×condition	0.01	1, 42	.933	< .001	.05
	Habitual×half	0.01	1, 42	.910	< .001	.05
	Habitual×site	0.14	1, 42	.794	.003	.07
	Habitual×condition×half	1.42	1, 42	.241	.03	.21
	Habitual×condition×site	0.08	1, 42	.894	.002	.06
	Habitual×half×site	0.27	1, 42	.649	.01	.08
	Habitual ×condition×half×site	0.14	1, 42	.837	.003	.07
Delta	Habitual	3.09	1, 42	.086	.07	.40
	Habitual×condition	0.11	1, 42	.745	.003	.06
	Habitual×half	0.17	1, 42	.681	.004	.07
	Habitual×site	3.11	1, 42	.071	.07	.48
	Habitual×condition×half	0.73	1, 42	.398	.02	.13
	Habitual×condition×site	0.95	1, 42	.383	.02	.20
	Habitual×half×site	0.81	1, 42	.404	.02	.16
	Habitual ×condition×half×site	0.06	1, 42	.874	.001	.06

Table F.3

Spectral power: F statistics, effect size (η^2), power, and significance levels (p) across frontal, central, and occipital electrode sites for the first and second half of the sleep period in slow wave sleep.

Spectral power		F	df	p	η^2	Power
Beta	Habitual	0.22	1, 42	.640	.01	.08
	Habitual×condition	0.02	1, 42	.900	< .001	.05
	Habitual×half	0.08	1, 42	.783	.002	.06
	Habitual×site	0.05	1, 42	.891	< .001	.06
	Habitual×condition×half	0.002	1, 42	.963	< .001	.05
	Habitual×condition×site	0.76	1, 42	.414	.02	.15
	Habitual×half×site	0.32	1, 42	.619	.01	.09
	Habitual ×condition×half×site	0.19	1, 42	.697	.004	.07
Alpha	Habitual	0.99	1, 42	.326	.02	.16
	Habitual×condition	0.04	1, 42	.848	.001	.05
	Habitual×half	0.001	1, 42	.976	< .001	.05
	Habitual×site	0.47	1, 42	.556	.01	.11
	Habitual×condition×half	0.11	1, 42	.739	.003	.06
	Habitual×condition×site	0.64	1, 42	.475	.02	.14
	Habitual×half×site	0.17	1, 42	.721	.004	.07
	Habitual ×condition×half×site	0.65	1, 42	.424	.02	.12
Sigma	Habitual	5.08	1, 42	.029*	.11	.60
	Habitual×condition	1.18	1, 42	.283	.03	.19
	Habitual×half	0.12	1, 42	.731	.003	.06
	Habitual×site	0.61	1, 42	.494	.01	.13
	Habitual×condition×half	1.31	1, 42	.259	.03	.20
	Habitual×condition×site	1.81	1, 42	.177	.04	.34
	Habitual×half×site	0.08	1, 42	.878	.002	.06
	Habitual ×condition×half×site	2.16	1, 42	.139	.05	.34
Theta	Habitual	0.03	1, 42	.873	.001	.05
	Habitual×condition	0.19	1, 42	.666	.004	.07
	Habitual×half	0.02	1, 42	.878	.001	.05
	Habitual×site	0.40	1, 42	.599	.01	.10
	Habitual×condition×half	0.19	1, 42	.668	.004	.07
	Habitual×condition×site	0.03	1, 42	.976	.001	.05
	Habitual×half×site	0.001	1, 42	.984	< .001	.05
	Habitual ×condition×half×site	0.43	1, 42	.589	.01	.11
Delta	Habitual	1.15	1, 42	.289	.03	.18
	Habitual×condition	0.17	1, 42	.685	.004	.07
	Habitual×half	1.37	1, 42	.249	.03	.21
	Habitual×site	0.57	1, 42	.502	.01	.12
	Habitual×condition×half	2.56	1, 42	.117	.06	.35
	Habitual×condition×site	0.88	1, 42	.417	.02	.20
	Habitual×half×site	0.40	1, 42	.586	.01	.10
	Habitual ×condition×half×site	0.10	1, 42	.877	.002	.06

Table F.4

Spectral power: F statistics, effect size (η^2), power, and significance levels (p) across frontal, central, and occipital electrode sites for the first and second half of the sleep period in REM sleep.

Spectral power		F	df	p	η^2	Power
Beta	Habitual	0.60	1, 42	.444	.01	.12
	Habitual×condition	0.01	1, 42	.940	< .001	.05
	Habitual×half	0.08	1, 42	.773	.002	.06
	Habitual×site	1.41	1, 42	.247	.03	.24
	Habitual×condition×half	3.05	1, 42	.088	.07	.40
	Habitual×condition×site	0.13	1, 42	.776	.003	.07
	Habitual×half×site	0.81	1, 42	.391	.02	.15
	Habitual ×condition×half×site	3.14	1, 42	.070	.07	.48
Alpha	Habitual	1.19	1, 42	.282	.03	.19
	Habitual×condition	0.88	1, 42	.353	.02	.15
	Habitual×half	0.30	1, 42	.588	.01	.08
	Habitual×site	0.60	1, 42	.463	.01	.12
	Habitual×condition×half	0.12	1, 42	.728	.003	.06
	Habitual×condition×site	0.12	1, 42	.772	.003	.06
	Habitual×half×site	0.26	1, 42	.634	.01	.08
	Habitual ×condition×half×site	0.04	1, 42	.858	.001	.06
Sigma	Habitual	0.99	1, 42	.325	.02	.16
	Habitual×condition	0.41	1, 42	.524	.01	.10
	Habitual×half	0.20	1, 42	.655	.01	.07
	Habitual×site	0.98	1, 42	.350	.02	.18
	Habitual×condition×half	0.001	1, 42	.978	< .001	.05
	Habitual×condition×site	0.48	1, 42	.539	.01	.11
	Habitual×half×site	0.29	1, 42	.656	.01	.09
	Habitual ×condition×half×site	0.19	1, 42	.782	.004	.08
Theta	Habitual	0.55	1, 42	.463	.01	.11
	Habitual×condition	0.04	1, 42	.844	.001	.05
	Habitual×half	0.05	1, 42	.822	.001	.06
	Habitual×site	0.02	1, 42	.934	.001	.05
	Habitual×condition×half	0.05	1, 42	.820	.001	.06
	Habitual×condition×site	0.32	1, 42	.659	.01	.09
	Habitual×half×site	0.57	1, 42	.497	.01	.12
	Habitual ×condition×half×site	0.09	1, 42	.875	.002	.06
Delta	Habitual	0.26	1, 42	.615	.01	.08
	Habitual×condition	0.46	1, 42	.502	.01	.10
	Habitual×half	0.44	1, 42	.509	.01	.10
	Habitual×site	0.06	1, 42	.872	.001	.06
	Habitual×condition×half	0.62	1, 42	.434	.02	.12
	Habitual×condition×site	0.09	1, 42	.812	.002	.06
	Habitual×half×site	0.01	1, 42	.964	< .001	.05
	Habitual ×condition×half×site	0.01	1, 42	.942	< .001	.05

APPENDIX G

Complete spectral analysis: Sex × acute effects

Complete spectral analysis for the acute effects of alcohol and sex on spectral power (beta, alpha, sigma, theta and delta) for each individual sleep stage (stage N2 sleep, stage N2 sleep, stage N3 sleep/SWS, REM sleep) for sex (male vs. female), acute condition (alcohol vs. placebo), half (first vs. second half of the sleep period), electrode site (frontal, central and occipital), and the interaction between them.

Table G.1

Spectral power: F statistics, effect size (η^2), power, and significance levels (p) across frontal, central, and occipital electrode sites for the first and second half of the sleep period in stage N1 sleep.

Spectral power		F	df	p	η^2	Power
Beta	Sex	0.02	1, 42	.901	< .001	.05
	Sex×condition	5.14	1, 42	.029*	.11	.60
	Sex×half	0.09	1, 42	.767	.002	.06
	Sex×site	0.28	1, 42	.749	.01	.09
	Sex×condition×half	0.004	1, 42	.947	< .001	.05
	Sex×condition×site	2.70	1, 42	.089	.06	.45
	Sex×half×site	1.34	1, 42	.265	.03	.24
	Sex×condition×half×site	0.49	1, 42	.547	.01	.12
Alpha	Sex	1.90	1, 42	.175	.04	.27
	Sex×condition	0.77	1, 42	.384	.02	.14
	Sex×half	0.29	1, 42	.594	.01	.08
	Sex×site	0.46	1, 42	.539	.01	.11
	Sex×condition×half	0.84	1, 42	.365	.02	.15
	Sex×condition×site	0.05	1, 42	.865	.001	.06
	Sex×half×site	0.64	1, 42	.455	.02	.13
	Sex×condition×half×site	1.85	1, 42	.179	.04	.28
Sigma	Sex	0.41	1, 42	.526	.01	.10
	Sex×condition	0.72	1, 42	.402	.02	.13
	Sex×half	0.08	1, 42	.786	.002	.06
	Sex×site	2.57	1, 42	.101	.06	.42
	Sex×condition×half	0.04	1, 42	.843	.001	.05
	Sex×condition×site	0.09	1, 42	.915	.002	.06
	Sex×half×site	4.78	1, 42	.014*	.10	.75
	Sex×condition×half×site	0.19	1, 42	.755	.01	.08
Theta	Sex	5.23	1, 42	.027*	.11	.61
	Sex×condition	0.02	1, 42	.898	< .001	.05
	Sex×half	0.59	1, 42	.446	.01	.12
	Sex×site	0.35	1, 42	.616	.01	.10
	Sex×condition×half	0.13	1, 42	.721	.003	.06
	Sex×condition×site	2.30	1, 42	.112	.05	.43
	Sex×half×site	3.33	1, 42	.060	.07	.51
	Sex×condition×half×site	0.84	1, 42	.400	.02	.16
Delta	Sex	0.47	1, 42	.496	.01	.10
	Sex×condition	1.12	1, 42	.295	.03	.18
	Sex×half	0.48	1, 42	.490	.01	.10
	Sex×site	1.63	1, 42	.208	.04	.28
	Sex×condition×half	0.18	1, 42	.671	.004	.07
	Sex×condition×site	0.20	1, 42	.763	.01	.08
	Sex×half×site	5.42	1, 42	.014	.11	.73
	Sex×condition×half×site	1.69	1, 42	.199	.04	.29

Table G.2

Spectral power: F statistics, effect size (η^2), power, and significance levels (p) across frontal, central, and occipital electrode sites for the first and second half of the sleep period in stage N2 sleep.

Spectral power		F	df	p	η^2	Power
Beta	Sex	0.20	1, 42	.658	.01	.07
	Sex×condition	0.31	1, 42	.579	.01	.09
	Sex×half	0.86	1, 42	.359	.02	.15
	Sex×site	1.07	1, 42	.334	.03	.21
	Sex×condition×half	3.07	1, 42	.087	.07	.40
	Sex×condition×site	0.40	1, 42	.587	.01	.10
	Sex×half×site	2.02	1, 42	.151	.05	.35
	Sex×condition×half×site	0.49	1, 42	.543	.01	.12
Alpha	Sex	4.41	1, 42	.042*	.10	.54
	Sex×condition	1.09	1, 42	.303	.03	.18
	Sex×half	2.75	1, 42	.105	.06	.37
	Sex×site	1.44	1, 42	.242	.03	.25
	Sex×condition×half	0.02	1, 42	.878	.001	.05
	Sex×condition×site	0.56	1, 42	.521	.01	.13
	Sex×half×site	1.39	1, 42	.253	.03	.24
	Sex×condition×half×site	0.99	1, 42	.349	.02	.18
Sigma	Sex	3.95	1, 42	.053	.09	.49
	Sex×condition	3.00	1, 42	.091	.07	.39
	Sex×half	1.16	1, 42	.688	.004	.07
	Sex×site	0.69	1, 42	.463	.02	.15
	Sex×condition×half	2.86	1, 42	.098	.06	.38
	Sex×condition×site	0.20	1, 42	.810	.01	.08
	Sex×half×site	14.33	1, 42	< .001**	.25	.99
	Sex×condition×half×site	4.15	1, 42	.030*	.09	.63
Theta	Sex	10.28	1, 42	.003*	.20	.88
	Sex×condition	1.27	1, 42	.267	.03	.20
	Sex×half	3.82	1, 42	.057	.08	.48
	Sex×site	0.51	1, 42	.540	.01	.12
	Sex×condition×half	0.01	1, 42	.928	< .001	.05
	Sex×condition×site	0.59	1, 42	.527	.01	.14
	Sex×half×site	4.32	1, 42	.036*	.09	.58
	Sex×condition×half×site	0.31	1, 42	.697	.01	.09
Delta	Sex	6.35	1, 42	.016*	.13	.69
	Sex×condition	1.58	1, 42	.216	.04	.23
	Sex×half	1.79	1, 42	.188	.04	.26
	Sex×site	0.84	1, 42	.396	.02	.16
	Sex×condition×half	0.01	1, 42	.932	< .001	.05
	Sex×condition×site	1.08	1, 42	.341	.03	.22
	Sex×half×site	1.24	1, 42	.284	.03	.22
	Sex×condition×half×site	0.93	1, 42	.365	.02	.17

Table G.3

Spectral power: F statistics, effect size (η^2), power, and significance levels (p) across frontal, central, and occipital electrode sites for the first and second half of the sleep period in slow wave sleep.

Spectral power		F	df	p	η^2	Power
Beta	Sex	2.78	1, 42	.103	.06	.37
	Sex×condition	3.24	1, 42	.079	.07	.42
	Sex×half	0.04	1, 42	.850	.001	.05
	Sex×site	0.45	1, 42	.566	.01	.11
	Sex×condition×half	2.53	1, 42	.119	.06	.34
	Sex×condition×site	0.23	1, 42	.689	.01	.08
	Sex×half×site	0.62	1, 42	.468	.01	.13
	Sex×condition×half×site	1.06	1, 42	.317	.03	.18
Alpha	Sex	2.13	1, 42	.152	.05	.30
	Sex×condition	1.22	1, 42	.276	.03	.19
	Sex×half	0.25	1, 42	.623	.01	.08
	Sex×site	1.46	1, 42	.239	.03	.25
	Sex×condition×half	1.37	1, 42	.248	.03	.21
	Sex×condition×site	0.79	1, 42	.418	.02	.16
	Sex×half×site	0.32	1, 42	.607	.01	.09
	Sex×condition×half×site	0.20	1, 42	.696	.01	.07
Sigma	Sex	3.49	1, 42	.069	.08	.45
	Sex×condition	1.81	1, 42	.186	.04	.26
	Sex×half	<0.001	1, 42	.983	<.001	.05
	Sex×site	0.21	1, 42	.734	.01	.08
	Sex×condition×half	3.12	1, 42	.085	.07	.41
	Sex×condition×site	0.67	1, 42	.491	.02	.15
	Sex×half×site	4.46	1, 42	.024*	.10	.66
	Sex×condition×half×site	1.49	1, 42	.229	.03	.22
Theta	Sex	12.53	1, 42	.001*	.23	.93
	Sex×condition	0.78	1, 42	.381	.02	.14
	Sex×half	9.29	1, 42	.004*	.18	.85
	Sex×site	0.03	1, 42	.922	.001	.05
	Sex×condition×half	5.41	1, 42	.025*	.11	.62
	Sex×condition×site	0.95	1, 42	.391	.02	.21
	Sex×half×site	5.31	1, 42	.020*	.11	.67
	Sex×condition×half×site	2.24	1, 42	.129	.05	.38
Delta	Sex	9.08	1, 42	.004*	.18	.84
	Sex×condition	4.04	1, 42	.051	.08	.50
	Sex×half	15.91	1, 42	<.001**	.28	.97
	Sex×site	1.44	1, 42	.242	.03	.25
	Sex×condition×half	3.22	1, 42	.080	.07	.42
	Sex×condition×site	6.16	1, 42	.003*	.13	.88
	Sex×half×site	5.54	1, 42	.015*	.12	.72
	Sex×condition×half×site	0.09	1, 42	.888	.002	.06

Table G.4

Spectral power: F statistics, effect size (η^2), power, and significance levels (p) across frontal, central, and occipital electrode sites for the first and second half of the sleep period in REM sleep.

Spectral power		F	df	p	η^2	Power
Beta	Sex	0.52	1, 42	.475	.01	.11
	Sex×condition	6.59	1, 42	.014*	.14	.71
	Sex×half	7.70	1, 42	.008*	.16	.77
	Sex×site	4.80	1, 42	.025*	.10	.64
	Sex×condition×half	2.31	1, 42	.136	.05	.32
	Sex×condition×site	6.06	1, 42	.012*	.13	.74
	Sex×half×site	8.23	1, 42	.004*	.16	.85
	Sex×condition×half×site	1.75	1, 42	.191	.04	.29
Alpha	Sex	3.83	1, 42	.057	.08	.48
	Sex×condition	0.61	1, 42	.438	.01	.12
	Sex×half	0.31	1, 42	.579	.01	.09
	Sex×site	0.76	1, 42	.404	.02	.14
	Sex×condition×half	0.35	1, 42	.559	.01	.09
	Sex×condition×site	0.05	1, 42	.862	.001	.06
	Sex×half×site	0.03	1, 42	.877	.001	.05
	Sex×condition×half×site	0.45	1, 42	.523	.01	.10
Sigma	Sex	5.80	1, 42	.021*	.12	.65
	Sex×condition	2.36	1, 42	.132	.05	.32
	Sex×half	2.12	1, 42	.153	.05	.30
	Sex×site	1.36	1, 42	.258	.03	.24
	Sex×condition×half	2.63	1, 42	.113	.06	.35
	Sex×condition×site	0.46	1, 42	.550	.01	.12
	Sex×half×site	2.07	1, 42	.150	.05	.33
	Sex×condition×half×site	1.56	1, 42	.220	.04	.29
Theta	Sex	10.33	1, 42	.003*	.20	.88
	Sex×condition	0.09	1, 42	.765	.002	.06
	Sex×half	4.22	1, 42	.046*	.09	.52
	Sex×site	0.004	1, 42	.982	< .001	.05
	Sex×condition×half	0.03	1, 42	.869	.001	.05
	Sex×condition×site	0.28	1, 42	.685	.01	.09
	Sex×half×site	0.84	1, 42	.392	.02	.16
	Sex×condition×half×site	0.55	1, 42	.463	.01	.11
Delta	Sex	13.20	1, 42	.001*	.24	.94
	Sex×condition	0.52	1, 42	.476	.01	.12
	Sex×half	2.60	1, 42	.114	.06	.35
	Sex×site	0.77	1, 42	.420	.02	.15
	Sex×condition×half	1.66	1, 42	.205	.04	.24
	Sex×condition×site	0.45	1, 42	.542	.01	.12
	Sex×half×site	0.36	1, 42	.591	.01	.09
	Sex×condition×half×site	0.35	1, 42	.592	.01	.09

APPENDIX H

Complete spectral analysis: Sex × habitual effects

Complete spectral analysis for the habitual effects of alcohol use and sex (male vs. female) on spectral power (beta, alpha, sigma, theta and delta) for each individual sleep stage (stage N1 sleep, stage N2 sleep, stage N3 sleep/SWS, REM sleep), for habitual alcohol use (habitual; heavy vs. light drinker), sex (male vs. female), condition (alcohol vs. placebo), half (first vs. second half of the sleep period), electrode site (frontal, central and occipital), and their interactions.

Table H.1

Spectral power: F statistics, effect size (η^2), power, and significance levels (p) across frontal, central, and occipital electrode sites for the first and second half of the sleep period in stage N1 sleep.

Spectral power		F	df	p	η^2	Power
Beta	Sex×habitual	3.98	1, 42	.053	.09	.50
	Sex×habitual×condition	0.04	1, 42	.852	.001	.05
	Sex×habitual×half	0.09	1, 42	.771	.002	.06
	Sex×habitual×site	4.71	1, 42	.013*	.10	.76
	Sex×habitual×condition×half	0.01	1, 42	.917	< .001	.05
	Sex×habitual×condition×site	0.29	1, 42	.685	.01	.09
	Sex×habitual×half×site	1.71	1, 42	.195	.04	.30
	Sex×habitual×condition×half×site	0.25	1, 42	.694	.01	.08
Alpha	Sex×habitual	0.81	1, 42	.374	.02	.14
	Sex×habitual×condition	2.29	1, 42	.138	.05	.32
	Sex×habitual×half	1.15	1, 42	.290	.03	.18
	Sex×habitual×site	0.43	1, 42	.555	.01	.10
	Sex×habitual×condition×half	0.92	1, 42	.344	.02	.16
	Sex×habitual×condition×site	0.20	1, 42	.701	.01	.07
	Sex×habitual×half×site	0.06	1, 42	.858	.001	.06
	Sex×habitual×condition×half×site	0.04	1, 42	.883	.001	.05
Sigma	Sex×habitual	0.14	1, 42	.710	.003	.07
	Sex×habitual×condition	1.67	1, 42	.203	.04	.24
	Sex×habitual×half	0.48	1, 42	.495	.01	.10
	Sex×habitual×site	0.78	1, 42	.423	.02	.16
	Sex×habitual×condition×half	0.28	1, 42	.598	.01	.08
	Sex×habitual×condition×site	0.96	1, 42	.361	.02	.18
	Sex×habitual×half×site	0.47	1, 42	.605	.01	.12
	Sex×habitual×condition×half×site	0.63	1, 42	.490	.02	.14
Theta	Sex×habitual	0.38	1, 42	.544	.01	.09
	Sex×habitual×condition	0.09	1, 42	.772	.002	.06
	Sex×habitual×half	2.12	1, 42	.153	.05	.30
	Sex×habitual×site	0.94	1, 42	.362	.02	.18
	Sex×habitual×condition×half	0.02	1, 42	.901	< .001	.05
	Sex×habitual×condition×site	0.32	1, 42	.709	.01	.10
	Sex×habitual×half×site	5.22	1, 42	.017*	.11	.70
	Sex×habitual×condition×half×site	0.01	1, 42	.957	< .001	.05
Delta	Sex×habitual	0.80	1, 42	.378	.02	.14
	Sex×habitual×condition	0.66	1, 42	.421	.02	.13
	Sex×habitual×half	0.47	1, 42	.496	.01	.10
	Sex×habitual×site	0.58	1, 42	.505	.01	.13
	Sex×habitual×condition×half	0.61	1, 42	.438	.01	.12
	Sex×habitual×condition×site	1.70	1, 42	.196	.04	.31
	Sex×habitual×half×site	0.24	1, 42	.710	.01	.08
	Sex×habitual×condition×half×site	0.72	1, 42	.449	.02	.15

Table H.2

Spectral power: F statistics, effect size (η^2), power, and significance levels (p) across frontal, central, and occipital electrode sites for the first and second half of the sleep period in stage N2 sleep.

Spectral power		F	df	p	η^2	Power
Beta	Sex×habitual	0.01	1, 42	.944	< .001	.05
	Sex×habitual×condition	1.08	1, 42	.304	.03	.17
	Sex×habitual×half	2.21	1, 42	.145	.05	.31
	Sex×habitual×site	0.47	1, 42	.575	.01	.12
	Sex×habitual×condition×half	1.02	1, 42	.318	.02	.18
	Sex×habitual×condition×site	0.05	1, 42	.887	.001	.06
	Sex×habitual×half×site	0.52	1, 42	.548	.01	.12
	Sex×habitual×condition×half×site	0.84	1, 42	.399	.02	.02
Alpha	Sex×habitual	1.35	1, 42	.253	.03	.21
	Sex×habitual×condition	0.11	1, 42	.746	.003	.06
	Sex×habitual×half	1.58	1, 42	.216	.04	.23
	Sex×habitual×site	0.02	1, 42	.939	< .001	.05
	Sex×habitual×condition×half	0.49	1, 42	.488	.01	.11
	Sex×habitual×condition×site	0.53	1, 42	.533	.01	.12
	Sex×habitual×half×site	0.99	1, 42	.351	.02	.18
	Sex×habitual×condition×half×site	0.52	1, 42	.527	.01	.12
Sigma	Sex×habitual	0.26	1, 42	.612	.01	.08
	Sex×habitual×condition	0.13	1, 42	.717	.003	.07
	Sex×habitual×half	1.73	1, 42	.196	.04	.25
	Sex×habitual×site	0.03	1, 42	.939	.001	.05
	Sex×habitual×condition×half	2.26	1, 42	.141	.05	.31
	Sex×habitual×condition×site	1.00	1, 42	.370	.02	.21
	Sex×habitual×half×site	0.74	1, 42	.449	.02	.16
	Sex×habitual×condition×half×site	0.02	1, 42	.963	< .001	.05
Theta	Sex×habitual	1.37	1, 42	.249	.03	.21
	Sex×habitual×condition	0.31	1, 42	.579	.01	.09
	Sex×habitual×half	2.90	1, 42	.096	.07	.38
	Sex×habitual×site	0.40	1, 42	.599	.01	.10
	Sex×habitual×condition×half	0.26	1, 42	.616	.01	.08
	Sex×habitual×condition×site	0.15	1, 42	.821	.004	.07
	Sex×habitual×half×site	1.72	1, 42	.197	.04	.27
	Sex×habitual×condition×half×site	1.05	1, 42	.345	.02	.21
Delta	Sex×habitual	0.01	1, 42	.936	< .001	.05
	Sex×habitual×condition	0.14	1, 42	.707	.003	.07
	Sex×habitual×half	0.52	1, 42	.475	.01	.11
	Sex×habitual×site	0.01	1, 42	.956	< .001	.05
	Sex×habitual×condition×half	1.58	1, 42	.216	.04	.23
	Sex×habitual×condition×site	0.04	1, 42	.950	.001	.06
	Sex×habitual×half×site	0.51	1, 42	.529	.01	.12
	Sex×habitual×condition×half×site	0.53	1, 42	.518	.01	.12

Table H.3

Spectral power: F statistics, effect size (η^2), power, and significance levels (p) across frontal, central, and occipital electrode sites for the first and second half of the sleep period in slow wave sleep.

Spectral power		F	df	p	η^2	Power
Beta	Sex×habitual	2.17	1, 42	.148	.05	.30
	Sex×habitual×condition	0.01	1, 42	.926	< .001	.05
	Sex×habitual×half	0.03	1, 42	.874	.001	.05
	Sex×habitual×site	1.03	1, 42	.340	.02	.19
	Sex×habitual×condition×half	0.07	1, 42	.787	.002	.06
	Sex×habitual×condition×site	0.23	1, 42	.689	.01	.08
	Sex×habitual×half×site	0.04	1, 42	.889	.001	.06
	Sex×habitual×condition×half×site	0.46	1, 42	.527	.01	.11
Alpha	Sex×habitual	3.09	1, 42	.086	.07	.40
	Sex×habitual×condition	0.48	1, 42	.494	.01	.10
	Sex×habitual×half	2.81	1, 42	.101	.06	.37
	Sex×habitual×site	1.67	1, 42	.203	.04	.28
	Sex×habitual×condition×half	1.00	1, 42	.324	.02	.16
	Sex×habitual×condition×site	0.78	1, 42	.421	.02	.16
	Sex×habitual×half×site	2.22	1, 42	.139	.05	.33
	Sex×habitual×condition×half×site	1.37	1, 42	.253	.03	.22
Sigma	Sex×habitual	1.93	1, 42	.172	.04	.27
	Sex×habitual×condition	0.30	1, 42	.588	.01	.08
	Sex×habitual×half	0.05	1, 42	.832	.001	.06
	Sex×habitual×site	0.43	1, 42	.583	.01	.11
	Sex×habitual×condition×half	0.19	1, 42	.662	.19	.07
	Sex×habitual×condition×site	1.07	1, 42	.340	.03	.21
	Sex×habitual×half×site	0.66	1, 42	.481	.02	.14
	Sex×habitual×condition×half×site	1.93	1, 42	.166	.04	.32
Theta	Sex×habitual	2.18	1, 42	.147	.05	.30
	Sex×habitual×condition	0.03	1, 42	.873	.001	.05
	Sex×habitual×half	3.11	1, 42	.085	.07	.41
	Sex×habitual×site	0.77	1, 42	.424	.02	.15
	Sex×habitual×condition×half	1.17	1, 42	.285	.03	.19
	Sex×habitual×condition×site	0.01	1, 42	.995	< .001	.05
	Sex×habitual×half×site	0.81	1, 42	.393	.02	.15
	Sex×habitual×condition×half×site	2.43	1, 42	.112	.06	.40
Delta	Sex×habitual	0.24	1, 42	.630	.24	.08
	Sex×habitual×condition	2.32	1, 42	.135	.05	.32
	Sex×habitual×half	1.82	1, 42	.185	.04	.26
	Sex×habitual×site	0.08	1, 42	.842	.002	.06
	Sex×habitual×condition×half	0.47	1, 42	.499	.01	.10
	Sex×habitual×condition×site	0.18	1, 42	.836	.004	.08
	Sex×habitual×half×site	0.42	1, 42	.573	.01	.10
	Sex×habitual×condition×half×site	0.77	1, 42	.447	.02	.14

Table H.4

Spectral power: F statistics, effect size (η^2), power, and significance levels (p) across frontal, central, and occipital electrode sites for the first and second half of the sleep period in REM sleep.

Spectral power		F	df	p	η^2	Power
Beta	Sex×habitual	0.19	1, 42	.669	.004	.07
	Sex×habitual×condition	0.44	1, 42	.510	.01	.10
	Sex×habitual×half	2.25	1, 42	.141	.05	.31
	Sex×habitual×site	0.07	1, 42	.842	.002	.06
	Sex×habitual×condition×half	1.91	1, 42	.174	.04	.27
	Sex×habitual×condition×site	0.03	1, 42	.906	.001	.05
	Sex×habitual×half×site	1.39	1, 42	.250	.03	.23
	Sex×habitual×condition×half×site	0.19	1, 42	.734	.01	.07
Alpha	Sex×habitual	1.38	1, 42	.247	.03	.21
	Sex×habitual×condition	0.02	1, 42	.880	.001	.05
	Sex×habitual×half	0.17	1, 42	.687	.004	.07
	Sex×habitual×site	0.24	1, 42	.660	.01	.08
	Sex×habitual×condition×half	0.15	1, 42	.704	.003	.07
	Sex×habitual×condition×site	0.57	1, 42	.481	.01	.12
	Sex×habitual×half×site	0.60	1, 42	.458	.01	.12
	Sex×habitual×condition×half×site	0.21	1, 42	.676	.01	.07
Sigma	Sex×habitual	2.77	1, 42	.103	.06	.37
	Sex×habitual×condition	0.91	1, 42	.346	.02	.15
	Sex×habitual×half	0.03	1, 42	.859	.001	.05
	Sex×habitual×site	0.70	1, 42	.448	.02	.14
	Sex×habitual×condition×half	0.28	1, 42	.598	.01	.08
	Sex×habitual×condition×site	0.51	1, 42	.525	.01	.11
	Sex×habitual×half×site	0.72	1, 42	.438	.02	.14
	Sex×habitual×condition×half×site	2.12	1, 42	.138	.05	.38
Theta	Sex×habitual	1.63	1, 42	.209	.04	.24
	Sex×habitual×condition	0.28	1, 42	.598	.01	.08
	Sex×habitual×half	1.71	1, 42	.198	.04	.25
	Sex×habitual×site	0.62	1, 42	.484	.02	.13
	Sex×habitual×condition×half	0.74	1, 42	.395	.02	.13
	Sex×habitual×condition×site	0.29	1, 42	.676	.01	.09
	Sex×habitual×half×site	5.87	1, 42	.012*	.12	.74
	Sex×habitual×condition×half×site	0.37	1, 42	.650	.01	.10
Delta	Sex×habitual	1.46	1, 42	.234	.03	.22
	Sex×habitual×condition	1.00	1, 42	.322	.02	.17
	Sex×habitual×half	0.58	1, 42	.449	.01	.12
	Sex×habitual×site	0.08	1, 42	.845	.002	.06
	Sex×habitual×condition×half	0.89	1, 42	.350	.02	.15
	Sex×habitual×condition×site	0.43	1, 42	.557	.01	.10
	Sex×habitual×half×site	0.47	1, 42	.532	.01	.12
	Sex×habitual×condition×half×site	0.77	1, 42	.404	.02	.15