SLEEP-WAKE DYSFUNCTION IN HUMAN ISCHAEMIC STROKE

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Abstract

Sleep-wake dysfunction is increasingly recognised as a key modifiable risk factor and consequence of ischaemic stroke. Chronic sleep-wake abnormalities, characterised by excessively long sleep duration or sleep disorders, increase the risk of ischaemic stroke. Following stroke, *de novo* sleep-wake impairment is common and associated with poor recovery. However, the pathogenesis and evolution of sleep-wake disturbances in stroke have been poorly characterised thus far, largely due to methodological limitations.

In this thesis, gold-standard sleep measurement tools and advanced MRI methodologies were applied to investigate the impact of chronic stroke on sleep-wake function. There were three primary research questions for this thesis, and each formed the conceptual framework for three major studies: (1) To what extent is sleep-wake dysfunction associated with both stroke risk and post-stroke evolution? (2) What are the neurodegenerative markers of sleep-wake after stroke? (3) What are the sleep architectural and sleep-respiratory characteristics of chronic stroke patients relative to healthy controls?

To address the first question, a scoping systematic review of over 5,000 studies was conducted in order to assess the bidirectional relationship between sleep and circadian rhythm dysfunction in human ischaemic stroke. A qualitative synthesis of the extant literature showed that excessively long sleep duration and sleep disorders significantly increase the risk of ischaemic stroke. On the other hand, acute stroke patients exhibit fragmented sleep architecture in the weeks following the incident event – potentially driven by newfound sleep disorders which may also be associated with post-stroke topography and recovery. These findings support a bidirectional relationship between sleep-wake dysfunction and ischaemic stroke with important clinical implications.

To expand on limitations of prior studies identified in the aforementioned systematic review, the associations between regional neurodegeneration and objectively measured sleep were investigated in a cohort of mild-to-moderate stroke patients and healthy controls from the Cognition and Neocortical Volume After Stroke (CANVAS) study. Stroke patients with excessively long sleep duration and poor sleep efficiency exhibited volumetric reductions to the thalamus and amygdala relative to healthy controls. Next, a novel method known as a whole brain fixel-based analysis was utilised to investigate fibre-specific white matter degeneration

in stroke patients with poor sleep. Stroke patients with excessively long sleep duration exhibited tract-specific neurodegeneration to the cortico-ponto-cerebellar tract. These findings suggest that poor sleep efficiency or long sleep duration may contribute to neurodegeneration following stroke.

The final study in this thesis aimed to characterise hemispheric sleep architecture and sleep-respiratory characteristics in stroke patients >4 years after their incident event using gold-standard polysomnography. In a subsample of patients from the CANVAS study, stroke patients and matched controls underwent overnight ambulatory polysomnography and completed an array of sleep and circadian questionnaires. Over half of all stroke patients in this sample exhibited undiagnosed moderate to severe obstructive sleep apnoea. Stroke patients had nearly 40% less restorative slow-wave sleep and potentially compensatory increases in lighter sleep stages relative to healthy controls. Sleep architectural disturbances were not attenuated by obstructive sleep apnoea. There were no sleep architectural differences in the stroke-affected versus healthy-hemisphere. These findings suggest that sleep impairment post-stroke is unlikely to be driven by comorbid obstructive sleep apnoea or the hemispheric distribution of stroke lesions. Furthermore, these results highlight the importance of formal sleep studies in stroke patients in order to identify undiagnosed obstructive sleep apnoea and fragmented sleep architecture.

The overall findings from this thesis offer valuable insight into the potential *in vivo* pathogenesis of sleep-wake dysfunction after stroke and the evolution of sleep abnormalities in the chronic stages of stroke. The clinical-pathogenic implications of sleep-wake dysfunction in stroke are unravelled, and a research agenda for future studies in this emerging field of medicine is outlined.

Declaration

This is to certify that:

(i) This thesis comprises only my original work towards the Doctorate of Philosophy, except where indicated in the preface;
(ii) due acknowledgement has been made in the text to all other materials used; and
(iii) the thesis is fewer than 100,000 words in total, exclusive of tables, bibliographies and appendices.

Elie Gottlieb

Preface

This thesis includes original research that was undertaken for the purpose of this PhD and does not include any research performed prior to my PhD candidature toward the conferment of other qualifications.

The following publications or works submitted for publication have been included in this thesis:

1. **Gottlieb E.,** Landau E., Baxter H., Werden E., Howard M.E., Brodtmann A. *The bidirectional impact of sleep and circadian rhythm dysfunction in human ischaemic stroke: a systematic review*. Sleep Medicine Reviews. 45: 54-69. doi: https://doi.org/10.1016/j.smrv.2019.03.003.

   The text in Chapter 3 (pages 20-55) is taken from the published article above (published by *Sleep Medicine Reviews* on 20 March 2019). My contributions to this work were in formulating hypotheses, study selection and conducting PRISMA guideline process, data synthesis and interpretation, and writing the manuscript. I particularly acknowledge the valuable contributions of Helen Baxter in guiding the development of review search criteria. I acknowledge the valuable contributions of all my co-authors in the preparation and revisions of this work. I additionally acknowledge Elizabeth Landau for her role as the second independent reviewer per PRISMA guidelines for study selection, data synthesis, and study risk of bias assessment. Finally, I acknowledge the contributions of the anonymous reviewers who provided valuable insight and useful suggestions to enhance this work. This paper is reproduced with permission from Elsevier Copyright Clearance Centre. The published paper is included in Appendix A.

2. **Gottlieb E**., Egorova N., Khlif M.S., Khan W., Werden E., Pase M.P., Howard M., Brodtmann A. *Regional neurodegeneration correlates with sleep-wake dysfunction after stroke.* SLEEP. 43 (9): 1-13. doi: https://doi.org/10.1093/sleep/zsaa054

   The text in Chapter 4 (pages 57-75) is taken from the published article above (published by *SLEEP* on 28 March 2020). My contributions to this work were in formulating the hypotheses, designing the experiment, data analysis and interpretation, and writing the manuscript. I acknowledge the valuable contributions of all co-authors toward this work

and in particular, Natalia Egorova, Mohamed Khlif, and Will Khan for their valuable contributions to the pre-processing of neuroimaging data. Finally, I acknowledge the contributions of the anonymous reviewers who provided valuable insight and suggestions for this work. This paper is reproduced with permission from Oxford University Press Copyright Clearance Centre. The published paper is included in Appendix A.

3. **Gottlieb E.,** Churilov L., Werden E., Churchward T., Pase M.P., Egorova N., Howard M., Brodtmann A. *Sleep-wake parameters can be detected in chronic stroke patients using a multi-sensor accelerometer: a validation study.* doi: https://jcsm.aasm.org/doi/10.5664/jcsm.8812. The text from Chapter 5 (pages 77-88) is taken from the work published by *Journal of Clinical Sleep Medicine* (Currently in-press, accepted on 16 September 2020). My contribution to this work was in formulating hypotheses, designing the experiments, recruitment of participants, data collection, data analysis, and writing the manuscript. I acknowledge the valuable contributions of all co-authors in preparing this work for submission, and in particular, Leonid Churilov for his statistical insight and the Austin Sleep Laboratory technologists for their assistance with polysomnography/EEG scoring.

4. **Gottlieb E.,** Werden E., Churchward T., Pase M.P., Egorova N., Howard M., Brodtmann A. *Sleep architectural dysfunction and undiagnosed obstructive sleep apnoea after chronic ischaemic stroke.* Submitted to *Stroke*. The text from Chapter 6 (pages 90-101) is taken from the above work submitted for publication to *Stroke* on 20 September 2020. My contribution to this work was in formulating hypotheses, designing the experiments, recruitment of participants, data collection, data analysis, and writing the manuscript. I acknowledge the valuable contributions of all co-authors in preparing this work for submission.

Figures or tables in this thesis that have been reproduced or adapted from sources other than my own publications have been cited accordingly within their respective legends.

Research Profile

Additional publications not included in this thesis and awards received during candidature are highlighted below.

1. **Gottlieb, E.**, Grima, N.A., Howard, M., Brodtmann, A., Pase, M.P. (2020) Unraveling the contributions of sleep dysfunction to Alzheimer's disease. In: Genetics, Neurology, Behavior, and Diet in Dementia. Elsevier; 539-552.

2. Egorova, N., **Gottlieb, E**., Khlif, M., Spratt, N., Brodtmann, A. (2019). Choroid plexus volume after stroke. International Journal of Stroke. 14 (9), 923-930.

3. Werden, E., Khlif, M., Bird, L., Cumming, T., Bradshaw, J., Khan, W., Pase, M., Restrepo, C., Veldsman, M., Egorova, N., Patel, S., **Gottlieb, E.,** Brodtmann, A. (2019). APOE epsilon-4 carriers show delayed recovery of verbal memory and smaller entorhinal volume in the first year after ischemic stroke. Journal of Alzheimer's Disease. 71 (1), 245-259.

Awards:

1. Wally & Jean Jackson Postgraduate Travel Award for Neuroimaging, Florey Institute
2. Mendelsohn Student Lecture Award (2nd place), University of Melbourne
3. Best E-Poster Presentation, European Stroke Organisation Conference, Milan, Italy
4. The Craig Drummond Neuroscience Award, University of Melbourne
5. Florey Postgraduate Institute Travel Award, Florey Institute
6. Olivia Newton-John Research Institute Scholarship (2nd place), Austin Health
7. Melbourne Research Scholarship (Fee-Remission), University of Melbourne

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I wish to thank the participants who so graciously and altruistically devoted their time and energy to my research. Their strength, resilience, and wisdom inspire me to continue the fight against stroke.

I would like to thank my colleagues from The Florey Institute of Neuroscience and Mental Health. Firstly, to the Clinical Cognitive Neuroscience Lab members past and present – particularly Gabby Jean, Laura Bird, Mohamed Khlif, Remika Mito, Carolina Restrepo, and Toby Cumming. It has been a privilege and a joy working with some of the most brilliant minds in stroke research. I wish to thank the entire AVERT team, in particular Julie Bernhardt, Kate Hayward, Ruby Smith, and Sharon Kramer, for their valuable discussions of my work and their infectious smiles.

I wish to thank my friends whom I've been lucky to meet during my time in Australia. To Venesha Rentham, I am so thankful to have shared this PhD journey with you. From a stranger, to a colleague, to a best friend, and to a sister – I thank you for your endless wisdom and laughter, and for constantly driving me nuts. I wouldn't have it any other way. I wish to thank Will Khan and Stanley Hung for their banter and friendship. Thank you for making my candidature so enjoyable.

I wish to thank my partner Alexandra, who, in addition to being an ideal subject for studying sleep, has brightened my life over the past year with endless laughter, support, and love.

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Abbreviations

ABRAS	Ascending brainstem reticular activating system
AHI	Apnoea-hypopnea index
ARI	Arousal index
CANVAS	Cognition And Neocortical Volume After Stroke Study
CCC	Lin's Concordance Coefficient
CT	Computed tomography
dMRI	Diffusion weighted imaging
IS	Ischaemic stroke
MRI	Magnetic resonance imaging
mRS	Modified Rankin Scale
NIHSS	National Institutes of Health Stroke Scale
NOS	Newcastle-Ottawa Scale
NREM	Non-rapid-eye-movement sleep
NREM-1	Non-rapid-eye-movement sleep stage 1
NREM-2	Non-rapid-eye-movement sleep stage 2
NREM-3	Non-rapid-eye-movement sleep stage 3 (AKA slow-wave sleep)
PLM	Periodic leg movements
PS	Post-stroke
PSG	Polysomnography
RBD	Rapid-eye-movement behaviour disorder
REM	Rapid-eye-movement sleep
RLS	Restless legs syndrome
RMAR	Reduced major axis regression
SA	Sleep architecture
SACRAS	Sleep And Circadian Rhythms After Stroke Study
SE	Sleep efficiency
SL	Sleep onset latency
SWS	Slow-wave-sleep
TIA	Transient ischaemic attack
TST	Total sleep time
WASO	Wake after sleep onset
WMH	White matter hyperintensities

Chapter 1
Introduction

"If sleep does not serve an absolutely vital function, then it is the biggest mistake the evolutionary process has ever made."
-Allan Rechtschaffen (1971)

1.1 Defining Sleep and Stroke

Sleep is behaviourally defined as the suspension of consciousness. Until recently, the function of sleep has perplexed scientists. Humans spend, on average, a third of their lives in this state of apparent passivity. Extended deprivation of sleep, both in human and rodent models, has been shown to be fatal [1,2]. It is now known that sleep is not the result of a simple attenuation of brain activity. For example, during rapid eye movement (REM) sleep, the human brain's activity is comparable to that of awakening [3]. Recent experimental evidence suggests that sleep may also play a critical neuroprotective and restorative role within the central nervous system [4]. As renowned sleep scientist Allan Rechtschaffen sagaciously commented, "If sleep does not serve an absolutely vital function, then it is the biggest mistake the evolutionary process has ever made." [5]. Here, Rechtschaffen refers to sleep's presumably essential biological function given the pronounced state of vulnerability exhibited in sleeping animals.

Sleep is electrophysiologically measured by neuronal voltage fluctuations of ionic currents within the brain. Polysomnography is the gold-standard and de-facto tool used to assess sleep in both the clinical and laboratory settings using a battery of simultaneous sensors [6]. These sensors generally allow for measurement of (1) brain activity using electroencephalography (EEG), (2) corneo-retinal standing potential to detect rapid-eye-movement (REM) using electrooculography (EOG), (3) muscle atonia using electromyography (EMG), (4) heart rate using electrocardiography (ECG), (5) blood oxygenation using pulse oximetry, and (6) and respiratory characteristics using nasal canula/thermistors. Traditionally, polysomnography is assessed in a laboratory setting, requiring participants to sleep in an unnatural environment. Ambulatory polysomnography is an alternative modality which allows for sleep-wake monitoring to occur at home. This method limits deleterious environmental stressors but may

be unfeasible in patients with severe sleep disorders (e.g., parasomnias) [7]. Alternative methods that are less intrusive include objective measures such as actigraphy or consumer-grade accelerometers, and subjective measures such as sleep diaries and self-report questionnaires. However, these methods may be unreliable in patients with severe sleep-wake abnormalities, neurological or psychiatric disease, or those with chronic sleep deprivation [8].

The impact of both acute and chronic sleep deprivation is widespread, and affects recovery at the cellular, network, and endocrine systems level [9]. Sleep deficits have also shown to impair psychomotor and cognitive performance [10]. In the United States alone, these sleep-related deficiencies have contributed to over 100,000 highway accidents each year, resulting in over 70,000 injuries and 1,500 fatalities [11]. The National Sleep Foundation reports that over 60 percent of Americans experience inadequate, unrefreshing, or problematic sleep patterns, and approximately 30 percent of individuals in the United States report experiencing symptoms of sleep disorders such as insomnia [11]. In Australia, inadequate sleep affecting daytime functioning has been reported in up to 45% of adults [12]. Despite increasing clinical and public awareness of the consequences of sleep problems, sleep-wake problems are on the rise; more Australian adults reported poor sleep in 2016's Sleep Health Foundation national survey when compared to an identical 2010 survey [12].

Recent compelling evidence suggests that sleep disorders are also strongly associated with neurological diseases [13]. Neurological disease affecting the ascending reticular activating system and thalamocortical tracts may directly contribute to sleep-wake dysfunction, although regions beyond these pathways have also shown to regulate sleep-wake function [14]. Similarly, sleep dysfunction may be implicated in the pathogenesis of neurodegenerative disease [15]. Less explored, however, is the relationship between sleep abnormalities and cerebrovascular disease such as stroke, the most common neurological cause of long-term disability in adulthood [16].

Stroke refers to an acute focal injury of the central nervous system by vascular cause. Atrophy, or premature neuronal death, following stroke is the result of impaired blood flow originating from either thrombotic or embolic obstructions (i.e., ischaemic stroke), or from haemorrhagic ruptures (i.e., haemorrhagic stroke) of a supplying artery. Following cerebral arterial blockage two zones of injury are differentiated: 1) the ischaemic core lesion, an area closest to the blocked artery where irreversible cell death occurs as a result of depleted oxygen and glucose, and 2) the peripheral ischaemic penumbra, tissue surrounding the core containing

hypoperfused, yet viable cerebral tissue. Although functional, behavioural and cognitive deficits following stroke are typically caused by damage arising from the core lesion and peripheral penumbra, dysfunction to corresponding neural networks are also implicated [17]. Depending on stroke topography, post-stroke severity, and pre-morbid vascular risk factors, distributed brain networks may be disturbed. We now believe that, following stroke, there is a cascade of neurodegeneration to regions responsible for sleep-wake function [18].

Anecdotal and clinical observations suggest that sleep-wake disturbances are common following stroke and are associated with poor functional outcomes [18]. Despite these preliminary findings, there are several limitations to studies assessing sleep-wake dysfunction in stroke. For example, stroke participants are often assessed in a clinical setting (e.g., hospital ward) and are impacted by confounding environmental stressors of the acute hospital setting. In addition, the use of polysomnography, the gold standard for sleep testing, is limited in the extant literature, resulting in an overreliance of subjective sleep measures (e.g., sleep diaries). Finally, advanced neuroimaging metrics which can be used to disentangle the potential *in vivo* pathogenesis of sleep dysfunction post-stroke are seldom used in combination with objectively measured sleep-wake recordings. These limitations will be thoroughly dissected and unravelled in Chapter 3's systematic review and form the conceptual framework for this thesis' primary questions which, thus far, remain unanswered:

1. Is there a bidirectional relationship between sleep-wake dysfunction and human ischaemic stroke?
2. To what extent is neurodegeneration to sleep-wake hubs in the brain associated with sleep-wake dysfunction after stroke?
3. Can a non-invasive, multi-sensor, and consumer-grade accelerometer accurately measure sleep-wake parameters in patients with stroke when compared with gold-standard polysomnography?
4. What are the macro-architectural characteristics of sleep and respiratory dysfunction in the chronic stages of stroke?

1.2 Thesis aim

There has been a recent surge in studies assessing sleep-wake dysfunction as both a key modifiable risk factor and consequence of aging and in disease. Recent studies have led to pioneering and exciting pre-clinical contributions in controlled animal studies. However, there are translational gaps in human sleep and neurological disease studies which have limited the generalisability of pre-clinical findings and hindered the development of post-stroke sleep treatments and guidelines. Furthermore, the extant literature has primarily focused on the impact of obstructive sleep apnoea on stroke risk and post-stroke evolution. Thus, the major aim of this thesis is to comprehensively characterise non-apnoea related sleep-wake dysfunction in human ischaemic stroke and unravel its potential pathogenesis using gold-standard sleep measurement tools and robust neuroimaging metrics.

This thesis is comprised of three independent, but interwoven aims. The aim of the first research study was to conduct a systematic review of the bidirectional impact of sleep and circadian rhythm dysfunction in human ischaemic stroke. Secondly, based on findings from this systematic review, I aimed to investigate the impact of excessively long sleep duration and poor sleep efficiency – measured using a validated accelerometer – on regional neurodegeneration in the sub-acute stage of stroke relative to healthy age- and sex-matched controls. Finally, the third aim was to determine whether post-stroke sleep and circadian rhythm dysfunction is chronically sustained or is a transient phenomenon by charting the macro-architectural sleep and circadian features of chronic stroke patients and healthy controls using gold-standard ambulatory polysomnography.

1.3 Outline of thesis chapters

Chapters 2 and 3 constitute the introductory background to this thesis and also form the conceptual framework for later experiments. In Chapter 2, I outline both the historical and present-day understanding of the neural circuitry, neurotransmission, and chemical substrates governing sleep in the brain. This brief review of the neural circuitry involved in sleep-wake function will dovetail results from Chapter 4 which pinpoint the potential neuroanatomical pathogenesis of post-stroke sleep-wake dysfunction. Next, I discuss recent compelling pre-clinical evidence implicating sleep as a primary mediator of neuroprotection after stroke in animal models. Finally, I synthesise and critique the growing body of clinical research investigating sleep-wake disturbances and disorders in stroke. In Chapter 3, titled *The*

bidirectional impact of sleep-wake dysfunction in human ischaemic stroke: a systematic review, I expand on the previous chapters literature review and conduct a scoping systematic review to assess the bidirectional impact of non-apnoea related sleep disorders, sleep architecture, and endogenous circadian rhythm dysfunction in ischaemic stroke. Chapter 3 also elaborates on significant gaps in the extant literature; in particular, the lack of *a priori* neuroanatomical hypotheses in sleep and stroke studies which should be used to probe the neuroanatomical correlates of sleep-wake dysfunction after stroke.

The second part of this thesis (Chapters 4-6) comprises the results of three major experiments undertaken for this thesis. In Chapter 4, titled *Regional neurodegeneration after stroke correlates with sleep-wake dysfunction after stroke*, data from the longitudinal and prospective Cognition and Neocortical Volume After Stroke study (CANVAS) were analysed to characterise the first post-stroke regional brain volumetric and whole-brain, fibre-specific, white matter markers of objectively measured sleep–wake dysfunction. This was a cross-sectional comparative study investigating the regional neurodegenerative correlates of excessively long sleep duration and poor sleep efficiency (measured using accelerometer) in stroke patients and healthy controls. In Chapters 5-6, I report on data I collected as part of a sub-study on 44 CANVAS participants (study title: Sleep and Circadian Rhythms After Stroke [SACRAS]). As part of the SACRAS study, polysomnographic, urinary melatonin/circadian rhythm, and an array of demographic and self-report data were collected in stroke patients and healthy controls. In Chapter 5 (*Validation of a multi-sensor accelerometer to detect sleep-wake parameters in patients with stroke),* I conduct robust concordance statistics to determine the validity of a novel multi-sensor armband – the same armband used to measure sleep from Chapter 4's study – relative to gold-standard polysomnography. Here, I assess the armband's clinical utility as a sleep monitor in stroke patients and in healthy controls. In Chapter 6, titled *Sleep architectural dysfunction and undiagnosed obstructive sleep apnoea after chronic ischaemic stroke*, I describe the final study results from this thesis. In this study, I characterise sleep architectural dysfunction, hemispheric sleep architecture, and sleep-respiratory abnormalities using ambulatory polysomnography to gauge whether or not, and to what extent, sleep-wake dysfunction is chronically sustained even >3 years after stroke when compared to healthy controls.

The third and final section of this thesis is comprised of Chapter 7 (*General Discussion),* which serves to summarise and synthesise the major findings of this thesis. Here, I highlight the

implications of sleep-wake dysfunction after stroke and propose a research agenda for future studies that could provide further insight into the characterisation, prevention, and treatment of sleep and circadian dysfunction in stroke.

Chapter 2

Background

2.1 Neural Circuitry Involved in Sleep-Wake Functioning

Brain regions involved in sleep and wakefulness were first uncovered in 1949 when researchers stimulated cholinergic neurons near the junction of the pons and midbrain. Activation to this area resulted in electroencephalographic (EEG) changes indicative of wakefulness and arousal; i.e., high frequency (15-60 Hz), low-amplitude (~30 uV) activity [19]. Findings from Magoun and Moruzzi were among the first to discover that wakefulness is not simply the result of heightened sensory input, rather it arises through systematic activation of specialised brain regions responsible for arousal and waking states [19]. This central arousal system in the brain is now known as the ascending reticular activating system and extends from the medulla and pons onto fibre tracts projecting toward thalamic nuclei and forebrain cholinergic systems (see Figure 2.1). Inhibition of the reticular activation system coupled with low-frequency electrical stimulation to the thalamus has shown to induce slow-wave sleep characterised by low frequency (0.5-4 Hz), high amplitude (100-150 uV) synchronous brain activity [3,20,21]. As will later be fully described, the thalamus' role in sleep-wake functioning involves generation of sleep spindles, K complexes, and neocortical high-amplitude, low frequency slow waves indicative of restorative non-rapid eye movement (NREM) sleep [14].

Additional evidence of sleep's interaction with thalamic and cortical brain regions was provided by investigations into the neuronal circuitry involved in rapid eye movement (REM) sleep [22]. Unlike NREM sleep, REM sleep electroencephalographic (EEG) recordings are similar to those of subjects in an awake state and are characterised by low-amplitude, mixed-frequency, and desynchronised activity.

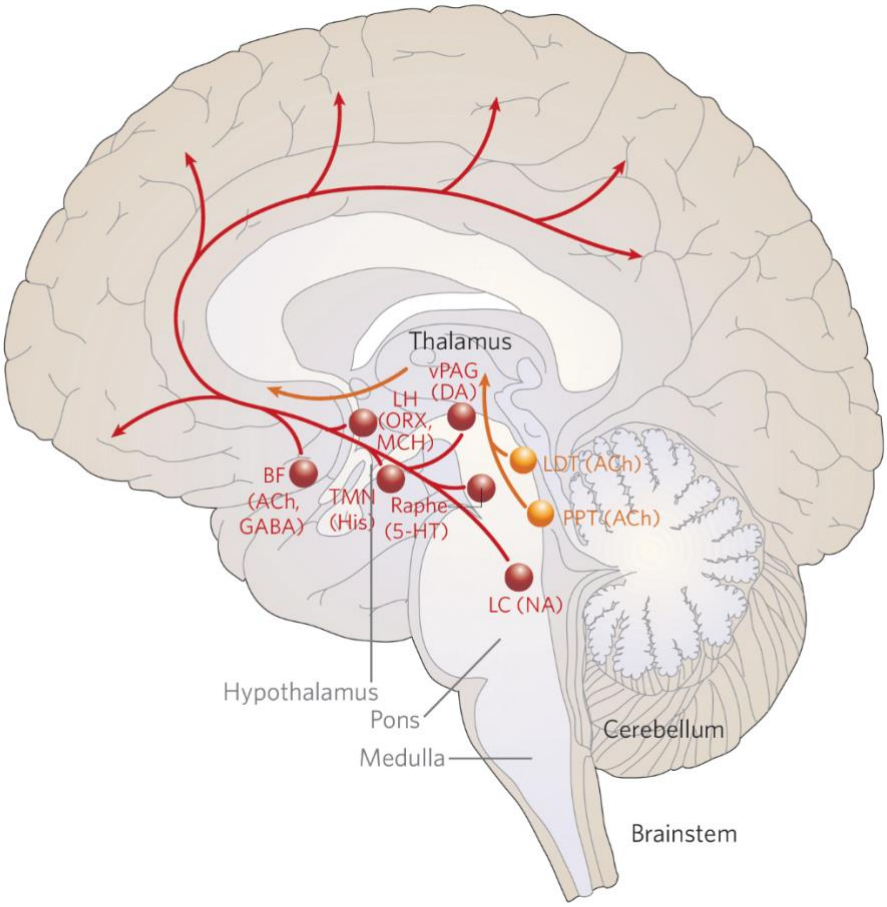

Figure 2.1. **The ascending reticular activating system.** Input to thalamic nuclei (orange) project from pontine cholinergic (ACh) cell groups, the pedunculopontine (PPT) and laterodorsal tegmental nuclei (LDT). A second pathway (red) activates the cerebral cortex to facilitate the processing of inputs from the thalamus through monoaminergic cell groups, including the tuberomammillary nucleus (TMN) containing histamine (His), dopamine (DA), the dorsal and median raphe nuclei containing serotonin (5-HT), and the locus coeruleus (LC) containing noradrenaline (NA). This pathway also receives projections from peptidergic neurons in the lateral hypothalamus (LHA) containing orexin (ORX) or melanin-concentrating hormone (MCH), and from basal forebrain (BF) neurons that contain GABA or ACh. Figure reproduced with permission from Saper, Scamelli, & Lu (2005) [23].

REM sleep is also differentiated by near-complete muscle atonia via activation of neurons within the locus coeruleus. The ballistic-like eye movements characteristic of REM sleep are

triggered by endogenously regulated signals arising from the pontine reticular formation transmitted to the motor region of the superior colliculus (see Figure 2.1) [24]. These collicular neuronal signals are projected onto the paramedial pontine reticular formation and the rostral interstitial nucleus. The low voltage, high frequency EEG changes that typify REM sleep are known as ponto-geniculo-occipital (PGO) waves and originate in the pontine reticular formation [25]. These signals are then propagated onto the lateral geniculate nucleus and the occipital lobe. The PGO waves representative of REM sleep provide yet another neural network by which brainstem nuclei impact activation of neocortical regions (see Figure 2.2) [21].

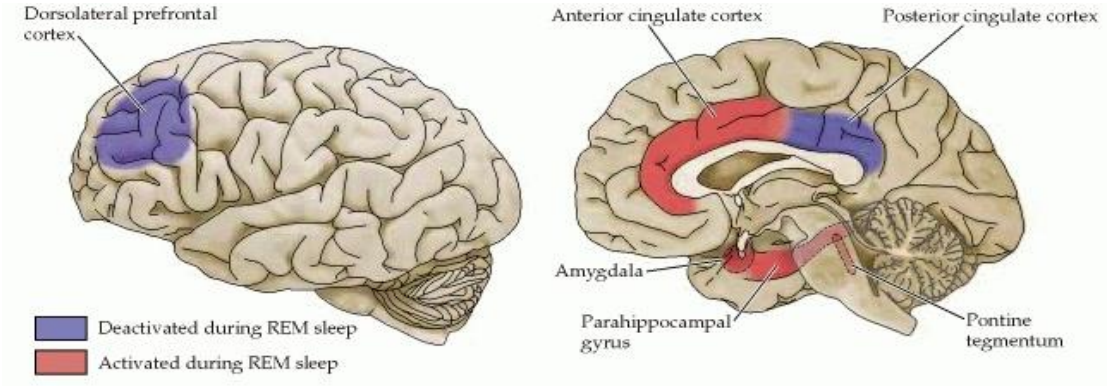

Figure 2.2. Diagram showing cortical regions where activity is increased or decreased during REM sleep. Reproduced with permission from Purves et al. (2010) [3].

With combined functional magnetic resonance imaging (fMRI) and positron emission topography (PET), researchers have identified key brain regions activated during REM sleep. Regions of subcortical activity during REM sleep include the anterior cingulate cortex, the amygdala, the parahippocampal gyrus, and the pontine tegmentum; decreased activity is particularly exhibited in the dorsolateral prefrontal cortex and the posterior cingulate cortex (see Figure 2.2) [25]. The increased activation of the limbic system along with decreased neocortical activity may explain the often nonsensical, yet highly emotional, nature of dreams occurring chiefly in REM sleep [26]. Damage to brain regions responsible for the activation of REM may lead to debilitating sleep disorders. For example, patients with brainstem infarcts had a significantly higher risk of developing REM behaviour disorder, a parasomnia involving decreased muscle atonia and "acting out" of dreams [27]. However, the impact of REM behaviour disorder on functional recovery and outcome following stroke is unknown.

The aforementioned studies reveal that a key component of the reticular activating system's modulation of sleep-wake mechanisms involve cholinergic nuclei, residing within the pons-midbrain junction of the brainstem. These cholinergic cells are components of a large, interconnected network, rather than a singular REM sleep "hub". Stimulating cholinergic nuclei within the pontine-midbrain junction causes a shift of EEG activity from high-amplitude, synchronised slow-waves to lower amplitude, high-frequency desynchronization similar to that of awakening and REM [28]. These findings suggest that cholinergic projections within the reticular activating system are the primary source of wakefulness and REM sleep, and deactivation to these networks is essential for initiation of slow-wave (NREM 3) and other NREM sleep stages. However, the neuronal basis for wakefulness and NREM sleep extends beyond these cholinergic neurons [20].

Monoaminergic network activity is also responsible for a spectrum of sleep-wake functioning ranging from deep sleep (e.g., slow-wave sleep) to high levels of alertness (e.g., sympathetic nervous system activation) (see Table 2.1). These monoaminergic brainstem networks include noradrenergic neurons residing within the locus coeruleus (modulated by the tuberomammillary nucleus responsible for the secretion of orexin, a wake-promoting peptide) and histaminergic neurons located within the hypothalamus' tuberomammillary nucleus responsible for awakening (which, when inhibited using antihistamines, causes drowsiness). The axons from these monoaminergic networks primarily target regions of the lateral hypothalamus, forebrain, and cerebral cortex where they terminate extensively within the prefrontal cortex. These cells groups are most active during arousal and wakefulness, declining during slow-wave and other NREM sleep stages, and completely fall silent during REM sleep (see Figure 2.2) [29-31]. Neurons within the ventrolateral preoptic nucleus (VLPO) periodically inhibit wakefulness and arousal systems [32]. These hypothalamic neurons of the VLPO are, in part, responsible for sleep onset and other NREM sleep-promoting networks.

Austrian neurologist Constantin von Economo first described the sleep-specific function of the VLPO when he reported symptoms of insomnia from patients with lesions to the preoptic region near the third ventricle [33]. Economo's findings were confirmed following investigations into the impact of experimental lesions of the preoptic basal forebrain on sleep [34]. Further subsequent studies revealed that GABAergic and galanin, an inhibitory neuromodulator of the VLPO, innervate regions of the ascending arousal system [35]. This population of neurons in the VLPO fire slowest during wakefulness (1-2Hz), twice as fast during stages 1-2 of NREM sleep

(4-8 Hz), and fastest at approximately 12-20Hz during slow-wave NREM sleep and REM sleep [36]. These findings suggest that VLPO neurons are part of a discrete sleep-promoting pathway responsible for inhibition of arousal systems contributing to the onset of sleep. To further test the impact of VLPO neurons on sleep function, cell-specific lesions of the VLPO revealed decreased NREM and REM sleep, as well as overall sleep duration by half [32].

Brainstem nuclei responsible	Neurotransmitter involved	Activity state of the relevant brainstem neurons
Wakefulness		
Cholinergic nuclei of pons-midbrain junction	Acetylcholine	Active
Locus coeruleus	Norepinephrine	Active
Raphe nuclei	Serotonin	Active
NREM Sleep		
Cholinergic nuclei of pons-midbrain junction	Acetylcholine	Decreased
Locus coeruleus	Norepinephrine	Decreased
Raphe nuclei	Serotonin	Decreased
REM Sleep Activation		
Cholinergic nuclei of pons-midbrain junction	Acetylcholine	Active (PGO waves)
Raphe nuclei	Serotonin	Inactive
REM Sleep Inhibition		
Locus coeruleus	Norepinephrine	Active

Tabe 2.1. Summary of the cellular mechanisms that govern sleep and wakefulness. Adapted with permission from Purves et al. (2010) [3,37].

Despite these findings, inhibition of the arousal systems during sleep must extend beyond the VLPO network given that experimental VLPO lesions only reduce sleep by approximately 50%. For example, evidence for the presence of sleep-promoting networks within the striatum

and globus pallidus has also been identified; lesions within these regions cause substantial increases in sleep fragmentation [38,39]. Indeed, the neural circuitry governing sleep and wakefulness involves complex modulation between the brainstem, thalamus, and cortex [32]. These regions, and others later described in Chapter 4, play a key role in the generation of electroencephalographic changes seen along the continuum of deep sleep to arousal and wakefulness [40]. Furthermore, damage to these regions may cause sleep-wake dysfunction and sleep disorders as described later in this review. The next section of this review will describe preclinical findings of the neuroprotective role of sleep after stroke.

2.2 Sleep modulates neuroprotection after stroke

Following ischaemic stroke, a cascade of physiological responses initiated by restriction of blood flow to the brain hinders recovery of cerebral tissue, particularly the ischaemic penumbra and distal networks. These events include excitotoxicity, the pathological process by which neuronal death is caused by overactivation of excitatory neurotransmitters such as glutamate. [41-43]. Preclinical findings suggest that forced wakefulness (sleep deprivation) impairs neurotransmitter receptor expression and function, as well as synaptic and membrane excitability in hippocampal neurons [44]. Sleep deprivation has been shown to further intensify extracellular glutamate concentrations and glutamate receptor levels which further contribute to excitotoxicity induced by ischaemia [45]. Similarly, long-term sleep deprivation may decrease antioxidative stress markers such as glutathione peroxidase and superoxide dismutase which may also intensify neuronal damage via free radical generation [46]. Furthermore, post-stroke proinflammatory responses are augmented by prolonged sleep deprivation [47]. The mechanisms underlying the function of sleep and the impact of sleep deprivation on neuronal injury such as stroke have only recently been discovered and point to sleep as having a neuroprotective function in the acute phases of stroke [48,49].

2.2.1 Sleep rebound is neuroprotective after stroke

Gao et al. (2010) provided direct evidence for the impact of sleep deprivation on stroke lesions and post-stroke sleep-modulated plasticity/recovery [50]. Rats subjected to 12 hours of sleep deprivation or three days of sleep disturbances in the acute phase of ischaemic stroke (induced by occlusion of the middle cerebral artery) had an increased infarct volume of 40% and 76% respectively. Sleep disturbances also significantly increased the expression of growth inhibiting genes, particularly *neurocan*, which has shown to inhibit axonal sprouting post-

stroke [48,50,51]. The peripheral ischaemic penumbra of sleep disturbed rodents contained significant reactive astrocytes and growth-inhibitory molecules such as *neurocan*, further hindering neuronal reconnection and recovery. Similarly, slow-wave sleep inducing stimulants such as gamma-hydroxybutyrate have shown to have the opposite effect and decrease *neurocan* induced by ischaemia [52]. These results further implicate *neurocan*, via increased NREM slow-wave sleep, as a potentially important molecule involved in sleep dependent post-stroke brain plasticity and recovery of the ischaemic penumbra and surrounding cerebral tissue.

Interestingly, inducing sleep deprivation in rodents prior to stroke is also associated with significant reductions in lesion volumes after seven days [47,53,54]. Indeed, pre-ischaemic sleep deprivation in rodents initiates compensatory processes by increasing sleep duration and deep sleep (slow-wave and REM sleep), a process known as sleep rebounding. The previous findings from Gao et al. (2010) and Zunzgenui et al. (2011) suggest that sleep rebound may modulate cerebral recovery [49,50]. Interestingly, Cam et al. (2013) demonstrated that pre-stroke sleep deprivation of 6 hours was associated with a 50% reduction in infarct volume in comparison to non-sleep deprived rodents after 7 days [53]. To investigate the causal relationship between sleep rebound and the neuroprotective effects of pre-stroke sleep deprivation, researchers allowed a group of rodents to sleep for 24 hours before inducing stroke. As expected, infarct volumes of rats allowed to sleep for 24 hours prior to the induction of stroke were significantly larger in comparison to the total sleep deprivation group (48.5 mm^3 vs. 28.8 mm^3; $p < 0.015$). These results suggest that removal of sleep rebound diminishes the neuroprotective effects of pre-ischaemic sleep deprivation. However, additional studies are needed to examine whether lesion volume reductions are longitudinally sustained.

The reduction of infarct volumes previously described is associated with significant increases in REM sleep. Specifically, both the latency of REM sleep and the amount of REM sleep bouts are associated with the intensity of pre-ischaemic sleep deprivation and lesion volume [55]. These findings suggest a potentially neuroprotective role of REM sleep following sleep deprivation pre-ischaemia. Alternatively, REM sleep may also be affected by neuroinflammation [56-58]. Recent investigators have confirmed these findings, but further note that the positive effects of sleep deprivation are not consistent at 24 hours and three days after inducing ischaemia. These findings suggest that sleep deprivation may delay the growth of infarction, which is at odds with the preceding findings. According to Pace et al. (2017), this theory is consistent with previous preconditioning treatments (e.g., short ischaemic preconditioning) which are

associated with increased neurogenesis; peaking cell proliferation following seven days of treatment [55,59]. Furthermore, additional studies suggest that NREM sleep promotes the proliferation of new cells and neurons, whereas longitudinal sleep deprivation reduces hippocampal cell volume and neurogenesis [60]. Taken together, sleep deprivation after ischaemia impairs neuroplasticity and is associated with increased lesion volumes. Inversely, sleep deprivation prior to ischaemia initiates compensatory sleep rebounding effects which may be neuroprotective [61].

2.2.2 Sleep-modulated pathways involved in neuroprotection after stroke

Stroke induces alterations in gene expression. To identify the genetic mechanisms underlying the potential neuroprotective role of sleep rebound after stroke, a recent study has utilized DNA oligonucleotide microarray analyses. Compared to animals that undergo ischaemia alone, sleep deprivation prior to ischaemia causes a significant reduction in the upregulation of genes involved in cell cycle regulation and immune response. Furthermore, findings from Pace et al. (2015) reveal an upregulation of a novel neuroendocrine pathway in sleep deprived rodents [62]. This pathway includes melanin concentrating hormones glycoprotein hormones-α-polypeptide and hypocretin and is exclusively activated in sleep deprivation induced ischaemia. These findings suggest that sleep deprivation prior to stroke may reprogram signalling responses to injury such as stroke. As previously described, short ischaemic preconditioning treatments may be neuroprotective and are associated with inhibition of cell cycle regulation and inflammation. Novel findings of a neuroendocrine pathway involved in sleep-modulated neuroprotection after stroke may reveal additional insights into neuroprotective ischaemic tolerance mechanisms [62].

2.2.3 Glymphatic system activation after stroke

Novel work by Xie et al. (2013) has shown that sleep serves a vital role maintaining brain metabolic homeostasis through activation of the glymphatic system [63]. The glymphatic system is a recently discovered functional waste clearance pathway consisting of para-arterial influx routes for cerebrospinal fluid (CSF) (see Figure 2.3) [64]. Unlike the peripheral lymphatic system which utilizes lymph vessels to recirculate excess interstitial proteins into the liver for degradation, the glymphatic system of the central nervous system contains perivascular channels formed by astroglial cells to facilitate elimination of soluble proteins and metabolites [64-66]. During slow-wave-sleep, a 60% increase in interstitial space causes CSF to recirculate and flood through the brain parenchyma to perivenous drainage pathways. In turn, convective

exchanges of CSF with interstitial fluid dramatically increase the removal rate of potentially toxic interstitial metabolic proteins [63].

Of particular interest for this thesis is the interstitial removal rate of β-amyloid (Aβ), a naturally occurring protein implicated in the pathogenesis of Alzheimer's disease and cerebral amyloid angiopathy which are risk factors for vascular cognitive impairment and stroke [67,68]. Prior experimental research on protein degradation within the central nervous system has focused on intracellular aggregation (i.e., proteasomal or lysosomal degradation) [69]. However, recent work has implicated toxic protein monomers, oligomers, and aggregates in interstitial fluid [70,71]. Experimental evidence suggests that soluble interstitial Aβ also impairs vascular reactivity and function [72,73]. The fundamental cause of longitudinal Aβ accumulation is still unknown, however preclinical work by Xie et al. (2013) has noted the implication for chronic sleep deprivation as a possible culprit. Using real-time assessments of tetramethylammonium diffusion and two-photon imaging in live mice, researchers have shown that natural sleep is associated with a significant increase in interstitial space [74]. This increase in interstitial space causes a cascade of events that increase the clearance rate of Aβ during slow-wave sleep. Experimental deletion of AQP4 channels responsible for glymphatic perfusion reduces clearance of exogenous Aβ by 65%, suggesting that convective movement of interstitial fluid is a substantial contributor to the removal of interstitial waste products and other products of cellular activity [64]. Chronic sleep deprivation may, therefore, contribute to the aggregation of Aβ, particularly in late adulthood given recent experimental findings indicating a ~80-90% decrease in glymphatic flow in aging mice [75].

Ischaemic stroke causes severe acute impairment of glymphatic perfusion 24 hours after ischaemia [76]. Glymphatic disruption may promote excitotoxicity of surrounding brain penumbra and prevent acute clearance of excitatory neurotransmitters. As previously described, a surge of excess glutamate is secreted after stroke (a process known as excitotoxicity) and elicits a myriad of signalling cascades that work synergistically to induce neuronal death [77]. The glymphatic system (activated primarily during slow-wave sleep) may therefore play a critical neuroprotective role via clearance of excess glutamate, and other deleterious molecules. According to Gaberel et al. (2014), the mechanisms responsible for glymphatic blockading after ischaemia may include a reduction of arterial pulsation as a result of vessel occlusion and compression by intravascular thrombus [76].

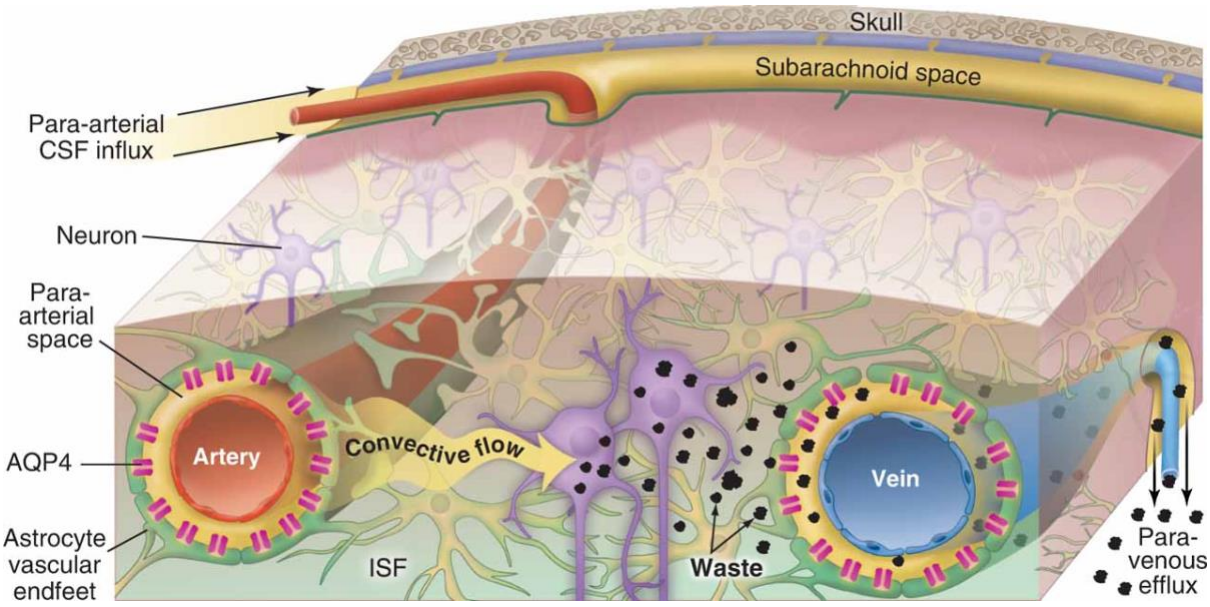

Figure 2.3. Schematic outline of the glymphatic system. Convective glymphatic fluxes of cerebrospinal fluid (CSF) and interstitial fluid (ISF) propel the waste products of neuron metabolism into the paravenous space, from which they are directed into lymphatic vessels and ultimately return to the general circulation for clearance by the kidney and liver. From Nedergaard, M. (2013). Garbage Truck of the Brain. Science, 340(6140), 1529-1530. Reproduced with permission from AAAS [65].

2.3 Clinical sleep-wake disturbances and disorders in stroke

Researchers have suggested that sleep-wake disorders present both a risk factor and a consequence of stroke that may modulate stroke recovery and outcome in humans [78]. Many factors contribute to the commonality of sleep disorders and sleep-wake disturbances following stroke: cerebral lesions may cause dysfunction in the sleep and respiratory regulatory centres [79]; consequences of stroke (mobility limitations, hypoxia, pain, etc.) may further compromise sleep [80]; and environmental factors associated with hospitalisation have shown to phase-shift circadian rhythms and deregulate sleep-wake patterns [81], particularly in intensive care units where disruption of sleep by hospital staff is common [82].

2.3.1 Sleep disordered breathing and stroke

The most widely investigated relationship between sleep disorders and stroke is sleep disordered breathing (SDB), particularly in the form of obstructive sleep apnoea (OSA). In a meta-analysis of 29 studies with over 2,300 cases of ischaemic stroke, haemorrhagic stroke, or transient ischaemic attack patients, 72%, 63%, or 38% respectively revealed SDB defined by an apnoea-hypopnea index of >5/h, >10/h, or >20/h [78,83]. Over 50% of these patients still

exhibited an apnoea-hypopnea index of >10/h four weeks after stroke. However, conflicting evidence regarding the association between SDB and stroke topography is common. While initial studies have reported no link between SDB and stroke topography, population-based and clinical cohorts have found significant associations between SDB and brainstem strokes, suggesting that lower cranial nerve dysfunction aggravates SDB [84,85].

Although OSA has long been confirmed as the most common form of SDB, stroke patients have recently been found to exhibit combinations of OSA and central types of SDB, particularly central sleep apnoea and Cheyne-Stokes breathing [86]. Meta-analyses of prospective clinical and population-based studies have further concluded that SDB is an independent stroke predictor, with stroke risk increasing with AHI [87]. Investigations into the mechanisms underlying elevated stroke risk in patients with SDB have shown that recurrent hypoxia in OSA causes intrathoracic pressure changes, sympathetic nervous system activation, and blood pressure spikes which, via oxidative stress and cerebral inflammation, may predispose individuals to drug-resistant arterial hypertension, atherosclerosis, cardiac arrhythmia, hypercoagulation, heart failure, and paradoxical embolisms [78,88]. Yet, we still do not fully understand the impact of stroke location on the severity and type of SDB, and the ways in which SDB contributes to changes in post-stroke sleep architecture.

2.3.2 Hypersomnia and insomnia in ischaemic stroke

Hypersomnia is common after stroke, usually after pontomesencephalic stroke. Characteristics range from sleep needs of >10 h/d, excessive daytime sleepiness as measured by the Epworth Sleepiness Scale (e.g., 28% of stroke survivors score >10 on the Epworth Sleepiness Scale), to major fatigue as measured by the Fatigue Severity Scale (with nearly half of participants reporting a Fatigue Severity Scale score of >4.0) [86]. Fatigue remains constant in the years following stroke [89], and retrospective meta-analyses have found that excessively long sleep, characteristic of hypersomnia, is an independent predictor of incident stroke, after adjustments for age, sex, vascular risk, and attributing comorbidities [90].

Furthermore, long sleep (>9 hours) has been linked to subcortical white matter hyperintensities, revealing that excessive sleep may result from cerebral small vessel disease, reflecting markers of subclinical atherosclerosis [91]. Inversely, insomnia is also common in the months following stroke and is found in 30-50% of sufferers [78]. Post-stroke insomnia is associated with poor life

satisfaction, depression, and stroke severity [86,92,93]. Although most post-stroke insomnia likely results from environmental factors (light, noise, novel environments), or comorbidities (SDB, depression, pain), insomnia has been hypothesized to also be directly related to brain damage given the near-complete loss of sleep found in patients suffering from pontomesencephalic stroke [94,95]. Few researchers have investigated sleep architecture in post-stroke insomnia. It has been observed that stroke affecting paramedian thalamic nuclei results in a near complete absence of sleep spindles [96]. Sleep deprivation (intended to mimic insomnia) in experimental stroke models may augment brain injury and impair neuroplasticity. Drugs promoting NREM and REM sleep have shown to have a positive effect on neuroplasticity and stroke recovery [97]. However, no research to our knowledge has examined these sleep-potentiated neurorestorative properties in humans following stroke.

Similar to results from hypersomnia literature, authors of recent meta-analyses have found that short sleep, characteristic of insomnia (defined by < 5-6 hours of sleep/night) is also an independent predictor of incident stroke after adjustment for age, sex, vascular risk factors, and comorbidities. These findings show that there may be a "U" based relationship between sleep duration and incident stroke, with increased risk resulting from insufficient (i.e., < 5-6 hours) or excessive (i.e., > 9 hours) sleep [98,99]. The underlying pathophysiological mechanisms driving these increased risks in stroke patients are not fully understood. For example, do excessively long sleepers exhibit fragmented sleep due to comorbid sleep disorders, or other reasons, resulting in long, yet poor quality sleep? Indeed, these prospective studies fail to distinguish sleep duration with more robust sleep variables (e.g., sleep latency, circadian stability, night-time awakenings, day-time naps, post-awakening latency, and sleep architecture as measured via polysomnography) and their possible impact on stroke risk and outcome.

2.3.3 Sleep architecture and ischaemic stroke

In normal aging, alterations in circadian and sleep homeostatic systems occur, and have shown to phase advance circadian rhythms, increase sleep disturbances, and change a variety of subjectively measured qualitatively sleep-wake parameters (e.g., increased fatigue) [100]. Sleep architectural fluctuations also include increased night-time awakenings, or wake after sleep onset, increased time spent in lower sleep stages (i.e., increased stages 1 and 2), and overall diminishment of slow-wave sleep and REM [101,102].

A small number of studies have identified relationships between topographic changes and sleep architecture post-stroke. However, these results vary in consistency and larger studies are required to confirm these findings. For example, authors investigating sleep EEG changes in the weeks following stroke have shown that compared to age and gender-matched adults, acute hemispheric stroke patients had significantly lower total sleep time, lower sleep efficiency, and lower amounts of NREM sleep stages 2-3 [103]. A recent meta-analysis of nine studies investigating stroke patients' EEG revealed acute reductions in total sleep time and sleep efficiency [101]. In patients with hemispheric stroke, changes in sleep EEG waveforms as sleep spindles and slow waves have been described [104].

These findings reflect a widely distributed neural network modulating sleep-wake function. Core lesions may cause either transient or chronic perturbations to distal neural networks responsible for sleep-wake functioning. No consistent associations have been found between stroke topography, stroke severity, and sleep architecture. Furthermore, no studies to date have investigated the sleep-wake correlates of regional post-stroke. Systematic searches and scoping reviews of the extant literature are warranted to better establish the bidirectional impact of sleep and circadian dysfunction in human ischaemic stroke.

2.4 Literature review conclusions

A bidirectional and complex relationship may exist between sleep and stroke. Chronic sleep dysfunction may contribute to the pathogenesis of risk factors associated with stroke, and ischaemic lesions may disrupt sleep's glymphatic and associative neuroprotective functions. Sufficient REM and slow-wave sleep may be critical in the acute and chronic stages of stroke, whereas sleep deprivation may drastically increase lesion volumes. Novel advancements in human brain imaging should be harnessed in order to unravel the potential mechanisms underlying sleep abnormalities after human ischaemic stroke. In particular, future work should assess the *in vivo* correlates of sleep-wake dysfunction after stroke. Longitudinal studies examining the evolution of sleep architecture and sleep-wake duration over damage to ipsilesional and contralesional brain regions (and varying stroke topographies) are warranted. Future research is necessary to assess a direct causal link between sleep promotion and both stroke prevention and post-stroke recovery.

Chapter 3

The bidirectional impact of sleep and circadian rhythm dysfunction in human ischaemic stroke: a systematic review

This chapter constitutes the first experimental study that was conducted as part of this thesis. The text in this chapter has been published as an original article in *Sleep Medicine Reviews* (Gottlieb et al., 2019), with an accompanying Guest Editorial by Professor Claudio Bassetti (Bassetti. C.L.A, 2019). See Appendix A for the full published paper, and the Preface for full disclosure.

3.1 Introduction

Anecdotally, sleep and circadian rhythm disturbances are common and potentially modifiable sequelae of ischaemic stroke (IS). Sleep-wake pathologies present both a risk factor and consequence of stroke. Chronic sleep and circadian dysfunction activate deleterious pathophysiological mechanisms (e.g., inflammation, autonomic nervous system activation with haemodynamic swings, hypothalamic-pituitary-adrenal axis activation), which may contribute to the pathogenesis of IS [105]. Inversely, lesions to sleep-wake networks and sleep disorders may compromise post-stroke recovery and sleep-potentiated neuroplasticity [106]. Furthermore, the glymphatic system, a pseudo-lymphatic perivascular network driven most efficiently by sleep, is compromised after human IS [107].

In pre-clinical studies, sleep deprivation after IS is associated with increased lesion volumes, and sleep deprivation prior to IS initiates compensatory rebound sleep that is neuroprotective [50,108]. Endogenous markers of circadian rhythms (i.e., melatonin) are suppressed after IS, and exogenous administration of melatonin is neuroprotective [109,110]. However, whether experimental findings translate to heterogeneous human stroke cohorts remains unclear.

Literature investigating stroke-related sleep dysfunction in humans has primarily focused on the impact of obstructive sleep apnoea on stroke risk and outcome [111,112]. In humans, a circadian variation in the timing of stroke onset is characterised by an increased incidence of all-stroke types in the morning (<6AM) and nadir during night-time [113]. However, the cause and neuroanatomical correlates of non-apnoea related sleep and endogenous sleep-potentiated circadian rhythm dysfunction in human IS remain unclear. Thus, the aim of the present review is to investigate the bidirectionality of non-apnoea sleep and circadian dysfunction in human IS. These aims will be stratified, where possible, to examine associations with post-stroke recovery, stroke topography, and time-course.

3.2 Methods

The systematic review was conducted in accordance with preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines [114]. The review was registered on the international prospective register of systematic reviews (PROSPERO) database (registration number: CRD42018079498).

3.2.1 Search strategy

The authors developed comprehensive search strategies to identify relevant studies pertaining to sleep architecture, sleep quality or duration, non-apnoea sleep disorders, circadian rhythms, and IS. Searches were conducted across MEDLINE (1946 - 7 August 2018, Ovid); Embase (1974 - 7 August 2018, Ovid); and PsycINFO (1806 - 7 August 2018, Ovid), and the Cochrane central register of controlled trials (CENTRAL) utilising a combination of subject headings and free-text created in collaboration with a clinical librarian. Subject headings were modified as required for translation to each database and included: sleep, circadian rhythms, sleep wake disorders, and stroke, with a broad list of free-text terms addressing sleep architecture, non-apnoea sleep disorders, circadian rhythms, and IS (see supplementary Figures S3.1-3.3 for search terms).

Non-ischaemic stroke types (i.e., haemorrhagic stroke and transient ischaemic attack) represent 15% of stroke cases and exhibit markedly different pathophysiology, neurological clinical evolution, and functional recovery/outcome [115]. Therefore, studies investigating only haemorrhagic stroke and/or TIA were excluded and considered outside the scope of this review.

Single case reports were not included in the review due to this study design's inherent low statistical validity and the availability of more robust evidence from other observational studies including cohort and case-control studies. Although meta-analyses were referenced to support findings from primary studies, they were excluded in our search strategy to avoid duplicate-inclusion and pooling of unstratified (non-ischaemic) stroke types. As case studies, systematic reviews and meta-analyses were to be excluded from the search results, the search strategy was limited to observational studies and clinical trials using established search filters [116] and the Emtree term "controlled study." There were no date or language restrictions applied. Removal of duplicate studies occurred prior to title and abstract screening. Authors scanned the reference

lists of included studies and searched for ongoing trials in the Australian New Zealand clinical trials registry and ClinicalTrials.gov.

3.2.2 Inclusion and exclusion criteria

Inclusion criteria were: observational studies or clinical trials; IS confirmed by CT or MRI; sleep assessed by polysomnography (PSG), actigraphy/accelerometer, or self-reported sleep-wake duration diaries; and circadian rhythm assessed via validated scale, actigraphy, or endogenous melatonin or metabolites (e.g., 6-sulphatoxymelatonin).

Exclusion criteria included: case studies, systematic reviews and meta-analyses; animal or tissue studies; self-reported stroke; homogenous haemorrhagic stroke or TIA cohorts; daytime alertness or sleepiness-specific outcomes only; sleep apnoea-specific outcomes; and indirect or non-sleep related circadian rhythmicity (e.g., shift work, heart rate, alertness).

Papers excluded on the basis of "wrong outcomes" (see Figure 3.1) refers to one or more of the following reasons: resting state daytime/awake electroencephalography (EEG); daytime sleepiness or fatigue outcomes only; indirect/proxy measures of circadian rhythms (e.g., pineal calcification, blood pressure, timing of stroke onset); traumatic brain injury or non-ischaemic-stroke potentiated lesions; and sleep apnoea outcomes only.

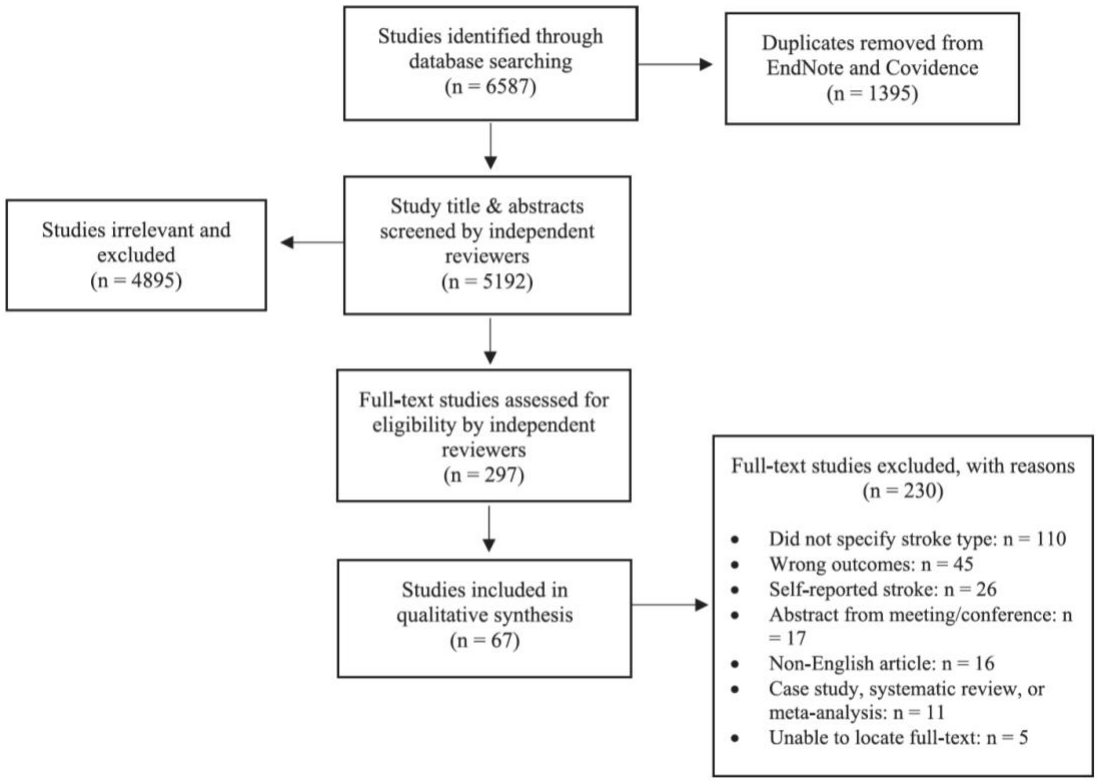

Figure 3.1. PRISMA flowchart of study selection process. n refers to number of studies.

3.2.3 Study selection

Titles and abstracts of potentially eligible citations were imported into Covidence, a web-based platform used to streamline the production of systematic reviews. Elie Gottlieb (EG) and Elizabeth Landau (EL) independently reviewed all titles and abstracts to determine initial eligibility. Full papers of eligible studies were independently assessed by EG and EL for inclusion. To achieve consensus, any conflicts raised between the reviewers were resolved through discussion with Amy Brodtmann (AB) and/or Mark Howard (MH).

3.2.4 Data extraction

Extracted variables were chosen based on the STROBE guidelines used for reporting observational studies [117]. Extracted data included: study identification/details; study design/setting; study demographics; stroke time (assessment administration); sleep or circadian rhythm measurement tool; stroke severity and topography (laterality, lesion location, stroke volume); adjustment variables; summarised and raw outcome data; and study quality assessment information. Data extraction for the entire sample was completed by EG. Twenty-five percent of the sample was randomly selected and independently extracted by EL;

agreement ratings between EG and EL were very good (92% for study characteristics and findings, 100% for study quality), and therefore did not warrant additional double-extraction. Missing data, or eligible studies that did not distinguish ischaemic and haemorrhagic stroke data, were requested from study authors. In studies supplying multiple covariate models, the most conservative (i.e., most adjusted variables) were exclusively selected. Confidence intervals (CI) are reported as 95%. Reported percentages are rounded to the nearest whole number. Raw or summarised statistically significant data are assumed as $p<.05$ unless otherwise specified.

3.2.5 Quality assessment

Critical appraisal of methodological quality for cohort and case-control studies was assessed using the Newcastle-Ottawa scale (NOS) [118], and the NOS tool adapted for cross-sectional studies. Studies were rated according to their selection criteria, comparability on the basis of design or analysis, and outcomes or exposures. Case-control and cohort studies were rated on a 1-9 scale. Ratings of 1-3 were scored as "low quality," 4-6 were scored as "moderate quality," and 7-9 were scored as "high quality." The NOS adapted for cross-sectional studies uses a 10-point scale; ratings of 1-3 were scored as "low quality," 4-7 were scored as "moderate quality," and 8-10 were scored as "high quality." Quality assessment scores are summarised in Tables 3.1-3.6. A breakdown of study-specific NOS results is presented in supplementary Tables S3.1-S3.3.

3.3 Results

A systematic search conducted on August 7, 2018 yielded 6587 citations. After removal of duplicates, 5192 unique citations were included in the title and abstract screening. Subsequently, 297 full-text studies were assessed for eligibility, of which 67 studies were included in the qualitative synthesis. Study characteristics, quality, and findings are summarised in Tables 3.1-3.6. Individual study stroke topography, stroke severity, and adjustment variables are reported in supplementary Tables S3.4-S3.9. Refer to Figure 3.1 for the complete PRISMA selection process.

Corresponding authors that did not distinguish stroke types were contacted for additional data or clarification if mention of stroke-stratification was included. A total of 43 authors were contacted for additional data and 12 authors responded to the request; 6 provided stratified data

or confirmed exclusive ischaemic stroke samples, and 6 were unable to provide the requested data.

3.3.1 Study characteristics

All studies were observational. Study quality was generally moderate (58%, n = 39 studies) or high (40%, n = 27 studies). One study was rated as low quality. The 67 included studies were published between 1992 and 2018, with over half published after 2012 and only 3 studies published before 2000. Sixteen percent of studies included Chinese populations (n = 11), while the other commonest populations were from Japan (n = 8), Switzerland (n = 8), and the United States (n = 7).

Studies were grouped into six categories according to directionality and outcomes: 1) sleep duration on risk of IS, 2) sleep disorders on risk of IS, 3) sleep architectural dysfunction on risk of IS, 4) impact of IS on sleep architecture, 5) impact of IS on sleep disorders, 6) impact of IS on circadian rhythms.

3.3.2 Sleep and circadian rhythm measures

Among studies investigating sleep disorders, 19 of 25 studies (76%) utilised validated diagnostic criteria. Studies investigating sleep duration as a risk factor for IS utilised self-report sleep measures with responses clustered into the following numerical groups: $\leq$6, 7, 8, 9, and $\geq$10 hours of sleep per night. Sleep architecture and quality was measured via PSG or EEG in 19 of 26 (73%) studies or by validated self-report sleep questionnaires in 5 of 26 (19%) studies. The remaining two (8%) studies utilised peripheral measures of generalised sleep disturbance (e.g., Nottingham health profile, patient-reported outcomes measurement information system). Circadian rhythms were most commonly assessed through endogenous melatonin serum or urinary melatonin metabolite, 6-sulfatoxymelatonin (6 of 9, 67%). The remaining studies utilised actigraphy (2 of 9, 22%) and a validated self-report chronotype questionnaire (1 of 9, 11%).

3.3.3 Primary findings

The 67 included studies investigated sleep dysfunction as a risk factor for IS (n = 20), and the impact, or consequence, of IS on sleep (n = 38) and circadian rhythms (n = 9). One study was included in two sections (Tables 3.4-3.5) as it measured both sleep disorders and sleep

architecture [119]. Thirty-one studies (46%) reported stroke topography, lesion volume, or other relevant neuroimaging measures (see Supplementary Tables S3.4-S3.9). Synthesised findings are presented in the following six sections according to directionality and outcomes.

3.3.4 Sleep duration as a risk factor for IS

Seven of eight studies (88%) reported a significant association between long-sleep duration, or ≥8 hours of sleep, and IS death [120-122] or incidence [123-126]. Study quality was high (63%, n = 5) to moderate (38%, n = 3). Hazard ratios (HRs) for long sleep duration risk ranged from 1.24 [123] to 3.90 [124]. HRs for sleep duration of >10 hours (n = 2 studies) ranged between 1.69 and 2.37 [121,122]. Nine or more hours of sleep (n = 4 studies) was associated with HRs between 1.24 and 1.94 [120,123,125,126]. Eight or more hours of sleep (n = 1 study) was associated with a 3.90-fold increased risk in IS incidence [124]. Inversely, Eguchi and colleagues (2010) reported an increased risk in IS risk in short sleep duration (<7.5 vs >7.5 hours of sleep) [127]. All studies (excluding [125], which only adjusted for age) included cerebrovascular risk factors as covariates. However, only two studies adjusted for depression or depressive symptoms [121,123]. Study characteristics and findings are summarised in Table 3.1.

3.3.5 Non-apnoea sleep disorders as a risk factor for IS

Non-apnoea sleep disorders, including restless legs syndrome (RLS) [128-130], REM sleep behaviour disorder (RBD) [131], hypersomnia [132], and insomnia [128,133-135] increase the risk of IS. Study quality was moderate (56%, n = 5) to high (44%, n = 4). Sleep-related movement disorders (i.e., RLS and periodic leg movements [PLM]) were associated with a 1.67, 2.04, and 3.89-fold increase in IS risk [128-130]. Insomnia was associated with a 1.19, 1.40, 1.75, and 1.79-fold increase in IS risk [128,133-135]. Participants with chronic insomnia had an increased risk of all-cause stroke compared to those in a remission group [30]. The presence of probable RBD, measured using a validated 13-item self-report questionnaire [136], was associated with a 1.93-fold increase in IS risk after adjusting for sleep measures and other potential confounders [131]. Hypersomnia was associated with a non-significant 1.87-fold increase in IS risk (HR = 1.87, CI: 0.60-5.80) [135]. Study characteristics and findings are summarised in Table 3.2.

3.3.6 Sleep architecture or quality as a risk factor for IS

No consistent associations were found in a heterogeneous sample of studies investigating sleep architecture [137,138] or sleep quality [139] and risk of IS. Study quality was moderate (66%, n = 2) to high (33%, n = 1). Poor sleep quality, measured using the PSQI, was associated with white matter hyperintensity (WMH) presence and severity (Odds Ratio [OR] = 2.44, CI: 1.26-4.71) [139]. However, no associations were found for silent lacunar infarction [139]. Long sleep duration with blood oxygenation saturation (SpO2) <95% was associated with increased microinfarction (OR = 3.88, CI: 1.10-13.76) [137]. Furthermore, increased slow-wave sleep (SWS) duration was associated with less generalised atrophy (OR= 0.32, CI: 0.10–1.03) [137]. No associations were found between sleep architecture and ischaemic stroke. In a TIA and all-cause stroke sample, patients with the longest nocturnal wake time and highest apnoea–hypopnea index (AHI) had an increased mortality risk (HR = 8.78, CI: 1.1–71.8; HR = 9.71, CI: 1.20–78.29) [138]. However, no statistically significant results were found when data were stratified by ischaemic stroke only [138]. Study characteristics and findings are summarised in Table 3.3.

3.3.7 Impact of IS on sleep architecture of quality

Sleep architecture and quality is compromised after IS [96,103,119,140-155]. Study quality was moderate (74%, n = 17) to high (26%, n = 6). Authors investigating sleep-potentiated stroke recovery found associations between sleep dysfunction and stroke severity or outcome [96,103,140,146,151,153,156]. Thirteen studies (57%) assessed sleep within 14 days after stroke [103,140,141,143-146,148,151-155]. Sleep architecture was objectively measured using PSG or high-definition EEG in 17 of 23 (74%) studies. Utilising PSG, sleep architectural variables impacted after IS, when compared to controls, ranged across studies from sleep efficiency (SE) and wake after sleep onset (WASO) [145,147], to total sleep time (TST), SE, non-rapid-eye-movement stage 2 sleep (NREM-2), SWS, and REM [154]. Sleep efficiency was reduced in 65% of studies (n = 11 of 17 studies) utilising PSG. Significant reductions to NREM-1, NREM-2, NREM-3 (SWS), and REM were reported in 12% (n = 2), 41% (n = 7), 35% (n = 6), and 35% (n = 6) of studies, respectively. Study characteristics and findings are summarised in Table 3.4.

Sleep architectural variables associated with post-stroke (PS) outcome, lesion volume, or topography varied across studies; SWS and REM correlated with stroke severity or functional outcome in five studies [146,147,151,153,154], and stroke topography was associated with sleep quality

or architecture in six studies [119,139,146,147,153,154]. IS patients had bilateral reductions in sleep spindles and sawtooth waves [96,103,144]. In both the acute (<10 days) and chronic (3-months) stage of stroke, SWS and theta activity over the contralesional hemisphere were significantly higher in the lateral temporo-parietal-occipital region and contralateral frontocentral region, respectively, which corresponded to the ipsilesional hemisphere [146,147]. Decreased REM percentage was associated with deep (versus superficial) lesions and was an independent predictor of functional outcome [151,153,154]. However, Manconi and colleagues (2014) reported no significant sleep architectural differences between supratentorial and infratentorial strokes [148]. Cortical lesions were associated with worse overall sleep quality [143]. These findings are inconsistent: Chen et al. (2015) reported left hemispheric and anterior circulation infarction associations with poorer sleep quality compared to right-sided and posterior circulation infarction, respectively [119]. In a small sample of mild-to-moderate extra-thalamic stroke, positive post-stroke (PS) outcome was associated with increased sleep efficiency (SE), total sleep time (TST), and NREM-2 sleep [103].

3.3.8 Impact of IS on non-apnoea sleep disorders

Sleep disorders were more common after IS when compared to normative averages or controls [119,132,157-163]. Study quality was mostly moderate (50%, n = 8) to high (44%, n = 7). One study was rated as low quality. Eight (50%) studies examined PS sleep-related movements disorders (n = 5 RLS [162,164-167], n = 3 PLM [157,168,169]; five studies examined PS insomnia [158-160,163,170]; one study examined PS REM sleep behaviour disorder [161]; one study examined PS hypersomnia [132]; one study examined all-cause (non-apnoea) sleep disorders [119]. Time from stroke to sleep assessment ranged significantly across studies from ≤2-days PS [166,168,169], to 3-months post stroke [157,158,160,161]. Study characteristics and findings are summarised in Table 3.5.

3.3.9 Prevalence of restless legs syndrome and period limb movements

One of six studies (17%) examining PS RLS prevalence included healthy controls [168]. Prevalence across studies ranged from 8% (n = 3) to 33% (n = 10) [169]. Four of six studies (67%) reported an RLS prevalence of ≤14.5% [164,166-168]. Two studies reported associations between RLS and PS symptoms or quality of life (QoL); RLS was negatively associated with QoL independent of functional outcome and depression, and stroke symptoms were significantly more severe in RLS patients as measured by the Barthel index and modified Rankin scale [164,165]. Two of three studies including neuroimaging-specific outcomes reported associations between

stroke topography and RLS; subcortical strokes (basal ganglia and/or corona radiata lesions) were associated with RLS, and a 17-fold increase in brainstem stroke-potentiated RLS was reported when accompanied with PS sensory symptoms (CI: 1.38-330.77) [166,167].

Among three studies investigating PS PLM, two included control groups and reported a greater quantity of PLMs detected on PSG when compared to healthy controls or TIA [157,168]. Associations between PLM and stroke topography were reported in one study; bivariate correlational analyses revealed that PLM index and lesion volume significantly correlated with increased WMHs [157]. However, in patients with supratentorial IS, no significant associations were found between IS topography and the presence of PLM [168].

3.3.10 Prevalence of insomnia after IS

No studies investigating PS insomnia included control groups. The prevalence of insomnia complaints after stroke ranged between 3.8% and 57% [158,170]. However, among studies utilising validated questionnaires, the prevalence of insomnia was 30%, 37.5%, and 44% [158-160]. No associations between insomnia, IS topography, PS severity or outcome were reported. Independent correlates of insomnia included anxiety and use of psychotropic drugs [158]. Insomnia symptoms were associated with depression and reduced quality of life [160,163]. These findings are supported by Glozier et al. (2017): patients with chronic insomnia (16%) after stroke had a 3.31, 3.60, and 6.75-fold increased rate of anxiety, disability, and depression, respectively [159].

3.3.11 Prevalence of rapid-eye-movement behaviour disorder after IS

Tang and colleagues (2014) reported that 10.9% of IS patients had symptoms of rapid-eye-movement behaviour disorder (RBD) using a validated RBD questionnaire [161]. Acute brainstem infarction was a significant independent predictor of RBD (OR = 3.68, CI:1.17–12.2). Infarct volume was significantly larger in non-RBD patients versus RBD-patients [161].

3.3.12 Impact of IS on circadian rhythms

Among studies measuring endogenous markers of circadian rhythmicity after acute IS (n = 6 studies), all reported significant reductions to melatonin compared to controls [171-176]. Study quality was generally moderate (67%, n = 6). Three studies (33%) were rated as high quality.

These findings are consistent for nocturnal serum melatonin [171-176], but not for the urinary melatonin metabolite, 6-sulphatoxymelatonin [173,174]. Circadian rhythm dysfunction was associated with IS severity or functional outcome in four of nine studies (44%) [175-178]. Backward logistic regression analyses revealed that nocturnal melatonin was independently associated with an increased probability of IS [172]. Comparable findings were reported in a PS insomnia sample; nocturnal serum concentrations of melatonin, GABA, and total antioxidants were lower in IS insomnia patients [176]. There was a significant interaction between NIHSS and melatonin that was associated with insomnia [176]. Study characteristics and findings are summarised in Table 3.6.

Two of three studies utilising actigraphy [178,179] or validated chronotype questionnaire [177] reported significant changes to circadian rhythms after IS. Self-reported chronotype, defined by mid-sleep time on work-free days corrected for sleep deficit on workdays (MSFsc), changed significantly after IS [177]. Changes to MSFsc after stroke were negatively correlated with stroke severity and outcome (NIHSS and mRS at hospital discharge) [177]. Interior circulatory strokes were associated with MSFsc delays, whereas posterior circulatory strokes were associated with advances of MSFsc [177]. Takekawa and colleagues (2007) reported fragmented circadian rhythms in non-ambulatory patients in the acute phase of IS [178]. However, Zuurbier and colleagues (2014) reported no significant associations between lacunar infarctions and actigraphy measured 24-hour circadian fragmentation (intradaily variability) in a large cohort study [179]. Increased white matter lesion volume and cerebral microbleeds were significantly correlated with circadian fragmentation [179].

Table 3.1. Summary of study characteristics and results of studies investigating sleep duration on ischaemic stroke risk.

Author, Year	Study quality (NOS score)	Design, follow-up period, outcome variable	Demographics (study country, gender, age)	Sleep measure	Ischaemic stroke outcome (Total N); Control N	Summary
Chen et al., 2008 [123]	High (7)	Cohort, 7.5 y f/u, IS incidence	USA; female: 100%, range: 50-79 y	Self-report (TST, ≤5, 6, 7, 8, 9, ≥10 h)	1166 (93175); 0	>9h sleep ↑ IS incidence
Eguchi et al., 2010 [127]	Moderate (4)	Cohort, 4 y f/u, IS incidence	Japan; female: 62.4%, mean: 69.9 y	Self-report sleep diary (difference b/w sleep and wake)	517 (932); 0	<7.5 h (vs >7.5 h) sleep ↑ IS incidence
Gianfagna et al., 2016 [125]	High (8)	Cohort, 17 y f/u, IS incidence	Italy; male: 100%, mean: 50.9 y	Self-report (TST, ≤5, 6, 7, 8, 9, ≥10 h)	96 (2277); 0	5 h, >9h sleep ↑ IS incidence
Ikehara et al., 2009 [121]	High (8)	Cohort, 14.3 y f/u, IS death	Japan; male: 56.7%, range: 40-79 y	Self-report (TST, ≤ 4, 5, 6, 7, 8, 9, ≥ 10 h)	1071 (98634); 0	>10h sleep ↑ IS death
Kakizaki et al., 2013 [122]	High (7)	Cohort, 13 y f/u, IS death	Japan; female: 51.8%, mean: 61.1 y	Self-report (TST: < 6, 7, 8, 9, > 10 h)	549 (49256); 0	>10h sleep ↑ IS risk death
Kawachi et al., 2016 [120]	Moderate (6)	Cohort, 16 y f/u, IS death	Japan; female: 51.4%, range: 35-97 y	Self-report (TST, ≤6, 7, 8, ≥9 h)	354 (27896); 0	>9h sleep ↑ IS death
Wen et al., 2016 [126]	High (7)	Case-control, nr, IS incidence	China; male: 54.4%, mean: 64.97 y	Self-report (TST)	223 (880); 547	≥9h sleep ↑ IS incidence
Zhang et al., 2008 [124]	Moderate (5)	Case-control, nr, IS incidence	China; male: 59.6%, mean: 63.5 y	Self-report (TST, ≤ 4, 4-6, 6-8, > 8 h)	245 (749); 282	>8h sleep ↑ IS incidence

Abbreviations: b/w = between, d = day(s), f/u=follow-up, h = hours, IS = ischaemic stroke, mo = month(s), NOS = Newcastle-Ottawa scale, nr = not reported, TST = total sleep time, y = year(s)

Table 3.2. Summary of study characteristics and results of studies investigating impact of non-apnoea sleep disorders on ischaemic stroke risk.

Author, Year	Study Quality (NOS score)	Design, follow-up period, outcome variable	Demographics (study country, gender, age)	Sleep disorders measure	IS outcome (Total N); control N	Summary
Canivet et al., 2014 [134]	High (7)	Cohort, 11 y f/u, insomnia symptoms prevalence	Sweden; 56.8% female, range: 45-69	4-item self-report questionnaire based on DSM-IV criteria	604 (13617); 0	Insomnia symptoms reported in 51.7% of IS pts, insomnia ↑ risk of all-cause CVD in pts with low socioeconomic status
Chou et al., 2017 [129]	High (7)	Cohort, 5 y f/u, PLM + RLS prevalence	Taiwan; 56.2% male, mean: 57.11 y	ICD-9-CM codes: 327.5 (PLM) and 333.9 (RLS)	137 (3020); 2416	PLM + RLS ↑ IS risk
Elwood et al., 2006 [128]	Moderate (5)	Cohort, 10 y f/u, sleep disturbance prevalence	UK; 100% male, range: 55-69 y	Wisconsin sleep questionnaire	103 (1874); 0	Insomnia ↑ IS, RLS ↑ IS
Frauscher et al., 2010 [180]	Moderate (4)	Case control, RBD prevalence and comorbidities in sleep disorder-PSG confirmed pts	Austria; demographics for RBD-confirmed pts only: 79% male, 57.7 y	PSG, ICSD-2 criteria	1 pontine infarction (34 RBD, 703 total); 0	4.8% (34 of 703) pts diagnosed with RBD, n=1 with pontine infarction (ns)

Huang et al., 2013 [135]	High (7)	Cohort, 9 y f/u, non-apnoea SD prevalence	Taiwan; 55.1% female. ≤ 35 y: 1%, 35-50 y: 7.6%, 50-65 s: 27.1%, > 65 y: 64.4%	ICD-9-CM codes: insomnia (780.5, 780.50, 780.52); hypersomnia (780.54); others (307.4, 780.55–780.56, 780.58–780.59)	9330 (144240); 94160	Insomnia ↑ IS risk, non-apnoea sleep disorders ↑ IS risk
Ma et al., 2017 [131]	Moderate (5)	Cohort, 3 y f/u, RBD prevalence	China; Demographics for total N listed only by RBD group. No RBD group: 81.9% male, mean: 53.9 y. RBD group: 86.9% male, mean: 54.3 y	13-item RBD questionnaire: Hong Kong	136 (12003); 0	RBD ↑ IS risk
Molnar et al., 2016 [130]	High (8)	Cohort, 8 y f/u, RLS incidence	USA; Demographics for total N only. 93% male, mean: 59.8 y	ICD-9-CM code: 333.94	397 (7392); 3696	RLS ↑ IS risk
Wang et al., 2016 [181]	Moderate (6)	Cohort, 85% of pts examined ≤ 3 mo PS, post-stroke depression associations with insomnia	China, 53% male, 68.7 y	Self-report (non-validated)	608 (608); 0	History of insomnia ↑ PS depression
Wu et al., 2014 [133]	Moderate (6)	Cohort, 4 y f/u, insomnia prevalence	Taiwan; Demographics listed only for all stroke types by insomnia status. Insomnia group: 53.5%	ICD-9-CM codes: 780.52, 307.41, 307.42	861 (85752); 64314	Insomnia ↑ IS risk, persistent insomnia vs. remission ↑ IS risk

			female, mean: 52 y. Non-insomnia group: 53.0% female, mean: 51 y			

Abbreviations: d = day(s), f/u = follow-up, ICD-9-CM = International classification of diseases ninth revision clinical modification, IS = ischaemic stroke, mo = month(s), NOS = Newcastle-Ottawa scale, PLM = periodic limb movements, RLS = restless legs syndrome, TIA = transient ischaemic attack, y = year(s)

Table 3.3. Summary of study characteristics and results of studies investigating sleep quality or sleep architecture on ischaemic stroke risk.

Author, Year	Study quality (NOS score)	Design, follow-up period, outcome variable	Demographics (study country, gender, age)	Sleep measure	Ischaemic Stroke Outcome (Total N); Control N	Summary
Del Brutto et al., 2015 [139]	High (9)	Cross-sectional, SQ in WMH & cerebral small vessel disease	Ecuador; Demographics listed for total N. 59% female, mean: 70 y	PSQI	28 LI, 154 WMH (237); 0	Poor SQ ↑ WMH
Gelber et al., 2015 [137]	Moderate (6)	Case control, PSG time to death 6.4 y, retrospective PSG associations after death	USA; 100% male, mean: 84 y	PSG	68 infarctions (167); 0	> sleep duration + SpO2 <95% ↑ microinfarction; > SWS ↓ generalised atrophy
*Ponsaing et al., 2017 [138]	High (8)	Cohort, mean stroke to PSG: 6 d, 19-37 mo f/u period, PSG associations of mortality in IS	Denmark; 63.5% male, mean: 70.25 y	PSG	48 (63); 0	Stratified IS results: no ↑ mortality risk related to PSG variables between IS survivors and non-survivors (*ns*).

Non-stratified stroke + TIA results: > AHI and nocturnal wake time ↑ mortality risk

*Note: Raw data for IS-stratified results were provided upon request by the corresponding authors and calculated according to study methodology by EG and EL. Study quality NOS scores are based solely on data reported in the original peer-reviewed manuscript.

Abbreviations: AHI = apnoea–hypopnea index , IS = ischaemic stroke, d = day(s), f/u = follow-up, ICD-9-CM = International classification of diseases ninth revision clinical modification, mo = month(s), PSQI = Pittsburgh sleep quality index, RLS = restless legs syndrome, SpO2 = blood oxygen saturation, SQ = sleep quality (subjective), SWS = slow-wave sleep (N3), WMH = white matter hyperintensities, y = year(s)

Table 3.4. Summary of study characteristics and results of studies investigating the impact of ischaemic stroke on sleep architecture and sleep quality.

Author, Year	Study Quality (NOS score)	Design, time of assessment administration, outcome variable	Demographics (study country, gender, age)	Sleep measure	Stroke outcome (Total N); Control N	Summary
Alvarez-Sabin et al., 2017 [182]	High (8)	Cross-sectional; nr, PSG in OSA pts with silent cerebral infarction (SCI) vs controls	Spain; 72.1% male, mean: 64.5 y	PSG	61 (183); 122	SCI SA vs controls: *ns*, OSA ↑ lacunar SCI
Bassetti & Aldrich, 2001 [103]	Moderate (6)	Case control; 11.7 d PS, PSG in acute hemispheric, extra-thalamic stroke vs TIA controls	USA; 66.67% male, mean: 62.1 y	PSG	24 (41); 17 TIA matched	IS SA vs TIA (control): TST min ↓ SE % ↓, N2 % ↓, N3-4 ↓. SA in good vs. bad IS outcome: TST ↑, SE % ↑, N2 ↑, sawtooth wave ratio ↑

Chen et al., 2015 [119]	Moderate (5)	Case control; nr, PSG in IS vs controls	China; 64.4% male, mean: 56.6 y	PSG, PSQI, ESS	101 (187); 86	IS SA vs control: TST min ↓, N1 % ↓, N3-4 % ↓, PSQI ↓, WASO % ↑, ESS score ↑, REM % ↑, SL min ↑, RL min ↑; Thalamic SA vs non-thalamic: N2 ↓, N3-4 ↑, SL ↓; Cerebral infarction SA vs subcortical, brainstem, cerebellum: TST ↓, SE ↓, N3-4 ↓, REM ↓, RL ↓, N1 ↑, SL ↑, WASO ↑
Gokkaya et al., 2005 [149]	Moderate (4)	Case control; 6 mo PS, Nottingham health profile (NHP) scores in IS vs controls	Turkey; 70% male, mean: 58.2 y	NHP	39 (108); 58	Chronic IS NHP sleep domain scores vs controls: ↑ (worse)
Giubilei et al., 1992 [151]	Moderate (5)	Case control; ≤ 5 hr + 3 w PS, PSG changes in acute + chronic IS vs controls	Italy; 55% male, mean: 66.3 y	PSG	18 (28); 10	IS SA vs control: REM min ↓, REM/NREM ratio ↓, REM bouts ↓, WASO ↑; ↓ acute REM correlated with worse PS outcome + severity; deep vs supervision lesions (acute): ↓ REM %
Hermann et al., 2008 [96]	High (7)	Cohort; ≤ 1 mo + 3-6 mo PS + ≥ 1 yr PS; stroke	Switzerland; 73.9% male, mean: 48.4 y	PSG, spectral EEG analysis (n=2), self-	46 (58); 12 (peripheral	IS SA vs control: N1 ↑, N2 ↓, spindle density ↓; SA + stroke

		mediated PSG evolution in paramedian thalamic stroke vs controls		report sleep duration	neurological disease controls)	topography PS: unilateral IS ↓ spindle density vs bilateral IS; self-report sleep needs PS ↑ (hypersomnia > in bilateral vs unilateral IS)
Jiang et al., 2013 [142]	Moderate (6)	Case control; ≤ 3 mo PS, PSG in IS + VCIND vs controls	China; 66.67% male, mean: 61 y	PSG, PSQI	48 (152); 48	IS SA vs control: TST ↓, SE ↓, SL ↑, SWS ↓, REM ↓, arousal index ↑, PSQI ↑ (worse)
Karaca, 2016 [150]	Moderate (5)	Cross-sectional; nr, Self-reported SQ in IS vs haemorrhagic stroke	Turkey; 60.9% male, mean: 60.2 y	PSQI	19 (23); 0	IS SQ (mean PSQI) score: 3.0. Regression to estimate PSQI variations: Beck depression inventory score (B = .035, CI: .004-.066), comorbidities (B = .901, CI: .048-1.754)
Katzan et al., 2018 [156]	Moderate (6)	Cohort; median 99 d PS, self-reported sleep disturbance after IS	USA; 54.9% male, mean: 62 y	PROMIS (Patient-Reported Outcomes Measurement Information System)	1195 (1195); 0	IS sleep disturbance scores ↑ (better) vs US population avg (49.2 vs 10.5, p = 0.02); 27.5% of IS pts with meaningfully worse scores (+5 points) vs avg population norms; sleep disturbance associated with worse PS outcome

* Klobučníková et al., 2016 [152]	High (7)	Case control, mean 4 d PS; PSG associations with EDS in acute IS	Slovakia; 56.8% male, mean: 68.36 y	PSG, ESS	93 (102); 0	PSG associations for EDS vs no EDS in IS: ↓ REM, ↑ respiratory disturbance index
Manconi et al., 2014 [148]	Moderate (6)	Cohort; admission + 3 mo PS, PSG in supratentorial vs infratentorial IS	Switzerland; 96% male, mean: 64.8 y	PSG	14 supratentorial IS (14 infratentorial IS); 0	Acute IS SA vs chronic: ↓ SE %, SL min ↑, REM latency ↑; Supratentorial IS SA vs infratentorial = *ns*
Muller et al., 2002 [147]	Moderate (5)	Case control; acute + subacute (not specified), PSG in acute hemispheric IS without sleep apnoea vs controls	Switzerland; 60% female, mean: 53 y	PSG	10 (20); 10	IS SA vs controls: WASO min ↑, SE % ↓; Positive correlation b/w SWS + stroke volume (r = 0.79); NREM SWA sleep/wakefulness ratio ↓ in IS vs control + correlated with NIHSS
Pace et al., 2018 [153]	High (8)	Cohort; ≤9 d PS; PSG evolution in IS + associations of functional outcome	Multicentre (Germany, Italy, Switzerland); 71.9% male, mean: 61.2 y	PSG, ESS	153 (153); 0	PSG associations with poor functional (mRS >2) vs good functional outcome (mRS ≤2): ↓ SE, ↓ REM sleep duration, ↑ REM latency, ↑ AHI; ↑ REM latency predictor of worse outcome PS
Poryazova et al., 2015 [146]	Moderate (4)	Case control; ≤ 10 d + ≤ 3 mo PS, HD sleep EEG in acute and chronic	Switzerland; 75% male, mean: 52 y	HD EEG	8 (16); 8	Acute + chronic IS SA: ↓ SWS, theta activity, spindle frequency ipsilesionally. SWS

		hemispheric IS vs controls				correlations: IS severity (NIHSS) + outcome (Barthel index)
Santamaria et al., 2000 [144]	Moderate (5)	Case control; 14 d PS, Sleep spindle in unilateral acute thalamic IS vs controls	Spain; 53.8% female, mean: 67 y	PSG	13 (31); 18	IS SA vs controls: TST min ↓, N2 % ↓, time in bed min ↓, bilateral sleep spindle ratios ↓
Siccoli et al., 2008 [145]	Moderate (4)	Case control; ≤ 8 d + ≤ 12 mo PS, PSG & cognition in acute and chronic hemispheric IS vs controls	Switzerland; 64% female, mean: 43 y	PSG	11 (16); 5	Acute IS SA vs. chronic IS or controls: SE % ↓, WASO min ↓
Siengsukon & Boyd, 2009 [183]	Moderate (5)	Case control mean 58.8 mo PS, SQ potentiated off-line motor learning in IS vs controls	USA, 50% female, mean: 62.6 y	Sleep log, PSQI, SSS	40 (80); 40	No significant differences between IS vs control average sleep time, PSQI, SSS (*ns*)
Siengsukon et al., 2015 [184]	Moderate (5)	Case control, ≥6 mo PS, SA potentiated offline motor learning in chronic IS vs controls	USA; 63.3% female, mean: 60.6 y	PSG, PSQI, SSS	20 (10); 30	IS SQ vs controls: no significant differences; SA offline motor learning associations in IS vs controls: ↑ SE, ↓ N3, ↑ REM weakly-to-moderately associated with ↑ offline motor learning (*ns*)

Suh, Choi-Kwon, & Kim, 2014 [143]	High (8)	Cross-sectional; 6.7 d PS, VHSS scores + topography in acute IS	South Korea; 58.9% male, mean: 62.3 y	VHSS, actigraphy (in 54 pts)	282 (282); 0	Multiple regression analysis of factors related to VHSS scores: cortical lesion location, diabetes mellitus, depression; SL: depression; night-time awakenings: depression
**Terzoudi et al., 2009 [154]	High (7)	Case control, ≤ 10 d PS, PSG in acute stroke vs controls in relation to outcome + topography	Greece; 64% male, mean: 61.8 y	PSG	45 (78); 16	SA in stroke (excl pts with SDB) vs controls: ↓ TST, ↓ SE, ↓ N2, ↓ SWS; Severe vs mild stroke deficits (NIHSS > 7 vs < 7): ↓ REM, % of N1 + REM negatively associated with stroke severity (NIHSS); ↓ REM % in brainstem, hemispheric, and multiple lesions (vs cerebellar lesions); worse outcome (Barthel index) associated with ↓ REM latency
Vock et al., 2002 [155]	Moderate (5)	Cohort; acute (1-8 d) + subacute (9-35 d) + chronic (5-24 mo) PS, longitudinal SA	Switzerland; 59.2% female,	PSG, sleep diary, ESS	40 (27); 13	IS SA abnormalities vs controls/published norms (no *p* values reported): 67% acute PS, 54% subacute PS,

		evolution in hemispheric IS				53% chronic PS; Acute IS SA vs chronic IS: TST ↑, SE ↓, WASO ↑; ↑ self-reported TST, ↑ WASO, ↑ N1, ↓ SE, associated with worse PS outcome (BI or mRS)
Wu et al., 2016 [141]	Moderate (4)	Cohort; 14 d + 3 mo PS, PSG in acute minor thalamic infarction versus controls	China; 70.4% male, mean: 61.4 y	PSG, PSQI, ESS	27 (39); 12	IS SA vs control: SL min ↓, SE % ↓, N2 % ↓, N3 % ↓
Zhang et al., 2014 [140]	Moderate (5)	Cross-sectional; 2 d + 3 mo PS, SQ in IS vs control	China; 70.3% male, mean: 35.9 y	PSQI	223 (381); 158	IS SQ (PSQI) ↓ vs controls (29.1 vs 47.1), < SQ ↑ 3-mo mRS scores

* Raw data for IS-stratified results were provided upon request by the corresponding authors and calculated according to study methodology by EG and EL. Study quality NOS scores are based solely on data reported in the original peer-reviewed manuscript.

** Results include both ischaemic stroke and haemorrhagic stroke. Authors reported no statistically significant differences in sleep architecture between either stroke types.

Abbreviations: AHI = apnea–hypopnea index BI = Barthel index, IS = ischaemic stroke, d = day(s), ESS = Epworth sleepiness scale, f/u = follow-up, ICD-9-CM = International classification of diseases ninth revision clinical modification, mo = month(s), MSLT = multiple sleep latency test, N1-4 = NREM stages 1-4, NHP = Nottingham health profile, NIHSS = National institutes of stroke scale (stroke severity), PS = post-stroke, PSG = polysomnography, PSQI = Pittsburgh sleep quality index, pts = patients, REM = rapid-eye-movement sleep, RL = rapid-eye-movement latency (total time to first REM bout), RLS = restless legs syndrome, SA = sleep architecture, SCI = silent cerebral infarction, SE = sleep efficiency, SL = sleep latency, SpO2 = blood oxygen saturation, SQ = sleep quality, SSS = Stanford sleepiness scale, SWA = slow-wave activity (ratio), SWS = slow-wave sleep (N3), TIA = transient ischaemic attack, VCIND = vascular cognitive impairment-no dementia, VHSS = Verran-snyder-halpern sleep scale, WASO = wake after sleep onset, WMH = white matter hyperintensities, y = year(s),

Table 3.5. Summary of study characteristics and results of studies investigating the impact of ischaemic stroke on non-apnoea sleep disorders.

Author, Year	Study quality (NOS score)	Design, time of assessment administration, outcome variable	Demographics (study country, gender, age)	Sleep measure	Stroke outcome (Total N); controls	Summary
Bassetti et al., 1996 [132]	Moderate (5)	Cohort; 6 pts < 5-weeks PS, 10 pts < 5-mo PS, 2 pts >1-y PS; PSG in paramedial thalamic IS + hypersomnia vs normative data	Switzerland; 83.3% male, age range: 16-60 y	PSG	12 (12); 0	IS + severe hypersomnia vs norms: N1 % ↑, N2 % ↓, N3-4 % ↓, sleep spindles ↓
Benbir, G. & Karadeniz, D., 2012 [168]	High (7)	Case-control; ≤2-d PS, PLM + RLS prevalence in supratentorial IS vs controls	Turkey; 62.9% male, mean: 68.1 y	PSG	35 (70); 35	PLM-index in male IS ↑ vs controls, IS topography + PLMs: *ns*. RLS in IS ↓ vs controls: 14.3% vs. 20%.
Benbir, G. & Karadeniz, D., 2013 [169]	High (8)	Cross-sectional; admission + 3-weeks + 3-mo PS, PLM + RLS prevalence and association with IS outcome	Turkey; 54.2% male, mean: 69.0 y	PSG, International Restless Legs Syndrome Study Group Diagnostic Criteria (IRLSSGC)	24 (All stroke, 2 RLS); 0	8% (n=2) PS RLS, > arousal-associated PLM-index at admission: ↑ NIHSS, ↓ Barthel scores at 3-mo PS

Boulos et al., 2017a [165]	Moderate (6)	Cohort; 3.9 + 110.4-d PS, RLS after IS and associations with PS QoL	Canada; Total N demographics reported (incl TIA), 51.1% female, mean: 67.4 y	Questionnaire based on IRLSSGC	48 (94); 0	24.4% (n=23, 10 IS) PS RLS. PS RLS ↓ (worse) QoL vs no RLS. RLS predictor of PS QoL score: baseline OR 0.28 (0.10-0.75), 2-6-month f/u OR 0.14 (0.02-0.82)
Boulos et al., 2017b [157]	High (8)	Cross-sectional; median 51 d PS, PLM and WMH incidence after IS	Canada; Total N demographics listed only, 57% male, mean: 63.7 y	Medical history, RLS diagnostic questionnaire (confirmed by sleep neurologist), PSG	16 (30); 14 (TIA)	IS PLM ↑ vs control, IS PLM-index ↑. PLM index + stroke volume correlated with ↑ WMHs.
Chen et al., 2015 [119]	Moderate (5)	Case-control; nr, PSG confirmed SD after IS vs controls	China; 64.4% male, mean: 56.67 y	PSG, PSQI, ESS	101 (187); 86	IS SD prevalence 77%, PS SD NIHSS ↑ vs no SD
Glozier et al., 2017 [159]	High (8)	Cohort; 28-d +, 6, 12-mo PS, self-reported insomnia after IS and associations with PS functional outcome	Australia; Total N demographics listed by insomnia vs no insomnia: insomnia: 57% male, 70% 46-65 y; no insomnia: 74% male, 79% 46-65 y	Karolinska Sleep Questionnaire	304 (368); 0	PS insomnia prevalence 30-37%, chronic insomnia prevalence 16%, chronic insomnia vs no insomnia: ↑ depression, ↑ anxiety, ↑ disability

Kim et al., 2017 [170]	Moderate (7)	Cohort; acute (not specified), insomnia after acute IS	South Korea; Total N (IS + haemorrhagic stroke) demographics only. 56.85% male mean: 65.63 y	Medical records	8205 (10625); 0	PS insomnia prevalence: IS = 305/8205 (3.8%), haemorrhage = 99/2420 (4.27%)
Lee et al., 2009 [167]	Moderate (6)	Cohort; 1-mo PS, RLS after IS	South Korea; 54% male, mean: 63.9 y	IRLSSGC	137 (All IS, 17 RLS); 0	PS RLS prevalence 12.4% (n=17); 94% (n=16) subcortical lesions
Leppavuori et al., 2002 [158]	High (8)	Cross-sectional, 3-mo PS, insomnia after IS	Finland; 50.9%, mean: 70.7 y	DSM-IV criteria	277 (All IS, 157 self-reported insomnia complaints); 0	Self-reported PS insomnia prevalence 57% (n=157), 37.5% (n=104) DSM-IV confirmed; pre-existing in 38.6% of IS, de novo in 18.1%. Independent correlates of de novo insomnia: ↑ dementia, ↑ psychotropic drugs, ↑ anxiety, ↑ Barthal index

Medeiros et al., 2011 [164]	Low (3)	Cohort; ≤15 d + 3-mo + 1-y PS, RLS in acute IS stroke and associations with PS outcomes	Brazil; 61.5% male, mean: 64.0 y	PSQI, IRLSSGC	96 (All IS, 12 RLS); 0	PS RLS prevalence 12.5% (n=12), 100% pre-existing). PS RLS SQ (PSQI) ↓ vs non-RLS. PS (3-12 mo) RLS outcome (Barthel index, mRS) ↓ vs non-RLS
Palomaki et al., 2003 [163]	Moderate (6)	Case-control; ≤14-d + 6, 12, and 18-mo PS, insomnia prevalence after IS and efficacy of mianserin for PS insomnia	Finland; Demographics by treatment condition only. Placebo group: 65.3% males, mean: 54.7 y. Mianserin group: 70.6% males, mean: 55.7 y	Hamilton Depression Scale (3-items related to insomnia), neurologist confirmation if score ≥1	100 (100); 49	PS confirmed insomnia prevalence 51% (n=51) of stroke patients with confirmed insomnia. PS insomnia ↑ poor life satisfaction. 2-mo placebo treatment ↑ insomnia
Rist et al., 2014 [162]	High (8)	Cross-sectional; nr, self-reported RLS after IS	France; Demographics for total N listed only by RLS group. No RLS: 59.7% female, mean: 71.6 y. RLS: 72.9%	3-item self-report questionnaire	88 (1035); 0	PS RLS prevalence: 21% (n=218). WML ↑ RLS risk

			female, mean: 71.6 y			
Ruppert et al., 2014 [166]	Moderate (5)	Cross-sectional; <2-d PS, RLS after brainstem IS	France; 60% male, mean aged 62.8 y	IRLSSGC	30 (30); 0	PS RLS prevalence: 10% (n=3). RLS + topography or severity: ns. RLS + PS sensory symptoms ↑ brainstem IS RLS
Tang et al., 2014 [161]	Moderate (5)	Cohort, 3-mo PS, RBD after IS	Hong Kong; Demographics by RBD status. RBD: 53.8% male, mean: 67.3 y. Non-RBD: 61.3% male, mean: 66.5 y	13-item RBD questionnaire	119 (119); 0	PS RBD prevalence: 10.9% (n=12). Brainstem IS ↑ RBD. IS volume in non-RBD ↑ vs. RBD
Tang et al., 2015 [160]	High (9)	Cross-sectional; 3-mo PS, insomnia after IS	Hong Kong; 60.4% male, mean: 66.1 y	7-item self-report questionnaire	336 (336); 0	PS insomnia prevalence: 44% (n=147); PS insomnia associated with ↓ QoL

Abbreviations: IS = ischaemic stroke, clinical modification, d = day(s), ESS = Epworth sleepiness scale, f/u = follow-up, ICD-9-CM = International classification of diseases, mo = month(s), ninth revision, nr = not reported, PS = post-stroke, PSG = polysomnography, PSQI = Pittsburgh sleep quality index, QoL = quality of life, RBD = rapid-eye-movement behaviour disorder, RLS = restless legs syndrome, RLSSGC =

International restless legs syndrome study group diagnostic criteria, SpO2 = blood oxygen saturation, SQ = sleep quality (subjective), SWS = slow-wave sleep (N3), WMH = white matter hyperintensities, y = year(s),

Table 3.6. Summary of study characteristics and results of studies investigating the impact of ischaemic stroke on circadian rhythms.

Author, year	Study quality (NOS score)	Design, time of assessment administration, outcome variable	Demographics (study country, gender, age)	Circadian rhythm measure	Stroke outcome (Total N); controls	Summary
Adamczak-Ratajczak et al., 2017 [171]	High (7)	Case control, ≤2-d PS, melatonin in acute IS vs controls	Poland; 100% male, mean: 53 y,	Melatonin serum	8 (29); 10	Melatonin amplitude + mesor ↓ after IS
Atanassova et al., 2009 [172]	High (7)	Cross-sectional matched case-control, 3-d PS, melatonin in acute IS vs controls	Bulgaria; 60.6% male, mean: 58.4 y	Melatonin serum	33 (68); 33	Melatonin ↓, cortisol ↑ after IS
Fiorina et al., 1999 [175]	Moderate (4)	Case control, nr, nocturnal and diurnal melatonin excretion in IS vs controls	Italy; 61.5% male, mean: 64.3 y	Urinary melatonin excretion	13 (18); 5	Nocturnal melatonin ↓, diurnal melatonin ns, after acute (3 d) and chronic (2 w) IS
Kantermann et al., 2014 [177]	Moderate (6)	Cross-sectional, 2-mo PS, chronotype (mid-sleep on work-free d corrected for sleep deficit on workdays;	Germany; 62.9% male, mean: 66.3 y	MCTQ	35 (35); 0	Chronotype (MSFsc) ↓ after anterior circulation IS, ↑ after posterior circulation; changes to MSFsc after IS negatively correlated with severity (NIHSS and mRS at discharge): chronotype

		MSFsc) after mild IS				correlation with IS severity: r=−0.565 for NIHSS at discharge, r =− 0.620 for mRS at discharge
Ritzenthaler et al., 2009 [174]	Moderate (6)	Cohort, <1-d PS, melatonin in IS vs controls	France; 69.3% male, age range: 18-50 y: 22.0%, 51-70 y: 36.2%, >70 y: 41.7%.	Melatonin serum, aMT6S	127 (343); 216	Melatonin ↓ after IS, aMT6S after IS ↓ (ns)
Ritzenthaler et al., 2013 [173]	Moderate (5)	Cohort; <1 day, 5-PS, melatonin in IS vs controls	France; 64.3% male, age range: 27.7-88.5 y (median: 73.1 y)	Melatonin serum, aMT6S	42 (232); 190	Melatonin, aMT6S ↓ after IS
Takekawa et al., 2007 [178]	Moderate (6)	Cohort, <7 d PS, circadian rhythm (actigraphy + rectal temperature) ambulatory vs. non-ambulatory pts after mild IS	Japan; No gender information provided. Mean: 68.4 y	Actigraphy, rectal temperature	50 (50); 0	mRS score ↓ in abberant circadian fragmentation group vs. normals: Admission mRS scores between normal, mild, severe/abberant CR groups: 2.8 vs. 2.9 vs. 4.8
Zhang et al., 2017 [176]	Moderate (5)	Case-control, N/A, melatonin in IS + insomnia vs controls	China; Demographics by inomnia group only. Non-insomnia group: 56% male, mean: 58.9 y. Insomnia group: 52% male, mean: 59.7 y	Melatonin serum, MEQ	25 (50); 25	Nocturnal melatonin, GABA, total antioxidants ↓ after IS (+ insomnia) vs. controls; melatonin ↑ NIHSS

Zuurbier et al., 2014 [179]	High (10)	Cohort study, 3 mo PS, circadian fragmentation (actigraphy - intradaily variability) in WML, LI, cerebral microbleeds	Netherlands; 58.1% male, mean: 59.2 y	Actigraphy	43 LI (970); 0	Circadian fragmentation ↑ WML volume + cerebral microbleeds. Circadian fragmentation + LI = ns

Abbreviations: IS = ischaemic stroke, aMT6s = 6-sulphatoxymelatonin (urinary melatonin metabolite), CR = circadian rhythm, d = days, GABA = gamma-aminobutyric acid, LI = lacunar infarction, MCTQ = Munich chronotype questionnaire, MEQ = morningingness-eveningness questionnaire, mo = months, mRS = modified Rankin scale (functional post-stroke outcome), MSFsc = mid-sleep on work-free days corrected for sleep deficit on workdays, NIHSS = National institutes of health stroke scale (stroke severity), ns = non-significant, PS = post-stroke, WML = white matter lesions, y = years

3.4 Discussion

3.4.1 Summary of findings, limitations, and clinical pathogenic implications

To our knowledge, this is the first systematic review to investigate the bidirectional impact of sleep and circadian dysfunction as both a risk factor and consequence of IS. Accumulating data from included studies suggest that chronic sleep dysfunction, characterised by long sleep duration or sleep disorders, significantly increases the risk of IS. Inversely, when compared to controls, IS is associated with sleep and endogenous circadian rhythm disruption which may be associated with IS topography and functional outcome.

We were unable to identify any studies that investigated objective or validated measures of sleep-potentiated circadian rhythm dysfunction as a risk factor for IS. Shift work disorder is a common circadian rhythm disorder and is an independent risk factor for all-cause stroke (RR R: 1.05, CI: 1.01 to 1.09) [185,186]. However, no screened IS studies utilised the only validated shift work disorder questionnaire created by Barger and colleagues (2012) [187].

Despite liberal inclusion criteria, a majority (70 %, n = 47) of studies examined sleep and circadian dysfunction *after* IS. Less than 30% of studies reported *a priori* neuroimaging hypotheses (e.g., IS topography, lesion volumes) related to PS outcome or severity. The most well-defined study designs and samples were from large prospective cohort studies investigating sleep duration and sleep disorders as risk factors for IS. Only one study was classified as low quality or as having a high-risk of bias.

3.4.2 Long sleep duration is a risk factor for IS

Prolonged sleep duration, characterised by eight or more hours of sleep per night, was associated with the highest stroke risk. Findings are consistent with recent meta-analyses reporting increased all-type stroke incidence for long versus short sleep duration [188-191]. Despite recent epidemiological evidence suggesting a U-shaped relationship between short sleep duration and all-cause mortality, our sample of studies did not corroborate these associations for short sleep duration and IS risk [125,192,193].

Depression or depressive symptoms were only adjusted for in two studies [121,123]. Given the frequency of hypersomnia and long-sleeping tendencies in individuals with depression, and the

frequency of depression after stroke, future studies investigating prospective associations with IS should include depression as a covariate, as well as other psychiatric comorbidities [194]. An important limitation is the widespread use of subjective, self-reported sleep duration, although no studies were classified as having a high risk of bias. The use of objective sleep measures (e.g., accelerometer or PSG) are especially necessary among the elderly and in patients with sleep disorders where misperception of sleep is well recognised [195,196]. Furthermore, the total hours of sleep duration were heterogeneously clustered and not measured as continuous variables. For example, while Giangfagna et al. (2016) grouped sleep duration into "≤5, 6, 7, 8, 9, or ≥10 h", Kawachi and colleagues (2016) used a restrictive "≤6, 7, 8, or ≥9 h" grouping [120,125]. No studies examined IS risk beyond ≥10h, thereby limiting potential findings for extreme sleep duration. Importantly, no studies included neuroimaging correlates of sleep duration risk, which may clarify the neuroanatomical basis of pathological long-sleep duration.

The underlying biological mechanisms supporting the association between chronic long-sleep duration and IS pathogenesis are unclear. One possible explanation may be stroke-related proinflammatory biomarkers such as C-reactive protein (CRP). Habitual long sleep duration is associated with elevations in CRP which have shown to significantly increase the risk of IS [197-199]. Furthermore, epidemiological evidence suggests an association between long-sleep duration and stroke-related risk factors including WMHs, atrial fibrillation, arterial atherosclerosis, and left ventricular masses [200-203]. Whether prolonged sleep duration is an independent causal risk factor for IS, or merely a marker of underlying poor health, remains unclear.

3.4.3 Bidirectional impact of sleep architectural and quality dysfunction in IS

Sleep architecture and self-reported sleep quality is compromised after IS. However, there is insufficient evidence among our sample of heterogeneous studies to suggest an association between longitudinal dysfunction to sleep architecture or subjective sleep quality and risk of IS. SWS duration measured in the contralesional hemisphere correlated with stroke volume and outcome. Furthermore, sleep architecture was most severely affected in thalamic and cortical strokes. These findings are consistent with neuroanatomical evidence; thalamocortical projections within the ascending reticular activating system are, in part, responsible for sleep-wake regulation [23].

There are important limitations among these studies. First, no studies included baseline (pre-stroke) polysomnographic characteristics to gauge the causal impact of IS on sleep dysfunction. A majority of studies using PSG also included small samples and did not report or justify effect size calculations. Next, control population types (i.e., TIA vs healthy age and gender-matched controls) were inconsistent across studies. IS populations were also heterogeneous; stroke severities, stroke topographies, and PS time-course differed across studies. Thus, the range and degree of sleep architectural disturbance may be attributed to the heterogeneity of infarct locations (topography) and volumes across studies. Furthermore, a majority of studies did not exclude patients taking known sleep architecture altering drugs (e.g., benzodiazepines, GABA agonists, serotonergic antagonists) or patients with *a priori* sleep disorder diagnoses. Finally, the decrease in SE may be due to deleterious environmental stressors associated with acute hospital care; namely, prolonged or insufficient light exposure, white noise, and overnight clinical interactions [204]. Although sleep architecture is compromised after IS, there is insufficient evidence to suggest a causal relationship between IS and sleep architectural dysfunction. Nonetheless, our findings are consistent with a recent review by Duss and colleagues (2017) postulating sleep-potentiated neuroprotection and neuroplasticity after IS [106].

3.4.4 Non-apnoea sleep disorders are risk factors for IS

Non-apnoea sleep disorders increase the risk of IS after controlling for covariates. Sleep-related movement disorders (i.e., RLS and PLM), insomnia, and self-reported RBD were associated with the highest risk. Furthermore, *de novo* sleep disorders were generally more common after IS when compared to normative averages or controls. However, conclusions for specific sleep disorders cannot be generalised given the small sample of included studies. Studies included relatively young samples (mean age: 55.3 years) with insufficient follow-up periods (mean follow-up period: 5.8 years) to reach peak IS risk ($\geq$ 65 years). Therefore, underestimation of IS risk is likely.

Prevalence of RLS after IS were in line with upper-ranges of normative averages (10-15%) [205]. However, acute and chronic IS symptoms were significantly more severe in patients with RLS. Topographically, subcortical strokes were associated with RLS, particularly when accompanied with PS sensory symptoms. These findings are consistent with a recent prospective study showing RLS as a significant predictor of all-type subcortical stroke [206]. Mechanistically, pre-clinical data also support these findings; subcortical basal ganglia nuclei

and dopaminergic dysfunction has been implicated in the pathogenesis of RLS [207]. The prevalence or severity of PLM, hypersomnia, insomnia, and RBD were generally greater after IS when compared to controls or normative averages [132,208-210]. Furthermore, brainstem infarction was a significant independent predictor of RBD.

In summary, non-apnoea sleep disorders increase the risk of IS after controlling for covariates. It is well established that sleep disorders contribute to sleep fragmentation, increased nocturnal arousals, and atypical sleep architecture. Thus, the proposed mechanisms for sleep disordered IS pathogenesis include sympathetic hyperactivity, hypothalamic pituitary adrenal axis activation, and deficiencies in central dopaminergic neurotransmission [207,211,212]. Longitudinal sleep-potentiated autonomic dysfunction may increase the prepathological risk of IS, and dysautonomia *after* IS may be exaggerated during sleep thereby obstructing PS recovery [213].

3.4.5 Circadian rhythms are disrupted after acute IS

Melatonin, an endogenous marker of circadian rhythms, is reduced after IS when compared to controls. Diminution of melatonin, and self-reported chronotypic changes, were associated with increased PS severity (NIHSS) and worse functional outcome at discharge (mRS). Importantly, nocturnal melatonin sampling occurred in light-controlled environments, thereby limiting the confounding effects of light exposure on pineal secretion of endogenous melatonin. No studies reported duration, intensity (lux), and wavelength (e.g., blue light, 540nm) of *daytime* light exposure – hence it was not feasible to determine whether altered circadian function was likely due to a direct impact of IS or secondary to altered environmental light exposure. No studies included pre-stroke or longitudinal measures of melatonin concentrations which limits directional and causal associations between circadian misalignment and IS. Importantly, the impact of potential sleep pathology after IS on circadian rhythmicity was not investigated in studies included in our sample. Circadian rhythm outcomes were not stratified by neuroanatomical IS topography and were heterogenous across studies. Focal suprahypothalamic lesions disrupt slow-wave-sleep potentiated elevations of growth hormone [214]. However, whether melatonin secretion in humans is impacted by focal lesions to the intergeniculate leaflet (which innervate the suprachiasmatic nucleus and pineal gland), or is disturbed as part of diffuse neurovascular injury or altered exposure to Zeitgebers, remains unclear.

The neuroprotective function of melatonin has been established in pre-clinical models of focal and diffuse brain ischaemia [109]. Melatonin initiates free radical scavenging and secondary antioxidant actions which exhibit a daily rhythm and are inhibited by light in humans [215]. In IS, the melatonin rhythm is impaired, with a reduction in nocturnal amplitude or a tendency to phase delay or advance. However, whether these effects are transient or chronically sustained requires further investigation. The radiological impact of varying stroke severities and topographies on melatonin secretion should be further evaluated using novel neuroimaging methods. The interplay of sleep pathology commonly reported after IS should also be measured in conjunction with endogenous circadian rhythm disruption.

Exogenous melatonin treatment in acute animal focal ischaemia has a neuroprotective effect [216]. Transcranial near-infrared light therapy has been implicated in photobiomodulation via normalisation of misaligned circadian rhythms and motor function recovery after embolic stroke in animals [217]. Thus, both exogenous melatonin supplementation and near-infrared light therapy should be assessed in randomised trials in acute human IS given their reported neuroprotective efficacy in pre-clinical models.

3.4.6 Limitations

Given the lack of homogeneity across studies and outcomes, there was limited scope for conducting a meta-analysis. Furthermore, findings from this review cannot be generalised across other stroke types (i.e., haemorrhagic, TIA) or varying stroke topographies given the marked differences in pathophysiology. Whenever possible, study-specific stroke topography and stroke severity characteristics have been reported in supplementary tables. An additional limitation is publishing or reporting biases of only *positive* findings.

The Newcastle Ottawa Scale is widely used and has been validated as a study quality assessment tool for non-RCTs [118]. However, the NOS may not give sufficient weight to validated (i.e., polysomnography) versus less informative or reliable sleep-measurement tools (e.g., actigraphy, sleep diary). It is therefore possible that a study scored as "high quality" utilises inferior sleep-measurement tools if other NOS criteria is met (e.g., exceptional sample size, sample representativeness, controls, and robust statistical methodology). Alternatively, a study utilising polysomnography may be scored as moderate or low-quality if accompanying NOS criteria is not fulfilled.

Finally, 43 screened studies investigating sleep or circadian dysfunction after stroke did not differentiate or stratify results by stroke type (e.g., TIA vs ischaemic vs haemorrhagic). Attempts were made to contact corresponding authors for addition stratified data or clarification. However, response rates were poor (28%, n = 12) and only six (14%) corresponding authors provided stratified data, thereby restricting our sample of included studies.

3.5 Conclusions

This systematic review revealed that long sleep duration and sleep disorders increase the risk of developing IS. Inversely, after IS, sleep and endogenous rhythm disruption is common and may be associated with IS severity and outcome. We were unable to identify any studies investigating the impact of longitudinal circadian rhythm dysfunction on IS risk. As evidenced by our study sample's heterogenous methodology, the direct assessment of sleep and circadian rhythms in IS is an emerging field in its infancy. Future studies should standardise sleep and circadian measurement methodology and incorporate *a priori* neuroimaging-specific outcomes. Additional recommendations are outlined in our research agenda.

3.5.1 Research agenda

Future studies investigating sleep and circadian dysfunction in human ischaemic stroke should address shortcoming described in pre-existing literature and specifically:

1. Longitudinal polysomnographic measurement of objective sleep architecture in conjunction with radiological measures of brain features (location, volume, activity) should be assessed to further establish the causal impact of chronic sleep dysfunction on ischaemic stroke
2. Direct and objective measures of circadian rhythms should be longitudinally assessed in large prospective cohorts to determine the impact of chronic circadian dysfunction on IS risk
3. Studies investigating sleep and ischaemic stroke should stratify results by strict delineations of homogenous stroke topography and severity
4. Observational follow-up periods should be extended to better determine the transient or sustained effects of post-stroke sleep and circadian dysfunction

5. Future clinical IS sleep research should control for important covariates including depression and other psychiatric comorbidities, stroke severity, stroke topography, and sleep-altering drugs
6. Future studies investigating circadian rhythms after ischaemic stroke should measure daytime environmental light exposure to determine whether this is the source of altered circadian function post-stroke
7. Exogenous melatonin supplementation and light therapy should be clinically evaluated in randomised trials of acute ischaemic stroke.

Chapter 4

Regional neurodegeneration correlates with sleep-wake dysfunction after stroke

In the previous chapter, I conducted a systematic review of the extant sleep, circadian rhythm, and stroke literature and identified a bidirectional relationship between sleep-wake dysfunction and ischaemic stroke. However, no studies included a priori neuroimaging hypotheses which limited our ability to determine the *in vivo* pathogenesis of sleep-wake dysfunction after stroke. This chapter explores the relationship between objectively measured sleep-wake dysfunction and regional neurodegeneration in stroke patients and healthy controls. The text in this chapter has been published as an original article in the journal *SLEEP* (Gottlieb et al., 2020). See Appendix A for the full published paper, and the Preface for full disclosure.

4.1 Introduction

Stroke affects over 15 million people annually and is a leading cause of long-term disability and death worldwide [218]. Sleep-wake dysfunction is bidirectionally associated with the pathogenesis and evolution of stroke and may be a modifiable cerebrovascular risk factor [219,220]. The authors of recent meta-analyses and systematic reviews pinpoint excessively long sleep duration, characterised by greater than eight hours of sleep, as an independent risk factor for ischaemic stroke incidence and death [219,221]. Pronounced sleep-wake pathology is described following infarction to thalamo-mesencephalic structures and is associated with impaired cognition and psychomotor performance [222,223]. However, manifestations of sleep-wake disturbances differ across studies and may be attributed to heterogeneous stroke aetiologies and regional brain volumes of affected sleep-wake structures [119,154,224]. Notwithstanding, the neuroanatomical circuitry responsible for sleep-wake dysfunction after stroke constitutes an enigma in the field. It is unclear whether post-stroke sleep deficits are due to focal infarction to sleep-wake structures, or diffuse and accelerated post-stroke brain atrophy to subcortical structures common after cerebrovascular disease [219,225,226]. Identification of neuroanatomical markers of sleep-wake dysfunction following stroke, through *a priori* neuroimaging hypotheses in conjunction with objectively measured sleep, is critical for the development of targeted treatments.

Pioneering contributions from Moruzzi and Magoun (1949) first identified the ascending brainstem reticular activating system (ABRAS) as principally responsible for sleep-wake function [227]. They theorised that diffuse cortical projections from the ABRAS synapsed in the thalamic midline and intralaminar nuclei. A decade following these findings it became doctrinaire that the thalamus was the arousal-promoting hub in the brain [228]. However, these

assumptions have been challenged by results from experimental ablation of the thalami. For example, athalamic cats and rodents do not exhibit alterations to behaviourally observable sleep-wake rhythms, with only minor electroencephalographic attenuations to sleep spindles [229]. In humans, severe arousal impairment is associated with thalamic strokes that extend into the midbrain and-or pontine tegmentum, whereas participants with focal thalamic lesions do not exhibit comparable arousal impairment [230]. Ablation to the dorsal striatum suppresses non-rapid-eye movement (NREM) sleep [231-233], and cerebellectomised cats demonstrate chronic drowsiness and decreased wakefulness [234]. These findings support the case for diffuse sleep-wake function in subcortical brain structures beyond the thalamus.

Seamless function of the "flip-flop" homeostatic sleep-wake switch is dependent upon inhibition of sleep-promoting structures (e.g., ventrolateral preoptic nucleus), and activation of arousal-promoting structures (e.g., pons) along the ABRAS [235]. Regional brain volume reductions after stroke, or neurodegeneration to thalamo-cortical ABRAS tract integrity, may exacerbate sleep problems already common among ageing populations [236]. While these processes are well-documented after experimental lesion in non-pathological animal models and in vitro, the volumetric and tractographic neuroanatomical markers of sleep-wake dysfunction following stroke remain unexplored in humans beyond small series case studies.

In this cross-sectional study, we describe the first post-stroke brain volumetric and fibre-specific white-matter correlates of objectively measured sleep in a cohort of ischaemic stroke participants (n = 112), imaged on average, 99 days (range: 44 – 158 days) after stroke. We characterised sleep dysfunction after stroke as excessively long (>8 hr) sleep duration (n=24) or poor sleep efficiency (<80%) (n=29). Our primary structural and fixel-based approach focused on long-sleep duration, given it is both a well-established ischaemic stroke risk factor and feature of post-stroke sleep deficits. We compared their results to healthy, age-matched controls with normal sleep duration (between 6 and 8 hours of sleep) (n = 25) or optimal sleep efficiency (greater than 80%) (n = 35). Regions of interest (ROI) were *a priori* selected on the basis of their established salient involvement in sleep-wake function, and their availability in FreeSurfer's automated subcortical parcellations based on the Desikan-Killiany Atlas [237]. We hypothesized that long sleep duration and poor sleep efficiency at 3-months post-stroke would be associated with reduced regional brain volumes of sleep-wake regions of interest (ROI). In a subset of participants with available diffusion magnetic resonance imaging (dMRI) (n = 93),

we conducted a whole brain fixel-based analysis (FBA) to examine long sleep-related differences in fibre-specific white matter pathways [238]. We hypothesised that stroke participants with excessively long sleep duration would exhibit extensive degeneration in key white matter pathways connecting the ABRAS.

4.2 Methods

4.2.1 *Participants*

Data from the prospective, longitudinal Cognition And Neocortical Volume After Stroke (CANVAS) study were analysed [239]. The CANVAS study includes participants with first-ever or recurrent ischaemic stroke within any circulation [240], aetiology [241], and no history of dementia or other neurodegenerative condition. The protocol and inclusion criteria for control participants were identical to stroke participants, except that control participants were stroke free. Participants were recruited from three hospitals in Melbourne, Australia: Austin Health, Eastern Health, Melbourne Health. The study was approved by each of the hospital's human research ethics committees in line with the Declaration of Helsinki [239,242]. Data from the 3-month post-stroke time-point (stroke n = 112, control n = 40) were used to avoid confounding environmental sleep stressors found in acute intensive care units, such as prolonged or insufficient light exposure, white noise, and overnight clinical interactions [243]. Participants with untreated obstructive sleep apnoea were excluded.

The presence of ischaemic stroke was a clinical diagnosis, radiologically confirmed on clinical computed tomography (CT) or magnetic resonance imaging (MRI) during the acute hospitalisation of the incident event. Stroke participants who were unable to undergo a 3T MRI scan or, because of severe aphasia, were unable to provide informed consent or follow basic instructions, were excluded. Participants with transient ischaemic attacks and no confirmed dMRI changes on MRI were excluded. As well, those with significant medical comorbidities precluding participation in cognitive-behavioural testing were excluded from participation.
Sleep-wake measurement

Sleep duration and sleep efficiency (the ratio of total sleep time to time in bed) were measured using BodyMedia's SenseWear armband (SWA) (mean wear time = 6.4 days, range = 1 – 13). Participants wore the SWA for approximately 1-week immediately following their dMRI

sequence assessment (mean: 99 days, range: 44 – 158 days post-stroke). The SWA is worn on the upper left arm and utilises a combination of accelerometry, near-body ambient skin temperature, heat flux, and galvanic skin response to measure sleep-wake. Validation of the SWA armband against gold-standard polysomnography has been conducted in healthy participants [244,245], adolescents [246], and in participants with obstructive sleep apnoea with an average sleep-wake epoch agreement of 80 $\pm$ 1.6% [247]. The accelerometer uses a microelectromechanical sensor which has a scale of ±2 g and a sensitivity of 167 mV/g. With respect to sleep duration, raw data output is binary (i.e., 1 = sleeping, 0 = awake). Physiological data are processed by proprietary algorithms to compute sleep duration and sleep efficiency. Sleep-wake estimations are computed in 1-minute epochs across a single main night-time sleep period. Averages were extracted using BodyMedia's software (InnerView, BodyMedia, Pittsburgh, PA).

4.2.2 Image acquisition and stroke lesion mapping

Whole brain images were acquired on a 3T Siemens Tim Trio Scanner with a 12-channel head coil (Siemens, Erlangen, Germany). The MR images for the presented analyses were acquired using a T1-weighted 3D magnetisation-prepared rapid gradient (MPRAGE) sequence with the following parameters: 160 sagital slices, repetition time RT = 1900 ms, echo time TE = 2.6 ms, inversion time TI = 900 ms, flip angle = 9°, matrix size = 256 × 256, voxel size = 1 × 1 × 1 mm^3 isotropic. High-resolution, 3D sampling perfection with application-optimised contrasts using different flip angle evolutions (SPACE)-fluid-attenuated inversion recovery (FLAIR) images were also acquired for white matter hyperintensity estimation and stroke lesion tracing: 160 sagittal slices, 1 mm thick, RT = 6000 ms, TE = 380 ms, 120° flip angle, and 256 x 256 acquisition matrix. Acquisition of dMRI images was performed using echo-planar imaging (EPI) with the following parameters: repetition time = 8400 ms, echo time = 110ms, voxel size = 2.5 × 2.5 × 2.5mm^3). Sixty diffusion weighted images (b=3000 s/mm^2) and eight images without a diffusion weighting (b=0) were acquired. For susceptibility induced distortion correction, a pair of non-diffusion weighted images with reverse phase encoding were also acquired.

Stroke lesion maps were generated in order to visualise the lesion localisation topography of the sample. Percentage overlay stroke lesion maps were delineated on fluid-attenuated inversion recovery (FLAIR) images for all stroke participants in the study (n=112) and were

not stratified by sleep metrics. Axial slices are displayed in conventional radiological format. Warm colours in yellow and red indicate areas of highest percentage overlap.

4.2.3 FreeSurfer pre-processing

Cortical reconstruction and volumetric segmentation were performed with the FreeSurfer image analysis suite (version 6.0) (http://surfer.nmr.mgh.harvard.edu/) [248]. FreeSurfer segmentation includes motion correction, removal of non-brain tissue, Talairach transformation, segmentation of subcortical white matter and deep grey matter structures, intensity normalisation, tessellation of the grey matter white matter boundary, topology correction, and surface deformation following intensity gradients. Subsequent pre-processing steps are based on the common information from the within-participant template and include skull stripping, Talairach transforms, atlas registration, creating spherical surface maps and parcellations [249]. Further technical details of FreeSurfer's cortical reconstruction and segmentation procedure have been described previously [250]. The unbiased template was created for each participant using the T1 MPRAGE scans collected each time-point [251]. Tissue segmentations for individual participants were visually inspected and corrected for quality assurance.

4.2.4 Whole brain fixel-based analysis

Diffusion-weighted imaging is the gold-standard method to assess white matter architecture *in vivo*. The vast majority of studies investigating sleep-potentiated white matter brain changes have analysed dMRI data using the diffusion tensor imaging (DTI) model [252-254]. Briefly, the DTI model posits that the structural integrity of white matter can be estimated by comparing metrics that are derived from a voxel: defined as a single sample, or data point, on a regularly spaced, three-dimensional grid. However, a major limitation of DTI is its limited ability to model and differentiate complex crossing fibre populations. These are present in approximately 90% of all white matter voxels and are likely particularly prevalent in sleep-related white matter tracts [255,256]. Thus, these voxel-averaged DTI metrics are now regarded as less sensitive in detecting abnormalities in the white matter. Newer methods look at fibre elements – known as fixels – across the whole brain. The term 'fixel' refers to fibre bundles or populations with potentially differing orientations that are present within a voxel. In contrast to DTI methods, these whole brain fixel-based analyses are regarded as being more sensitive to differences

within the orientation of specific fibre populations, and may characterise neurodegenerative differences to fibre populations within voxels more robustly [238,257,258]. A fixel-based analysis can be used to estimate total intra-axonal volume differences in the tissue microstructure (fibre density, FD) and the fibre-bundle cross-section macrostructure (fibre cross-section, FC). We use a combined fibre density and bundle cross-section (fibre density and cross-section, FDC) metric to assess both the micro- and macro-architecture of sleep-related white matter neurodegeneration.

4.2.5 dMRI pre-processing

dMRI data was pre-processed using MRtrix3 (https://www.mrtrix.org) and MRtrix3Tissue (https://3tissue.github.io) [259]. dMRI images were preprocessed by denoising the data [260], removing Gibbs ringing artefact [261], field map correction of eddy-current distortions [262], motion correction [263], and bias-field correction (N4, http://stnava.github.io/ANTs/). After these initial pre-processing steps, fibre orientation response functions (FODs) were obtained using Single-Shell 3-Tissue Constrained Spherical Deconvolution, with group-averaged response functions for white matter, grey matter, and cerebrospinal fluid tissue compartments. These response functions (+b=0) were directly estimated from the dMRI data themselves yielding group average anisotropic single fibre white matter response functions (b≠0) and isotropic grey matter and cerebrospinal fluid response functions using an unsupervised method [264]. Spatial correspondence for tissue specific FOD's was achieved by generating a population template using a subset of 30 participants (15 stroke participants, 15 healthy controls) using an optimised non-linear transformation model [265]. Subsequently, each individual FOD image was non-linearly registered to the template using an FOD-guided registration method and a bespoke automated method was used to intensity normalise and bias-field correct all FOD images from each tissue compartment [266,267].

4.2.6 *Choice of brain regions for volumetric analyses*

Regional volume estimates were generated from FreeSurfer default cortical and subcortical parcellations based on the Desikan-Killiany Atlas [237]. For these ROI analyses, we focused on the following structures given their involvement in sleep-wake function: bilateral (left and right) thalami, bilateral caudate, bilateral putamen, bilateral hippocampi, bilateral amygdala, bilateral accumbens, bilateral pallidum, and brainstem.

4.2.7 Statistical analyses

Statistical analyses were conducted in MATLAB (2018a). All analyses were two-tailed and a critical p-value of 0.05 was used. Differences between groups on demographic and clinical variables were examined using independent samples *t*-tests (continuous variables, parametrically distributed scores), Mann-Whitney *U* tests (continuous variables, non-parametrically distributed scores), and Fisher Exact tests (categorical variables).

We analysed the effect of sleep-wake variables (long sleep duration, n = 24; poor sleep efficiency, n=29) on ipsi (on the same hemisphere as the lesion) and contralesional (opposite hemisphere to the lesion) thalamic, caudate, putamen, hippocampus, amygdala, accumbens, pallidum, and brainstem volumes using a univariate linear regressions model both between- (stroke versus control) and within- (stroke versus stroke) group. Healthy controls with optimal sleep characteristics (normal sleep duration: between 6-8 hours of sleep, n=25; and optimal sleep efficiency: $\geq$80%, n=35) were selected as comparators. Stroke participants with lesions or infarcts in any ROIs were excluded from volumetric analyses in order to reduce the direct effects of peri-infarct involution and atrophy within the infarct site.

For each ROI, we compared groups using a base linear regression model, with age, sex, education, and total intracranial volume (TIV) included as covariates. Body mass index (BMI) and depression were added as covariates in an extended model. The linear regression model was implemented using the MATLAB function, fitlm, with default settings (e.g., 'modelspec', 'linear'; 'RobustOpts', 'off'). We did not correct for multiple testing as the analyses were exploratory. We, therefore, provided unadjusted effect sizes for all volumetric comparisons and included only a priori-selected regions of interest. Age was included to account for loss of brain volume due to normal aging; sex to control for sexual dimorphism; education to adjust for its protective effect on cerebral structures; BMI to correct for risk of undiagnosed obstructive sleep apnoea [268]; depression to control for psychiatric hypersomnia mediating long sleep duration; and TIV to control for head size variations.

In stroke participants with available dMRI data (n=93), a whole-brain fixel-based analysis was conducted in order to identify tracts with altered white matter fibre integrity. We utilised a combined measure of fibre density and cross-section (FDC) in the long sleep duration (> 8 hr, n = 20) and normal (between > 6 hr and < 8 hr) sleep duration (n = 59) groups versus controls

(n = 40). Herein, we use the term whole-brain fixel-based analysis to refer to a comparison of all white matter fixels identified within the brain. Statistical comparisons of fibre density and fibre bundle cross-section (FDC) between groups were performed at each white matter fixel by a General Linear Model, comparing (i) long sleep duration (> 8 hr) in stroke participants versus healthy controls; (ii) long sleep duration versus normal sleep duration (< 8 hr) in stroke participants; and (iii) normal sleep duration (between > 6 and < 8 hr) in stroke participants versus healthy controls. With respect to nuisance covariates, we undertook a minimalist approach and included age, sex, and TIV in accordance with previously published whole-brain fixel-based analysis work [258]. Connectivity-based smoothing and statistical inference was performed using connectivity-based fixel enhancement (CFE), using 2 million streamlines from the template tractogram, and with default smoothing parameters (smoothing = 10 mm full-width at half-maximum, C = 0.5, E = 2, H = 3) [238]. Note that in CFE, smoothing is preferentially applied along structurally connected fixels, ensuring that fixel-based metrics are locally smoothed with fixels belonging to the same fibre tract. Family-wise error (FWE)-corrected P-values were then assigned to each fixel using non-parametric permutation testing over 5000 permutations [269].

Significant fixels (FWE-corrected P-value < 0.05) were then displayed using the mrview tool in MRtrix3. To better appreciate the fibre pathways implicated, significant fixels were displayed on the template-derived tractogram, in which streamlines were cropped to only those fixels that were significant. Significant streamlines were colour-coded either by streamline orientation (left-right: red, inferior-superior: blue, anterior-posterior: green), or by the effect size expressed (thresholded from 0 to 40 percent) as a percentage relative to healthy controls or normal sleepers' group. Both whole-brain fixel-based statistical analyses and visualizations were performed in MRtrix3.

4.3 Results

4.3.1 *Participant demographics*

Demographic, cerebrovascular, mood, and stroke characteristics between participants with stroke and healthy controls, and between excessively long versus normal stroke sleepers, are listed in Tables 4.1-4.3. Stroke characteristics in participants with poor versus optimal sleep

efficiency are listed in Table S4.1. Demographic, cerebrovascular, and sleep characteristics in participants with missing versus available dMRI data are listed in Table S4.2.

Control participants had attained a higher level of education, higher National Adult Reading Test IQ (NART) scores, and a lower prevalence of atrial fibrillation (Table 4.1). Participants with stroke had reduced sleep efficiency relative to controls (p = 0.033, mean: 82.92 vs. 85.58). No other sleep-wake variables significantly differed between groups (e.g., mean sleep duration, percentage of long sleepers [>480 mins], percentage of short sleepers [< 360 mins], mean days SWA worn, Table 4.2).

Demographics	Stroke (*N* = 112)	No.	Control (*N* = 40)	No.	*p*
Age in years, M ± SD	68.18 (11.41)	112	68.83 (6.63)	40	0.923†
Sex, male *n* (%)	79 (71%)	112	25 (63%)	40	0.428‡
Education in years, M ± SD	12.82 (3.80)	112	15.48 (4.53)	40	0.001†
Body mass index, M ± SD	27.91 (4.37)	112	26.58 (3.77)	40	0.091§
NART-FSIQ, M ± SD	111.95 (10.78)	102	118.71 (9.85)	39	0.001†
Hypertension diagnosis, *n* (%)	71 (63%)	112	17 (43%)	40	0.026‡
Hyperlipidemia diagnosis, *n* (%)	48 (43%)	112	14 (35%)	40	0.455‡
Atrial fibrillation diagnosis, *n* (%)	23 (21%)	112	1 (3%)	40	0.005‡
Ischemic heart disease, *n* (%)	12 (11%)	112	2 (5%)	40	0.357‡
Type 2 diabetes mellitus, *n* (%)	27 (24%)	112	4 (10%)	40	0.068‡
High alcohol intake (>14 standard drinks per week), *n* (%)	14 (13%)	112	7 (18%)	40	0.435‡
Depression diagnosis, *n* (%)	11 (10%)	112	4 (10%)	40	1‡
ApoE_e4 (≥1 allele), *n* (%)	20 (20%)	98	4 (11%)	38	0.216‡

ApoE, apolipoprotein E allele; NART-FSIQ, National Adult Reading Test-Full Scale; No., number of participants included in each variable without missing data; M, mean; SD, standard deviation.
†Mann Whitney *U* test.
‡Fisher's exact test.
§Independent samples *t*-test.

Table 4.1. Demographic characteristics of stroke and all control participants. Reproduced with permission from original publication.

Sleep variables	Stroke (*N* = 112)	Control (*N* = 40)	*p*
Sleep efficiency ratio, M (SD)	82.92 (7.23)	85.58 (5.14)	0.033†
Average sleep duration in mins, M (SD)	428.80 (75.61)	435.15 (65.05)	0.592†
Long sleepers (≥8 h), *n* (%)	24 (21%)	9 (23%)	1‡
Short sleepers (≤6 h), *n* (%)	17 (15%)	6 (15%)	1‡
Days SenseWear worn, mean (SD)	6.32 (1.49)	6.13 (1.55)	0.953†

M, mean; SD, standard deviation.
†Mann Whitney *U* test.
‡Fisher exact test.

Table 4.2. Sleep characteristics in stroke and control participants. Reproduced with permission from original publication.

4.3.2 Stroke characteristics

Long-sleepers were more disabled at admission (79% of long-sleepers with modified Rankin Scale [mRS] 0-2 at baseline versus 84% non-long sleepers, p=0.05) and at time of diffusion imaging 3 months after stroke (again 79% versus 92%, p=0.038) (see Table 4.3).

No significant differences in stroke characteristics were found between stroke participants with poor (<80%) versus optimal (>80%) sleep efficiency (see supplementary Table S4.2).

Stroke characteristics	Sleep duration ≥8 h (*n* = 24)	No.	Sleep duration <8 h (*n* = 88)	No.	*p*
Infarct volume, mean (mm^3)	5,957.92	24	7,275.43	88	0.676†
Oxfordshire criteria, *n* (%)		24		88	0.39‡
Lacunar (LACI)	4 (17%)		13 (15%)		
Posterior (POCI)	7 (29%)		31 (35%)		
Partial anterior (PACI)	12 (50%)		44 (50%)		
Total anterior (TACI)	1 (4%)		0 (0%)		
Stroke side, *n* (%)		24		88	0.601‡
Left	7 (29%)		32 (36%)		
Right	17 (71%)		53 (60%)		
Bilateral	0 (0%)		3 (4%)		
Tissue plasminogen activator administered, *n* (%)	3 (13%)	24	11 (13%)	88	1‡
mRS (0–2 vs. 3–4) Baseline, *n* (%)	19 (79%)	24	74 (84%)	88	0.05‡
mRS (0–2 vs. 3–4) 3 months, *n* (%)	19 (79%)	24	81 (92%)	88	0.038‡
NIHSS Baseline, M (SD)	3.38 (3.29)	24	3.05 (2.69)	88	0.655§
NIHSS 3 months, M (SD)	1.08 (1.79)	24	.83 (1.38)	88	0.525§
Days from stroke to 3-month review, M (range)	99.88 (23–158)	24	100.72 (44–460)	82	0.457†

M, mean; No., number of participants included in each variable without missing data; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; SD, standard deviation.
†Mann Whitney *U* test.
‡Fisher's exact test.
§Independent samples *t*-test.

Table 4.3. Stroke characteristics in participants with long versus non-long sleep duration. Reproduced with permission from original publication.

4.3.3 Regional brain volume differences

Stroke participants with long sleep duration (n=24) had lower volumes in the contralesional amygdala (B=-129.56, SE=60.73, p=0.03) and trending in the ipsilesional thalamus (B=-383.40, SE=191.95, p=0.052), and larger contralesional pallidum (B=109.95, SE=53.72, p=0.04) when compared to controls with normal sleep duration (between >6 and <8 hr, n = 25) (see Table 4.4). No significant brain volumetric differences were found in stroke participants with long versus normal sleep duration (see Table S4.3).

Stroke participants with poor sleep efficiency (n=29) had lower volumes in the ipsilesional thalamus (B=-332.73, SE=112.04, p=0.004) and contralesional hippocampus (B=-186.98, SE=92.42, p=0.04) when compared to healthy controls with normal sleep efficiency (>80%, n = 35). Amygdaloid volumes were numerically smaller but did not reach significance (B=-85.97, SE=50.76, p=0.09). Larger volumes in stroke participants were found for the bilateral caudate (ipsi: B=301.36, SE=127.82, p=0.02; contra: B=293.48, SE=88.87, p=0.001). The contralesional pallidum volumes were numerically larger but did not reach significance (B=84.55, SE=48.09, p=0.08) (see Table 4.5).

Stroke participants with poor sleep efficiency had lower ipsilesional amygdala volumes (B=-123.62.62, SE=56.32, p=0.03) when compared to stroke participants with optimal sleep efficiency (see Table S4.4).

Region of interest	Est	SE	g (CI)	*p*
Accumbens—Ipsi	−6.68	29	0.18 (−0.38, 0.74)	0.81
Accumbens—Contra	−32.8	30.19	0.46 (−0.1, 1.03)	0.27
Amygdala—Ipsi	83.23	70.11	−0.17 (−0.73, 0.39)	0.23
Amygdala—Contra	−129.56	60.73	0.6 (0.03, 1.18)	0.03†
Brainstem	−511.81	521.91	0.33 (−0.23, 0.9)	0.32
Caudate—Ipsi	−99.9	124.11	0.14 (−0.43, 0.72)	0.42†
Caudate—Contra	152.47	126.44	−0.21 (−0.78, 0.36)	0.23
Hippocampus—Ipsi	−84.65	107.35	0.31 (−0.25, 0.88)	0.43
Hippocampus—Contra	−99.06	92.37	0.41 (−0.16, 0.98)	0.28
Pallidum—Ipsi	27.89	57.84	−0.04 (−0.6, 0.52)	0.63
Pallidum—Contra	109.95	53.72	−0.41 (−0.98, 0.15)	0.04
Putamen—Ipsi	−181.87	220.31	0.28 (−0.3, 0.87)	0.41
Putamen—Contra	167.55	154.82	−0.24 (−0.83, 0.34)	0.28
Thalamus—Ipsi	−383.4	191.95	0.64 (0.06, 1.25)	0.052
Thalamus—Contra	24.98	181.88	0.16 (−0.42, 0.74)	0.89

Stroke participants with lesions in ROIs were excluded (*n* = 3 thalamus, *n* = 1, hippocampus, *n* = 2 caudate, *n* = 3 putamen).
†Signifies use of extended model (including BMI and PHQ-9).

Table 4.4. Regional brain volumetric differences in stroke participants with long (≥8 h) sleep duration (n = 24) versus healthy controls with normal (between >6 and <8 h) sleep duration (n = 25). Reproduced with permission from original publication.

Region of interest	Est	SE	g (CI)	*p*
Accumbens—Ipsi	−24.94	25.09	0.21 (−0.29, 0.7)	0.32
Accumbens—Contra	−37.34	26.2	0.33 (−0.17, 0.82)	0.15
Amygdala—Ipsi	−49.86	59.62	0.13 (−0.36, 0.63)	0.4
Amygdala—Contra	−85.97	50.76	0.18 (−0.31, 0.67)	0.09†
Brainstem	−484.7	467.87	0.06 (−0.43, 0.55)	0.3
Caudate—Ipsi	301.36	127.82	−0.53 (−1.05, −0.03)	0.02
Caudate—Contra	293.48	88.87	−0.76 (−1.28, −0.25)	0.001
Hippocampus—Ipsi	−72.25	95.48	0.3 (−0.19, 0.8)	0.45†
Hippocampus—Contra	−186.98	92.42	0.35 (−0.14, 0.85)	0.04
Pallidum—Ipsi	28.51	46.57	−0.18 (−0.68, 0.32)	0.54
Pallidum—Contra	84.55	48.09	−0.41 (−0.91, 0.09)	0.08
Putamen—Ipsi	−105.3	158.29	0.05 (−0.44, 0.55)	0.5
Putamen—Contra	140.21	145.97	−0.34 (−0.84, 0.16)	0.34
Thalamus—Ipsi	−332.73	112.04	0.35 (−0.16, 0.86)	0.004
Thalamus—Contra	−105.49	120.09	0.02 (−0.48, 0.52)	0.38

Stroke participants with lesions to ROIs were excluded (n = 2 thalamus, n = 1 caudate, n = 1 putamen, n = 1 pallidum).
†Signifies use of extended model (including BMI and PHQ-9).

Table 4.5. Regional brain volume differences in stroke participants with poor (<80%) sleep efficiency (n=29) versus healthy controls with optimal (≥80%) sleep efficiency (n=35). Reproduced with permission from original publication.

4.3.4 Whole brain fibre-specific white matter differences

Figure 4.1 shows the whole brain fixel-based analysis streamline segments associated with significant fibre tract-specific FDC decreases in stroke participants with long sleep duration (>8 hr) compared to healthy controls. Streamline segments were cropped from the template tractogram to include only those corresponding to fixels that exhibited a significant (FWE-corrected P-value <0.05) difference in the FDC metric in the stroke group, coloured by effect size (percent decrease) and fibre orientation.

Stroke participants with long sleep duration exhibited FDC reductions within the right thalamocortical tract in regions projecting to the ABRAS when compared to healthy controls. Bilateral degeneration to the corticopontocerebellar tract was extensive, with some fibre regions (e.g., superior cerebellar peduncle) exhibiting FDC reductions of up to 40%. Bilateral pontine degeneration was observed along the cerebellar peduncles, particularly at the decussation of the superior cerebellar peduncle.

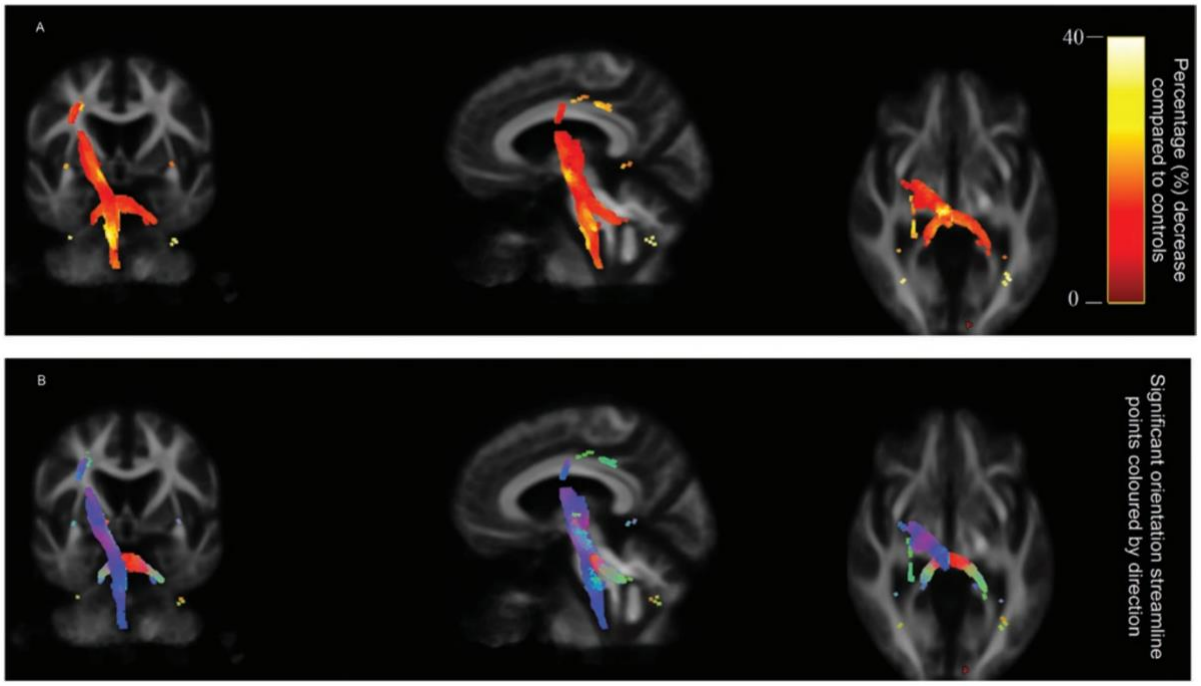

Figure 4.1. Whole-brain FBA of stroke participants with long sleep duration (>8 h, n = 20) compared with healthy controls (n = 40) revealing significant neurodegeneration to the corticopontocerebellar tract among long sleepers. Streamline segments were cropped from the template tractogram to include only streamline points that correspond to significant fixels (FWE-corrected p-value < 0.05). Streamlines were coloured by percentage effect (thresholded from 0% to 40%) decrease in the stroke group compared with the healthy control group for FDC. Significant orientation streamline points are coloured by direction (anterior–posterior: green; superior–inferior: blue; left–right: red). Reproduced with permission from original publication.

Figure 4.2 shows FDC reductions and orientation in the normal sleep (between > 6 and <8 hr) stroke group compared to all healthy controls. White matter degeneration was extensive across the whole-brain and most apparent along the corpus collosum, inferior fronto-occipital fasciculus, and cingulum. Visually comparing the patterns of white matter degeneration in the 'long-sleep stroke vs. control' and 'normal sleep stroke vs. control' analyses, we observed spatially distinct results, with only some overlap across certain pontine fibre tracts; however, the distribution in the normal sleeping stroke participants was less extensive (i.e., no cortico-cerebellar projections) and the percentage effect reductions did not exceed 20 %. No significant whole-brain FBA differences were found between the long-sleep stroke versus normal-sleep stroke groups.

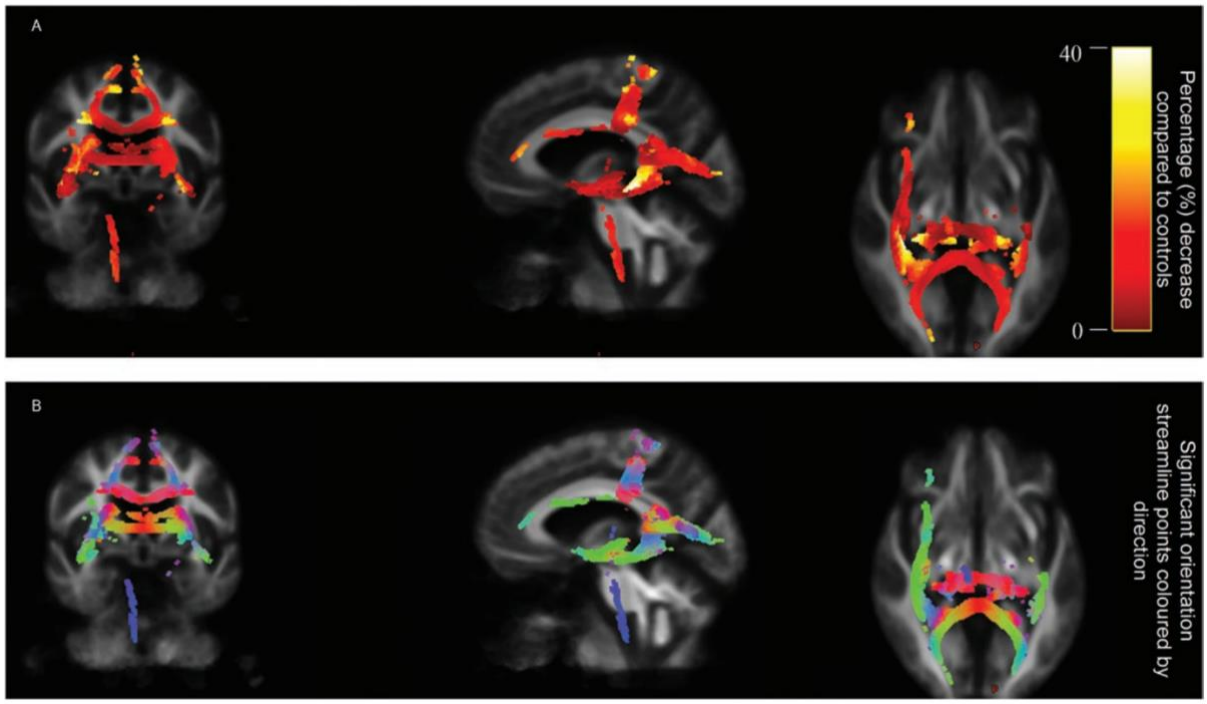

Figure 4.2. Whole-brain FBA of stroke participants with normal sleep duration (between >6 and < 0.05, n = 59) compared with healthy controls (n=40) revealing widespread degeneration across the whole brain and most apparent within the corpus callosum, inferior fronto-occipital fasciculus, and cingulum. Streamline segments were cropped from the template tractogram to include only streamline points that correspond to significant fixels (FWE-corrected p-value < 0.05). Streamlines were coloured by percentage effect (thresholded from 0% to 40%) decrease in the stroke group compared with the healthy control group for FDC. Significant orientation streamline points are coloured by direction (anterior–posterior: green; superior–inferior: blue; left–right: red). Reproduced with permission from original publication.

4.4 Discussion

The present study identified sleep-wake correlates of regional brain volumetric and white matter degeneration after stroke. The major disease-related findings included the following: (i) stroke participants with long sleep duration and poor sleep efficiency generally exhibited subcortical regional brain volume reductions relative to healthy, optimal sleeping, controls; (ii) fibre-specific white matter degeneration to the corticopontocerebellar tract was associated with long sleep duration after stroke compared to controls and was different from white matter degeneration pattern observed in normally sleeping stroke participants compared to controls; and (iii) stroke participants with long sleep duration were more disabled at admission and 3-months post-stroke compared to non-long sleepers. This exploration of the volumetric and fibre-specific white matter sleep-wake correlates offers valuable insight into the potential neuroanatomical pathogenesis of post-stroke sleep disruption. These findings add to the growing literature implicating sleep-wake dysfunction as markers of poor cerebrovascular

health. Hereon, we describe the potential clinicopathological implications of sleep-related vascular neurodegeneration and attempt to corroborate experimental and clinical mechanistic, neuroanatomical findings.

4.4.1 *The potential for reduced regional brain volumes to drive sleep-wake dysfunction*

To explicitly investigate how sleep dysfunction contributes to neurodegeneration beyond the effect of stroke infarction itself, we examined volumetric differences of *a priori* selected ROIs in stroke participants with excessively long duration and poor sleep efficiency. Stroke participants with long sleep duration exhibit reduced regional volumes of the contralesional amygdala and trending ipsilesional thalamus when compared to controls. Poor sleep efficiency after stroke was associated with reduced regional volumes of the ipsilesional thalamus and contralesional hippocampus when compared to controls with optimal sleep efficiency. Finally, stroke participants with poor sleep efficiency exhibited reduced ipsilesional amygdala volume when compared to stroke participants with optimal sleep efficiency. Given the cross-sectional design of the present study, we are unable to pinpoint causation or directionality. However, we have previously reported a bidirectional relationship between sleep disruption and stroke [219], and here, we propose that post-stroke sleep dysfunction in the form of excessive sleep duration or poor sleep efficiency is associated with degeneration to sleep-wake ROIs. In addition, we posit that subcortical sleep-wake structures, which appear to be differentially affected and vulnerable to accelerated brain volume loss after stroke, may drive sleep-wake dysfunction after stroke, independent of lesion location (see Figure 4.3).

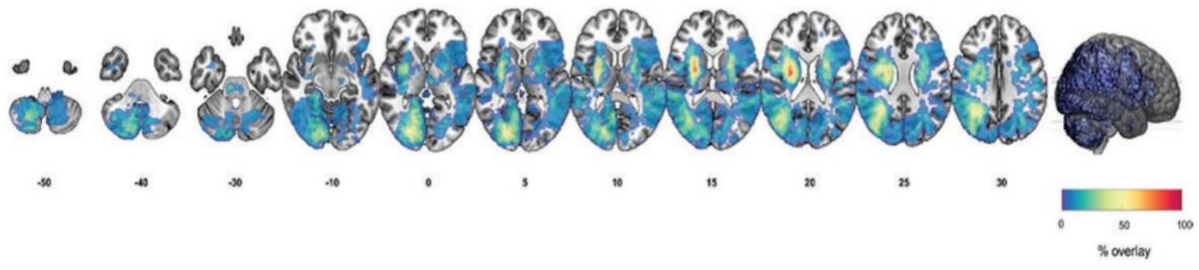

Figure 4.3. Lesion localisation mapping of participants with stroke diagnosis. Percentage overlay stroke lesion maps were delineated on FLAIR images for all stroke participants in the study (N = 112). Axial slices are displayed in conventional radiological format. Warm colors in yellow and red indicate areas of the highest percentage overlap. Reproduced with permission from original publication.

Regions in which we found volumetric reductions associated with long-sleep duration and poor sleep efficiency, including the thalamus, amygdala, and hippocampus play critical roles in sleep-wake functioning. Several authors have reviewed in detail the neurobiological mechanisms subserving local sleep-wake regulation in animal models and healthy subjects [270]. They have established that the sleep-wake system is mediated by a diffuse and complex multi-hierarchical neural network [271,272]. Interactions between various subcortical structures initiate global changes in neural states via, but not limited to, the dorsal ABRAS, a key hub of neuronal sleep-wake circuitry. Beyond the ABRAS, however, human PET studies also demonstrate the functional neuroanatomical role of amygdalo-cortical interactions for REM sleep [273], and hippocampal networks for orchestrating sleep-related oscillatory activities [271,274,275]. The ABRAS consists of a myriad of brainstem nuclei that project to the cortex via thalamic and extra-thalamic neurotransmitter-specific pathways [276]. These pathways include pontine serotonergic fibres [277], norepinephrine synthesis from the pontine locus coeruleus [278], dopaminergic fibres from the ventral tegmentum [279], cholinergic fibres from the caudal midbrain and rostral pons [280], and rostral pontine glutamatergic fibres [281]. While not statistically significant, regional brainstem volume was reduced in stroke participants with sleep-wake dysfunction across all experimental conditions.

While neuroanatomical markers of poor sleep efficiency have not been explored post-stroke, volumetric correlates of long-sleep duration after stroke have been described in small series case studies involving focal brain lesions and *de novo* hypersomnia and narcolepsy. These case reports show that focal ischaemic brain lesions that affect the ABRAS are associated with arousal inhibition. For example, severe hypersomnia is a presenting symptom of acute paramedian thalamic stroke and accompanied by NREM fragmentation and impaired cognition [282-285]. Hypersomnolence and narcolepsy have also been proposed as the primary manifestation of midbrain strokes that extend into the thalamus or from degenerative pontine lesions [230,286]. Indeed, focal lesions to the thalamus that extend into the posterior fossa/ABRAS region have an acute effect on sleep-wake activity; however, we excluded participants with infarction in our ROIs (see Figure 4.3 for lesion localisation mapping of all stroke participants). It is important to note that these case reports largely occur in the hyper-acute to acute stages of stroke where deleterious environmental stressors of acute hospital care may confound sleep and circadian measures – either by inducing overnight sleep deprivation which, in turn, triggers excessive sleep rebound, or by altered circadian exposure to Zeitgebers [287]. Here, we show that

sleep-wake associated reductions to regional brain volumes of subcortical sleep-wake structures may *not* be transient – occurring in the chronic stages of stroke (approximately 3-months after incident) in participants with long sleep duration and poor sleep efficiency independent of environmental stressors, confounding comorbidities, and lesion location.

Cerebrovascular disease has been associated with accelerated global brain volume loss, yet subcortical sleep-wake structures appear to be particularly susceptible to vascular neurodegeneration [288]. For example, preliminary findings of subcortical atrophy to the striatum and thalamus have previously been described following cerebral infarction [226,289-291]. Furthermore, stroke may cause delayed brain atrophy in the ipsilesional hemisphere – degeneration likely related to the area of acute ischaemia [290]. Interestingly, we did not observe any discernible difference in the proportion of contralesional or ipsilesional structures affected in poor sleepers. These findings suggest that volumetric reductions identified in poor stroke sleepers are unlikely to be driven directly by stroke lesions and may be driven by vascular risk factors [292]. The direction and cause of this degeneration is difficult to gauge within the current design; pre-morbid sleep dysfunction may exacerbate neurodegeneration in susceptible populations with vascular risk factors [293,294].

Harris and colleagues report that post-stroke hypersomnia is associated with functional independence measure scores 16-points below the mean and a ten-fold increased risk of requiring aged care home [282]. We also identified a functional recovery deficit, as stroke participants with long sleep duration had significantly higher mRS scores at admission and 3-months post-stroke when compared to normal sleepers. The proposed pathophysiological mechanisms subserving the observed relationship between long sleep duration and reduced neurological recovery are numerous and may be associated with confounders which were included as covariates (e.g., depression, sleep apnoea) and-or true mediators of the effect (e.g., shortened photoperiod/phase advanced circadian rhythms, lethargy, systemic inflammation, degeneration as a proxy/manifestation of post-stroke disability) [295]. Alternatively, the demonstrable reductions to sleep efficiency seen in our stroke sample may also be associated with fragmentation to slow-wave sleep, a principle driver of glymphatic clearance function in the brain [63]. Compromised glymphatic activation after stroke may impair extracellular clearance of toxic solutes (e.g., glutamate) and contribute to neuronal excitotoxicity, thereby exacerbating neurological deficits [107].

Less explicable are the significant volumetric *increases* to the contralesional pallidum in stroke participants with long sleep duration, and bilateral caudate in stroke participants with poor sleep efficiency. A possible contributor to these observed increases could be a function of endogenous brain remodelling whereby intense axonal sprouting, dendritic branching, and synaptogenesis occurs in the post-acute ischaemic phase [296]. In a small sample of 28 participants, Abela and colleagues found grey matter volume expansion within the caudate nucleus [297]. Extensive white matter hyperintensities, common in stroke participants, have also been associated with increased brain volume changes in cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) and may be caused by global increases in cerebral water content [298]. Here, the injured brain exhibits a re-emergence of an ontogenetic state: glial, and especially astrocytic, expansion assuages neuronal excitability and enables synaptic plasticity. However, it is unclear why either the pallidum or caudate are exclusively selected; glial cells and neuroblasts provide basic trophic support independent of brain region and have low selectivity for specific neuronal populations [299].

4.4.2 *Cortico-ponto-cerebellar tract degeneration may mediate long sleep duration*

We employed a fixel-based analysis to characterise white-matter fibre density and bundle cross-section (i.e., morphological changes) associated with long sleep duration after stroke. In contrast to other diffusion tensor imaging modes such as fractional anisotropy or mean diffusivity, fixel-based analyses can resolve crossing fibres which occur in approximately 60-90% of adult human brain tissue. Crossing fibres may be particularly prevalent in complex multi-hierarchical sleep-wake tracts of interest such as the ABRAS [255]. We found that stroke participants with long sleep duration exhibit bilateral white matter degeneration to the cortico-ponto-cerebellar tract when compared to healthy controls. Furthermore, stroke participants with normal sleep duration (between 6-8 hours) displayed a widespread distribution of white matter reduction, suggesting specificity of the corticopontocerebellar tract for excessive sleep duration after stroke.

Unlike the ABRAS, which contains no cerebellar projections, the corticopontocerebellar tract contains key afferent pontine fibres which synapse in the cerebellar cortex via the cerebellar peduncles. Briefly, thalamocortical fibres project to the dentate nucleus through the superior cerebellar peduncle and cross midline at the level of the midbrain to synapse at the ventrolateral

thalamus. Thalamic afferents descend adjacent to the corticospinal tracts and synapse in the medulla [300].

The bilateral pontocerebellar degeneration among our stroke participants with long sleep duration has important sleep-wake implications. Firstly, the pons, and particularly the locus coeruleus located within the rostral pons near the pons-midbrain junction, is a key sleep-wake node [280,301]. Orexin-1 receptors found in the locus coeruleus promote sleep-state stability [302]. Orexin-receptor knockout mice exhibit behavioural hypersomnolence similar to those of human narcolepsy [303,304]. In humans, pontine lesions are associated with locked-in syndrome and hypersomnia [305]. In the present study, five participants suffered focal pontine lesions and all exhibited long sleep duration, suggesting that pontine degeneration and focal stroke topography may be associated with the genesis of long sleep duration.

While injury to corticopontocerebellar tract is mainly associated with ataxia and weakness, arousal impairment may also be related to muscular activation, potentially mediated by degeneration to the descending reticular activating system and thalamocortical tracts [306]. Interestingly, while not known to generate endogenous sleep oscillations, the cerebellum contains significant sleep-wake gene expressions in the brain [307] yet has been characterised as "uncharted land" in sleep research [308]. Cell populations known to impact arousal project to the cerebellum, such as cholinergic inputs from the pons and peduncles, and dopaminergic inputs originating in the ventral tegmental area [308]. Our finding of cerebellar degeneration in excessively long sleepers aligns with convincing evidence from investigations of spinocerebellar ataxias such as Machado-Joseph disease and sleep dysfunction [309]. Participants with Machado-Joseph disease, a spinocerebellar ataxia syndrome characterised by neurodegeneration to the cerebellum and its reciprocal thalamocortical fibre projections, exhibit both REM and NREM-arousal dysfunction [310]. Moreover, experimental ablation of the superior peduncle, the main cerebellar output pathway, and a region we found associated with extensive degeneration in long sleepers, causes increased drowsiness and decreased wakefulness [234]. An fMRI case study on a patient Kleine-Levin syndrome, a rare idiopathic hypersomnia characterised by exceptionally long sleep duration, identified reduced thalamic and pontine functional connectivity indicative of ABRAS degeneration [311]. Together, these findings substantiate our results and pinpoint a neuroanatomical basis and potential biomarker for excessively long sleep duration, nested within the corticopontocerebellar tract.

4.4.3 *Alerting therapies for stroke-related hypersomnolence*

Recovery of hypersomnolence after stroke has shown to be concurrent with recovery of injury to the ABRAS in case reports [312-314]. Pharmacological treatment of hypersomnolence after stroke through eugeroics/wakefulness-promoting agents (i.e., modafinil, amphetamines) or monoamine oxidase inhibitors has not, to our knowledge, been studied. As the aetiology and pathophysiology of non-stroke related hypersomnia remains unclear, treatment may require a combined sleep-behavioural intervention (CBT-i), circadian light therapy, and eugeroic pharmacological intervention [315]. Development of interventions for post-stroke related hypersomnia is warranted and should target the neural substrates of structures which we found were associated with sleep-wake dysfunction.

4.4.4 Limitations

The cross-sectional design of the present study limited our ability to investigate the directionality or causation of sleep-potentiated brain changes. In addition, our sleep measures were limited to sleep duration and sleep efficiency; polysomnographic-EEG measures provide more specific sleep architectural data. Given our exclusive use of accelerometer, we were unable to confirm whether other sleep disorders beyond sleep-apnoea were driving our sleep-duration findings (e.g., narcolepsy). We were unable to examine volumetric correlates of the hypothalamus or ventrolateral preoptic nucleus, a key sleep-wake region of interest, due to its exclusion from FreeSurfer's validated atlas which we used to generate our regional volumes. Additional limitations lie in our stroke sample: our cohort included relatively mild strokes; we were unable to obtain pre-stroke or post-mortem imaging; and we did not have useable dMRI imaging for all participants.

4.4.5 Conclusions and future directions

Our findings suggest that stroke participants with post-stroke sleep dysfunction in the form of long sleep duration and poor sleep efficiency exhibit a subcortical pattern of regional brain volume reduction and white matter degeneration to the corticopontocerebellar tract. To further characterise the neuroanatomical pathogenesis of post-stroke sleep dysfunction, future work should incorporate longitudinal polysomnography, the gold-standard for sleep measurement, to identify sleep architectural signatures or disorders which may, over time, underlie long-sleep duration and poor sleep efficiency after stroke. Future work with larger subsamples of stroke

participants with sleep-wake dysfunction should also examine the relationship between the dMRI indices and sleep-wake parameters using a correlational methodology to reveal whether there is, for example, a linear decrease in FDC metrics with linearly increasing sleep duration. Studies informed by our exploratory whole-brain findings could further explore FDC differences in specific *a priori* defined tracts within the corticopontocerebellar region. In addition, future studies should chart the neuropsychological and psychomotor changes likely subserving sleep-potentiated brain changes after stroke [223]. Finally, longitudinal examination of pharmacological or behavioural treatment of sleep disruption to abate post-stroke vascular neurodegeneration and neurological disability is warranted.

Chapter 5

Sleep-wake parameters can be detected in chronic stroke patients using a multi-sensor accelerometer: a validation study

Longitudinal and prospective measurement of sleep after chronic stroke remains poorly characterised due to a lack of validated objective and ambulatory sleep measurement tools in neurological populations. In this Chapter, I conduct a validation study of a multi-sensor sleep monitor, the SenseWear Armband, in ischaemic stroke patients and controls using at-home polysomnography. The text in this chapter has been published as an original article in the *Journal of Clinical Sleep Medicine* (in press, Gottlieb et al., 2020).

5.1 Introduction

Stroke is a leading cause of long-term disability and death worldwide [218]. Sleep-wake dysfunction is bidirectionally associated with the pathogenesis and evolution of stroke and may be a key modifiable risk factor for stroke [220,316]. Excessively long sleep duration characterised by greater than eight hours of sleep is an independent risk factor and consequence of ischaemic stroke [190], [317]. Inversely, sleep efficiency is significantly reduced in patients with stroke and positively correlated with post-stroke recovery [101]. Despite the rise in interest in sleep-wake dysfunction as a modifiable risk factor for stroke , the tools used to measure sleep-wake after stroke are heterogeneous [316]. Poor validation methodologies of existing wearable sleep technology have limited their use in larger, prospective studies conducted in ambulatory settings [318].

Polysomnography, despite being recognised as the gold standard for sleep-wake detection, is intrusive and generally conducted for only 1-5 nights [319]. The use of polysomnography is therefore unsuitable for prospective cohort studies requiring longitudinal sleep-wake measurement. Sleep diaries and validated sleep-wake questionnaires are inherently subjective and potentially unreliable in populations with neurological disease, where sleep-state misperception may be a feature of sleep-wake pathology [320]. The development and validation of ambulatory, objective, and non-invasive sleep-wake monitors is warranted. Recent guidelines have established a set of best practices for validation studies [319]. Whether ambulatory sleep-wake monitors accurately and reliably detect sleep-wake states in stroke populations is unclear, particularly given stroke patients often display abnormal sleep architecture and a higher prevalence of sleep disorders [101].

Traditional sleep-wake wearables solely utilise accelerometery to estimate sleep via micromovement detection. Recent advances in wearable technologies have enabled the use of multi-sensor arrays to robustly quantify sleep-wake parameters. For example, the BodyMedia Sensewear Armband™ (SWA, BodyMedia Inc., Pittsburgh, PA, USA) utilises a dual-axis accelerometer, galvanic skin response sensors, heat flux sensors, skin temperature sensors, and a near-body ambient temperature sensor to provide a more comprehensive breadth of physiological observations to enhance the accuracy of sleep estimation [321]. Previous validation of the SWA armband against polysomnography has been conducted in healthy participants [244,245], adolescents [246], and in patients with obstructive sleep apnoea [322], but not in clinical

populations with neurological disorders. The present validation study was designed to assess the clinical utility of the SWA as a sleep monitor against ambulatory at-home polysomnography (home-PSG) in participants with stroke and healthy controls by addressing the agreement between the SWA and home-PSG both at the patient and epoch-by-epoch level.

5.2 Materials and methods

5.2.1 Participants

Participants were recruited from the Cognition and Neocortical Volume After Stroke (CANVAS) study cohort. The CANVAS study includes participants with first-ever or recurrent ischaemic stroke within any circulation [323] or aetiology [241], and no history of dementia or other neurodegenerative condition. The protocol and inclusion criteria for control participants were identical to stroke participants, except that control participants did not have a history of stroke. Patients were recruited from three hospitals in Melbourne, Australia: Austin Health, Eastern Health, Melbourne Health. The study was approved by each hospital's human research ethics committee in line with the Declaration of Helsinki [242]. Patients with untreated or diagnosed obstructive sleep-apnoea were excluded. Patients with narcolepsy and those taking medications with a primary effect on sleep architecture, as measured by EEG during the time of the study, were excluded. Ischaemic stroke was a clinical diagnosis and radiologically confirmed on clinical computed tomography or magnetic resonance imaging (MRI) during acute hospitalisation for the event. Patients were excluded if they were unable to undergo a 3T MRI scan; were unable to provide informed consent due to severe aphasia; were diagnosed with transient ischaemic attack or failed to have their stroke confirmed on CT or MRI; or had significant medical comorbidities precluding participation in cognitive-behavioural testing. Participants were recruited, on average, 4.10 years post-stroke (SD: 0.91).

5.2.2 *Sleep-wake protocol*

The protocol for the present study was split into two time-points. During time-point 1, participants wore the SWA and completed a 16-item sleep diary for at least one week. Time-point 1 sleep data provided an "average" sleep-day used to schedule participants' at-home polysomnography examination. During time-point 2, participants were fitted with an ambulatory home-PSG device (Somté PSG version 2.0, Compumedics, Limited, Abbostford, Victoria, Australia) and wore, in tandem, the SWA for 1-night at home. Participants completed a 16-item sleep diary and an array of demographic, mood, and sleep-circadian questionnaires.

The SWA was attached to the upper right arm according to manufacturer recommendations. The SWA utilises a combination of accelerometry, near-body ambient skin temperature, heat flux, and galvanic skin response to measure sleep-wake. The accelerometer includes a microelectromechanical sensor, which has a scale of ±2 g and a sensitivity of 167 mV/g. With respect to sleep duration, raw data output is binary (i.e., 1 = sleeping, 0 = awake). Sleep-wake averages from time-point 2 were extracted using BodyMedia software (InnerView, BodyMedia, Pittsburgh, PA) and used as primary validation outcome variables.

Home-PSG was conducted under the supervision of a a trained sleep scientist in accordance with the AASM manual version 2.6 [324] and 2020 ANZSSA/ASA guidelines [325]. Profusion PSG Sleep Software (V4.5 Build 468, Compumdics Limited, Abbotsford, Vic, Australia) was used to analyse sleep. Six-lead EEG placement was used in accordance to the international 10–20 system (F4-M1, C4-M1, O2-M1; F3-M2, C3-M2, O1-M2). For stroke patients, ipsilesional and contralesional hemisphere EEG were scored independently due to the potential effects of infarction and regional brain volume loss on unihemispheric sleep [317, 326].

Sleep and respiratory scoring were completed by an experienced research-grade sleep scientist. The scientist remained blinded to the healthy versus lesioned hemisphere until both hemispheric sleep-wake analyses were completed. Upon completion of independent bi-hemispheric sleep-wake analyses, the scientist was unblinded to the lesioned hemisphere and utilised the contralesional hemisphere's sleep-wake states and arousal events for scoring respiratory events that were used in subsequent calculations, such as the apnoea–hypopnoea index (AHI). Thus, sleep-wake variables were scored (blindly) in the ipsilesional and contralesional hemispheres by the sleep scientist to allow for comparisons based on lesion location, whereas respiratory parameters were scored contralesionally to allow for comparison between healthy controls and stroke participants, in which case the health-state of the hemisphere used could be a confounder for respiratory events [327,328]. In addition to EEG, the following were recorded via home-PSG: electrooculogram (EOG – left and right placement), electromyogram (EMG – mentalis/submentalis), electrocardiogram (ECG – modified lead II), pulse oximetry (PO –SaO2), respiration (oro-nasal airflow – nasal canula), respiratory inductance plethysmography (RIP – chest and abdominal wall movement), and leg EMG.

5.2.3 Patient macro-level outcomes

Total sleep time, sleep onset latency, wake after sleep onset, and sleep efficiency (the ratio of total sleep time to time in bed) were included as patient-level macro measures of sleep-wake. Total sleep time and sleep efficiency were automatically computed using SWA's proprieatary software (Body Media® InnerView® Research Software). Sleep onset latency was manually calculated using subjectively measured "lights out" time assessed from sleep diary time which was confirmed with the SWA's detection of first "lay" time. Wake after sleep onset was manually calculated as periods of wakefulness after first defined sleep onset.

5.2.4 Epoch-by-epoch micro-level outcomes

Epoch-by-epoch analyses and harmonisation of SWA and home-PSG data were conducted in accordance with previously published SWA validation methodologies [245,247,329]. The binary (1 = sleeping, 0 = awake) SWA's sleep-wake estimations were computed in 1-minute epochs across a single main night-time sleep period. Home-PSG sleep-wake data were analysed in 30-sec segments (epochs) and were used as the reference comparator for the SWA. PSG sleep epochs (NREM 1-3 and REM) and wake epochs were converted to binary (sleep = 1, wake = 0) to mirror SWA output binary data. As the SWA is limited to 1-minute epoch sampling, each 1-min SWA epoch was divided into two 30-sec epochs to mirror PSG epochs as previously reported. For example, a 1-minute SWA sleep epoch was converted to two 30-sec sleep epochs to match home-PSG epochs. SWA and home-PSG data exports were synchronised on the same network of computers to ensure time-zone outputs were matched between measures. Secondary manual checks of time synchronisation for each epoch were conducted when binary SWA and home-PSG data were aligned.

5.2.5 *Statistical analyses*

Statistical analyses were conducted in SPSS Version 26 (IBM Corp., Armonk, NY, USA) and Stata 15IC (Stata Corp., College Station, TX, USA). Reduced major axis regressions and concordance statistics (i.e., Bland Altman, Lin's concordance coefficients) were conducted in Stata. Epoch-by-epoch agreements, Cohen's kappa coefficients, and demographic and clinical comparisons were computed in SPSS. All analyses were two-tailed and a critical p-value of 0.05 was used. Continuous variables were summarised by median (Mdn) and interquartile ranges (IQR), and mean and standard deviation (SD). Categorical variables were summarised

by number (n) and percent. Mann-Whitney U tests were used for comparisons between continuous measures as normality testing can be severely underpowered in small samples. Fisher exact tests were used for 2x2 categorical variables.

For the patient macro-level analysis, the agreement between SWA and PSG in total sleep time, sleep onset latency, sleep efficiency, and wake after sleep onset was estimated using Lin's concordance correlation coefficients (CCC) and further investigated using Bland-Altman limits of agreement and Reduced Major Axis regression (RMAR) [330]. The RMAR yields a slope and an intercept. A slope different from 1 is indicative of the presence of proportional bias, when the magnitude is disagreement between two methods increases or decreases proportionally to the measured values. Under the absence of proportional bias, an intercept different from 0 is indicative of the presence of fixed bias, when the magnitude is disagreement between two methods is constant across the range of measured values. The results of RMAR are reported as scatterplots that include both the line of perfect concordance and the fitted RMAR line.

For the epoch-by-epoch micro-level analysis, sensitivity and specificity of SWA to correctly identify individual epochs as "sleep" or "wake" on PSG were estimated. Epoch-by-epoch agreement between home-PSG and the SWA were estimated for individual patients using Cohen's Kappa coefficient, where $k = 1$ demonstrates perfect agreement and $k = 0$ demonstrates agreement based on chance alone. Viera and Garrett's (2005) kappa scoring interpretation for agreement between measures was used [331].

5.3 Results

A total of 44 participants (28 stroke patients, 16 healthy controls) underwent simultaneous overnight home-PSG and SWA monitoring. One stroke patient was excluded due to SWA data loss. Polysomnographically measured total sleep time, sleep efficiency, sleep onset latency, and wake after sleep onset were not statistically different between groups (ipsilesional-stroke versus control). Stroke patients had a higher prevalence of moderate-to-severe obstructive sleep apnoea (defined as apnoea–hypopnea index [AHI] > 15/hr: 57% vs 38%, $p = 0.09$) and higher arousal index (ARI) compared to controls (20 vs 12.50, $p=0.03$). Participant demographics, stroke characteristics and sleep metrics for stroke participants and healthy controls are summarised in Table 5.1. Stroke characteristics are listed in supplementary Table S5.1.

	Stroke (N=28)	Control (N=16)	p
Demographic characteristics			
Age in years, Mdn (IQR)	70 (63.25, 77)	76 (71.50, 77.50)	0.07[a]
Sex, male n (%)	22 (79%)	10 (63%)	0.30[b]
Education in years, Mdn (IQR)	12.50 (10.75, 15.25)	16 (10.75, 18)	0.19[a]
Body mass index, Mdn (IQR)	28.02 (26, 30.53)	25 (23, 26)	0.87a
NART-FSIQ, Mdn (IQR)	112.30 (104.30, 120.80)	119.30 (111.05, 124.15)	0.19[a]
Family history of stroke, n (%)	9 (32%)	5 (31%)	1[b]
Family history of dementia, n (%)	6 (21%)	6 (38%)	0.30[b]
Depression diagnosis, n (%)	3 (11%)	2 (13%)	1[b]
Hyperlipidaemia diagnosis, n (%)	10 (36%)	8 (50%)	0.53[b]
Hypertension diagnosis, n (%)	13 (46%)	6 (38%)	0.75[b]
Ischaemic heart disease, n (%)	2 (7%)	2 (13%)	0.61[b]
Atrial fibrillation diagnosis, n (%)	3 (11%)	0 (0%)	0.29[b]
Type 2 diabetes mellitus, n (%)	5 (18%)	0 (0%)	0.14[b]
High alcohol intake (> 14 standard drinks per week), n (%)	2 (7%)	2 (13%)	0.61[b]
ApoE_e4 (≥1 allele), n (%)	7 (25%)	1 (6%)	0.22[b]
PHQ-9, Mdn (IQR)	3 (1.25, 5.75)	1 (1, 2)	0.039[a]
GAD-7, Mdn (IQR)	0.50 (0, 3.5)	0 (0, 1)	0.16[a]
PSG measured sleep-respiratory characteristics			
Total sleep time, min, Mdn (IQR)	319.50 (280.50, 375.75)	319 (278.37, 341.75)	0.59[a]
Sleep efficiency, ratio, Mdn (IQR)	70.50 (60.75, 78.62)	72.75 (57.37, 78.00)	0.73[a]

Sleep onset latency, min, Mdn (IQR)	8.00 (3.62, 16.37)	14.25 (9.37, 18.00)	0.08[a]
Wake after sleep onset, min, Mdn (IQR)	119.50 (94.25, 168.00)	110.50 (90.12, 189.87)	0.75[a]
Apnea–hypopnea index/hr, Mdn (IQR)	25.00 (9.25, 33.25)	10.00 (7.0, 21.25)	0.09[a]
Arousal index/hr, Mdn (IQR)	20.00 (13.00, 27.75)	12.50 (10.25, 19.75)	0.03[a]
Moderate-severe OSA, n (%)	16 (57%)	6 (38%)	0.09[b]

Table 5.1. Participant demographics and sleep-respiratory characteristics of all stroke participants and healthy controls. ApoE: apolipoprotein E allele; GAD-7: General Anxiety Disorder 7-item questionnaire, IQR: interquartile range (25^{th}, 75^{th} quartiles) M: mean; NART-FSIQ: National Adult Reading Test-Full Scale; Mdn: median; MOSA: obstructive sleep apnoea ; PHQ-9: Patient Health questionnaire 9-item; SD, standard deviation. a: Mann-Whitney U Test, b: Fisher Exact Test

5.3.1 *Patient macro-level outcomes*

In stroke patients with total sleep time scored both ipsi- and contra-lesionally, we found *moderate-to-fair agreement* (CCC = 0.49) between the SWA and home-PSG. Reduced major axis results for concordance of all sleep metrics in stroke patients between the SWA and home-PSG are summarised in Table 5.2 and plotted in Figure 5.1. There was no evidence of proportional bias (slope = 0.99). We observed a fixed bias for total sleep time (intercept = -76.67); the SWA systematically overestimated sleep time by approximately 77 minutes at a consistent, rather than changing, amount (i.e., proportional bias) across magnitude. We observed *poor agreement* (CCC < 0.40) between the SWA and home-PSG for all other measured sleep metrics, including sleep efficiency, wake after sleep onset, and sleep onset latency. The SWA overestimated sleep efficiency by 14.78 with evidence of proportional bias (RMAR slope = 1.41, intercept -49.58). The SWA wake after sleep onset by approximately 63 minutes with evidence of proportional bias (RMAR slope=1.36, intercept 40.44). The SWA underestimated sleep onset latency by 3.51 minutes and we observed evidence of proportional bias (RMAR slope=1.78, intercept -2.16).

Sleep Variable	Mean Difference in Minutes (SD)	95% Limits of Agreement (Bland & Altman)	CCC (95% CI)	RMA Slope	RMA Intercept
Ipsilesional					
Total sleep time	-77.22 (71.28)	-216.93 to 62.48	0.49 (0.28 to 0.71)	0.99	-76.67
Sleep efficiency	-14.78 (14.33)	-42.88 to 13.32	0.23 (0.01 to 0.44)	1.41	-49.58
Wake after sleep	63.59 (60.79)	-55.56 to 182.74	0.30 (0.08 to 0.52)	1.36	40.44
Sleep onset latency	3.51 (10.23)	-16.53 to 23.57	0.16 (-0.13 to 0.46)	1.78	-2.16
Contralesional					
Total sleep time	-80.15 (70.16)	-217.67 to 57.37	0.48 (0.26 to 0.70)	0.97	-68.71
Sleep efficiency	-15.15 (14.74)	-44.03 to 13.74	0.21 (-.01 to 0.42)	1.42	-50.87
Wake after sleep	65.04 (60.83)	-54.19 to 184.26	0.30 (0.09 to 0.52)	1.38	40.42
Sleep onset latency	2.93 (10.18)	-17.02 to 22.87	0.03 (-0.30 to 0.36)	1.58	-1.31

Table 5.2. Comparison of concordance between polysomnography and SenseWear armband in ipsi- and contralesionally scored stroke participants. CCC: Lin's concordance coefficients, CI: confidence interval (lower, upper limit), RMA: reduced major axis regression, SD: standard deviations

Comparison of concordance in healthy controls for SWA and home-PSG are summarised in Table 5.3 and plotted in Supplementary Figure S5.1. We observed *poor agreement* (CCC < 0.40) between the SWA and home-PSG for all sleep metrics in healthy controls, including total sleep time, sleep efficiency, wake after sleep onset, and sleep onset latency. Comparison of concordance in healthy controls for SWA and home-PSG are summarised in Table 5.3 and plotted in Supplementary Figure S5.1. Similar to the comparison of concordance between the SWA and home-PSG in stroke patients, we observed fixed bias in healthy controls for total sleep time (slope = 0.99, intercept = -94.04). Proportional bias was observed for sleep efficiency (slope = 2.05, intercept = -115.74), wake after sleep onset (slope = 2.07, intercept =33.35), and sleep onset latency (slope = 1.13, intercept = 6.71).

Sleep Variable	Mean Difference in Minutes (SD)	95% Limits of Agreement (Bland & Altman)	CCC (95% CI)	RMA Slope	RMA Intercept
Total sleep time	-99.88 (56.52)	-210.65 to 10.90	0.10 (-0.07 to 0.26)	0.99	-94.04
Sleep efficiency	-21.06 (11.89)	-44.37 to 2.25	0.03 (-0.07 to 0.14)	2.05	-115.74
Wake after sleep	80.63 (55.94)	-29.01 to 190.26	0.04 (-0.10 to 0.19)	2.07	33.35
Sleep onset latency	7.68 (7.94)	-7.87 to 23.24	0.37 (0.06 to 0.69)	1.13	6.71

Table 5.3. Comparison of concordance between polysomnography and SenseWear armband in healthy control participants. CCC: Lin's concordance coefficients, CI: confidence interval (lower, upper limit), RMA: reduced major axis regression, SD: standard deviations

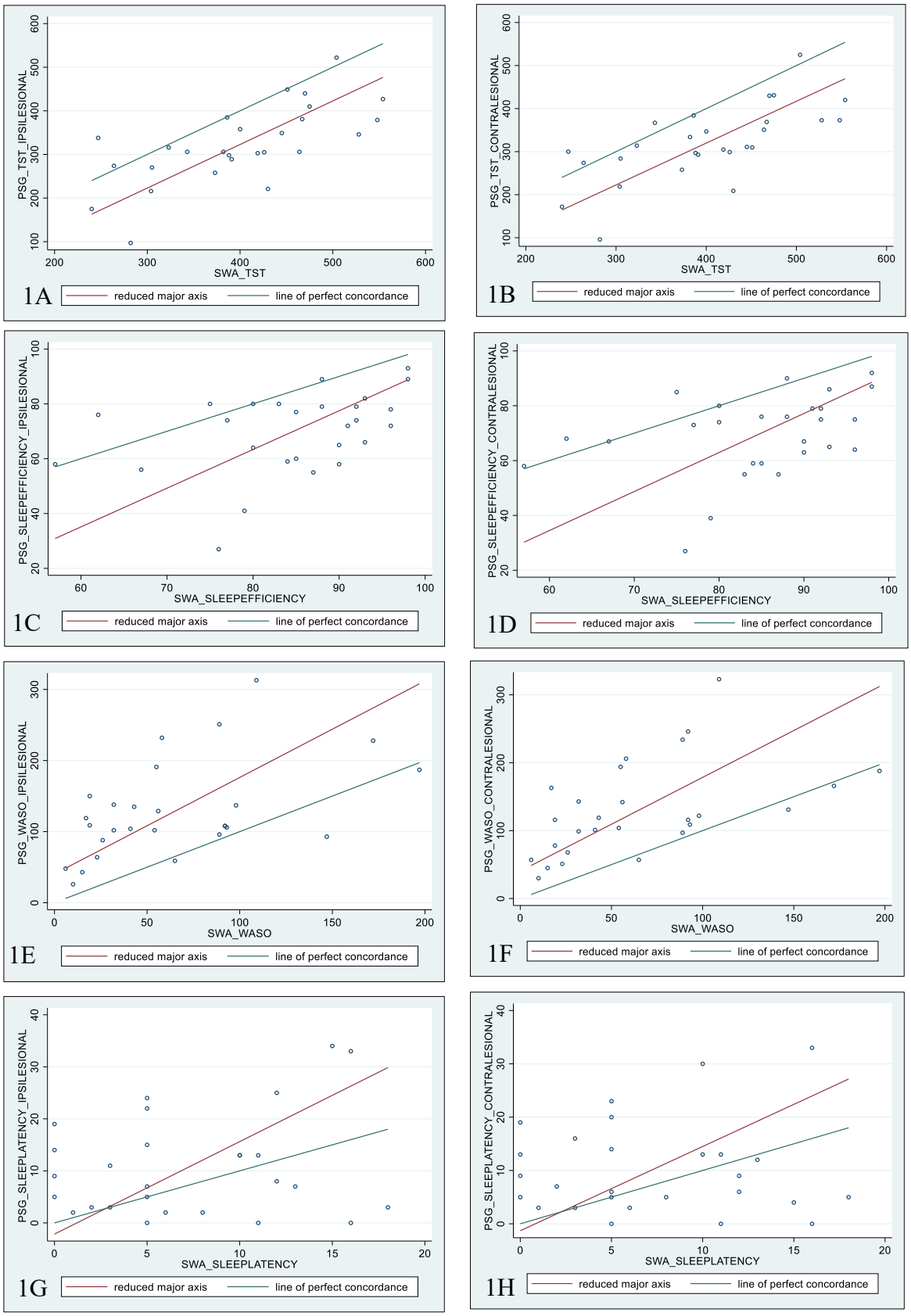

Figure 5.1: Reduced major axis regression plots of polysomnographically scored contra- and ipsi-lesional total sleep time (A-B), sleep efficiency (C-D), wake after sleep onset (E-F), and sleep onset latency (G-H) versus Sensewear Armband scores.

5.3.2 *Epoch-by-epoch micro-level analyses*

Group summaries of average within-participant epoch-by-epoch agreement characteristics for stroke patients and healthy controls are presented in Table 5.4. No significant differences in within-patient epoch-by-epoch agreement between stroke patients and healthy controls were identified. Crude agreement between home-PSG and SWA was 78.21% for stroke patients and 74.20% for controls.

Median sensitivity of the SWA (i.e., agreement for sleep detection) was high (95.90%) for stroke patients and for controls (95.70%). Average specificity for the SWA (i.e., agreement for wake detection) was fair for stroke patients (40.45%) and moderate (45.60%) for controls. Cohen's kappa coefficients revealed fair agreement (0.31) between SWA and home-PSG in stroke patients and moderate agreement (0.42) in controls.

Agreement Measure	Stroke (N=27)	Control (N=16)	P
Crude agreement, Mdn (IQR)	78.21 (73.21, 81.45)	74.20 (70.90, 77.96)	0.25[a]
Kappa coefficient, Mdn (IQR)	0.31 (0.10, 0.44)	0.42 (0.33, 0.49)	0.16[a]
Sensitivity %, Mdn (IQR)	95.90 (84.98, 97.35)	95.70 (88.15, 97.90)	0.87[a]
Specificity %, Mdn (IQR)	40.45 (18.97, 54.57)	45.60 (34.05, 55.25)	0.18[a]

Table 5.4. Within-participant epoch-by-epoch agreement measures in stroke patients and healthy controls. M: mean, Mdn: median, IQR: interquartile range (25^{th}, 75^{th} quartiles), SD: standard deviation
a: Mann-Whitney U Test

5.4 Discussion

Stroke is a common condition with high morbidity and mortality. Disordered sleep in stroke is linked to important clinical outcomes [218]. This is the first study to undertake a robust evaluation of ambulatory and non-invasive sleep monitoring devices that will enable objective measurement of the impact of sleep-related interventions to improve sleep in stroke. We assessed the concordance, specificity, and sensitivity of the SenseWear armband (SWA)

against ambulatory at-home polysomnography (home-PSG) in ischaemic stroke patients and healthy controls using robust validation statistics. Despite an acceptable (>78%) average within-patient epoch-by-epoch agreement in stroke patients, the SWA did not exceed moderate-to-fair agreement (CCC $\geq$0.50) for any measured sleep variables. Interestingly, the variability in agreement between the SWA and at-home PSG was consistent between stroke patient's ipsilesional versus contralesionally scored sleep. Unihemispheric sleep EEG changes over the ipsilesional hemisphere have previously been described following acute stroke [326]. Our null hemispheric findings suggest that, irrespective of stroke localisation, the SWA's sleep detection is unlikely to be influenced by stroke hemisphere in the chronic stages of stroke. Additionally, we observed proportional bias according to the RMAR for all sleep variables excluding total sleep time. In line with previous validation studies, total sleep time was the most robustly quantified sleep variable computed by the SWA. We observed no evidence of proportional bias for total sleep time; however, a fixed bias was evident and the SWA systematically overestimated total sleep time by 77 minutes. The variability in agreement between home-PSG and SWA for all sleep variables was extensive and the SWA performed poorest for sleep measures requiring discrimination of wakefulness. For example, accurate measurement of sleep onset latency, an index of time elapsed from lights-out to sleep onset, requires differentiation of mere laying/quiet restfulness from sleep initiation.

Unlike the more frequently used Bland Altman analysis, the RMAR allowed us to quantify both fixed and proportional biases between the SWA and home-PSG [332,333]. By separating the fixed and proportional biases of the SWA, we were able to determine whether the SWA gave differing values relative to home-PSG across a whole range of measurement, and/or whether the SWA estimation diverged progressively. Our results suggest that the measurement of total sleep time using the SWA diverge from home-PSG across a whole measurement range in a consistent amount across magnitude. Thus, the SWA's overestimation of total sleep time may be easier to rectify (i.e., transform) when compared to sleep-wake variables with proportional bias such as sleep efficiency, wake after sleep onset, and sleep onset latency [334].

Although the SWA includes additional biosensors (e.g., galvanic scale, near body temperature, heat flux), which may enhance sleep-wake discrimination beyond micromovement detection via traditional accelerometer, we observed relatively low specificity (i.e., wake detection) of 40% for the SWA in stroke patients [329]. Previous validation work comparing tri-axial versus

uni-axial accelerometers showed a higher epoch-by-epoch agreement in the tri-axial device, while a uni-axial device exhibited higher concordance for WASO and total sleep time [335]. The proprietary sleep-wake measurement algorithms of the SWA prevented us from exploring biosensors that may be contributing to poor specificity (i.e., wakefulness) detection.

The armband nature of the SWA potentially provides a novel solution to sleep measurement in clinical populations with upper limb injuries such as stroke. Relative to wrist-worn monitors, placement of the SWA on the upper-arm minimises noise associated with small micro-movements of the wrist [336]. Although the SWA has previously shown to outperform other consumer wrist worn accelerometers such as the Fitbit and Jawbone Up, it remains unclear whether the armband versus wrist-worn nature of the SWA or its additional sensors are responsible for enhanced sleep-wake detection due to the device's proprietary-blackbox algorithms [337]. Furthermore, no studies to date have assessed the SWA as a sleep monitor in patients spinal cord injury or stroke where upper limb injury is pervasive. However, the SWA has been used to assess energy expenditure in stroke patients with conflicting results. Manns and Haennel (2012) found *good* agreement (ICC = 0.70) in a small sample of 12 chronic stroke patients when comparing energy expenditure measured by the SWA and the StepWatch Activity Monitor [338]. In the acute stages of stroke (within 7 days of stroke), however, Kramer and colleagues (2018) found poor agreement (CCC < 0.40) between the SWA placed on the unaffected arm and the metabolic cart [339]. Neither study compared the concordance of the SWA between the unaffected versus affected arm. It is therefore unclear whether upper limb impairment contributed to the SWA's performance. Future studies systematically assessing the SWA's sleep-wake detection in populations with upper limb injuries are warranted.

Reduced agreement and increased variability between polysomnography and the SWA generally occurred in unison with poorer sleep and increased wakefulness. For example, large variability and lack of concordance was particularly evident when sleep efficiency was <80% (Figures 1C-1D), and a similar trend was observed for >100 mins of wake after sleep onset (Figures 1E-1F). Previous validation studies of the SWA have been undertaken in a range of populations including healthy adults [321] and patients with obstructive sleep apnoea [322]. We are the first to examine the validity of the SWA in patients with a neurological disorder where sleep architectural disruption due to infarction and de novo sleep disorders such as OSA are common. Unexpectedly, we found a high prevalence of previously undiagnosed moderate-to-

severe OSA in both samples. Despite excluding participants with previously diagnosed OSA, over half of all stroke patients exhibited undiagnosed moderate-to-severe OSA defined as AHI ≥ 15. The high prevalence of OSA in our stroke sample is unsurprising; post-stroke OSA prevalence ranges from 44% to 72% [340]. In addition to our validation findings, our respiratory-PSG derived finding highlights the importance of formal sleep studies in stroke patients in order to identify undiagnosed OSA. Interestingly, both our neurologically-intact controls and stroke patients exhibited relatively poor sleep-wake quality (i.e., sleep efficiency <70%) and comparable SWA-PSG concordance – potentially due to a lack of habituation period for a single night of polysomnography.

Nonetheless, our epoch-by-epoch agreement and systematic biases are comparable to prior validation work. For example, Soric et al. and Roane et al. reported high individual variability in the SWA's estimation of total sleep time and an overestimation of total sleep time by >60 minutes [246,329]. However, this is in sharp contrast to Sharif and colleagues work revealing near-perfect agreement (whole sample ICC = 0.92) for all sleep variables measured in a heterogenous obstructive sleep apnoea sample [322]. A binary epoch-by-epoch agreement rating was not assessed by Sharif and colleagues. However, similar to our findings, lower agreement and widening of variability between the SWA and PSG was also generally observed in participants with sleep efficiency <60 [322]. The significant differences in agreement between our findings may therefore be due to our sample's poorer sleep efficiency (70 vs 73-79) and longer total sleep time (319 vs 187-290). These findings suggest that caution is warranted when utilising the SWA in populations with excessive nighttime awakenings and fragmentation mediating poor sleep efficiency.

5.4.1 *Limitations*

An analytical limitation of the present study was that the SWA and home-PSG recorded sleep at differing epochs which required potentially imperfect matching. Specifically, 30-second epochs were recorded for the home-PSG, whereas the SWA recorded sleep in 1-minute epochs. Thus, in our epoch-by-epoch analysis, we divided the SWA outputs to correspond with each 30-second PSG epoch. This may have introduced bias into our SWA's epoch-by-epoch agreement rate, including an overestimation of discordance with home-PSG. Additional limitations lie in our sample which was relatively small. However, our sample size of 44 participants was comparable, or larger, than previous published SWA validation studies that

included epoch-by-epoch analyses [245,247,329]. Our sample also included patients with mild stroke severity (baseline National Institute of Health Stroke Scale score, mean = 2.96). As sleep-wake dysfunction after stroke parallels stroke severity, the SWA may perform worse in a larger, more heterogeneous stroke sample with moderate-severe stroke severity. Our study protocol only included a single sleep night with no PSG habituation period. Although our use of at-home ambulatory PSG may have remediated the deleterious environmental stressors associated with in-lab PSG studies, multi-night validation protocols should be prioritised when viable. Furthermore, the limiting nature of propriety black-box algorithms common in consumer devices prevented us from identifying which biosensors were responsible for the SWA's poor wake detection. Finally, a potential limitation is our use of a single scorer for sleep staging. To minimise scorer bias we utilised an experienced research-grade sleep scientist with an extensive track record of satisfactory participation in an external analysis quality assurance program. Furthermore, the use of a single scorer has the advantage of avoiding inter-scorer variability. We also limited the confounding effects of variably classified events by assessing epochs binarily as sleep or wake, rather than comparing sleep sub-types/stages which are prone to inter-scorer variability and errors (i.e., differentiating awake/NREM-1, NREM-1/NREM-2, and NREM-2/NREM-3 sleep) [341].

5.4.2 *Conclusions and future direction*

Overall, the SWA shows promise as an ambulatory tool to measure sleep-wake at a group-level. Specificity at an individual-level, however, is only moderate-fair and warrants caution when used as a diagnostic tool or in populations with significant sleep-wake fragmentation. This is especially the case if sleep-wake variables beyond total sleep time (e.g., sleep onset latency, sleep efficiency, and wake after sleep onset) are used as primary outcome measures. It is important to assess sleep-wake parameters beyond total sleep time in stroke populations; although stroke patients often exhibit long sleep duration, sleep may be fragmented with increased wake after sleep onset and poor sleep efficiency [48,342]. Similarly, sleep architecture may be disturbed after stroke [342]. Earlier work suggests that stroke patients exhibit alterations to NREM-3/slow-wave sleep, which may be mediated by sleep disorders such as obstructive sleep apnoea [326]. Nonetheless, there are several advantages of the SWA over traditional PSG [319,343], which generally mirror those of actigraphy and include: longitudinal-prospective monitoring in a naturalistic environment; ambulatory and non-invasive; cost-effective; an ability to discriminate periods when the device is not worn; and limited effect on sleep

architecture (i.e., habituation period not needed. Future validation studies are warranted in heterogenous stroke populations in order to examine the effect of variable stroke severities (and stroke topographies) on device performance. In addition, future studies should examine the SWA in tandem with more recently developed and open-source (non-proprietary) multi-sensor ambulatory sleep-wake technologies to establish which array of biosensors and software contribute to optimal (>90%) specificity and sensitivity detection [344].

Chapter 6
Sleep architectural dysfunction and undiagnosed sleep apnoea after chronic ischaemic stroke

In previous chapters, I presented data identifying sleep-wake abnormalities and regional neurodegeneration after sub-acute stroke. However, it remains unclear whether sleep-wake disturbances are transient post-stroke, limited to the acute stages of the incident event. In this chapter, I characterise sleep architectural dysfunction, sleep-respiratory parameters, and hemispheric sleep differences in ischaemic stroke patients 4-years after their incident event relative to healthy matched controls using gold-standard polysomnography. The text in this chapter has been submitted as a manuscript to *Stroke*, for which the full disclosure is available in the Preface.

6.1 Introduction

Globally there are eighty million stroke survivors which are at an elevated risk for sleep disorders [220]. Both stroke and sleep disorders are associated with increased risk of all cause dementia [345]. Sleep-wake dysfunction has recently been proposed both as a key modifiable risk factor and consequence of ischaemic stroke in pre-clinical and human studies [316]. Rodents subjected to intermittent sleep disturbances after ischaemic stroke exhibit deficits to both functional recovery and morphological brain markers [346]. Conversely, slow-wave sleep (SWS, non-rapid eye movement sleep stage 3 [NREM-3]) enhancement accelerates neurological recovery following stroke [347]. In humans, it has been posited that slow-wave oscillations during sleep entrain a pseudo-lymphatic state drawing cerebrospinal fluid into and out of the brain parenchyma which may be neuroprotective [348]. Ischaemic burden may contribute to impaired extracellular clearance of neurotoxic solutes, thereby exacerbating neurodegeneration and hindering recovery perhaps by impairment of the sleep dependent glymphatic system [349,350,351]. *De novo* sleep architectural suppression and sleep disorders are associated with worse post-stroke severity and poor functional outcome [316]. We have shown that chronic sleep-wake dysfunction after sub-acute stroke is associated with regional neurodegeneration. However, the duration and prevalence of post-stroke sleep-wake dysfunction beyond the acute phases of stroke has not been fully described; whether sleep-wake dysfunction exists in chronically recovered stroke patients warrants further investigation. Furthermore, it is unclear whether chronic post-stroke changes to neighbouring sleep-wake hubs are associated with sleep architectural impairments across both hemispheres, or whether they are restricted to the lesioned hemisphere. We aimed to characterize sleep architecture and sleep-respiratory features after chronic stroke ($\geq$3 years post-stroke), relative to healthy controls, and examine hemispheric differences in sleep architecture.

6.2 Methods

Forty-four participants (28 ischaemic stroke, 16 healthy age- and sex-matched controls) were recruited from the Cognition and Neocortical Volume After Stroke (CANVAS) study. CANVAS is a multicentre, prospective, observational cohort study following people with ischaemic stroke with serial cognitive testing and brain MRI scanning. Details regarding the CANVAS study protocol and methodology have been previously described in detail [239]. A sample frame, or targeted sample, was used to diversify the sample's stroke topography and lesion characteristics for enhanced generalizability. Healthy controls were informally matched

for age and sex following recruitment of all stroke participants. We calculated mean age and sex distribution of stroke patients and selected control participants from the CANVAS database of volunteers who had similar characteristics.

The CANVAS study includes patients with clinical strokes in any circulation, radiologically confirmed using clinical MRI or CT. Participants need to be aged greater than 18 years of age and be able to have cognitive testing and an MRI scan. Inclusion criteria for healthy controls were identical to stroke patients excluding a stroke diagnosis. Exclusion criteria include significant medical comorbidities precluding participation in cognitive testing or making survival of the longitudinal study (three years) unlikely; normal exclusion criteria for MRI (e.g., implanted metal, severe claustrophobia); pre-existing dementia; and pregnancy. Additional exclusion criteria for the present sub-study included use of medications with a primary effect on sleep architecture as measured by EEG (e.g., benzodiazepines, selective serotonin reuptake inhibitors) during the time of the study; and narcolepsy or severe REM-behaviour disorder making use of ambulatory polysomnography unfeasible. Participants were recruited from three hospital networks in Melbourne, Australia: Austin Health, Eastern Health, Melbourne Health.

The present study was split into two time-points over a 2-week period. During time-point one, participants wore a validated accelerometer (the SenseWear Armband) and completed a 16-item sleep diary for at least one week [322]. Sleep data collected during time-point one provided an "average" sleep-day used to schedule a participant's overnight at-home polysomnography examination. During time-point 2, participants were fitted with an ambulatory polysomnography device (Somté PSG version 2.0, Compumedics, Limited, Abbotsford, Victoria, Australia) and wore, in tandem, the SenseWear Armband for 1-night at home. Upon completion of overnight polysomnography, participants returned the devices and completed an array of demographic, health, mood, and sleep-circadian questionnaires.

Ambulatory polysomnography was recorded using Compumedics Somté PSG. Polysomnographic fittings and staging were completed in accordance with the American Academy of Sleep Medicine [324] (AASM) and Australasian guidelines [325] . Six-lead EEG placement were used in accordance to the international 10–20 system (F4-M1, C4-M1, O2-M1; F3-M2, C3-M2, O1-M2). Sleep architectural and sleep-respiratory variables were scored

by a single research-grade sleep technologist who remained blinded to both the group and, if a stroke participant, the healthy and stroke-affected hemisphere.

Bi-hemispheric sleep staging studies were de-identified, and the order of studies scored was randomized. For stroke patients, ipsilesional and contralesional hemisphere EEG were scored independently to assess potential hemispheric sleep architectural differences. The sleep technologist remained blinded to the healthy versus stroke-affected hemisphere's EEG until both hemispheric staging (i.e., a. F4-C4-O2, b. F3-C3-O1) were independently scored. Upon completion of independent uni-hemispheric EEG scoring, the sleep technologist was unblinded to the ipsilesional/lesioned hemisphere and utilized the contralesional/healthy hemisphere for scoring respiratory parameters and arousal events. The following measures were used: nasal and mouth airflow detection (thermistor and oro-nasal airflow – nasal canula), abdominal and thoracic respiratory efforts (respiratory inductance plethysmography – chest and abdominal wall movement), and pulse oximetry (SaO2) for respiratory parameters; electrooculogram (left and right placement), electromyogram (mentalis/submentalis), electrocardiogram (modified lead II), and leg EMG (left and right leg placement).

We assessed generalized anxiety and depression severity using the Generalized Anxiety Disorder-7 scale [352] and the Patient Health Questionnaire-9 scale [353], respectively. The Epworth Sleepiness Scale [354] was used to measure sleep traits, while the Karolinska Sleepiness Scale [355] was used to measure sleep states. The Fatigue Assessment Scale [356] measured fatigue and the Apnoea Predictions Questionnaire [357] [358] was used to screen for obstructive sleep apnoea. The Insomnia Severity Index screened [359] for insomnia pathology, and the Morningness-Eveningness Questionnaire [360]was used as a proxy for circadian functioning and chronotype. Lastly, the National Institute of Health Stroke Scale provided current scoring of stroke severity.

6.2.1 Standard protocol approvals, registrations, and patient consents

The study was approved by each of the hospital's human research ethics committees in line with the Declaration of Helsinki and informed consent was obtained from all participants.

6.2.2 Statistical analyses

Statistical analysis was performed with SPSS version 26 (IBM Corp., Armonk, NY, USA). Data were summarized by the mean and standard deviation (SD) and number and percent for categorical variables. Differences in continuous clinical, demographic, vascular risk, and sleep-wake variables were assessed using independent samples t-tests if normally distributed. If normality tests failed, Mann Whitney U tests were used. Fisher exact tests were used to compare 2 × 2 categorical data. For between-group sleep architecture comparisons, stroke patients ipsi- and contra-lesionally scored EEG were averaged and compared with controls left and right hemisphere averaged EEG. Post-hoc comparisons of significant sleep variables were conducted using a univariate General Linear Model (analysis of covariance [ANCOVA]) controlling for the apnoea-hypopnea index (AHI) to determine whether sleep-apnoea severity could explain the variance in sleep architectural differences between groups. Levene's test and normality checks were carried out to ensure assumptions were met. Effect sizes, standard errors, p values, and 95% confidence intervals (CIs) were reported for primary outcome analyses. For non-parametric analyses, effect sizes were calculated using the Wilcoxon-Mann-Whitney generalized odds ratio, a rank-based and assumption-free effect size measure[361]. All analyses were two-tailed and levels of α were set at 0.05.

6.2.3 Data sharing statement

Anonymized original data will be shared by reasonable request from any qualified investigator after inquiry.

6.3 Results

6.3.1 Participant demographics and stroke characteristics

Twenty-eight stroke patients (mean age 69.6 ± 7.35, 19 right sided, 22 male) and 16 healthy controls were included. Demographic, cerebrovascular, and mood characteristics of participants with stroke and healthy controls are listed in Table 6.1. Stroke participants reported a higher degree of self-reported depressive symptoms relative to healthy controls. No other demographic characteristics, cerebrovascular risk factors, or mood characteristics were significantly different between groups. Stroke characteristics including stroke severity, post-stroke disability, stroke aetiology, and lesion topography are listed in Table 6.2.

Demographics	**Stroke (N=28)**	**Control (N=16)**	**p**
Age in years, M ± SD	69.61 (7.35)	73.75 (7.10)	0.07[a]
Sex, male n (%)	22 (79%)	10 (63%)	0.30[b]
Education in years, M ± SD	13.29 (4.00)	15.18 (4.67)	0.19[a]
BMI, M ± SD	26.65 (3.77)	25.50 (4.37)	0.87[c]
NART-FSIQ, M ± SD	112.90 (4.01)	117.70 (8.50)	0.19[a]
Handedness, right n (%)	27 (96%)	14 (88%)	0.54[b]
Self-reported history of obstructive sleep apnoea, n (%)	0 (0%)	3 (18.75%)	0.71[b]
Moderate-severe OSA, n (%), M ± SD	16 (57%)	6 (38%)	0.09[b]
Family history of stroke, n (%)	9 (32%)	5 (31%)	1[b]
Family history of dementia, n (%)	6 (21%)	6 (38%)	0.30[b]
Depression diagnosis, n (%)	3 (11%)	2 (13%)	1[b]
Hyperlipidaemia diagnosis, n (%)	10 (36%)	8 (50%)	0.53[b]
Hypertension diagnosis, n (%)	13 (46%)	6 (38%)	0.75[b]
Ischaemic heart disease, n (%)	2 (7%)	2 (13%)	0.61[b]
Atrial fibrillation diagnosis, n (%)	3 (11%)	0 (0%)	0.29[b]
Type 2 diabetes mellitus, n (%)	5 (18%)	0 (0%)	0.14[b]
High alcohol intake (> 14 standard drinks per week), n (%)	2 (7%)	2 (13%)	0.61[b]
ApoE_e4 (≥1 allele), n (%)	7 (25%)	1 (6%)	0.22[b]
PHQ-9, M ± SD	3.50 (2.82)	1.63 (1.54)	0.039[c]
GAD-7, M ± SD	3.00 (5.42)	0.81 (1.33)	0.16[c]

Table 6.1. Demographic characteristics in stroke patients and healthy controls. BMI = body mass index; GAD-7 = generalized anxiety disorder questionnaire 7-item; M = mean; n = number; NART = National adult reading test-IQ; PHQ-9 = patient health questionnaire 9-item; SD = standard deviation; **a:** Mann-Whitney U Test, **b**: Fisher Exact Test, **c**: Independent Samples T-Test

Variable		**Mean/N (SD/%)**
Years post-stroke*, M ± SD		4.10 (0.91)
Lesion volume, mm^3 M ± SD		13724 (21998)
TPA administered, M ± SD		3 (11%)
Baseline NIHSS, M ± SD		3.0 (2.0)
NIHSS at PSG, M ± SD		1.5 (1.0)
Baseline mRS, M ± SD		1.4 (0.5)
mRS at PSG, M ± SD		0.9 (0.7)
Stroke side, n (%)	Right	19 (69%)
	Bilateral	2 (7%)
	Left	7 (25%)
Oxfordshire Criteria, n (%)	POCI	10 (36%)
	TACI	0 (0%)
	PACI	15 (54%)
	LACI	3 (11%)
TOAST Classification, n (%)	Large-artery	6 (21%)
	Cardioembolic	9 (32%)
	Small-vessel (lacune)	5 (18%)
	Other determined aetiology	2 (7%)
	Undetermined/unknow	4 (14%)

Table 6.2 Stroke characteristics. LACI = lacunar infarct; M = mean; mRS = modified Rankin scale; n = number; NIHSS = National Institutes of Health stroke scale; PACI = partial anterior cerebral infarct; POCI = posterior cerebral infarct; SD = standard deviation. * = Time from stroke onset/MRI confirmation to polysomnography examination.

6.3.2 Subjective measurement of sleep, respiratory, and circadian rhythms

Composite scores of self-reported sleep-wake questionnaire differences in stroke patients and healthy controls are listed in Table 6.3. Stroke patients had higher scores on the Morningness-Eveningness Questionnaire, which was indicative of a 'moderate' morning chronotype relative to healthy controls' 'definite' morning chronotype (p=0.01). We observed a trend towards higher (worse) Epworth Sleepiness Scale scores in stroke patients (5.53 vs 3.69, p = 0.06) relative to healthy controls. A compositive index from the Apnoea Predictions Questionnaire was not significantly different between stroke patients and healthy controls.

Scale	**Stroke (N=28)**	**Control (N=16)**	***p***	**Effect size (95% CI*)**
Epworth Sleepiness Scale, M ± SD	5.53 (3.40)	3.69 (2.38)	0.06[a]	0.69[c] (-0.10, 3.79)
Karolinska Sleepiness Scale, M ± SD	4.64 (1.45)	3.39 (1.73)	0.15[a]	0.80[c] (-.28, 1.69)
Fatigue Assessment Scale, M ± SD	19.39 (7.03)	18.46 (7.35)	0.68[a]	0.13[c] (-3.68, 5.54)
Apnoea Prediction Questionnaire (MAP Index), M ± SD	0.75 (0.72)	0.66 (0.82)	0.8[b]	0.78[d] (0.38, 1.59)
Insomnia Severity Index, M ± SD	3.57 (3.04)	2.44 (2.39)	0.21[a]	0.39[c] (-0.65, 2.92)
Morningness-Eveningness Questionnaire, M ± SD	65.82 (13.36)	76.63 (9.20)	0.01[b]	0.20[d] (0.08.0.49

Table 6.3. Subjective sleep-wake characteristics in stroke patients and healthy controls. a: Independent Samples T-Test; b: Mann-Whitney U Test; c: Effect size calculated Hedges' g; d: Effect size calculated using Wilcoxon-Mann-Whitney generalized odds ratio [361] = Ln[(U/(N1*N2))/(1-(U/(N1*N2))]. *95% confidence interval (upper limit, lower limit).

6.3.3 Sleep architecture and sleep-respiratory differences between stroke patients and healthy controls

Sleep architectural variables and sleep-respiratory characteristics between stroke patients and healthy controls are listed in Table 6.4. Despite no difference in total sleep time (stroke: 320.57 min vs control: 306.31 min, p=0.54), sleep efficiency (stroke: 69.50 vs control: 68.81, p=0.87), or wake after sleep onset (stroke: 129.28 min vs control: 122.87 min, p=0.75), stroke participants had reduced NREM-3/SWS (66.25 min vs 99.26 min, p=0.02), increased NREM 1-2 (NREM-1: 48.43 vs 28.95, p=0.03; NREM-2: 142.61 vs 115.87, p=0.02), and a higher arousal index (21.46 vs 14.43, p=0.03) relative to healthy controls. Fifty-seven percent of stroke patients (n=16) had undiagnosed moderate to severe sleep apnoea (AHI $\geq$15). Stroke patients had over 8 more apnoea-hypopnea events per hour of sleep (AHI: 21.46 vs 14.43) relative to controls, although this difference was not statistically significant (p=0.09).

Variables	**Stroke (N=28)**	**Control (N=16)**	***p***	**Effect size (95% CI*)**
Total sleep time, min, M ± SD	320.57 (85.17)	306.31 (47.90)	0.54[a]	0.20[d] (-32.57, 61.09)
Sleep efficiency, ratio, M ± SD	69.50 (14.28)	68.81 (11.44)	0.87[a]	0.05[d] (-7.74, 9.12)
Sleep onset latency, min, M ± SD	10.35 (8.35)	15.31 (8.80)	0.07[a]	0.57[d] (-10.34, 0.43)
Wake after sleep onset, min, M ± SD	129.28 (64.70)	122.87 (53.99)	0.75[b]	0.89[e] (0.42, 1.85)
NREM-1, min, M ± SD	48.43 (29.89)	28.95 (16.77)	0.03[b]	0.44[e] (0.20, 0.94)
NREM-2, min, M ± SD	142.61 (48.31)	115.87 (29.82)	0.02[a]	0.66[d] (2.94, 50.53)
NREM-3/SWS, min, M ± SD	66.25 (45.55)	99.26 (45.29)	0.02[a]	0.72[d] (-61.77, 4.26)
REM, min, M ± SD	64.44 (27.35)	64.36 (32.28)	0.67[b]	0.85[e] (0.41, 1.76)
SWS latency, min, M ± SD	23.01 (43.13)	14.06 (12.76)	0.68[b]	0.86[e] (0.42, 1.76)

REM latency, min, M ± SD	114.73 (76.47)	124.21 (79.65)	0.44[b]	0.75[e](0.36, 1.55)
Total awakenings, M ± SD	33.50 (12.83)	33.06 (12.71)	0.98[b]	0.99[e] (0.47, 2.05)
Apnoea–hypopnea index/hr, M ± SD	24.00 (17.32)	15.73 (13.83)	0.09[b]	0.53[e] (0.25, 1.12)
Arousal index/hr, M ± SD	21.46 (10.92)	14.43 (6.61)	0.03[b]	0.43[e] (0.20, 0.92)

Table 6.4. Unadjusted sleep architectural differences between stroke patients and healthy controls. a: Independent Samples T-Test, b: Mann-Whitney U Test, c: Fisher Exact Test; d: Effect size calculated Hedges' g; e: Effect size calculated using Wilcoxon-Mann-Whitney generalized odds ratio[361] = Ln[(U/(N1*N2))/(1-(U/(N1*N2))]; *95% confidence interval (upper limit, lower limit).

Post-hoc one-way ANCOVA summary data of estimated marginal mean NREM 1-3 differences between stroke patients and healthy controls, after controlling for obstructive sleep apnoea severity (AHI), are listed in Table 6.5 and Figure 6.1. Stroke participants had more NREM-2 (estimated marginal mean difference: 32.84 min) after controlling for AHI ($F[2,41]=6.01$, $p=0.019$, partial eta^2: 0.12). Inclusion of AHI as a covariate attenuated the significance of increased NREM-1 ($F[2,41]=3.25$, estimated marginal mean difference=15.47, $p=0.07$) and reduced NREM-3 in stroke ($F[2,41]=3.43$, estimated marginal mean difference=-26.39, $p=0.079$); however, effect sizes and estimated marginal means remained similar between unadjusted (NREM-1 WMW GenOR=0.44 [moderate effect]; NREM-3/SWS Hedge's g=0.72 [moderate effect]) and AHI-adjusted/ANCOVA models (NREM-1 partial eta^2 = 0.074 [moderate effect]; NREM-3 partial eta^2 = 0.077 [moderate effect]).

Dependent Variable	Estimated Marginal Means (Std. Error)		Mean Difference	Std. Error	P	95% Confidence Interval		Partial Eta Squared
	Stroke	Control				Lower	Upper	
NREM-1, min	46.41 (4.56)	32.49 (6.09)	15.47	7.71	0.079	-1.66	29.49	0.074
NREM-2, min	144.83 (7.92)	111.99 (10.56)	32.84	13.38	0.019	5.8	59.87	0.128
NREM-3, min	68.66 (8.43)	95.05 (11.24)	-26.39	14.25	0.071	-55.17	2.39	0.077

Table 6.5. Assessing sleep-architectural differences in an ANCOVA model adjusting for OSA severity (AHI).

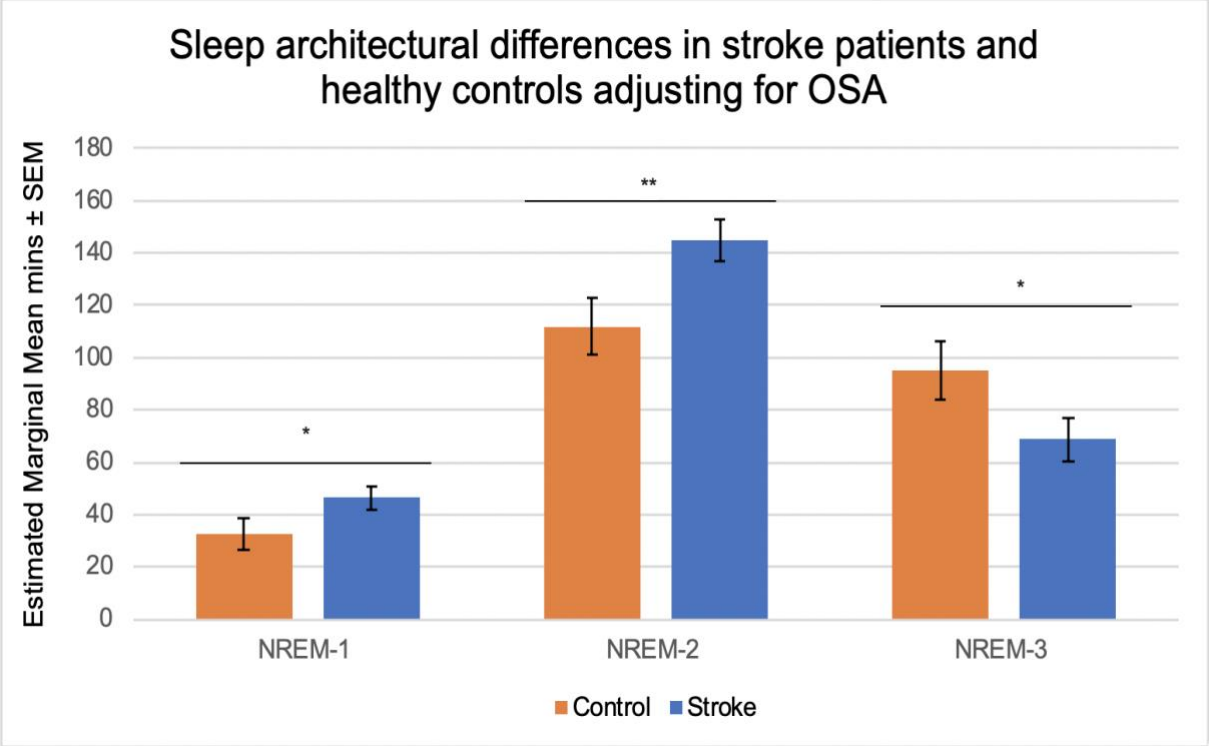

Figure 6.1. Bar graph of sleep architectural differences between stroke patients and healthy controls adjusted for obstructive sleep apnoea severity (AHI). SEM = standard error of the mean; ***** = $p > 0.05$, $\eta_p^2 > 0.07$; ****** = $p < 0.05$, $\eta_p^2 > 0.07$

6.3.4 Macroarchitectural sleep differences between ipsilesional and contralesional EEG

Uni-hemispheric sleep-EEG characteristics in ipsi- versus contra-lesional hemispheres in stroke patients are shown in Figure 6.2. We observed no significant differences in total time of sleep architectural variables between ipsi-lesionally and contra-lesionally scored EEG.

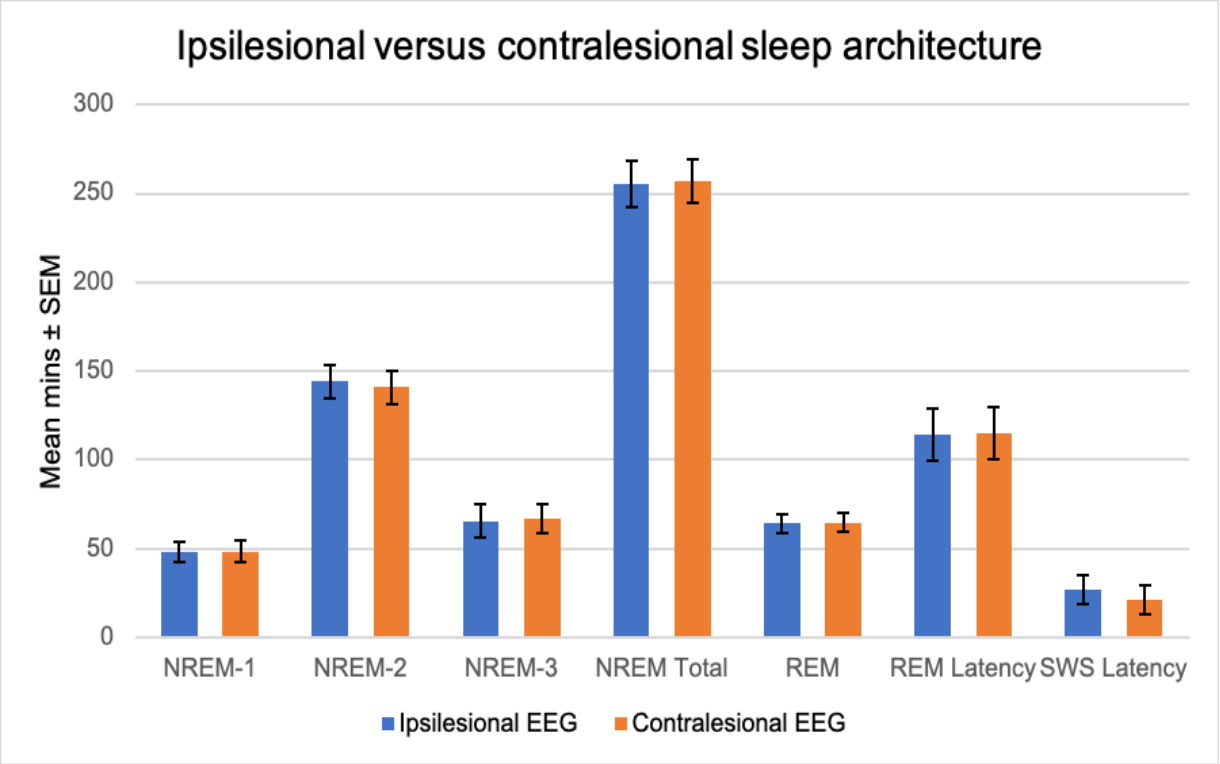

Figure 6.2. Hemispheric sleep-EEG characteristics in ipsi- versus contra-lesional hemispheres. Non-significant ($p>0.05$ for all ipsi- versus contra-lesional comparisons) sleep architectural EEG differences between stroke lesion hemisphere (ipsilesional, shown in blue) versus healthy hemisphere (contralesional, shown in orange) measured in mean minutes with standard error bars.

6.4 Discussion

We found that stroke survivors 4 years after their clinical event had significantly less slow-wave sleep, increased lighter non-REM sleep stages 1-2 and higher arousal indices relative to controls, but had comparable total sleep time and sleep efficiency. Interestingly, although no patients in this sample reported a history of sleep apnoea, 57% of stroke patients were found to have moderate-to-severe OSA. Whilst controlling for OSA attenuated the significance to SWS and NREM-2, the effect sizes and estimated marginal means remained consistent between unadjusted and adjusted models. This suggests that OSA alone is unlikely to be mediating the reductions to SWS observed in our stroke sample. Despite preliminary exploratory evidence

indicating an effect of acute stroke topography and lesion volumes on sleep architecture [103,326], we found no significant differences in hemispheric sleep architecture between stroke patients' ipsilesional and contralesional hemispheres. These findings suggest that hemispheric stroke infarction is unlikely to be driving sleep architectural dysfunction after stroke.

Stroke patients had nearly 40% less SWS and significantly more NREM 1-2 sleep relative to healthy controls. Other authors have reported that sleep architecture is generally lighter [96,103,119] (i.e., greater amount of NREM 1-2) and less consolidated [326,342,362] (i.e., greater arousal indices potentially suppressing NREM-3) when compared to controls in the acute and sub-acute stages of stroke [316]. Sleep efficiency abnormalities after stroke have been commonly reported in in the acute settings due to deleterious environmental stressors associated with acute hospital care [316]. To our knowledge, this is the first study to show that sleep-wake disturbances exist even 4 years after the incident event in chronically recovered stroke patients. Interestingly, stroke patients and control participants reported comparable sleep quality using established questionnaires, with only trending differences to self-reported sleepiness. Despite the absence of self-reported sleep abnormalities, sleep architectural dysfunction should be considered a key modifiable sequela in stroke patients.

SWS disruptions may play a pivotal role in post-stroke neuroplasticity, neuroprotection, and waste clearance from the brain [48,351]. For example, neuroplasticity-dependent consolidation of newly acquired procedural and declarative memories is compromised following reduced SWS [48,362,363]. The potential pathophysiological mechanisms driving reductions in SWS and increased arousals may be related to atrophy to subcortical sleep–wake structures (e.g., thalamus, hippocampus, and amygdala) and white-matter tracts (e.g., corticopontocerebellar tract) [317]. Post-stroke neurodegeneration to the ascending reticular activating system may therefore impair sleep-wake homeostasis regulated by multi-hierarchical orexinergic[364], adenosinergic[232], and cholinergic[365] neuromodulatory systems.

The inclusion of AHI as a covariate in our post-hoc analyses attenuated the statistical significance of reductions to SWS seen in our stroke patients. This was likely due to a drop in study power, and relatively small sample size, as evinced by our moderate effect sizes and comparable estimated marginal means when compared to our unadjusted comparisons. These

findings suggest that obstructive sleep apnoea is unlikely to fully mediate the relationship between stroke and sleep architectural impairment.

Stroke patients had significantly more arousals and more apnoea-hypopnea events per hour, although the latter was not statistically significant. Over half of the stroke patients in the sample exhibited moderate to severe obstructive sleep apnoea, relative to 38% of healthy controls. A recent study examining sleep using actigraphy in chronic stroke patients found that 17% of patients self-reported a history of OSA, relative to just 3% of healthy controls [222]. Participants from this study were comparable to our sample in both age (69.94 $\pm$ 6.64) and BMI (28.32 $\pm$ 5.08), however our study contained more men which may, in part, explain the higher rate of OSA [366]. The high prevalence of OSA in our stroke sample is not surprising; up to 80% of acute stroke patients have a sleep disorder, and post-stroke OSA prevalence ranges from 44% to 72% [340]. OSA is an independent risk factor and associated with the pathogenesis of stroke, even after controlling for cerebrovascular risk factors including diabetes, hypertension, hyperlipidaemia, and atrial fibrillation [367] [368]. Interestingly, despite the increased prevalence of undiagnosed OSA among stroke patients, our sample's mean Epworth Sleepiness score of 5.8 and BMI of 26.6 indicate that our sample was generally neither subjectively sleepy nor obese. These findings are consistent with previous work showing a dissociation of OSA severity from hypersomnolence and obesity in stroke patients [369]. OSA is associated with the evolution of stroke severity, likely related to post-stroke sympathetic hyperactivity [370,371]. Given the cross-sectional design of the present study and the lack of premorbid OSA diagnoses, we are unable to conclude causation or directionality of OSA onset; whether infarction to subcortical-brainstem structures was associated with the pathogenesis of *de novo* OSA is unclear [372].

Interestingly, no stroke patients reported a history of OSA, and we observed relatively moderate self-reported Apnoea Predictions Screener scores with no significant differences between-groups. Despite obtaining multiple comprehensive interviews assessing sleep habits and qualitative sleep complaints with patients, it is important to note that self-reported sleep may be inaccurate in stroke populations. Sleep-state misperception, the mismatch between subjective and objective sleep, is a feature of neurological disease and in patients with insomnia and excessive daytime sleepiness [373,320]. Patients with primary insomnia exhibit significant arousal instability and misperceive sleep onset latency as significantly longer and total sleep time as significantly shorter [374]. Interestingly, however, sleep complaints are usually

exaggerated (i.e., subjectively rated worse than objectively quantified) rather than *underestimated* as seen in our sample [375]. This underestimation of sleep-wake disturbance (indicated by our sample's poor sleep efficiency, high rate of OSA, and reduced SWS) may be a form of psychological adaption to chronic sleep-wake dysfunction. In a landmark study conducted by Buysse and colleagues (1991), healthy elderly subjects adapted their perception of objectively disturbed sleep over time [376]. These findings indicate that measures of habitual sleep quality do not strongly correlate with polysomnographic characteristics – particularly in patients with chronic and objectively confirmed sleep pathology. Formal objective sleep studies are therefore warranted in chronic stroke patients, even in the absence of self-reported history of sleep-wake disturbance or sleep disorders.

We found no significant differences in sleep architecture between the stroke-affected versus unaffected hemisphere. Despite these null findings, there are several key explanations to consider. Earlier exploratory work investigating hemispheric sleep differences post-stroke utilized high-density EEG of 128-EEG sensors [326]. For example, in a small sample of 8 unilateral stroke patients, Poryazova and colleagues used high-density EEG and found topographical differences to slow-wave activity and theta activity in sleep comparing the ipsi- versus contra-lesional hemisphere, and in patients versus healthy controls [326]. Given our use of ambulatory at-home PSG, it was not feasible to include a HD-EEG configuration. Three EEGs per hemisphere, as configured in most ambulatory PSG hardware, may therefore be too crude of a measurement tool to discriminate hemispheric sleep architectural differences [155]. Our findings suggest that if hemispheric sleep differences do exist in the chronic stage of stroke, they should be assessed via sleep *micro*architecture (e.g., power spectra) rather than *macro*architecture (e.g., total minutes of SWS). Hemispheric sleep differences may be nuanced after stroke, requiring robust measurement of EEG frequency and amplitude rather than global time measures. A final explanation is that our stroke sample was too heterogenous, lacking sufficient patients with infarcts to sleep-wake hubs and patients with moderate-severe stroke severity/volumes, thereby overwhelming our ability to discriminate any stroke-potentiated hemispheric sleep differences.

Limitations of our study include a relatively small sample size and, as is common in human stroke studies, variable stroke topographies and lesion volumes. With a larger, more homogenous stroke sample (i.e., infarctions to key sleep-wake brain structures), higher

statistical power could have been obtained. Sleep-wake dysfunction after stroke parallels stroke severity [316] and our stroke sample included patients with relatively mild stroke severity (baseline NIHSS = 2.96). We may have therefore underestimated the effects of sleep-wake dysfunction after stroke. A larger sample with more moderate-to-severe stroke severities may exhibit more widespread sleep architectural differences when compared to healthy controls. Finally, the cross-sectional design of the present study limited our ability to determine the directionality or causation of stroke-related sleep changes; whether these sleep and respiratory disturbances were *de novo* or existed prior to stroke-onset is unclear. However, we have previously reported a bidirectional relationship between sleep-wake dysfunction and stroke [316].

Our study shows that stroke patients 4 years after their stroke exhibit SWS reductions and potentially compensatory increases to lighter sleep stages (NREM 1-2) and arousal. Although no patients self-reported a history of OSA, almost 60% of our patients exhibited moderate-to-severe OSA. We did not identify any hemispheric sleep differences in stroke patients when comparing sleep architecture ipsi- and contralesionally. These findings suggest that OSA and hemispheric distributions of stroke lesions are unlikely to be fully mediating contributors to sleep disturbances post-stroke. Formal sleep studies are warranted in chronic stroke patients in order to detect undiagnosed OSA or sleep architectural dysfunction, even in the absence of self-reported history of sleep disorders or normal sleep quality.

Chapter 7

General Discussion

The purpose of this thesis was to characterise sleep architectural dysfunction after stroke by applying gold-standard sleep-wake measurement tools and novel neuroimaging techniques. The first aim of this thesis was to systematically synthesise existing evidence examining the bidirectional impact of non-apnoea sleep and circadian pathology in stroke and describe limitations and gaps of the extant literature. The second aim expanded on limitations of prior work identified in the systematic review and delineated the impact of sleep-wake dysfunction on regional neurodegeneration beyond the effects of stroke infarction itself. The final aim was to assess whether sleep architectural disturbances after stroke are transient as suggested by previous work, or are potentially chronic sequelae even after >4 years post-stroke.

These aims were achieved by conducting three experiments that centred upon sleep and circadian rhythm measurement in stroke patients and healthy controls. The first primary experiment (Chapter 4) obtained objective sleep-wake and neuroimaging data from the pre-existing longitudinal prospective CANVAS study (Cognition And Neocortical Volume After Stroke). To further characterise sleep-wake dysfunction in this cohort (Chapter's 5-6), I recruited participants into the CANVAS sub-study, SACRAS (Sleep And Circadian Rhythms After Stroke). In this study, a sub-set of CANVAS participants underwent ambulatory polysomnography, bi-hemispheric EEG, urinary melatonin assay, and completed an array of sleep, circadian, and mood questionnaires.

In this final chapter, I reiterate the primary methodologies and findings associated with each of my primary aims and their respective limitations. Next, I discuss the overarching implications of sleep-wake abnormalities in stroke patients and call for the characterisation, prevention, and treatment of sleep problems in stroke patients and those with vascular risk factors. Finally, I propose a research agenda for future work in sleep and stroke and discuss additional planned experiments that may further shed light on sleep and circadian rhythm dysfunction after stroke.

7.1 Summary of primary findings

A range of methodologies were used to assess sleep-wake dysfunction after stroke. In the first primary experiment of this thesis, accelerometer and diffusion-structural MRI metrics were obtained from the longitudinal Cognition and Neocortical Volume After Stroke (CANVAS) study. Pre-existing cross-sectional data from CANVAS' 3-month post-stroke time-point were analysed to chart neuroanatomical markers of sleep-wake dysfunction assessed via

accelerometer. In the subsequent studies described in Chapters 5-6, gold-standard polysomnography and urinary melatonin measurements were collected as part of the CANVAS sub-study, the Sleep and Circadian Rhythms After Stroke (SACRAS) study. Together, the SACRAS sub-study and the pre-existing CANVAS study's rich dataset enabled robust and comprehensive characterisation of sleep-wake dysfunction in stroke patients and healthy controls, which potentially allows broader conclusions to be drawn. In particular, how sleep abnormalities may contribute to vascular brain burden and subsequent neurodegeneration.

In Study 1 (Chapter 3), a scoping systematic review was conducted in order to assess the bidirectional relationship between non-apnoea sleep disorders, sleep architecture, circadian rhythms and ischaemic stroke. The most robust finding from this review was from large, prospective cohort studies assessing the relationship between habitual sleep duration or sleep disorders on stroke risk. Synthesised data from included studies showed that chronic sleep-wake dysfunction, characterised as excessively *long*, rather than short, sleep duration (>8 hours of sleep per night) was associated with largest increased risk of ischaemic stroke incidence or death. Similarly, insomnia, restless legs syndrome, and REM behaviour disorder significantly increased ischaemic stroke risk. On the other hand, among studies utilising polysomnography to assess sleep *after* stroke, sleep architecture was significantly fragmented (i.e., reduced sleep efficiency) and suppressed (i.e., reduced NREM-3 and REM sleep) in the acute and sub-acute stages of stroke. In addition, sleep disorders including hypersomnia, REM behaviour disorder, insomnia, and restless legs syndrome were observed *de novo* after stroke. Finally, among studies measuring endogenous circadian rhythms post-stroke, all found significant reductions to nocturnal serum melatonin or urinary melatonin metabolites. These findings suggest that sleep-wake dysfunction is both a risk factor and consequence of stroke with important clinical implications.

Indeed, Professor Claudio Bassetti, a renowned scientist in the field of sleep and stroke, recently noted in a guest editorial of our review: *"…the evidence of a significant link between sleep and stroke is sufficiently strong to call for more awareness and stronger interdisciplinary collaborations between sleep, circadian and stroke scientists and clinicians in this emerging field of medicine.*[377]*"*

Our review also outlined a research agenda for future studies in order to address the shortcomings of prior sleep and stroke research in humans. We noted that future work should assess the neuroanatomical features of sleep-wake dysfunction after stroke in order to establish the potential *in vivo* pathogenesis of sleep abnormalities in patients.

In Study 2 (Chapter 4), I explored the impact of excessively long sleep duration or poor sleep efficiency measured using the SenseWear armband on regional brain volumes and fibre-specific white matter integrity, controlling for lesion characteristics and comorbidities. By applying a recently developed diffusion-weighted imaging technique known as a whole brain fixel-based analysis, specific fibre tracts were identified that exhibited fibre density and cross-sectional reductions in stroke patients with sleep-wake dysfunction. Stroke patients with long sleep duration exhibited neurodegeneration to the corticopontocerebellar tract when compared to age- and sex-matched controls. Stroke patients with long sleep duration and poor sleep efficiency also had smaller ipsilesional thalamus and contralesional amygdala volumes when compared to controls with optimal sleep characteristics. Interestingly, we also found that stroke patients with excessively long sleep duration were more disabled (significantly higher modified Ranking Scale scores at stroke baseline and 3-months post-incident) relative to non-long sleepers. These findings suggest that excessively long sleep duration after stroke may be a marker of brain volume loss and subsequent disability, although causality has not yet been determined. We do not yet know if treatments to alter sleep duration will have an effect on abating neurodegeneration after stroke.

In Study 3 (Chapter 5), I conducted a validation study and compared several sleep variables (e.g., total sleep time, sleep efficiency, wake after sleep onset, and sleep onset latency measured) measured using the SenseWear armband (SWA) against gold-standard polysomnography. Robust concordance statistics were employed and showed that the SWA had an acceptable average epoch-by-epoch agreement and high sensitivity/sleep detection relative to polysomnography. Importantly for this thesis (and Chapter 4's conclusions), total sleep time was the most robustly quantified sleep-wake variable. However, the SWA exhibited only fair specificity/wake detection, which was especially evident when sleep efficiency was <80%. Caution is therefore warranted when the SWA is used for sleep variables requiring wake discrimination (i.e., sleep onset latency, sleep efficiency) or in populations with significant sleep-wake fragmentation.

The final research chapter of this thesis (Study 4, Chapter 6) explored polysomnographically measured sleep architecture, sleep-respiratory, and bi-hemispheric sleep in stroke patients 4 years after their incident event. Stroke patients exhibited significant sleep-wake dysfunction (i.e., more arousals, less slow-wave sleep) relative to controls. In addition, stroke patients had high rates of undiagnosed moderate to severe OSA. These findings were especially alarming since stroke patients and controls reported comparable sleep quality. We observed no difference between ipsilesional versus contralesional sleep architecture. This study highlighted the importance of administering formal sleep studies in chronic stroke patients in order to objectively identify undiagnosed sleep dysfunction, irrespective of lesion characteristics or self-reported sleep abnormalities.

The proceeding three sections of this General Discussion will synthesise the aforementioned findings in the broader context; exploring how, through the amalgamation of these studies, we have furthered our understanding of sleep and stroke. Section 7.2 highlights the necessity for both the prevention and treatment of non-apnoea sleep disturbances in stroke patients given sleep's bidirectional impact on stroke as shown in Studies 1 and 4. Section 7.3 will delve into the pathophysiological mechanisms driving sleep abnormalities after stroke. Finally, Section 7.4 will briefly discuss this thesis' overall limitations and provide a research agenda for future studies.

7.2 Moving beyond OSA and stroke: the role of non-apnoea sleep-wake dysfunction in stroke

Stroke recurrence remains unacceptably high, in up to 40% of patients over a 10-year period [378]. Thrombolytic drugs and devices have revolutionised the quality of care and recovery of qualified stroke patients in the acute and sub-acute settings. Nonetheless, immense challenges remain in altering the trajectory of stroke evolution for those patients who either do not qualify for thrombolytic treatments or remain disabled after treatment. Modifying stroke risk factors can also potentially alleviate accumulating disabilities associated with stroke recurrence. Modifiable ischaemic stroke risk factors have traditionally included hypertension, smoking status, waist-to-hip ratio, diet risk score, physical activity, diabetes, binge alcohol consumption, psychosocial stress and depression. The ground-breaking international case–control INTERSTROKE study found that modifiable risk factors explain 90% of stroke risk [379]. Given

these findings, the investigation of novel risk factors – particularly modifiable behavioural factors – has emerged as an area of active research [380].

There remains a critical gap in clinician awareness of non-apnoea sleep-wake dysfunction in stroke. Are we neglecting a modifiable risk factor and sequela of stroke? For the first time since its inception, the American Heart Association guidelines include a new chapter on sleep [378]. However, the report focuses on the already well-recognised impact of sleep disordered breathing (especially OSA) on stroke and cardiovascular disease. Non-apnoea sleep disorders, sleep architectural disturbances, and comprehensive sleep treatment options beyond CPAP remain virtually unexplored in established clinical practice and stroke guidelines.

7.2.1 Obstructive sleep apnoea and stroke

Sleep dysfunction is amenable to treatment and sleep disorders are estimated to be present in over 50% of stroke patients [381]. The most common sleep disorder associated with stroke is OSA, with an estimated prevalence of up to 70% [382]. In the longitudinal prospective Sleep Heart Health Study, an AHI $\geq$15 (i.e., moderate to severe OSA) was 30% more common among ischaemic stroke patients relative to individuals who remained stroke free [383]. Multiple studies suggest that OSA is not a consequence of brain injury. Rather, OSA is a pre-existing condition prior to stroke incidence [381,382]. For example, Parra et al.'s prospective study (2000) showed a similar frequency and severity of OSA both before and after stroke and TIA, suggesting it is unrelated to brain infarction [382]. Over 50% of stroke patients also exhibit sustained sleep disordered breathing (AHI > 10) even after 3 months post-stroke. Importantly, however, unlike other sleep disorders such as insomnia, hypersomnia, and REM behaviour disorder, OSA prevalence and severity is generally not associated with stroke aetiology or topography [384]. Furthermore, randomised control trials assessing the treatment and prevention of OSA in stroke using gold-standard CPAP have demonstrated largely disappointing and mixed results.

In the multi-centre Sleep Apnea Cardiovascular Endpoints (SAVE) trial, CPAP treatment was not associated with the prevention of recurrent cerebrovascular events after a mean follow-up of 3.7 years [385]. However, in a subsequent propensity score-matched analysis, participants with higher CPAP adherence (≥4 hours) had a lower risk of stroke compared with controls (relative risk: 2.29; 95% CI: 1.05–4.99). A recent meta-analysis of 7 randomised controlled trials found that treatment with CPAP for a mean 3.5 hours per night did not significantly reduce the

incidence of major cardiovascular events after, on average, 37 months of follow-up [386]. However, analogous to McEvoy et al.'s findings (2016), participants with extended CPAP use of $\geq$ 4 hours exhibited a decreased incidence of major cardiovascular events. Similar findings have been shown among studies assessing the impact of CPAP treatment in OSA patients on functional recovery *after* stroke. CPAP adherence and study retention in previous studies have been insufficient to delineate clear neurological or functional benefits among stroke patients with OSA. Unfortunately, long-term CPAP adherence is exceptionally low in stroke patients, with estimates ranging from 12 to 25% [381]. In addition to poor CPAP compliance, prior trials examining CPAP use in stroke patients have been extremely limited by 1) relatively small sample sizes (excluding the SAVE trial, where only half of included participants were stroke survivors), 2) short follow-up periods, and 3) exclusion of patients with severe OSA (AHI/hr > 30).

While future work assessing high CPAP adherence in OSA is promising for stroke, the investigation of sleep's impact on stroke should extend beyond OSA. For example, non-apnoea sleep disorders are bidirectionally associated with stroke and often require less invasive treatment methods. Indeed, as discussed in Study 1 and Study 4, the characterisation and treatment of non-apnoea sleep disorders and sleep architectural dysfunction represent a critically understudied area of the stroke literature and neurotherapeutics relative to OSA and CPAP. In addition, unlike OSA, several non-apnoea sleep disorders are associated with stroke topography and may provide novel targets for stroke recovery and prevention.

7.2.2 The bidirectional impact of non-apnoea sleep-wake dysfunction in stroke: A neglected modifiable risk factor and sequela of stroke

In a retrospective study of over 94,000 participants, those with any non-apnoea sleep disorder (N = 47,080) had a 20% increased risk of incident ischaemic stroke relative to controls after adjusting for age, sex, and cerebrovascular comorbidities (adjusted HR: 1.19; CI: 1.14–1.24) [135]. In Study 1, we found that prolonged sleep duration, sleep-related movement disorders, insomnia, and REM behaviour disorder generally increased the risk of ischaemic stroke. Furthermore, *de novo* sleep disorders and sleep architectural dysfunction were common in the acute and sub-acute stages of stroke when compared to normative averages or controls. In Study 4, we expanded on these findings and showed that sleep architectural disturbances may not be transient after stroke and exist even >4 years after the incident event after controlling

for OSA. Here, the discussion will emphasise the most robust findings from studies investigating post-stroke non-apnoea sleep disorders, sleep architectural dysfunction in stroke, and current treatment options. For brevity purposes, the focus will be on insomnia (and short sleep duration), hypersomnia (and excessively long sleep duration), and sleep architecture.

7.2.3 Insomnia and short sleep duration in stroke

Insomnia has recently shown to be associated with cardiovascular disease, metabolic syndromes, and stroke [316,387,388]. Unlike habitual short sleep duration (which is often attributed to deleterious environmental circumstances or lifestyle habits), patients with insomnia report non-restorative sleep and difficulty maintaining or initiating sleep. Interestingly, although the impact of habitual short sleep duration on ischaemic stroke remains unclear, clinically diagnosed insomnia and insomnia symptoms have been associated with increased ischaemic stroke risk. In Study 1, we showed that insomnia was associated with a 1.19, 1.40, 1.75, and 1.79-fold increase in ischaemic stroke risk [316]. The relationship between insomnia and stroke is, however, confounded by patients underlying psychological and physiological comorbidities. After adjusting for numerous potential confounders, the significance of some relationships was attenuated. For example, in a large cohort of 17,604 participants followed over 14 years, Helbig and colleagues (2015) found that neither short sleep duration nor insomnia symptoms were predictors of stroke after controlling for comorbidities [389]. Contrariwise, both Wu et al. (2014) and Hsu et al. (2015) reported a significantly increased risk of stroke (adjusted HR range: 1.54 - 1.85) in insomnia patients diagnosed according to the International Classification of Diseases codes [133,390]. Furthermore, insomnia symptoms have been reported in up to 57% of stroke patients – de novo in up to 18% – and are often associated with reduced quality of life post-stroke [391]. In rare cases, stroke topography or lesion location may be responsible for *de novo* insomnia. Duss and colleagues (2018) note that thalamo-mesencephalic and tegmental pontine damage may drive insomnia symptoms after stroke [392]. Authors of a recent meta-analysis investigating post-stroke insomnia reported a pooled prevalence of 38% (CI: 30.1 – 46.5) and 32% (CI: 18.5–47.64) among studies using validated assessment tools [393]. Interestingly, Baylan and colleagues (2020) reported a higher post-stroke insomnia prevalence at 18-months (48.9%) compared to 12-months (38.4%) [393]. Glozier and colleagues (2017) showed that those with insomnia at 12-months post-stroke were significantly more likely to be depressed (OR: 6.75, 95% CI: 2.78–16.4), anxious (OR: 3.31, 95% CI: 1.54–7.09), and disabled (OR: 3.60, 95% CI: 2.07–6.25) relative to patients without insomnia [394]. Given this bidirectional link between

insomnia and stroke, does treatment of insomnia prevent stroke or accelerate post-stroke recovery? Unfortunately, the efficacy of insomnia treatment on the risk of stroke has not be adequately assessed.

7.2.4 Insomnia treatment – stroke risk and post-stroke outcomes

In a large hospital-based case-control study with 752 stroke patients and 760 controls, Zhu and colleagues (2016) reported a significant decrease in ischaemic stroke risk among patients taking gamma-aminobutyric acid agonists (adjusted OR: 0.48; CI: 0.32 – 0.72) [395]. In contrast, long term use of benzodiazepines appears to increase cognitive dysfunction and stroke. In a matched retrospective study of nearly 39,000 patients on benzodiazepine therapy and controls, higher annual dosage or time spent on benzodiazepines was associated with an increased risk of stroke [396]. Taipale and colleagues (2015) also found that benzodiazepine use was associated with an increased risk of ischaemic stroke (HR: 1.21; CI: 1.02 – 1.44) [397]. Studies investigating non-pharmacological treatment options such as cognitive behavioural therapy-insomnia (CBT-I) are warranted for both stroke prevention and post-stroke outcomes. Authors of recent small pilot studies (N = $\leq$ 15) have recently reported promising results for CBT-I as both a feasible and efficacious intervention for post-stroke insomnia [398,399]. Large treatment effects were observed for insomnia, depression, and quality of life and were maintained after therapy cessation. Together, these findings highlight the need for large, prospective studies evaluating the effect of both CBT-I and novel hypnotics (e.g., orexin receptor antagonists, see Clark et al. 2020) on stroke risk and post-stroke outcomes [400].

7.2.5 Hypersomnia and excessively long sleep in stroke

In addition to insomnia, Studies 1 and 2 showed that excessively long sleep duration and hypersomnia may be risk factors and consequences of stroke. Recent evidence has suggested a "U" shaped relationship between habitual sleep duration and stroke risk. That is, both excessively short (<6) and long (>8) sleep increase stroke risk [188]. However, in Study 1, we found that seven of eight studies reported a significant association between *long* sleep duration, but not short sleep, and stroke risk after controlling for cerebrovascular risk factors. Significant hazard ratios for habitual long sleep duration and stroke risk ranged from 1.24 – 3.90, and 1.69 – 2.37 for stratified sleep duration of >10 hours per night [316]. Our findings have been supported by recent work showing a "J" shaped dose-response association between sleep duration and

stroke [190,401]. In addition to long sleep duration, hypersomnia was associated with 1.87-fold increase in ischaemic stroke risk (HR: 1.87; CI: 0.60-5.80), although this relationship was non-significant potentially due to a lack of power [135]. Relative to normative data, *de novo* hypersomnia is more common *after* ischaemic stroke and associated with reduced slow-wave sleep [402]. The lack of restorative slow-wave sleep in patients with hypersomnia may, in part, explain the increased prevalence of excessive daytime sleepiness and fatigue in stroke patients [402]. Stroke topography may also be associated with the pathogenesis of hypersomnia. For example, patients with infarction to the paramedian thalamus often exhibit severe hypersomnolence and excessive daytime sleepiness [78,403]. In addition to stroke topography, both OSA and depression are often comorbid with hypersomnia. Vascular risk factors such as obesity, physical inactivity (potentially due to post-stroke disability), and diabetes mellitus are also associated with hypersomnia and daytime sleepiness [404].

Critical questions remain regarding the link between excessively long sleep duration, hypersomnia, and stroke. Is excessive sleep an independent causal risk factor and consequence of stroke, or merely a marker of underlying poor health? Should clinicians recommend patients to sleep *less*? These questions reaffirm the need for experimental studies investigating the mechanisms responsible for hypersomnia's effect on stroke risk and outcome. For example, Bassetti and colleagues (1996) reported that the adverse effects of excessively long sleep duration may be caused by excessive time spent in lighter stages of sleep (i.e., NREM 1-2), and insufficient restorative slow-wave sleep [402]. In Study 4, we showed similar sleep architectural disturbances relative to controls. Additional explanations for the pathophysiological mechanisms driving excessively long sleep duration will be discussed in Section 7.3.

7.2.6 Hypersomnia treatment and functional recovery after stroke

Despite limited mechanistic data currently available, improvements in post-stroke hypersomnia have been observed with pharmacological treatment. Post-stroke hypersomnia and excessive daytime sleepiness may be alleviated with modafinil, methylphenidate, dopaminergic agents, and, in the case of comorbid clinical depression, a stimulating antidepressant [403,405]. Interestingly, experimental data suggests that these eugeroic wake promoting pharmacological interventions – especially methylphenidate and levodopa, a dopamine replacement agent – may also promote functional recovery after stroke [406,407]. The potential impact of hypersomnia or

self-reported long sleep duration on physical and cognitive recovery independent of comorbidities remains inadequately assessed in stroke patients. Future studies should examine the pathophysiological mechanisms underlying hypersomnia and stroke, and whether long-term treatment of hypersomnia or long sleep duration reduces stroke risk.

7.2.7 Sleep macro- and micro-architectural impairment in stroke

Findings from Study 1 and 4 suggest that sleep-EEG abnormalities are a primary sequela of stroke. The range and degree of sleep architectural disturbances after stroke likely depend on stroke topography (infarct location) and time of appearance during stroke recovery. Environmental stressors associated with acute stroke wards also play a key role in affecting sleep-wake patterns. Authors of a recent meta-analysis found that stroke patients have significantly reduced total sleep time and sleep efficiency within the first 2-weeks of stroke [101]. Reports on post-stroke NREM and REM sleep are less consistent. In Study 1, we showed that lighter sleep stages (i.e., NREM-1 and NREM-2) were reduced in only 12% (n = 2) and 41% (n = 7) studies, respectively. In fact, several studies showed increased NREM-1 and NREM-2 up to 1-year post-stroke [96,103]. Hermann and colleagues (2008) also note that the persistence of higher sleep needs after chronic stroke may reflect incomplete recovery [96]. We corroborated these findings in Study 4; up to 4 years after stroke, patients still exhibited increased NREM 1-2 relative to controls. Unlike NREM 1-2, most authors report reductions to slow-wave sleep during the acute phase following either supratentorial or brainstem strokes [103,342]. It remains unclear whether, and to what extent, *a priori* sleep disorders are responsible for these sleep architectural disturbances. Furthermore, several studies did not exclude patients taking drugs with an established influence on sleep EEG [316]. In Study 4, we show that OSA does not fully explain the sleep architectural abnormalities seen in stroke patients free from sleep altering medication use.

In addition to sleep macro-architecture (total time spent in NREM 1-3 and REM), sleep microstructure (e.g., sleep spindles, local slow-wave activity) may be impaired after stroke and associated with stroke topography. For example, Gottselig and colleagues (2002) found reduced sleep spindles after thalamic and supratentorial strokes, but not after brainstem strokes [408]. Poryazova et al. (2015) also identified reduced spindle frequency range in stroke patients ipsilesional hemisphere when compared to controls [326]. Local slow-wave activity is another microarchitectural sleep characteristic that may be altered after stroke.

Increased slow-wave activity over the ipsilesional hemisphere and reduced contralesional slow-wave activity were reported in the acute and chronic (three months) stages of stroke. Furthermore, Porazova et al. (2015) found that both stroke severity and post-stroke outcome were associated with hemispheric slow-wave activity [326]. In Study 4, we observed no significant differences in macro-architecture between stroke patients ipsi- versus contra-lesional hemispheres. However, the use of high-density EEG in future chronic stroke studies may yield results similar to those identified by Poryazova and colleagues. It remains unclear whether sleep architectural disturbances pre-date stroke or are risk factors for stroke.

In Study 1, we found no consistent associations in a small sample of studies investigating sleep architectural disturbances and risk of ischaemic stroke. Interestingly, however, Gelber and colleagues (2015) found that retrospectively measured increased slow-wave sleep duration was associated with less generalised brain atrophy after death (OR: 0.32; CI: 0.10 = 1.03) [137]. Del Brutto et al. (2015) also showed that poor subjective sleep quality was associated with increased risk of white matter hyperintensities (OR: 2.44; CI: 1.26 – 4.71) [139] . Together, these findings pinpoint a bidirectional relationship between sleep architectural dysfunction (particularly slow-wave sleep reductions) and stroke. More data are necessary to test the hypothesis of a causal link between sleep (and its modulation/enhancement) and stroke recovery.

7.2.8 Slow-wave sleep enhancing treatments for post-stroke outcomes

Slow-wave sleep is amenable to enhancement through pharmacological methods, non-invasive brain stimulation tools such as tDCS (transcranial direct current stimulation), rTMS (repetitive transcranial magnetic stimulation), and acoustic cueing [409-411]. The use of tDCS and rTMS to improve stroke recovery via long-term cortical stimulation has produced largely null results [412]. However, studies investigating the potential impact of brain stimulation tools to modulate and enhance endogenous slow-wave sleep are warranted. Acoustic cueing has also recently emerged as a non-invasive and safe slow-wave sleep enhancing tool. Diep and colleagues (2020) recently showed that an automated acoustic cueing device enhanced slow-wave activity and improved executive function [409]. According to ClinicalTrials.gov, a clinical trial is currently underway to assess whether acoustic cueing during slow-wave sleep may improve motor rehabilitation outcomes in stroke patients (ClinicalTrials.gov Identifier: NCT03684603). An additional trial entitled “Sleep as a model to understand and manipulate cortical activity in

order to promote neuroplasticity and functional recovery after stroke" is currently underway which will use a range sleep enhancement tools in both experimental (using optogenetic approaches) and human models to assess sleep-potentiated stroke recovery (**http://p3.snf.ch/project-160803**). Although the advent of these trials is encouraging, the accumulating evidence from the extant literature and our findings from Study 1 and Study 4 suggest a bidirectional relationship between sleep architectural disturbances and stroke; tailored interventions for slow-wave sleep enhancement are warranted for both stroke recovery and stroke prevention.

7.2.9 The future of sleep medicine in stroke: A call to action

In Study 1, we showed that non-apnoea sleep disorders and sleep architectural disturbances are associated with both stroke risk and post-stroke outcomes. Importantly, the aforementioned non-apnoea sleep variables are responsive to non-invasive treatment which may improve post-stroke outcomes. In Study 4, stroke patients exhibited nearly half the amount of restorative slow-wave sleep relative to controls. Fortunately, slow-wave sleep can also be enhanced through non-invasive methods. Nonetheless, although most stroke patients exhibit sleep disorders or sleep architectural dysfunction, only 6% of stroke survivors are offered formal sleep examinations, and less than 3% complete polysomnography in the 3-months following stroke [381,413]. This lack of sleep testing after stroke is unacceptable. The evidence of a significant association between sleep and stroke is stroke enough to call for more clinical awareness, interdisciplinary collaboration, and revisions to sleep-stroke guidelines.

7.3 Unravelling the pathophysiological mechanisms driving disturbed sleep in stroke

A primary aim of this thesis was to explicitly investigate how sleep dysfunction contributes to neurodegeneration beyond the effects of direct infarction. Until Study 2, it remained unclear whether post-stroke sleep pathology was due to focal lesions to sleep-wake nodes in the brain, or to accelerated post-stroke neurodegeneration. Probing the *in vivo* associations of sleep-wake dysfunction with neuroimaging correlates after stroke provided an aperture through which neuroanatomical pathogeneses may be explored. In Section 2.1, I showed that there is a widely distributed and complex neural network regulating sleep-wake control. Damage to one area of the network may cause perturbations in the expression or maintenance of NREM sleep and

wakefulness. In Study 4, we showed that these perturbations exist even in the chronic stages of stroke relative to neurologically intact controls. Here, I synthesise the neuroanatomical findings from Study 2 and propose potential pathophysiological mechanisms – including subcortical vascular neurodegeneration, impaired glymphatic clearance, sympathetic hyperactivity, and autonomic dysfunction – which may be involved in the pathogenesis of sleep-wake dysfunction in stroke. Together, these deleterious mechanisms may not only impair sleep after stroke, but also incite a vicious cascading cycle further aggravating post-stroke cognition, functional recovery, and quality of life.

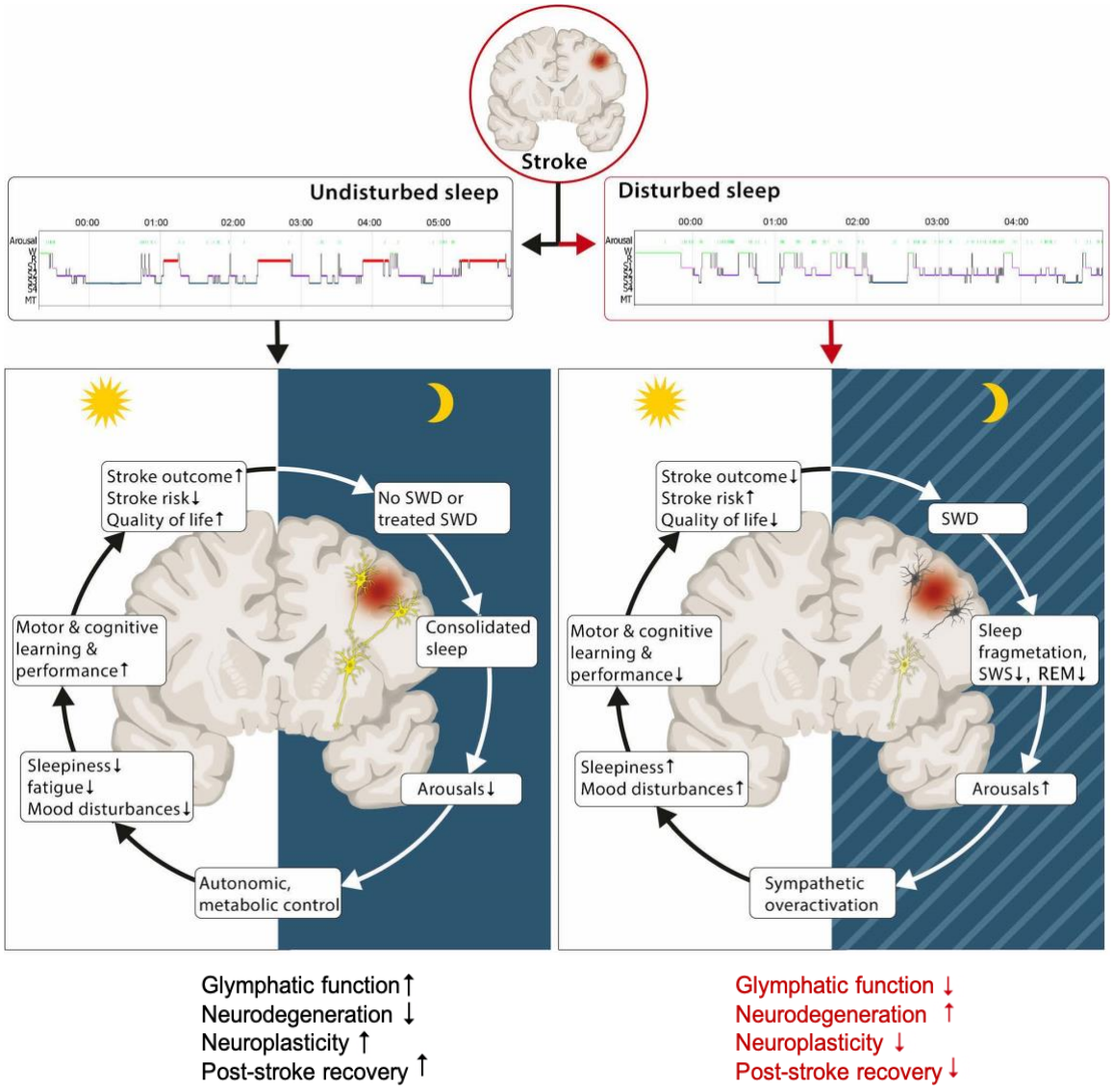

Figure 7.1. The role of sleep-wake disturbances and their treatment on post-stroke recovery. Each circle illustrates either the effect of undisturbed sleep on stroke (left), or the impact of disturbed sleep on various mechanisms involved in post-stroke recovery (right). Abbreviations: SWD: sleep-wake disturbances, SWS: slow-wave sleep. Adapted from Duss et al. (2018) [392].

7.3.1 Post-stroke sleep and arousal impairment reflect thalamocortical damage

Sleep-wake dysfunction after stroke is likely multifactorial in origin, arising from both neurological factors related to stroke (e.g., lesion location, stroke severity, OSA, vascular neurodegeneration) and neuropsychological factors impacting sleep (e.g., depression, pain). Furthermore, environmental factors associated with acute hospital care (e.g., noise, loss of Zeitgebers, altered light exposure) may also impair sleep after stroke. In Study 2, we showed that excessively long sleep duration and poor sleep efficiency were associated with neurodegeneration to key sleep-wake regions *even after* controlling for lesion characteristics, comorbid depression, and OSA. These findings suggest that changes in post-stroke sleep continuity are likely driven, in part, by damage to sleep-wake structures in the brain unrelated to direct infarction or comorbidities. However, when considering the different ways in which structural and tract-specific degeneration may relate to sleep-wake dysfunction in stroke, there are several different models that can be conceptualised.

It is possible that pre-morbid vascular burden may contribute to subcortical brain volume loss to sleep-wake structures long before stroke occurs. For example, Carmichael and Wainford (2015) note that hypertension is a hallmark of vascular pathology and may be evoked by hypothalamic dysfunction – a structure also known to regulate sleep homeostasis [414]. Recent evidence also suggests that disturbed sleep and type 2 diabetes may be a potential nexus for neurodegeneration via hyperglycaemia generated advanced glycated end products [415]. Thalamic resting state functional disruption has also been described in patients with diabetes [416]. Inversely, long term sleep-wake dysfunction may contribute to fluctuations in sympathetic/parasympathetic hyperactivity related to arousal further affecting the homeostatic regulation of blood glucose and insulin levels [417]. These processes may leave the brain susceptible to the effects of vascular subcortical neurodegeneration, thus further exacerbating sleep-wake pathology. In these models, it is unclear whether (1) pre-morbid sleep dysfunction exacerbates neurodegeneration in those with vascular risk factor or; (2) vascular risk factors which were significantly elevated in CANVAS' stroke sample including hypertension, diabetes, and atrial fibrillation – also associated with OSA, see [418] – trigger neurodegeneration to primary sleep-wake centres in the brain. Prospective pre-stroke experimental designs with post-stroke follow-up are required to gauge the direction and causation of sleep-stroke related neurodegeneration in humans.

On the other hand, stroke is associated with accelerated global brain volume loss after the incident event, and subcortical structures responsible for sleep-wake function are especially susceptible to neurodegeneration. For example, Stebbins and colleagues (2008) found significant thalamic atrophy in ischaemic stroke patients with cognitive impairment [291]. Tamura and colleagues also identified shrinkage of the ipsilesional thalamus up to 1 year post-stroke [290]. Zhang and colleagues (2012) review suggests that selective secondary neurodegeneration to ipsilesional regions may occur after focal cerebral infarction [288]. Interestingly, in Study 2, we observed no discernible difference in the proportion of either contralesional or ipsilesional structures affected in poor stroke sleepers. Given our exclusion of patients with lesions in any of our regions of interest, any sleep-potentiated structural or tractographic reductions are unlikely to be driven by stroke infarction and may be more closely associated with vascular risk factors. However, the relationship between regional neurodegeneration and sleep-wake dysfunction in stroke may be far more complex than any aforementioned binary ("either or") explanations or models.

Synergistic and bidirectional mechanisms are likely compounding these associations. Pre-morbid vascular burden may drive neurodegeneration to subcortical thalamocortical nuclei thereby impairing sleep-wake homeostasis, and ischaemic stroke may accelerate atrophy to susceptible distal nodes responsible for sleep-wake function. The convergence of both pre-morbid and post-stroke neurodegeneration to sleep-arousal networks may explain the long-term post-stroke sleep architectural deficits (reduced slow-wave sleep and increased arousals) identified in Study 4. Indeed, we found fibre-specific white matter degeneration to the corticopontocerebellar tract in stroke patients with excessively long sleep duration 3-months after their incident event in Study 2. In a sub-sample of these patients followed-up approximately 4 years post-stroke, we found significantly reduced slow-wave sleep and increased arousal. Thalamocortical projections from the corticopontocerebellar tract are responsible for the generation of slow-wave oscillations. Perhaps corticopontocerebellar degeneration in stroke patients is a marker of not only excessively long sleep and arousal impairment, but also subsequent slow-wave oscillatory deregulation due to thalamocortical damage. Whether corticopontocerebellar degeneration is associated with reductions to slow-wave sleep warrants further investigation and will be discussed in section 7.4's research agenda. Fortunately, all SACRAS participants from Study 4 have MRI data available from their longitudinal CANVAS assessments. Beyond neuroanatomical associations, reductions to

slow-wave sleep after stroke may also have important implications for sleep's restorative function in the brain.

7.3.2 Slow-wave sleep reductions and glymphatic system impairment in stroke

The demonstrable reductions to slow-wave sleep identified in Study 4 may play a key role in the brain's endogenous "rinse cycle". The mammalian brain lacks an anatomically defined lymphatic system. Xie and colleagues (2013) identified a specialised pseudo-lymphatic route in the brain responsible for convective exchanges of cerebrospinal fluid and interstitial fluid [63,348]. This "glymphatic system", aptly named for its dependence on glial aquaporin-4 channels, is responsible for removing deleterious interstitial molecules from the brain parenchyma and is most efficiently driven by delta waves characteristic of slow-wave sleep. Critical questions still remain about the glymphatic system's function (see Haugland et al. for review [419]). Unconscious states were induced by ketamine/xylazine which, although may mimic sleep, are not precisely the same as "natural" homeostatic-induced sleep. Nonetheless, cerebrospinal fluid convection in the glymphatic system is proportional to the amplitude and frequency of slow-wave activity, whereas high amounts of norepinephrine indicative of wakefulness is associated with reductions to glymphatic cerebrospinal fluid influx (see Figure 7.2).

Although research on sleep and the glymphatic system remains in its infancy, there has been an explosion of recent interest given its potential therapeutic role in neurological disease. To date, research on the glymphatic system and sleep has focused on glymphatic clearance of pathological protein species in Alzheimer's disease. For example, in a recently published book chapter review [420], I discuss the mechanisms by which sleep facilitates glymphatic clearance of amyloid-beta and hyperphosphorylated tau proteins, two pathognomonic features of Alzheimer's disease. Less explored, however, is the potential for the glymphatic system and sleep to drive deleterious molecules out of the brain parenchyma following stroke. Using contrast-enhanced MRI, Gaberel and colleagues (2014) showed that the glymphatic system is transiently inhibited after ischaemic stroke and subarachnoid haemorrhage [351]. Spontaneous arterial recanalisation restored glymphatic function after embolic ischaemic stroke.

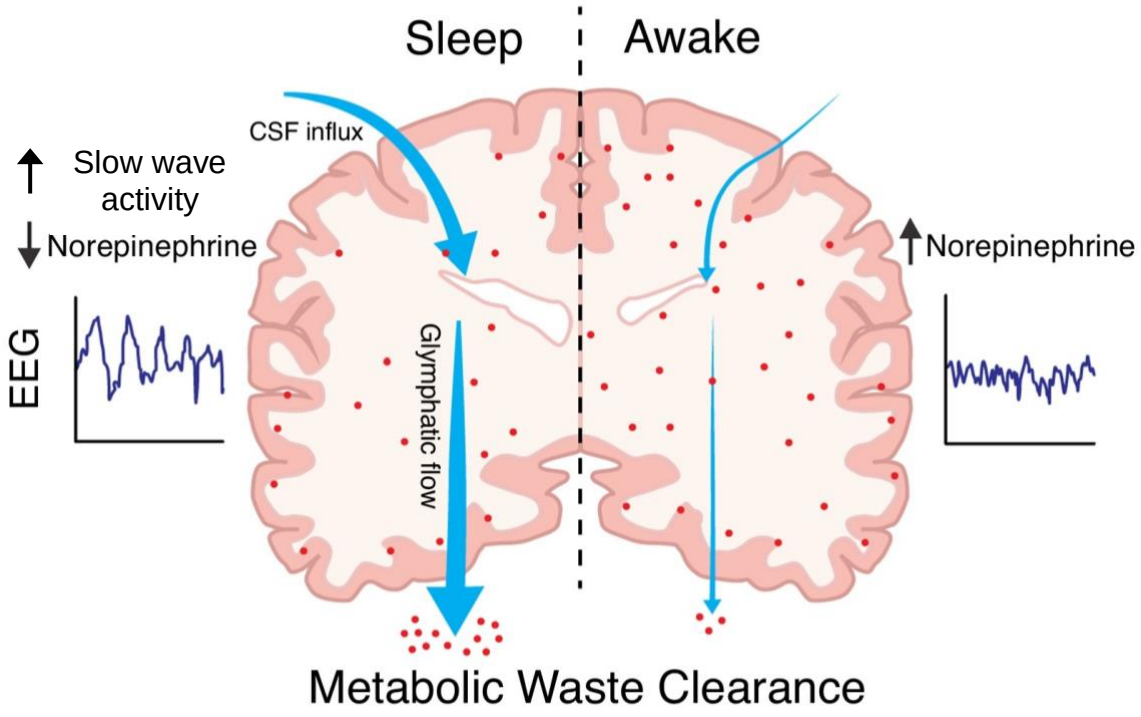

Figure 7.2. The relationship between the glymphatic system and sleep-wake function. During anaesthesia-induced states of slow-wave and low norepinephrine tone (left) cerebrospinal fluid enters the brain parenchyma, interchanges with interstitial fluid and clears the brain of waste metabolites. In wakefulness and in pharmacologically induced states of high norepinephrine tone (right), glymphatic cerebrospinal fluid influx decreases, and clearance of metabolic waste products from the brain is attenuated. Adapted from Haugland et al. (2020) [419].

Interestingly, these findings have not been corroborated in a landmark study recently published in *Science* [421]. Using multi-modal in vivo imaging in rodents, Mestre et al. (2020) found that, after stroke, cerebrospinal fluid rapidly flows into perivascular spaces within the brain causing spreading ischaemic oedema [421]. This aberrant cerebrospinal fluid influx is dependent upon aquaporin-4 water channels expressed in glial cells – the key contributors to glymphatic activation. Furthermore, histological samples of postmortem human brain tissue exhibited increased fluid accumulation in the cerebral ventricles. Berezuk and colleagues (2015) examined the association between Virchow-Robin spaces (i.e., perivascular spaces) and polysomnography-derived sleep parameters in a small sample of 26 patients with cerebrovascular disease [422]. Enlarged Virchow-Robin volumes were associated with poor sleep efficiency, wake after sleep onset, and slow-wave sleep. Interestingly, in a collaborative project with Egorova et al. (2019), we also identified lateral ventricular enlargement measured at 3- and 12-months post-stroke, with accelerated expansion in stroke patients ipsilesional ventricles

[423]. These findings challenge our understanding of the pathogenesis of post-stroke oedema and pinpoint glymphatic enhancement as a potential candidate for acute stroke treatment.

Impaired glymphatic activity in the acute stages of stroke may prevent clearance of deleterious interstitial molecules or trigger oedema. On the other hand, chronic slow-wave sleep reductions after stroke, as identified in Study 4, may contribute to long-term glymphatic suppression and accelerate amyloid-beta deposition – further promoting neurodegeneration and Alzheimer's disease pathogenesis. Future work is needed to examine the association between post-stroke glymphatic disruption and sleep architecture.

7.3.3 A perfect storm: hypoxemia, sympathetic hyperactivity, and impaired cerebral haemodynamics in stroke patients with obstructive sleep apnoea

Thus far, this discussion has focused on the pathogenesis of non-apnoea sleep-wake dysfunction in stroke. However, in Study 4, we found that nearly 60% of stroke patients exhibited undiagnosed moderate to severe OSA. Although the sleep architectural deficits seen in these patients were not attenuated by OSA severity, both stroke risk and post-stroke recovery are independently associated with OSA as discussed in Section 7.2.1. Many authors have contributed to comprehensive reviews of the pathophysiological mechanisms responsible for OSA increasing stroke risk (see [424] for a scoping review). The impact of OSA on post-stroke recovery, however, warrants discussion given our findings from Study 4. A recent prospective study assessing the impact of OSA on post-stroke recovery also identified a high prevalence (60%) of OSA after stroke [425]. Stroke patients with OSA in this study also had poor neurological and functional recovery [425]. Furthermore, Sahlin and colleagues (2008) identified an increased risk of death after stroke among patients with OSA relative to controls (HR: 1.76; CI: 1.05-2.95) [426]. The exact mechanisms by which the presence of OSA after stroke may hinder neurological recovery remain unclear and may include intermittent hypoxemia of the ischaemic penumbra, impaired cerebral haemodynamics, and sympathetic hyperactivity [381].

Pizza et al. (2012) examined cerebral haemodynamic changes in a small sample of eleven patients with acute middle cerebral artery stroke and OSA using near-infrared spectroscopy [427]. During an apnoeic event, stroke patients exhibited asymmetrical (hemispheric) patterns of cerebral oxygenation and significantly reduced haemoglobin concentrations [427]. In an earlier study, Pizza and colleagues (2010) showed that cerebral haemodynamic consequences of OSA

may lead to aberrant cerebral blood flow velocity and subsequent brain tissue hypoxia [428]. OSA severity is also associated with intermittent surges in systolic and diastolic blood pressure during the hyperacute (≤ 72 hours) stages of stroke, while OSA-related non-dipping blood pressure and intracranial pressure is associated with stroke severity and poorer post-stroke recovery [429]. Together, OSA may cause fluctuations in blood pressure, impaired cerebral haemodynamics, and hypoxemia/reoxygenation. These deleterious consequences of OSA may subject stroke patients to prolonged sympathetic hyperactivity and fragmented sleep (i.e., reduced slow-wave sleep and increased arousals) as shown in Chapter 4. Finally, OSA is associated with cognitive deficits after stroke including a decline in executive function, memory impairment, and excessive daytime sleepiness [430]. Conversely, cognitive function is improved following CPAP treatment in subacute stroke patients with OSA [431]. Randomised controlled trials are warranted in order to assess whether CPAP treatment mitigates the detrimental neurological effects associated with OSA and improves functional recovery after stroke.

7.4 Limitations and future directions

Study-specific limitations have been described in their respective chapters, while potential future directions to this work have been alluded to in the previous sections of this chapter. In this section, I briefly discuss the overarching limitations of this work and additional planned or proposed experiments that could provide additional insight into the field of sleep and stroke in the future.

7.4.1 Cross-sectional study designs

The primary research components of this thesis (Studies 2, 3, and 4) constituted three cross-sectional studies aimed at characterising sleep-wake dysfunction in stroke patients during a single time-point. Utilising a breadth of methodologies greatly improved our understanding of sleep after stroke, however, we did not address the temporal pattern of sleep-wake evolution after stroke. Findings from Study 4 suggest that sleep-wake dysfunction is unlikely to resolve following acute stroke. However, given Study 4's relatively small sample size, caution is warranted when generalising our findings until replicated in larger prospective cohort studies. Longitudinal polysomnography should be conducted in larger, more heterogenous stroke samples (e.g., various stroke aetiologies) to assess sleep architectural impairment from the

acute hospitalisation of the incident event until the chronic stages of stroke. Other aspects of sleep, and the consequences of poor sleep (e.g., alertness, napping, daytime sleep), should also be assessed. Circadian and continuous activity monitoring should be used to assess sleep timing and napping behaviours, as well as daytime alertness. If combined with radiological measures of stroke and brain features (i.e., lesion location and volume, regional brain integrity, stroke aetiology), the causal impact of stroke on sleep architecture may be elucidated. For example, as part of a case study, Jang and colleagues (2016) charted the evolution of the ascending reticular activating system in a stroke patient suffering from hypersomnia using diffusion tensor imaging at 3-, 4-, 12-, and 24-months post-stroke [313,314]. Fascinatingly, recovery of self-reported hypersomnia was concurrent with recovery of the injured ascending reticular activating system following neurotropic drugs and physical therapy [313]. The CANVAS study protocol includes collection of sleep-wake (measured using the SenseWear Armband), MRI, PET, and neuropsychological data from 3-months, 1-year, 3-years, and 5-years post-stroke [239]. This rich source of longitudinal data will allow us to chart the temporal patterns of sleep changes post-stroke using objective sleep measurement tools and advanced MRI metrics. Future work investigating spatio-temporal changes to sleep-related brain markers may allow more causal conclusions to be drawn regarding sleep's hypothesised neuroprotective function after stroke.

7.4.2 Exploring associations between post-stroke dementia and sleep

In Study 2, sleep-wake dysfunction was associated with regional neurodegeneration. However, we did not examine whether these sleep-related brain changes have a clinically meaningful impact on cognition or subsequent dementia. Stroke and dementia are interconnected; up to two-thirds of stroke patients experience cognitive impairment, and more than one-third develop dementia after five years [432]. Sleep plays a vital role in memory consolidation and cognitive functioning (see [433] and [236] for reviews). Sleep architectural impairment, especially slow-wave sleep impairment, may therefore be a nexus for post-stroke dementia. The recent discovery of the glymphatic system also has exciting therapeutic implications for post-stroke dementia and sleep. In Study 4, we showed significantly decreased slow-wave sleep – the primary driver for glymphatic function and clearance of pathological protein species involved in Alzheimer's pathogenesis – relative to controls. We will be able to examine the relationship between sleep, cognition, and amyloid-beta deposition after stroke using the CANVAS and SACRAS databases. An understanding of whether sleep-wake dysfunction after stroke is associated with

cognitive impairment and amyloid beta aggregation may help guide the development of sleep-modifying therapies. Furthermore, stratifying patients by cerebrovascular risk factor profiles may provide observational insight into the association between sleep impairment and vascular neurodegeneration.

7.4.3 The future of sleep measurement and medicine

In Study 2, we utilised the SenseWear armband, a consumer-grade sleep and activity monitor, to measure sleep. Our findings from Study 3 suggest that, similar to other consumer-grade accelerometers, the clinical utility of the SenseWear armband may be limited in populations with significant sleep-wake fragmentation. Our use of the SenseWear armband is therefore a methodological limitation of Study 2. Gold-standard polysomnography should be prioritised when viable, particularly in populations with sleep-wake dysfunction. In Study 4, we utilised ambulatory polysomnography with 6-lead EEG to monitor sleep architecture and respiratory. Since the 1960s, polysomnography has been used in both clinical and research settings to monitor sleep. To this day, polysomnography remains the gold-standard for sleep architectural measurement. However, recent advancements in biosensor technologies, "big data", EEG pre-processing, machine learning, and artificial intelligence have revolutionised the future of sleep data and sleep medicine [434]. With these advancements in mind, future studies assessing sleep architecture after stroke should move beyond binary EEG staging and sleep macro-architecture (e.g., "either NREM 1-3 *or* REM"). Indeed, we should assess sleep *micro*architecture using high-density EEG to chart not just sleep architectural duration, but also sleep-EEG *power*. Power spectral density can be used to quantify the amount of oscillatory activity for various EEG frequencies. For example, local sleep reductions due to focal infarction can be detected using high-density EEG and spectral analysis [326]. Traditional 3- to 6-lead EEG placement and binary sleep scoring may not be sufficiently sensitive to detect focal changes to hemispheric sleep as noted in Study 4. Furthermore, continuous rather than nightly measurement of sleep-wake EEG using ambulatory non-invasive monitors may be used to assess the evolution of sleep architecture after stroke. Thus far, the application of high-density EEG and advanced EEG pre-processing methods to both clinical practice and clinical studies are lagging. Fortunately, sleep medicine continues to leverage expertise across health and human-computer sciences to bridge the gap between state-of-the-art sleep-monitoring technologies and clinical reality. It will be fascinating to follow the development of innovative sleep technologies and apply novel techniques to further our understanding of sleep in stroke.

7.5 Conclusions

The overall findings from this work suggest that sleep-wake dysfunction is a key sequela of ischaemic stroke. Stroke patients exhibit significantly reduced slow-wave sleep, increased arousals, and remarkably high rates of undiagnosed obstructive sleep apnoea. Inversely, chronic sleep dysfunction, characterised by excessively long sleep duration or non-apnoea sleep disorders, may significantly increase the risk of ischaemic stroke. Utilising advanced MRI metrics and a validated accelerometer to assess the *in vivo* pathogenesis of sleep-wake dysfunction, we showed that excessively long sleep duration and poor sleep efficiency are associated with regional neurodegeneration after stroke. Together, these findings strengthen our understanding of sleep-wake dysfunction and highlight the need for more clinical and empirical awareness of this vital aspect to sleep and stroke medicine. Hopefully, a recent surge in sleep and stroke studies, a new chapter on sleep in the American Heart Association's 2019 report, and this thesis' primary findings may serve as a stepping-stone for future work in this emerging field of medicine.

This thesis was introduced with a sagacious quote by sleep pioneer, Allan Rechtshaffen: "*If sleep does not serve an absolutely vital function, then it is the biggest mistake the evolutionary process has ever made.*" Now, I echo this statement in the hopes that someday we may fully apprehend the complex relationship between sleep and stroke, and wield sleep as a therapeutic for both stroke prevention and post-stroke recovery.

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Appendices

Appendix A: Published Papers

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Contents lists available at ScienceDirect

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CLINICAL REVIEW

The bidirectional impact of sleep and circadian rhythm dysfunction in human ischaemic stroke: A systematic review

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SUMMARY

Sleep and circadian rhythm disruption are potentially modifiable risk factors and consequences of ischaemic stroke. Pre-clinical evidence suggests a direct effect of sleep and endogenous circadian rhythm dysfunction on lesion volumes and post-stroke recovery. In humans, sleep and stroke literature has focused primarily on obstructive sleep apnoea. However, the bidirectional impact of non-apnoea related sleep disorders, sleep architecture, and endogenous circadian rhythm dysfunction in ischaemic stroke remains unclear. A systematic search of publications in three major databases from inception to August 7 2018 identified 67 studies meeting inclusion criteria. Long sleep duration or sleep disorders significantly increased the risk of ischaemic stroke. Inversely, ischaemic stroke was associated with sleep architectural and endogenous circadian rhythm disruption which were generally associated with post-stroke severity and functional outcome. Importantly, no studies examined direct measures of circadian rhythm dysfunction as a risk factor for ischaemic stroke. Most studies were moderate to high quality. However, methodology and stroke characteristics (e.g., stroke topography, stroke severity) were heterogenous thereby limiting generalisable conclusions. Furthermore, *a priori* neuroimaging outcomes in conjunction with sleep and circadian features were seldom assessed. The clinical pathogenic implications and methodological limitations of studies are discussed, and a research agenda for future studies is outlined.

Introduction

Anecdotally, sleep and circadian rhythm disturbances are common and potentially modifiable sequelae of ischaemic stroke (IS). Sleep-wake pathologies present both a risk factor and consequence of stroke. Chronic sleep and circadian dysfunction activate deleterious pathophysiological mechanisms (e.g., inflammation, autonomic nervous system activation with haemodynamic swings, hypothalamic-pituitary-adrenal axis activation), which may contribute to the pathogenesis of IS [1]. Inversely, lesions to sleep-wake networks and sleep disorders may compromise post-stroke recovery and sleep-potentiated neuroplasticity [2]. Furthermore, the glymphatic system, a pseudo-lymphatic perivascular network driven most efficiently by sleep, is compromised after human IS [3].

In pre-clinical studies, sleep deprivation after IS is associated with increased lesion volumes, and sleep deprivation prior to IS initiates compensatory rebound sleep that is neuroprotective [4,5]. Endogenous markers of circadian rhythms (i.e., melatonin) are suppressed after IS, and exogenous administration of melatonin is neuroprotective [6,7]. However, whether experimental findings translate to heterogeneous human stroke cohorts remains unclear.

Literature investigating stroke-related sleep dysfunction in humans has primarily focused on the impact of obstructive sleep apnoea on stroke risk and outcome [8,9]. In humans, a circadian variation in the timing of stroke onset is characterised by an increased incidence of all-stroke types in the morning (<6AM) and nadir during night-time [10]. However, the cause and neuroanatomical correlates of non-apnoea related sleep and endogenous sleep-potentiated circadian rhythm dysfunction in human IS remain unclear. Thus, the aim of the present review is to investigate

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Abbreviations

AHI	Apnoea–hypopnea index
IS	Ischaemic stroke
mRS	Modified Rankin scale
NIHSS	National Institutes of Health Stroke scale
NOS	Newcastle-Ottawa scale
NREM	Non-rapid-eye-movement sleep
PLM	Periodic leg movements
PS	Post-stroke
PSG	Polysomnography
RBD	Rapid-eye-movement behaviour disorder
REM	Rapid-eye-movement sleep
RLS	Restless legs syndrome
SA	Sleep architecture
SE	Sleep efficiency
SL	Sleep onset latency
SWS	Slow-wave-sleep
TIA	Transient ischaemic attack
TST	Total sleep time
WASO	Wake after sleep onset
WMH	White matter hyperintensities

the bidirectionality of non-apnoea sleep and circadian dysfunction in human IS. These aims will be stratified, where possible, to examine associations with post-stroke recovery, stroke topography, and time-course.

Methods

The systematic review was conducted in accordance with preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines [11]. The review was registered on the international prospective register of systematic reviews (PROSPERO) database (registration number: CRD42018079498).

Search strategy

The authors developed comprehensive search strategies to identify relevant studies pertaining to sleep architecture, sleep quality or duration, non-apnoea sleep disorders, circadian rhythms, and IS. Searches were conducted across MEDLINE (1946 – 7 August 2018, Ovid); Embase (1974 – 7 August 2018, Ovid); and PsycINFO (1806 – 7 August 2018, Ovid), and the Cochrane central register of controlled trials (CENTRAL) utilising a combination of subject headings and free-text created in collaboration with a clinical librarian. Subject headings were modified as required for translation to each database and included: sleep, circadian rhythms, sleep wake disorders, and stroke, with a broad list of free-text terms addressing sleep architecture, non-apnoea sleep disorders, circadian rhythms, and IS (see Supplementary Figs. S1–3 for search terms).

Non-ischaemic stroke types (i.e., haemorrhagic stroke and transient ischaemic attack) represent 15% of stroke cases and exhibit markedly different pathophysiology, neurological clinical evolution, and functional recovery/outcome [12]. Therefore, studies investigating only haemorrhagic stroke and/or TIA were excluded and considered outside the scope of this review.

Single case reports were not included in the review due to this study design's inherent low statistical validity and the availability of more robust evidence from other observational studies including cohort and case–control studies. Although meta-analyses were referenced to support findings from primary studies, they were excluded in our search strategy to avoid duplicate-inclusion and pooling of unstratified (non-ischaemic) stroke types. As case studies, systematic reviews and meta-analyses were to be excluded from the search results, the search strategy was limited to observational studies and clinical trials using established search filters [13] and the Emtree term "controlled study." There were no date or language restrictions applied. Removal of duplicate studies occurred prior to title and abstract screening. Authors scanned the reference lists of included studies and searched for ongoing trials in the Australian New Zealand clinical trials registry and ClinicalTrials.gov.

Inclusion and exclusion criteria

Inclusion criteria were: observational studies or clinical trials; IS confirmed by CT or MRI; sleep assessed by polysomnography (PSG), actigraphy/accelerometer, or self-reported sleep-wake duration diaries; and circadian rhythm assessed via validated scale, actigraphy, or endogenous melatonin or metabolites (e.g., 6-sulphatoxymelatonin).

Exclusion criteria included: case studies, systematic reviews and meta-analyses; animal or tissue studies; self-reported stroke; homogenous haemorrhagic stroke or TIA cohorts; daytime alertness or sleepiness-specific outcomes only; sleep apnoea-specific outcomes; and indirect or non-sleep related circadian rhythmicity (e.g., shift work, heart rate, alertness).

Papers excluded on the basis of "wrong outcomes" (see Fig. 1) refers to one or more of the following reasons: resting state daytime/awake electroencephalography (EEG); daytime sleepiness or fatigue outcomes only; indirect/proxy measures of circadian rhythms (e.g., pineal calcification, blood pressure, timing of stroke onset); traumatic brain injury or non-ischaemic-stroke potentiated lesions; and sleep apnoea outcomes only.

Study selection

Titles and abstracts of potentially eligible citations were imported into Covidence, a web-based platform used to streamline the production of systematic reviews. EG and EL independently reviewed all titles and abstracts to determine initial eligibility. Full papers of eligible studies were independently assessed by EG and EL for inclusion. To achieve consensus, any conflicts raised between the reviewers were resolved through discussion with AB and/or MH.

Data extraction

Extracted variables were chosen based on the STROBE guidelines used for reporting observational studies [14]. Extracted data included: study identification/details; study design/setting; study demographics; stroke time (assessment administration); sleep or circadian rhythm measurement tool; stroke severity and topography (laterality, lesion location, stroke volume); adjustment variables; summarised and raw outcome data; and study quality assessment information. Data extraction for the entire sample was completed by EG. Twenty-five percent of the sample was randomly selected and independently extracted by EL; agreement ratings between EG and EL were very good (92% for study characteristics and findings, 100% for study quality), and therefore did not warrant additional double-extraction. Missing data, or eligible studies that did not distinguish ischaemic and haemorrhagic stroke data, were requested from study authors. In studies supplying multiple covariate models, the most conservative (i.e., most adjusted variables) were exclusively selected. Confidence intervals (CI) are reported as 95%. Reported percentages are rounded to the nearest

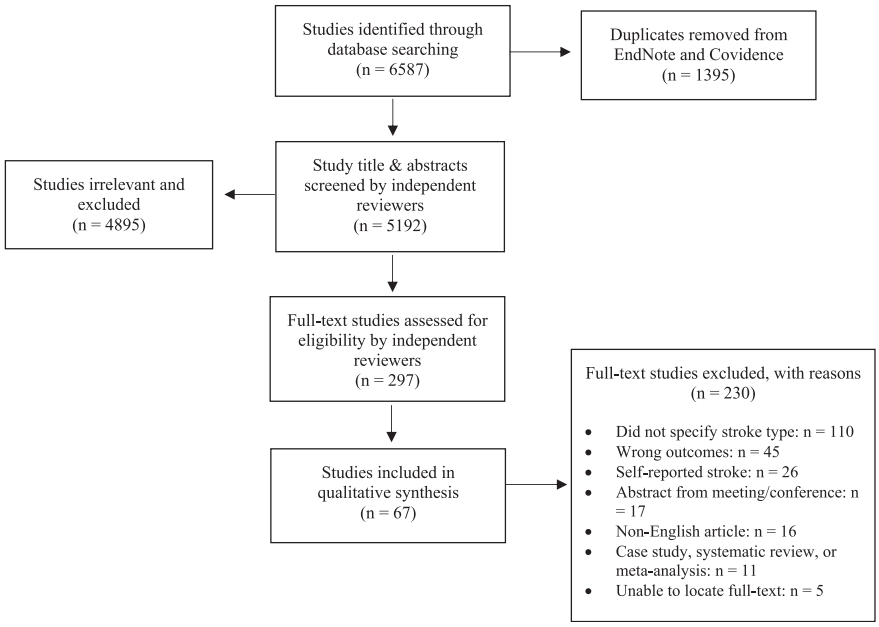

Fig. 1. PRISMA flowchart of study selection. *n* refers to number of studies.

whole number. Raw or summarised statistically significant data are assumed as $p < 0.05$ unless otherwise specified.

Quality assessment

Critical appraisal of methodological quality for cohort and case–control studies was assessed using the Newcastle-Ottawa scale (NOS) [15], and the NOS tool adapted for cross-sectional studies. Studies were rated according to their selection criteria, comparability on the basis of design or analysis, and outcomes or exposures. Case-control and cohort studies were rated on a 1–9 scale. Ratings of 1–3 were scored as "low quality," 4–6 were scored as "moderate quality," and 7–9 were scored as "high quality." The NOS adapted for cross-sectional studies uses a 10-point scale; ratings of 1–3 were scored as "low quality," 4–7 were scored as "moderate quality," and 8–10 were scored as "high quality." Quality assessment scores are summarised in Tables 1–6. A breakdown of study-specific NOS results is presented in Supplementary Tables S1–S3.

Results

A systematic search conducted on August 7, 2018 yielded 6587 citations. After removal of duplicates, 5192 unique citations were included in the title and abstract screening. Subsequently, 297 full-text studies were assessed for eligibility, of which 67 studies were included in the qualitative synthesis. Study characteristics, quality, and findings are summarised in Tables 1–6. Individual study stroke topography, stroke severity, and adjustment variables are reported in Supplementary Tables S4–S9. Refer to Fig. 1 for the complete PRISMA selection process.

Corresponding authors that did not distinguish stroke types were contacted for additional data or clarification if mention of stroke-stratification was included. A total of 43 authors were contacted for additional data and 12 authors responded to the request; six provided stratified data or confirmed exclusive ischaemic stroke samples, and six were unable to provide the requested data.

Study characteristics

All studies were observational. Study quality was generally moderate (58%, n = 39 studies) or high (40%, n = 27 studies). One study was rated as low quality. The 67 included studies were published between 1992 and 2018, with over half published after 2012 and only three studies published before 2000. Sixteen percent of studies included Chinese populations (n = 11), while the other commonest populations were from Japan (n = 8), Switzerland (n = 8), and the United States (n = 7).

Studies were grouped into six categories according to directionality and outcomes: 1) sleep duration on risk of IS, 2) sleep disorders on risk of IS, 3) sleep architectural dysfunction on risk of IS, 4) impact of IS on sleep architecture, 5) impact of IS on sleep disorders, 6) impact of IS on circadian rhythms.

Sleep and circadian rhythm measures

Among studies investigating sleep disorders, 19 of 25 studies (76%) utilised validated diagnostic criteria. Studies investigating sleep duration as a risk factor for IS utilised self-report sleep measures with responses clustered into the following numerical groups: ≤6, 7, 8, 9, and ≥10 h of sleep per night. Sleep architecture and quality was measured via PSG or EEG in 19 of 26 (73%) studies or by validated self-report sleep questionnaires in five of 26 (19%) studies. The remaining two (8%) studies utilised peripheral measures of generalised sleep disturbance (e.g., Nottingham health profile, patient-reported outcomes measurement information system). Circadian rhythms were most commonly assessed through endogenous melatonin serum or urinary melatonin metabolite, 6-sulfatoxymelatonin (6 of 9, 67%). The remaining studies utilised actigraphy (2 of 9, 22%) and a validated self-report chronotype questionnaire (1 of 9, 11%).

Primary findings

The 67 included studies investigated sleep dysfunction as a risk factor for IS (n = 20), and the impact, or consequence, of IS on sleep (n = 38) and circadian rhythms (n = 9). One study was included in

Table 1
Summary of study characteristics and results of studies investigating sleep duration on ischaemic stroke risk.

Author, Year	Study quality (NOS score)	Design, follow-up period, outcome variable	Demographics (study country, gender, age)	Sleep measure	Ischaemic stroke outcome (Total N); Control N	Summary
Chen et al., 2008 [20]	High (7)	Cohort, 7.5 y f/u, IS incidence	USA; female: 100%, range: 50–79 y	Self-report (TST, ≤5, 6, 7, 8, 9, ≥10 h)	1166 (93175); 0	>9h sleep ↑ IS incidence
Eguchi et al., 2010 [24]	Moderate (4)	Cohort, 4 y f/u, IS incidence	Japan; female: 62.4%, mean: 69.9 y	Self-report sleep diary (difference b/w sleep and wake)	517 (932); 0	<7.5 h (vs >7.5 h) sleep ↑ IS incidence
Gianfagna et al., 2016 [22]	High (8)	Cohort, 17 y f/u, IS incidence	Italy; male: 100%, mean: 50.9 y	Self-report (TST, ≤5, 6, 7, 8, 9, ≥10 h)	96 (2277); 0	5 h, >9h sleep ↑ IS incidence
Ikehara et al., 2009 [18]	High (8)	Cohort, 14.3 y f/u, IS death	Japan; male: 56.7%, range: 40–79 y	Self-report (TST, ≤ 4, 5, 6, 7, 8, 9, ≥10 h)	1071 (98634); 0	>10h sleep ↑ IS death
Kakizaki et al., 2013 [19]	High (7)	Cohort, 13 y f/u, IS death	Japan; female: 51.8%, mean: 61.1 y	Self-report (TST: < 6, 7, 8, 9, >10 h)	549 (49256); 0	>10h sleep ↑ IS risk death
Kawachi et al., 2016 [17]	Moderate (6)	Cohort, 16 y f/u, IS death	Japan; female: 51.4%, range: 35–97 y	Self-report (TST, ≤6, 7, 8, ≥9 h)	354 (27896); 0	>9h sleep ↑ IS death
Wen et al., 2016 [23]	High (7)	Case-control, nr, IS incidence	China; male: 54.4%, mean: 64.97 y	Self-report (TST)	223 (880); 547	≥9h sleep ↑ IS incidence
Zhang et al., 2008 [21]	Moderate (5)	Case-control, nr, IS incidence	China; male: 59.6%, mean: 63.5 y	Self-report (TST, ≤ 4, 4–6, 6–8, >8 h)	245 (749); 282	>8h sleep ↑ IS incidence

Abbreviations: b/w = between, d = day(s), f/u = follow-up, h = hours, IS = ischaemic stroke, mo = month(s), NOS = Newcastle-Ottawa scale, nr = not reported, TST = total sleep time, y = year(s).

two sections (Tables 4 and 5) as it measured both sleep disorders and sleep architecture [16]. Thirty-one studies (46%) reported stroke topography, lesion volume, or other relevant neuroimaging measures (see Supplementary Tables S4–S9). Synthesised findings are presented in the following six sections according to directionality and outcomes.

Sleep duration as a risk factor for IS (n = 8)

Seven of eight studies (88%) reported a significant association between long-sleep duration, or ≥8 h of sleep, and IS death [17–19] or incidence [20–23]. Study quality was high (63%, n = 5) to moderate (38%, n = 3). Hazard ratios (HRs) for long sleep duration risk ranged from 1.24 [20] to 3.90 [21]. HRs for sleep duration of >10 h (n = 2 studies) ranged between 1.69 and 2.37 [18,19]. Nine or more hours of sleep (n = 4 studies) was associated with HRs between 1.24 and 1.94 [17,20,22,23]. Eight or more hours of sleep (n = 1 study) was associated with a 3.90-fold increased risk in IS incidence [21]. Inversely, Eguchi and colleagues (2010) reported an increased risk in IS risk in short sleep duration (<7.5 vs >7.5 h of sleep) [24]. All studies (excluding [22], which only adjusted for age) included cerebrovascular risk factors as co-variates. However, only two studies adjusted for depression or depressive symptoms [18,20]. Study characteristics and findings are summarised in Table 1.

Non-apnoea sleep disorders as a risk factor for IS (n = 9)

Non-apnoea sleep disorders, including restless legs syndrome (RLS) [25–27], REM sleep behaviour disorder (RBD) [28], hypersomnia [29], and insomnia [25,30–32] increase the risk of IS. Study quality was moderate (56%, n = 5) to high (44%, n = 4). Sleep-related movement disorders (i.e., RLS and periodic leg movements [PLM]) were associated with a 1.67, 2.04, and 3.89-fold increase in IS risk [25–27]. Insomnia was associated with a 1.19, 1.40, 1.75, and 1.79-fold increase in IS risk [25,30–32]. Participants with chronic insomnia had an increased risk of all-cause stroke compared to those in a remission group [30]. The presence of probable RBD, measured using a validated 13-item self-report questionnaire [33], was associated with a 1.93-fold increase in IS risk after adjusting for sleep measures and other potential confounders [28]. Hypersomnia was associated with a non-significant 1.87-fold increase in IS risk (HR = 1.87, CI: 0.60–5.80) [32]. Study characteristics and findings are summarised in Table 2.

Sleep architecture or quality as a risk factor for IS (n = 3)

No consistent associations were found in a heterogeneous sample of studies investigating sleep architecture [34,35] or sleep quality [36] and risk of IS. Study quality was moderate (66%, n = 2) to high (33%, n = 1). Poor sleep quality, measured using the PSQI, was associated with white matter hyperintensity (WMH) presence and severity (Odds Ratio [OR] = 2.44, CI: 1.26–4.71) [36]. However, no associations were found for silent lacunar infarction [36]. Long sleep duration with blood oxygenation saturation (SpO2) <95% was associated with increased microinfarction (OR = 3.88, CI: 1.10–13.76) [34]. Furthermore, increased slow-wave sleep (SWS) duration was associated with less generalised atrophy (OR = 0.32, CI: 0.10–1.03) [34]. No associations were found between sleep architecture and ischaemic stroke. In a TIA and all-cause stroke sample, patients with the longest nocturnal wake time and highest apnoea–hypopnea index (AHI) had an increased mortality risk (HR = 8.78, CI: 1.1–71.8; HR = 9.71, CI: 1.20–78.29) [35]. However, no statistically significant results were found when data were

Table 2
Summary of study characteristics and results of studies investigating impact of non-apnoea sleep disorders on ischaemic stroke risk.

Author, Year	Study Quality (NOS score)	Design, follow-up period, outcome variable	Demographics (study country, gender, age)	Sleep disorders measure	IS outcome (Total N); control N	Summary
Canivet et al., 2014 [31]	High (7)	Cohort, 11 y f/u, insomnia symptoms prevalence	Sweden; 56.8% female, range: 45-69	4-item self-report questionnaire based on DSM-IV criteria	604 (13617); 0	Insomnia symptoms reported in 51.7% of IS pts, insomnia ↑ risk of all-cause CVD in pts with low socioeconomic status
Chou et al., 2017 [26]	High (7)	Cohort, 5 y f/u, PLM + RLS prevalence	Taiwan; 56.2% male, mean: 57.11 y	ICD-9-CM codes: 327.5 (PLM) and 333.9 (RLS)	137 (3020); 2416	PLM + RLS ↑ IS risk
Elwood et al., 2006 [25]	Moderate (5)	Cohort, 10 y f/u, sleep disturbance prevalence	UK; 100% male, range: 55−69 y	Wisconsin sleep questionnaire	103 (1874); 0	Insomnia ↑ IS, RLS ↑ IS
Frauscher et al., 2010 [79]	Moderate (4)	Case control, RBD prevalence and comorbidities in sleep disorder-PSG confirmed pts	Austria; demographics for RBD-confirmed pts only: 79% male, 57.7 y	PSG, ICSD-2 criteria	1 pontine infarction (34 RBD, 703 total); 0	4.8% (34 of 703) pts diagnosed with RBD, n = 1 with pontine infarction (ns)
Huang et al., 2013 [32]	High (7)	Cohort, 9 y f/u, non-apnoea SD prevalence	Taiwan; 55.1% female. ≤ 35 y: 1%, 35−50 y: 7.6%, 50−65 s: 27.1%, >65 y: 64.4%	ICD-9-CM codes: insomnia (780.5, 780.50, 780.52); hypersomnia (780.54); others (307.4, 780.55−780.56, 780.58−780.59)	9330 (144240); 94160	Insomnia ↑ IS risk, non-apnoea sleep disorders ↑ IS risk
Ma et al., 2017 [28]	Moderate (5)	Cohort, 3 y f/u, RBD prevalence	China; Demographics for total N listed only by RBD group. No RBD group: 81.9% male, mean: 53.9 y. RBD group: 86.9% male, mean: 54.3 y	13-item RBD questionnaire: Hong Kong	136 (12003); 0	RBD ↑ IS risk
Molnar et al., 2016 [27]	High (8)	Cohort, 8 y f/u, RLS incidence	USA; Demographics for total N only. 93% male, mean: 59.8 y	ICD-9-CM code: 333.94	397 (7392); 3696	RLS ↑ IS risk
Wang et al., 2016 [80]	Moderate (6)	Cohort, 85% of pts examined ≤ 3 mo PS, post-stroke depression associations with insomnia	China, 53% male, 68.7 y	Self-report (non-validated)	608 (608); 0	History of insomnia ↑ PS depression
Wu et al., 2014 [30]	Moderate (6)	Cohort, 4 y f/u, insomnia prevalence	Taiwan; Demographics listed only for all stroke types by insomnia status. Insomnia group: 53.5% female, mean: 52 y. Non-insomnia group: 53.0% female, mean: 51 y	ICD-9-CM codes: 780.52, 307.41, 307.42	861 (85752); 64314	Insomnia ↑ IS risk, persistent insomnia vs. remission ↑ IS risk

Abbreviations: d = day(s), f/u = follow-up, ICD-9-CM = International classification of diseases ninth revision clinical modification, IS = ischaemic stroke, mo = month(s), NOS = Newcastle-Ottawa scale, PLM = periodic limb movements, RLS = restless legs syndrome, TIA = transient ischaemic attack, y = year(s).

Table 3
Summary of study characteristics and results of studies investigating sleep quality or sleep architecture on ischaemic stroke risk.

Author, Year	Study quality (NOS score)	Design, follow-up period, outcome variable	Demographics (study country, gender, age)	Sleep measure	Ischaemic Stroke Outcome (Total N); Control N	Summary
Del Brutto et al., 2015 [36]	High (9)	Cross-sectional, SQ in WMH & cerebral small vessel disease	Ecuador; Demographics listed for total N. 59% female, mean: 70 y	PSQI	28 LI, 154 WMH (237); 0	Poor SQ ↑ WMH
Gelber et al., 2015 [34]	Moderate (6)	Case control, PSG time to death 6.4 y, retrospective PSG associations after death	USA; 100% male, mean: 84 y	PSG	68 infarctions (167); 0	> sleep duration + SpO2 <95% ↑ microinfarction; > SWS ↓ generalised atrophy
[a]Ponsaing et al., 2017 [35]	High (8)	Cohort, mean stroke to PSG: 6 d, 19–37 mo f/u period, PSG associations of mortality in IS	Denmark; 63.5% male, mean: 70.25 y	PSG	48 (63); 0	Stratified IS results: no ↑ mortality risk related to PSG variables between IS survivors and non-survivors (*ns*). Non-stratified stroke + TIA results: > AHI and nocturnal wake time ↑ mortality risk

Abbreviations: AHI = apnoea–hypopnea index, IS = ischaemic stroke, d = day(s), f/u = follow-up, ICD-9-CM = International classification of diseases ninth revision clinical modification, mo = month(s), PSQI = Pittsburgh sleep quality index, RLS = restless legs syndrome, SpO2 = blood oxygen saturation, SQ = sleep quality (subjective), SWS = slow-wave sleep (N3), WMH = white matter hyperintensities, y = year(s).
[a] Note: Raw data for IS-stratified results were provided upon request by the corresponding authors and calculated according to study methodology by EG and EL. Study quality NOS scores are based solely on data reported in the original peer-reviewed manuscript.

stratified by ischaemic stroke only [35]. Study characteristics and findings are summarised in Table 3.

Impact of IS on sleep architecture or quality (n = 23)

Sleep architecture and quality is compromised after IS [16,37–54]. Study quality was moderate (74%, n = 17) to high (26%, n = 6). Authors investigating sleep-potentiated stroke recovery found associations between sleep dysfunction and stroke severity or outcome [37,43,47,49,50,52,55]. Thirteen studies (57%) assessed sleep within 14 days after stroke [37,38,40–43,45,47,49,51–54]. Sleep architecture was objectively measured using PSG or high-definition EEG in 17 of 23 (74%) studies. Utilising PSG, sleep architectural variables impacted after IS, when compared to controls, ranged across studies from sleep efficiency (SE) and wake after sleep onset (WASO) [42,44], to total sleep time (TST), SE, non-rapid-eye-movement stage 2 sleep (NREM-2), SWS, and REM [53]. Sleep efficiency was reduced in 65% of studies (n = 11 of 17 studies) utilising PSG. Significant reductions to NREM-1, NREM-2, NREM-3 (SWS), and REM were reported in 12% (n = 2), 41% (n = 7), 35% (n = 6), and 35% (n = 6) of studies, respectively. Study characteristics and findings are summarised in Table 4.

Sleep architectural variables associated with post-stroke (PS) outcome, lesion volume, or topography varied across studies; SWS and REM correlated with stroke severity or functional outcome in five studies [43,44,49,52,53], and stroke topography was associated with sleep quality or architecture in six studies [16,36,43,44,52,53]. IS patients had bilateral reductions in sleep spindles and sawtooth waves [41,47,50]. In both the acute (<10 days) and chronic (3-months) stage of stroke, SWS and theta activity over the contralesional hemisphere were significantly higher in the lateral temporo-parietal-occipital region and contralateral frontocentral region, respectively, which corresponded to the ipsilesional hemisphere [43,44]. Decreased REM percentage was associated with deep (versus superficial) lesions and was an independent predictor of functional outcome [49,52,53]. However, Manconi and colleagues (2014) reported no significant sleep architectural differences between supratentorial and infratentorial strokes [45]. Cortical lesions were associated with worse overall sleep quality [40]. These findings are inconsistent: Chen et al. (2015) reported left hemispheric and anterior circulation infarction associations with poorer sleep quality compared to right-sided and posterior circulation infarction, respectively [16]. In a small sample of mild-to-moderate extra-thalamic stroke, positive post-stroke (PS) outcome was associated with increased sleep efficiency (SE), total sleep time (TST), and NREM-2 sleep [47].

Impact of IS on non-apnoea sleep disorders (n = 16)

Sleep disorders were more common after IS when compared to normative averages or controls [16,29,56–62]. Study quality was mostly moderate (50%, n = 8) to high (44%, n = 7). One study was rated as low quality. Eight (50%) studies examined PS sleep-related movements disorders (n = 5 RLS [61,63–66], n = 3 PLM [56,67,68]; five studies examined PS insomnia [57–59,62,69]; one study examined PS REM sleep behaviour disorder [60]; one study examined PS hypersomnia [29]; one study examined all-cause (non-apnoea) sleep disorders [16]. Time from stroke to sleep assessment ranged significantly across studies from ≤2-days PS [65,67,68], to 3-months post stroke [56,57,59,60]. Study characteristics and findings are summarised in Table 5.

Prevalence of restless legs syndrome (RLS) and periodic limb movements (PLM) after IS (n = 8)

One of six studies (17%) examining PS RLS prevalence included healthy controls [67]. Prevalence across studies ranged from 8% (n = 3) to 33% (n = 10) [56,68]. Four of six studies (67%) reported an RLS prevalence of ≤14.5% [63,65–67]. Two studies reported associations between RLS and PS symptoms or quality of life (QoL); RLS was negatively associated with QoL independent of functional outcome and depression, and stroke symptoms were significantly more severe in RLS patients as measured by the Barthel index and modified Rankin scale [63,64]. Two of three studies including neuroimaging-specific outcomes reported associations between stroke topography and RLS; subcortical strokes (basal ganglia and/or corona radiata lesions) were associated with RLS, and a 17-fold increase in brainstem stroke-potentiated RLS was reported when accompanied with PS sensory symptoms (CI: 1.38–330.77) [65,66].

Among three studies investigating PS PLM, two included control groups and reported a greater quantity of PLMs detected on PSG when compared to healthy controls or TIA [56,67]. Associations between PLM and stroke topography were reported in one study; bivariate correlational analyses revealed that PLM index and lesion

Table 4
Summary of study characteristics and results of studies investigating the impact of ischaemic stroke on sleep architecture and sleep quality.

Author, Year	Study Quality (NOS score)	Design, time of assessment administration, outcome variable	Demographics (study country, gender, age)	Sleep measure	Stroke outcome (Total N); Control N	Summary
Alvarez-Sabin et al., 2017 [81]	High (8)	Cross-sectional; nr, PSG in OSA pts with silent cerebral infarction (SCI) vs controls	Spain; 72.1% male, mean: 64.5 y	PSG	61 (183); 122	SCI SA vs controls: *ns*, OSA ↑ lacunar SCI
Bassetti & Aldrich, 2001 [47]	Moderate (6)	Case control; 11.7 d PS, PSG in acute hemispheric, extra-thalamic stroke vs TIA controls	USA; 66.67% male, mean: 62.1 y	PSG	24 (41); 17 TIA matched	IS SA vs TIA (control): TST min ↓ SE % ↓, N2% ↓, N3-4 ↓. SA in good vs. bad IS outcome: TST ↑, SE % ↑, N2 ↑, sawtooth wave ratio ↑
Chen et al., 2015 [16]	Moderate (5)	Case control; nr, PSG in IS vs controls	China; 64.4% male, mean: 56.6 y	PSG, PSQI, ESS	101 (187); 86	IS SA vs control: TST min ↓, N1% ↓, N3-4% ↓, PSQI ↓, WASO % ↑, ESS score ↑, REM % ↑, SL min ↑, RL min ↑; Thalamic SA vs non-thalamic: N2 ↓, N3-4 ↑, SL ↓; Cerebral infarction SA vs subcortical, brainstem, cerebellum: TST ↓, SE ↓, N3-4 ↓, REM ↓, RL ↓, N1 ↑, SL ↑, WASO ↑
Gokkaya et al., 2005 [46]	Moderate (4)	Case control; 6 mo PS, Nottingham health profile (NHP) scores in IS vs controls	Turkey; 70% male, mean: 58.2 y	NHP	39 (108); 58	Chronic IS NHP sleep domain scores vs controls: ↑ (worse)
Giubilei et al., 1992 [49]	Moderate (5)	Case control; ≤ 5 hr + 3 w PS, PSG changes in acute + chronic IS vs controls	Italy; 55% male, mean: 66.3 y	PSG	18 (28); 10	IS SA vs control: REM min ↓, REM/NREM ratio ↓, REM bouts ↓, WASO ↑; ↓ acute REM correlated with worse PS outcome + severity; deep vs supervision lesions (acute): ↓ REM %
Hermann et al., 2008 [50]	High (7)	Cohort; ≤ 1 mo + 3–6 mo PS + ≥ 1 yr PS; stroke mediated PSG evolution in paramedian thalamic stroke vs controls	Switzerland; 73.9% male, mean: 48.4 y	PSG, spectral EEG analysis (n = 2), self-report sleep duration	46 (58); 12 (peripheral neurological disease controls)	IS SA vs control: N1 ↑, N2 ↓, spindle density ↓; SA + stroke topography PS: unilateral IS ↓ spindle density vs bilateral IS; self-report sleep needs PS ↑ (hypersomnia > in bilateral vs unilateral IS)
Jiang et al., 2013 [39]	Moderate (6)	Case control; ≤ 3 mo PS, PSG in IS + VCIND vs controls	China; 66.67% male, mean: 61 y	PSG, PSQI	48 (152); 48	IS SA vs control: TST ↓, SE ↓, SL ↑, SWS ↓, REM ↓, arousal index ↑, PSQI ↑ (worse)
Karaca, 2016 [48]	Moderate (5)	Cross-sectional; nr, Self-reported SQ in IS vs haemorrhagic stroke	Turkey; 60.9% male, mean: 60.2 y	PSQI	19 (23); 0	IS SQ (mean PSQI) score: 3.0. Regression to estimate PSQI variations: Beck depression inventory score (B = 0.035, CI: 0.004–0.066), comorbidities (B = 0.901, CI: 0.048–1.754)
Katzan et al., 2018 [55]	Moderate (6)	Cohort; median 99 d PS, self-reported sleep disturbance after IS	USA; 54.9% male, mean: 62 y	PROMIS (Patient-Reported Outcomes Measurement Information System)	1195 (1195); 0	IS sleep disturbance scores ↑ (better) vs US population avg (49.2 vs 10.5, p = 0.02); 27.5% of IS pts with meaningfully worse scores (+5 points) vs avg population norms; sleep disturbance associated with worse PS outcome
[a] Klobučníková et al., 2016 [51]	High (7)	Case control, mean 4 d PS; PSG associations with EDS in acute IS	Slovakia; 56.8% male, mean: 68.36 y	PSG, ESS	93 (102); 0	PSG associations for EDS vs no EDS in IS: ↓ REM, ↑ respiratory disturbance index
Manconi et al., 2014 [45]	Moderate (6)	Cohort; admission + 3 mo PS, PSG in supratentorial vs infratentorial IS	Switzerland; 96% male, mean: 64.8 y	PSG	14 supratentorial IS (14 infratentorial IS); 0	Acute IS SA vs chronic: ↓ SE %, SL min ↑, REM latency ↑; Supratentorial IS SA vs infratentorial = *ns*
Muller et al., 2002 [44]	Moderate (5)	Case control; acute + subacute (not specified), PSG in acute hemispheric IS without sleep apnoea vs controls	Switzerland; 60% female, mean: 53 y	PSG	10 (20); 10	IS SA vs controls: WASO min ↑, SE % ↓; Positive correlation b/w SWS + stroke volume (r = 0.79); NREM SWA sleep/wakefulness ratio ↓ in IS vs control + correlated with NIHSS
Pace et al., 2018 [52]	High (8)	Cohort; ≤9 d PS; PSG evolution in IS + associations of functional outcome	Multicentre (Germany, Italy, Switzerland); 71.9% male, mean: 61.2 y	PSG, ESS	153 (153); 0	PSG associations with poor functional (mRS >2) vs good functional outcome (mRS ≤2): ↓ SE, ↓ REM sleep duration, ↑ REM latency, ↑ AHI; ↑ REM latency predictor of worse outcome PS
Poryazova et al., 2015 [43]	Moderate (4)	Case control; ≤ 10 d + ≤ 3 mo PS, HD sleep EEG in acute and chronic hemispheric IS vs controls	Switzerland; 75% male, mean: 52 y	HD EEG	8 (16); 8	Acute + chronic IS SA: ↓ SWS, theta activity, spindle frequency ipsilesionally. SWS correlations: IS severity (NIHSS) + outcome (Barthel index)
Santamaria et al., 2000 [41]	Moderate (5)	Case control; 14 d PS, Sleep spindle in unilateral acute thalamic IS vs controls	Spain; 53.8% female, mean: 67 y	PSG	13 (31); 18	IS SA vs controls: TST min ↓, N2% ↓, time in bed min ↓, bilateral sleep spindle ratios ↓
Siccoli et al., 2008 [42]	Moderate (4)	Case control; ≤ 8 d + ≤ 12 mo PS, PSG & cognition in acute and chronic hemispheric IS vs controls	Switzerland; 64% female, mean: 43 y	PSG	11 (16); 5	Acute IS SA vs. chronic IS or controls: SE % ↓, WASO min ↓

Siengsukon & Boyd, 2009 [82]	Moderate (5)	Case control mean 58.8 mo PS, SQ potentiated off-line motor learning in IS vs controls	USA, 50% female, mean: 62.6 y	Sleep log, PSQI, SSS	40 (80); 40	No significant differences between IS vs control average sleep time, PSQI, SSS (*ns*)
Siengsukon et al., 2015 [83]	Moderate (5)	Case control, ≥6 mo PS, SA potentiated offline motor learning in chronic IS vs controls	USA; 63.3% female, mean: 60.6 y	PSG, PSQI, SSS	20 (10); 30	IS SQ vs controls: no significant differences; SA offline motor learning associations in IS vs controls: ↑ SE, ↓ N3, ↑ REM weakly-to-moderately associated with ↑ offline motor learning (*ns*)
Suh, Choi-Kwon, & Kim, 2014 [40]	High (8)	Cross-sectional; 6.7 d PS, VHSS scores + topography in acute IS	South Korea; 58.9% male, mean: 62.3 y	VHSS, actigraphy (in 54 pts)	282 (282); 0	Multiple regression analysis of factors related to VHSS scores: cortical lesion location, diabetes mellitus, depression; SL: depression; night-time awakenings: depression
[b]Terzoudi et al., 2009 [53]	High (7)	Case control, ≤ 10 d PS, PSG in acute stroke vs controls in relation to outcome + topography	Greece; 64% male, mean: 61.8 y	PSG	45 (78); 16	SA in stroke (excl pts with SDB) vs controls: ↓ TST, ↓ SE, ↓ N2, ↓ SWS; Severe vs mild stroke deficits (NIHSS > 7 vs < 7): ↓ REM, % of N1 + REM negatively associated with stroke severity (NIHSS); ↓ REM % in brainstem, hemispheric, and multiple lesions (vs cerebellar lesions); worse outcome (Barthel index) associated with ↓ REM latency
Vock et al., 2002 [54]	Moderate (5)	Cohort; acute (1−8 d) + subacute (9 −35 d) + chronic (5−24 mo) PS, longitudinal SA evolution in hemispheric IS	Switzerland; 59.2% female,	PSG, sleep diary, ESS	40 (27); 13	IS SA abnormalities vs controls/published norms (no *p* values reported): 67% acute PS, 54% subacute PS, 53% chronic PS; Acute IS SA vs chronic IS: TST ↑, SE ↓, WASO ↑; ↑ self-reported TST, ↑ WASO, ↑ N1, ↓ SE, associated with worse PS outcome (BI or mRS)
Wu et al., 2016 [38]	Moderate (4)	Cohort; 14 d + 3 mo PS, PSG in acute minor thalamic infarction versus controls	China; 70.4% male, mean: 61.4 y	PSG, PSQI, ESS	27 (39); 12	IS SA vs control: SL min ↓, SE % ↓, N2% ↓, N3% ↓
Zhang et al., 2014 [37]	Moderate (5)	Cross-sectional; 2 d + 3 mo PS, SQ in IS vs control	China; 70.3% male, mean: 35.9 y	PSQI	223 (381); 158	IS SQ (PSQI) ↓ vs controls (29.1 vs 47.1), < SQ ↑ 3-mo mRS scores

Abbreviations: AHI = apnea−hypopnea index BI = Barthel index, IS = ischaemic stroke, d = day(s), ESS = Epworth sleepiness scale, f/u = follow-up, ICD-9-CM = International classification of diseases ninth revision clinical modification, mo = month(s), MSLT = multiple sleep latency test, N1-4 = NREM stages 1−4, NHP = Nottingham health profile, NIHSS = National institutes of stroke scale (stroke severity), PS = post-stroke, PSG = polysomnography, PSQI = Pittsburgh sleep quality index, pts = patients, REM = rapid-eye-movement sleep, RL = rapid-eye-movement latency (total time to first REM bout), RLS = restless legs syndrome, SA = sleep architecture, SCI = silent cerebral infarction, SE = sleep efficiency, SL = sleep latency, SpO2 = blood oxygen saturation, SQ = sleep quality, SSS = Stanford sleepiness scale, SWA = slow-wave activity (ratio), SWS = slow-wave sleep (N3), TIA = transient ischaemic attack, VCIND = vascular cognitive impairment-no dementia, VHSS = Verran-snyder-halpern sleep scale, WASO = wake after sleep onset, WMH = white matter hyperintensities, y = year(s).

[a] Raw data for IS-stratified results were provided upon request by the corresponding authors and calculated according to study methodology by EG and EL. Study quality NOS scores are based solely on data reported in the original peer-reviewed manuscript.

[b] Results include both ischaemic stroke and haemorrhagic stroke. Authors reported no statistically significant differences in sleep architecture between either stroke types.

Table 5
Summary of study characteristics and results of studies investigating the impact of ischaemic stroke on non-apnoea sleep disorders.

Author, Year	Study quality (NOS score)	Design, time of assessment administration, outcome variable	Demographics (study country, gender, age)	Sleep measure	Stroke outcome (Total N); controls	Summary
Bassetti et al., 1996 [29]	Moderate (5)	Cohort; 6 pts < 5-weeks PS, 10 pts < 5-mo PS, 2 pts >1-y PS; PSG in paramedial thalamic IS + hypersomnia vs normative data	Switzerland; 83.3% male, age range: 16–60 y	PSG	12 (12); 0	IS + severe hypersomnia vs norms: N1% ↑, N2% ↓, N3-4% ↓, sleep spindles ↓
Benbir, G. & Karadeniz, D., 2012 [67]	High (7)	Case-control; ≤2-d PS, PLM + RLS prevalence in supratentorial IS vs controls	Turkey; 62.9% male, mean: 68.1 y	PSG	35 (70); 35	PLM-index in male IS ↑ vs controls, IS topography + PLMs: *ns*. RLS in IS ↓ vs controls: 14.3% vs. 20%.
Benbir, G. & Karadeniz, D., 2013 [68]	High (8)	Cross-sectional; admission + 3-weeks + 3-mo PS, PLM + RLS prevalence and association with IS outcome	Turkey; 54.2% male, mean: 69.0 y	PSG, International Restless Legs Syndrome Study Group Diagnostic Criteria (IRLSSGC)	24 (All stroke, 2 RLS); 0	8% (n = 2) PS RLS, > arousal-associated PLM-index at admission: ↑ NIHSS, ↓ Barthel scores at 3-mo PS
Boulos et al., 2017a [64]	Moderate (6)	Cohort; 3.9 + 110.4-d PS, RLS after IS and associations with PS QoL	Canada; Total N demographics reported (incl TIA), 51.1% female, mean: 67.4 y	Questionnaire based on IRLSSGC	48 (94); 0	24.4% (n = 23, 10 IS) PS RLS. PS RLS ↓ (worse) QoL vs no RLS. RLS predictor of PS QoL score: baseline OR 0.28 (0.10–0.75), 2–6-month f/u OR 0.14 (0.02–0.82)
Boulos et al., 2017b [56]	High (8)	Cross-sectional; median 51 d PS, PLM and WMH incidence after IS	Canada; Total N demographics listed only, 57% male, mean: 63.7 y	Medical history, RLS diagnostic questionnaire (confirmed by sleep neurologist), PSG	16 (30); 14 (TIA)	IS PLM ↑ vs control, IS PLM-index ↑. PLM index + stroke volume correlated with ↑ WMHs.
Chen et al., 2015 [16]	Moderate (5)	Case-control; nr, PSG confirmed SD after IS vs controls	China; 64.4% male, mean: 56.67 y	PSG, PSQI, ESS	101 (187); 86	IS SD prevalence 77%, PS SD NIHSS ↑ vs no SD
Glozier et al., 2017 [58]	High (8)	Cohort; 28-d +, 6, 12-mo PS, self-reported insomnia after IS and associations with PS functional outcome	Australia; Total N demographics listed by insomnia vs no insomnia: insomnia: 57% male, 70% 46–65 y; no insomnia: 74% male, 79% 46–65 y	Karolinska Sleep Questionnaire	304 (368); 0	PS insomnia prevalence 30–37%, chronic insomnia prevalence 16%, chronic insomnia vs no insomnia: ↑ depression, ↑ anxiety, ↑ disability
Kim et al., 2017 [69]	Moderate (7)	Cohort; acute (not specified), insomnia after acute IS	South Korea; Total N (IS + haemorrhagic stroke) demographics only. 56.85% male mean: 65.63 y	Medical records	8205 (10625); 0	PS insomnia prevalence: IS = 305/8205 (3.8%), haemorrhage = 99/2420 (4.27%)
Lee et al., 2009 [66]	Moderate (6)	Cohort; 1-mo PS, RLS after IS	South Korea; 54% male, mean: 63.9 y	IRLSSGC	137 (All IS, 17 RLS); 0	PS RLS prevalence 12.4% (n = 17); 94% (n = 16) subcortical lesions
Leppavuori et al., 2002 [57]	High (8)	Cross-sectional, 3-mo PS, insomnia after IS	Finland; 50.9%, mean: 70.7 y	DSM-IV criteria	277 (All IS, 157 self-reported insomnia complaints); 0	Self-reported PS insomnia prevalence 57% (n = 157), 37.5% (n = 104) DSM-IV confirmed; pre-existing in 38.6% of IS, de novo in 18.1%. Independent correlates of de novo insomnia: ↑ dementia, ↑ psychotropic drugs, ↑ anxiety, ↑ Barthal index
Medeiros et al., 2011 [63]	Low (3)	Cohort; ≤15 d + 3-mo + 1-y PS, RLS in acute IS stroke and associations with PS outcomes	Brazil; 61.5% male, mean: 64.0 y	PSQI, IRLSSGC	96 (All IS, 12 RLS); 0	PS RLS prevalence 12.5% (n = 12), 100% pre-existing). PS RLS SQ (PSQI) ↓ vs non-RLS. PS (3–12 mo) RLS outcome (Barthel index, mRS) ↓ vs non-RLS
Palomaki et al., 2003 [62]	Moderate (6)	Case-control; ≤14-d + 6, 12, and 18-mo PS, insomnia prevalence after IS and efficacy of mianserin for PS insomnia	Finland; Demographics by treatment condition only. Placebo group: 65.3% males, mean: 54.7 y. Mianserin group: 70.6% males, mean: 55.7 y	Hamilton Depression Scale (3-items related to insomnia), neurologist confirmation if score ≥1	100 (100); 49	PS confirmed insomnia prevalence 51% (n = 51) of stroke patients with confirmed insomnia. PS insomnia ↑ poor life satisfaction. 2-mo placebo treatment ↑ insomnia
Rist et al., 2014 [61]	High (8)	Cross-sectional; nr, self-reported RLS after IS	France; Demographics for total N listed only by RLS group. No RLS: 59.7% female, mean: 71.6 y. RLS: 72.9% female, mean: 71.6 y	3-item self-report questionnaire	88 (1035); 0	PS RLS prevalence: 21% (n = 218). WML ↑ RLS risk
Ruppert et al., 2014 [65]	Moderate (5)	Cross-sectional; <2-d PS, RLS after brainstem IS	France; 60% male, mean aged 62.8 y	IRLSSGC	30 (30); 0	PS RLS prevalence: 10% (n = 3). RLS + topography or severity: ns. RLS + PS sensory symptoms ↑ brainstem IS RLS

Tang et al., 2014 [60]	Moderate (5)	Cohort, 3-mo PS, RBD after IS	Hong Kong: Demographics by RBD status. RBD: 53.8% male, mean: 67.3 y. Non-RBD: 61.3% male, mean: 66.5 y	13-item RBD questionnaire	119 (119); 0	PS RBD prevalence: 10.9% (n = 12). Brainstem IS ↑ RBD. IS volume in non-RBD ↑ vs. RBD
Tang et al., 2015 [59]	High (9)	Cross-sectional; 3-mo PS, insomnia after IS	Hong Kong: 60.4% male, mean: 66.1 y	7-item self-report questionnaire	336 (336); 0	PS insomnia prevalence: 44% (n = 147); PS insomnia associated with ↓ QoL

Abbreviations: IS = ischaemic stroke, clinical modification, d = day(s), ESS = Epworth sleepiness scale, f/u = follow-up, ICD-9-CM = International classification of diseases, mo = month(s), ninth revision, nr = not reported, PS = post-stroke, PSG = polysomnography, PSQI = Pittsburgh sleep quality index, QoL = quality of life, RBD = rapid-eye-movement behaviour disorder, RLS = restless legs syndrome, RLSSGC = International restless legs syndrome study group diagnostic criteria, SpO2 = blood oxygen saturation, SQ = sleep quality (subjective), SWS = slow-wave sleep (N3), WMH = white matter hyperintensities, y = year(s).

volume significantly correlated with increased WMHs [56]. However, in patients with supratentorial IS, no significant associations were found between IS topography and the presence of PLM [67].

Prevalence of insomnia after IS (n = 5)

No studies investigating PS insomnia included control groups. The prevalence of insomnia complaints after stroke ranged between 3.8% and 57% [57,69]. However, among studies utilising validated questionnaires, the prevalence of insomnia was 30%, 37.5%, and 44% [57–59]. No associations between insomnia, IS topography, PS severity or outcome were reported. Independent correlates of insomnia included anxiety and use of psychotropic drugs [57]. Insomnia symptoms were associated with depression and reduced quality of life [59,62]. These findings are supported by Glozier et al. (2017): patients with chronic insomnia (16%) after stroke had a 3.31, 3.60, and 6.75-fold increased rate of anxiety, disability, and depression, respectively [58].

Prevalence of rapid-eye-movement behaviour disorder after IS (RBD) (n = 1)

Tang and colleagues (2014) reported that 10.9% of IS patients had symptoms of rapid-eye-movement behaviour disorder (RBD) using a validated RBD questionnaire [60]. Acute brainstem infarction was a significant independent predictor of RBD (OR = 3.68, CI: 1.17–12.2). Infarct volume was significantly larger in non-RBD patients versus RBD-patients [60].

Impact of IS on circadian rhythms (n = 9)

Among studies measuring endogenous markers of circadian rhythmicity after acute IS (n = 6 studies), all reported significant reductions to melatonin compared to controls [70–75]. Study quality was generally moderate (67%, n = 6). Three studies (33%) were rated as high quality. These findings are consistent for nocturnal serum melatonin [70–75], but not for the urinary melatonin metabolite, 6-sulphatoxymelatonin [72,73]. Circadian rhythm dysfunction was associated with IS severity or functional outcome in four of nine studies (44%) [74–77]. Backward logistic regression analyses revealed that nocturnal melatonin was independently associated with an increased probability of IS [71]. Comparable findings were reported in a PS insomnia sample; nocturnal serum concentrations of melatonin, GABA, and total antioxidants were lower in IS insomnia patients [75]. There was a significant interaction between NIHSS and melatonin that was associated with insomnia [75]. Study characteristics and findings are summarised in Table 6.

Two of three studies utilising actigraphy [77,78] or validated chronotype questionnaire [76] reported significant changes to circadian rhythms after IS. Self-reported chronotype, defined by mid-sleep time on work-free days corrected for sleep deficit on workdays (MSFsc), changed significantly after IS [76]. Changes to MSFsc after stroke were negatively correlated with stroke severity and outcome (NIHSS and mRS at hospital discharge) [76]. Interior circulatory strokes were associated with MSFsc delays, whereas posterior circulatory strokes were associated with advances of MSFsc [76]. Takekawa and colleagues (2007) reported fragmented circadian rhythms in non-ambulatory patients in the acute phase of IS [77]. However, Zuurbier and colleagues (2014) reported no significant associations between lacunar infarctions and actigraphy measured 24-hour circadian fragmentation (intradaily variability) in a large cohort study [78]. Increased white matter lesion volume and cerebral microbleeds were significantly correlated with circadian fragmentation [78].

Table 6
Summary of study characteristics and results of studies investigating the impact of ischaemic stroke on circadian rhythms.

Author, year	Study quality (NOS score)	Design, time of assessment administration, outcome variable	Demographics (study country, gender, age)	Circadian rhythm measure	Stroke outcome (Total N); controls	Summary
Adamczak-Ratajczak et al., 2017 [70]	High (7)	Case control, ≤2-d PS, melatonin in acute IS vs controls	Poland; 100% male, mean: 53 y,	Melatonin serum	8 (29); 10	Melatonin amplitude + mesor ↓ after IS
Atanassova et al., 2009 [71]	High (7)	Cross-sectional matched case–control, 3-d PS, melatonin in acute IS vs controls	Bulgaria; 60.6% male, mean: 58.4 y	Melatonin serum	33 (68); 33	Melatonin ↓, cortisol ↑ after IS
Fiorina et al., 1999 [74]	Moderate (4)	Case control, nr, nocturnal and diurnal melatonin excretion in IS vs controls	Italy; 61.5% male, mean: 64.3 y	Urinary melatonin excretion	13 (18); 5	Nocturnal melatonin ↓, diurnal melatonin ns, after acute (3 d) and chronic (2 w) IS
Kantermann et al., 2014 [76]	Moderate (6)	Cross-sectional, 2-mo PS, chronotype (mid-sleep on work-free d corrected for sleep deficit on workdays; MSFsc) after mild IS	Germany; 62.9% male, mean: 66.3 y	MCTQ	35 (35); 0	Chronotype (MSFsc) ↓ after anterior circulation IS, ↑ after posterior circulation; changes to MSFsc after IS negatively correlated with severity (NIHSS and mRS at discharge): chronotype correlation with IS severity: $r = -0.565$ for NIHSS at discharge, $r = -0.620$ for mRS at discharge
Ritzenthaler et al., 2009 [73]	Moderate (6)	Cohort, <1-d PS, melatonin in IS vs controls	France; 69.3% male, age range: 18–50 y: 22.0%, 51–70 y: 36.2%, >70 y: 41.7%.	Melatonin serum, aMT6S	127 (343); 216	Melatonin ↓ after IS, aMT6S after IS ↓ (ns)
Ritzenthaler et al., 2013 [72]	Moderate (5)	Cohort; <1 d, 5- PS, melatonin in IS vs controls	France; 64.3% male, age range: 27.7–88.5 y (median: 73.1 y)	Melatonin serum, aMT6S	42 (232); 190	Melatonin, aMT6S ↓ after IS
Takekawa et al., 2007 [77]	Moderate (6)	Cohort, <7 d PS, circadian rhythm (actigraphy + rectal temperature) ambulatory vs. non-ambulatory pts after mild IS	Japan; No gender information provided. Mean: 68.4 y	Actigraphy, rectal temperature	50 (50); 0	mRS score ↓ in abberant circadian fragmentation group vs. normals: Admission mRS scores between normal, mild, severe/abberant CR groups: 2.8 vs. 2.9 vs. 4.8
Zhang et al., 2017 [75]	Moderate (5)	Case-control, N/A, melatonin in IS + insomnia vs controls	China; Demographics by inomnia group only. Non-insomnia group: 56% male, mean: 58.9 y. Insomnia group: 52% male, mean: 59.7 y	Melatonin serum, MEQ	25 (50); 25	Nocturnal melatonin, GABA, total antioxidants ↓ after IS (+insomnia) vs. controls; melatonin ↑ NIHSS
Zuurbier et al., 2014 [78]	High (10)	Cohort study, 3 mo PS, circadian fragmentation (actigraphy - intradaily variability) in WML, LI, cerebral microbleeds	Netherlands; 58.1% male, mean: 59.2 y	Actigraphy	43 LI (970); 0	Circadian fragmentation ↑ WML volume + cerebral microbleeds. Circadian fragmentation + LI = ns

Abbreviations: IS = ischaemic stroke, aMT6s = 6-sulphatoxymelatonin (urinary melatonin metabolite), CR = circadian rhythm, d = days, GABA = gamma-aminobutyric acid, LI = lacunar infarction, MCTQ = Munich chronotype questionnaire, MEQ = morningingness-eveningness questionnaire, mo = months, mRS = modified Rankin scale (functional post-stroke outcome), MSFsc = mid-sleep on work-free days corrected for sleep deficit on workdays, NIHSS = National institutes of health stroke scale (stroke severity), ns = non-significant, PS = post-stroke, WML = white matter lesions, y = years.

Discussion

Summary of findings, limitations, and clinical pathogenic implications

To our knowledge, this is the first systematic review to investigate the bidirectional impact of sleep and circadian dysfunction as both a risk factor and consequence of IS. Accumulating data from included studies suggest that chronic sleep dysfunction, characterised by long sleep duration or sleep disorders, significantly increases the risk of IS. Inversely, when compared to controls, IS is associated with sleep and endogenous circadian rhythm disruption which may be associated with IS topography and functional outcome.

We were unable to identify any studies that investigated objective or validated measures of sleep-potentiated circadian rhythm dysfunction as a risk factor for IS. Shift work disorder is a common circadian rhythm disorder and is an independent risk factor for all-cause stroke (RR R: 1.05, CI: 1.01 to 1.09) [84,85]. However, no screened IS studies utilised the only validated shift work disorder questionnaire created by Barger and colleagues (2012) [86].

Despite liberal inclusion criteria, a majority (70%, n = 47) of studies examined sleep and circadian dysfunction *after* IS. Less than 30% of studies reported *a priori* neuroimaging hypotheses (e.g., IS topography, lesion volumes) related to PS outcome or severity. The most well-defined study designs and samples were from large prospective cohort studies investigating sleep duration and sleep disorders as risk factors for IS. Only one study was classified as low quality or as having a high-risk of bias.

Long sleep duration is a risk factor for IS

Prolonged sleep duration, characterised by eight or more hours of sleep per night, was associated with the highest stroke risk. Findings are consistent with recent meta-analyses reporting increased all-type stroke incidence for long versus short sleep duration [87–90]. Despite recent epidemiological evidence suggesting a U-shaped relationship between short sleep duration and all-cause mortality, our sample of studies did not corroborate these associations for short sleep duration and IS risk [22,91,92].

Depression or depressive symptoms were only adjusted for in two studies [18,20]. Given the frequency of hypersomnia and long-sleeping tendencies in individuals with depression, and the frequency of depression after stroke, future studies investigating prospective associations with IS should include depression as a covariate, as well as other psychiatric comorbidities [93]. An important limitation is the widespread use of subjective, self-reported sleep duration, although no studies were classified as having a high risk of bias. The use of objective sleep measures (e.g., accelerometer or PSG) are especially necessary among the elderly and in patients with sleep disorders where misperception of sleep is well recognised [94,95]. Furthermore, the total hours of sleep duration were heterogeneously clustered and not measured as continuous variables. For example, while Giangfagna et al. (2016) grouped sleep duration into "≤5, 6, 7, 8, 9, or ≥10 h", Kawachi and colleagues (2016) used a restrictive "≤6, 7, 8, or ≥9 h" grouping [17,22]. No studies examined IS risk beyond ≥10h, thereby limiting potential findings for extreme sleep duration. Importantly, no studies included neuroimaging correlates of sleep duration risk, which may clarify the neuroanatomical basis of pathological long-sleep duration.

The underlying biological mechanisms supporting the association between chronic long-sleep duration and IS pathogenesis are unclear. One possible explanation may be stroke-related proinflammatory biomarkers such as C-reactive protein (CRP). Habitual long sleep duration is associated with elevations in CRP which have shown to significantly increase the risk of IS [96–98]. Furthermore, epidemiological evidence suggests an association between long-sleep duration and stroke-related risk factors including WMHs, atrial fibrillation, arterial atherosclerosis, and left ventricular masses [99–102]. Whether prolonged sleep duration is an independent causal risk factor for IS, or merely a marker of underlying poor health, remains unclear.

Bidirectional impact of sleep architectural and quality dysfunction in IS

Sleep architecture and self-reported sleep quality is compromised after IS. However, there is insufficient evidence among our sample of heterogenous studies to suggest an association between longitudinal dysfunction to sleep architecture or subjective sleep quality and risk of IS. SWS duration measured in the contralesional hemisphere correlated with stroke volume and outcome. Furthermore, sleep architecture was most severely affected in thalamic and cortical strokes. These findings are consistent with neuroanatomical evidence; thalamocortical projections within the ascending reticular activating system are, in part, responsible for sleep-wake regulation [103].

There are important limitations among these studies. First, no studies included baseline (pre-stroke) polysomnographic characteristics to gauge the causal impact of IS on sleep dysfunction. A majority of studies using PSG also included small samples and did not report or justify effect size calculations. Next, control population types (i.e., TIA vs healthy age and gender-matched controls) were inconsistent across studies. IS populations were also heterogenous; stroke severities, stroke topographies, and PS time-course differed across studies. Thus, the range and degree of sleep architectural disturbance may be attributed to the heterogeneity of infarct locations (topography) and volumes across studies. Furthermore, a majority of studies did not exclude patients taking known sleep architecture altering drugs (e.g., benzodiazepines, GABA agonists, serotonergic antagonists) or patients with *a priori* sleep disorder diagnoses. Finally, the decrease in SE may be due to deleterious environmental stressors associated with acute hospital care; namely, prolonged or insufficient light exposure, white noise, and overnight clinical interactions [104]. Although sleep architecture is compromised after IS, there is insufficient evidence to suggest a causal relationship between IS and sleep architectural dysfunction. Nonetheless, our findings are consistent with a recent review by Duss and colleagues (2017) postulating sleep-potentiated neuroprotection and neuroplasticity after IS [2].

Non-apnoea sleep disorders are risk factors for IS

Non-apnoea sleep disorders increase the risk of IS after controlling for covariates. Sleep-related movement disorders (i.e., RLS and PLM), insomnia, and self-reported RBD were associated with the highest risk. Furthermore, de novo sleep disorders were generally more common after IS when compared to normative averages or controls. However, conclusions for specific sleep disorders cannot be generalised given the small sample of included studies. Studies included relatively young samples (mean age: 55.3 years) with insufficient follow-up periods (mean follow-up period: 5.8 years) to reach peak IS risk (≥65 years). Therefore, underestimation of IS risk is likely.

Prevalence of RLS after IS were in line with upper-ranges of normative averages (10–15%) [105]. However, acute and chronic IS symptoms were significantly more severe in patients with RLS. Topographically, subcortical strokes were associated with RLS,

particularly when accompanied with PS sensory symptoms. These findings are consistent with a recent prospective study showing RLS as a significant predictor of all-type subcortical stroke [106]. Mechanistically, pre-clinical data also support these findings; subcortical basal ganglia nuclei and dopaminergic dysfunction has been implicated in the pathogenesis of RLS [107].

The prevalence or severity of PLM, hypersomnia, insomnia, and RBD were generally greater after IS when compared to controls or normative averages [29,108–110]. Furthermore, brainstem infarction was a significant independent predictor of RBD.

In summary, non-apnoea sleep disorders increase the risk of IS after controlling for covariates. It is well established that sleep disorders contribute to sleep fragmentation, increased nocturnal arousals, and atypical sleep architecture. Thus, the proposed mechanisms for sleep disordered IS pathogenesis include sympathetic hyperactivity, hypothalamic pituitary adrenal axis activation, and deficiencies in central dopaminergic neurotransmission [107,111,112]. Longitudinal sleep-potentiated autonomic dysfunction may increase the prepathological risk of IS, and dysautonomia *after* IS may be exaggerated during sleep thereby obstructing PS recovery [113].

Circadian rhythms are disrupted after acute IS

Melatonin, an endogenous marker of circadian rhythms, is reduced after IS when compared to controls. Diminution of melatonin, and self-reported chronotypic changes, were associated with increased PS severity (NIHSS) and worse functional outcome at discharge (mRS). Importantly, nocturnal melatonin sampling occurred in light-controlled environments, thereby limiting the confounding effects of light exposure on pineal secretion of endogenous melatonin. No studies reported duration, intensity (lux), and wavelength (e.g., blue light, 540 nm) of *daytime* light exposure – hence it was not feasible to determine whether altered circadian function was likely due to a direct impact of IS or secondary to altered environmental light exposure. No studies included pre-stroke or longitudinal measures of melatonin concentrations which limits directional and causal associations between circadian misalignment and IS. Importantly, the impact of potential sleep pathology after IS on circadian rhythmicity was not investigated in studies included in our sample. Circadian rhythm outcomes were not stratified by neuroanatomical IS topography and were heterogenous across studies. Focal suprahypothalamic lesions disrupt slow-wave-sleep potentiated elevations of growth hormone [114]. However, whether melatonin secretion in humans is impacted by focal lesions to the intergeniculate leaflet (which innervate the suprachiasmatic nucleus and pineal gland), or is disturbed as part of diffuse neurovascular injury or altered exposure to Zeitgebers, remains unclear.

The neuroprotective function of melatonin has been established in pre-clinical models of focal and diffuse brain ischaemia [6]. Melatonin initiates free radical scavenging and secondary antioxidant actions which exhibit a daily rhythm and are inhibited by light in humans [115]. In IS, the melatonin rhythm is impaired, with a reduction in nocturnal amplitude or a tendency to phase delay or advance. However, whether these effects are transient or chronically sustained requires further investigation. The radiological impact of varying stroke severities and topographies on melatonin secretion should be further evaluated using novel neuroimaging methods. The interplay of sleep pathology commonly reported after IS should also be measured in conjunction with endogenous circadian rhythm disruption.

Exogenous melatonin treatment in acute animal focal ischaemia has a neuroprotective effect [116]. Transcranial near-infrared light therapy has been implicated in photobiomodulation via normalisation of misaligned circadian rhythms and motor function recovery after embolic stroke in animals [117]. Thus, both exogenous melatonin supplementation and near-infrared light therapy should be assessed in randomised trials in acute human IS given their reported neuroprotective efficacy in pre-clinical models.

Limitations

Given the lack of homogeneity across studies and outcomes, there was limited scope for conducting a meta-analysis. Furthermore, findings from this review cannot be generalised across other stroke types (i.e., haemorrhagic, TIA) or varying stroke topographies given the marked differences in pathophysiology. Whenever possible, study-specific stroke topography and stroke severity characteristics have been reported in supplementary tables. An additional limitation is publishing or reporting biases of only *positive* findings.

The Newcastle Ottawa Scale is widely used and has been validated as a study quality assessment tool for non-RCTs [15]. However, the NOS may not give sufficient weight to validated (i.e., polysomnography) versus less informative or reliable sleep-measurement tools (e.g., actigraphy, sleep diary). It is therefore possible that a study scored as “high quality” utilises inferior sleep-measurement tools if other NOS criteria is met (e.g., exceptional sample size, sample representativeness, controls, and robust statistical methodology). Alternatively, a study utilising polysomnography may be scored as moderate or low-quality if accompanying NOS criteria is not fulfilled.

Finally, 43 screened studies investigating sleep or circadian dysfunction after stroke did not differentiate or stratify results by stroke type (e.g., TIA vs ischaemic vs haemorrhagic). Attempts were made to contact corresponding authors for addition stratified data or clarification. However, response rates were poor (28%, n = 12) and only six (14%) corresponding authors provided stratified data, thereby restricting our sample of included studies.

Conclusions

This systematic review revealed that long sleep duration and sleep disorders increase the risk of developing IS. Inversely, after IS, sleep and endogenous rhythm disruption is common and may be associated with IS severity and outcome. We were unable to identify any studies investigating the impact of longitudinal circadian rhythm dysfunction on IS risk. As evidenced by our study sample's heterogenous methodology, the direct assessment of sleep and circadian rhythms in IS is an emerging field in its infancy. Future studies should standardise sleep and circadian measurement methodology and incorporate *a priori* neuroimaging-specific outcomes. Additional recommendations are outlined in our research agenda.

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Practice points

A systematic review investigating the bidirectional impact of sleep and circadian rhythm dysfunction after ischaemic stroke revealed the following:

1. This literature generally consisted of moderate to high quality studies. However, methodology (e.g., stroke to sleep and circadian assessment times, follow-up periods, measurement tools) and stroke characteristics (e.g., stroke topography, stroke severity) were heterogenous.
2. Long sleep duration and sleep disorders increase the risk of ischaemic stroke. Inversely, when compared to controls, ischaemic stroke is associated with sleep architectural and endogenous circadian rhythm disruption.
3. Post-stroke sleep architectural and circadian rhythm abnormalities may be associated with post-stroke severity and functional outcome.
4. The range and degree of sleep architectural disturbances reported after ischaemic stroke are likely due to varied infarct locations and volumes across studies.
5. There is a major gap in the circadian rhythm and stroke literature; we were unable to locate any studies investigating direct measures of circadian rhythm dysfunction as a risk factor for IS.

Research agenda

Future studies investigating sleep and circadian dysfunction in human ischaemic stroke should address shortcoming described in pre-existing literature and specifically:

1. Longitudinal polysomnographic measurement of objective sleep architecture in conjunction with radiological measures of brain features (location, volume, activity) should be assessed to further establish the causal impact of chronic sleep dysfunction on ischaemic stroke.
2. Direct and objective measures of circadian rhythms should be longitudinally assessed in large prospective cohorts to determine the impact of chronic circadian dysfunction on IS risk.
3. Studies investigating sleep and ischaemic stroke should stratify results by strict delineations of homogenous stroke topography and severity.
4. Observational follow-up periods should be extended to better determine the transient or sustained effects of post-stroke sleep and circadian dysfunction.
5. Future clinical IS sleep research should control for important covariates including depression and other psychiatric comorbidities, stroke severity, stroke topography, and sleep-altering drugs.
6. Future studies investigating circadian rhythms after ischaemic stroke should measure daytime environmental light exposure to determine whether this is the source of altered circadian function post-stroke.
7. Exogenous melatonin supplementation and light therapy should be clinically evaluated in randomised trials of acute ischaemic stroke.

Conflicts of interest

The primary author acknowledges the University of Melbourne Faculty of Medicine, Dentistry and Health Sciences for a Melbourne Research Scholarship supporting a doctoral degree but neither benefited from this systematic review.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.smrv.2019.03.003.

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ORIGINAL ARTICLE

Regional neurodegeneration correlates with sleep–wake dysfunction after stroke

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Abstract

Sleep–wake disruption is a key modifiable risk factor and sequela of stroke. The pathogenesis of poststroke sleep dysfunction is unclear. It is not known whether poststroke sleep pathology is due to focal infarction to sleep–wake hubs or to accelerated poststroke neurodegeneration in subcortical structures after stroke. We characterize the first prospective poststroke regional brain volumetric and whole-brain, fiber-specific, white matter markers of objectively measured sleep–wake dysfunction. We hypothesized that excessively long sleep (>8 h) duration and poor sleep efficiency (<80%) measured using the SenseWear Armband 3-months poststroke (n = 112) would be associated with reduced regional brain volumes of a priori-selected sleep–wake regions of interest when compared to healthy controls with optimal sleep characteristics (n = 35). We utilized a novel technique known as a whole-brain fixel-based analysis to investigate the fiber-specific white matter differences in participants with long sleep duration. Stroke participants with long sleep (n = 24) duration exhibited reduced regional volumes of the ipsilesional thalamus and contralesional amygdala when compared with controls. Poor sleep efficiency after stroke (n = 29) was associated with reduced ipsilesional thalamus, contralesional hippocampus, and contralesional amygdala volumes. Whole-brain fixel-based analyses revealed widespread macrostructural degeneration to the corticopontocerebellar tract in stroke participants with long sleep duration, with fiber reductions of up to 40%. Neurodegeneration to subcortical structures, which appear to be vulnerable to accelerated brain volume loss after stroke, may drive sleep–wake deficiencies poststroke, independent of lesion characteristics and confounding comorbidities. We discuss these findings in the context of the clinicopathological implications of sleep-related neurodegeneration and attempt to corroborate previous mechanistic-neuroanatomical findings.

Statement of Significance

Sleep–wake dysfunction is bidirectionally associated with the incidence and evolution of stroke. The pathogenesis of sleep–wake dysfunction after stroke is unclear. Here, we examined regional brain volumes and fiber-specific white matter differences in stroke participants with sleep–wake dysfunction. Stroke participants with excessively long sleep duration and poor sleep efficiency had smaller regional brain volumes when compared to healthy controls with optimal sleep. Stroke participants with long sleep duration exhibited neurodegeneration to the corticopontocerebellar tract and had poorer poststroke neurological recovery. The results suggest that sleep dysfunction may contribute to neurodegeneration beyond the effects of direct infarction and may be a key modifiable target for abating brain volume loss after stroke.

Key words: stroke; sleep duration; sleep efficiency; regional brain volume; ascending arousal system; neurodegeneration; neuroimaging

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Introduction

Stroke affects over 15 million people annually and is a leading cause of long-term disability and death worldwide [1]. Sleep–wake dysfunction is bidirectionally associated with the pathogenesis and evolution of stroke and may be a modifiable cerebrovascular risk factor [2, 3]. The authors of recent meta-analyses and systematic reviews pinpoint excessively long sleep duration, characterized by greater than 8 hours of sleep, as an independent risk factor for ischemic stroke incidence and death [2, 4]. Pronounced sleep–wake pathology is described following infarction to thalamo-mesencephalic structures and is associated with impaired cognition and psychomotor performance [5, 6]. However, manifestations of sleep–wake disturbances differ across studies and may be attributed to heterogeneous stroke etiologies and regional brain volumes of affected sleep–wake structures [7–9]. Notwithstanding, the neuroanatomical circuitry responsible for sleep-wake dysfunction after stroke represents something of an enigma. It is unclear whether poststroke sleep deficits are due to focal infarction to sleep–wake structures, or diffuse and accelerated poststroke brain atrophy to subcortical structures common after cerebrovascular disease [2, 10, 11]. Identification of neuroanatomical markers of sleep–wake dysfunction following stroke, through a priori neuroimaging hypotheses in conjunction with objectively measured sleep, is critical for the development of targeted treatments.

Pioneering contributions from Moruzzi and Magoun first identified the ascending brainstem reticular activating system (ABRAS) as principally responsible for sleep–wake function [12]. They theorized that diffuse cortical projections from the ABRAS synapsed in the thalamic midline and intralaminar nuclei. A decade following these findings it became doctrinaire that the thalamus was the arousal-promoting hub in the brain [13]. However, these assumptions have been challenged by results from experimental ablation of the thalami. For example, athalamic cats and rodents do not exhibit alterations to behaviorally observable sleep–wake rhythms, with only minor electroencephalographic attenuations to sleep spindles [14]. In humans, severe arousal impairment is associated with thalamic strokes that extend into the midbrain and/or pontine tegmentum, whereas participants with focal thalamic lesions do not exhibit comparable arousal impairment [15]. Ablation to the dorsal striatum suppresses non-rapid-eye movement (NREM) sleep [16–18], and cerebellectomized cats demonstrate chronic drowsiness and decreased wakefulness [19]. These findings support the case for diffuse sleep–wake function in subcortical brain structures beyond the thalamus.

Seamless function of the "flip-flop" homeostatic sleep–wake switch is dependent upon inhibition of sleep-promoting structures (e.g. ventrolateral preoptic nucleus) and activation of arousal-promoting structures (e.g. pons) along the ABRAS [20]. Regional brain volume reductions after stroke, or neurodegeneration to thalamo-cortical ABRAS tract integrity, may exacerbate sleep problems already common among aging populations [21]. While these processes are well-documented after experimental lesion in non-pathological animal models and in vitro, the volumetric and tractographic neuroanatomical markers of sleep–wake dysfunction following stroke remain unexplored in humans beyond small series case studies.

In this cross-sectional study, we describe the first poststroke brain volumetric and fiber-specific white matter correlates of objectively measured sleep in a cohort of ischemic stroke participants (n = 112), imaged on average, 99 days (range: 44–158 days) after stroke. We characterized sleep dysfunction after stroke as excessively long (>8 h) sleep duration (n = 24) or poor sleep efficiency (<80%) (n = 29). Our primary structural and fixel-based approach focused on long sleep duration, given it is both a well-established ischemic stroke risk factor and feature of poststroke sleep deficits. We compared their results to healthy, age-matched controls with normal sleep duration (between 6 and 8 h of sleep) (n = 25) or optimal sleep efficiency (greater than 80%) (n = 35). Regions of interest (ROI) were a priori selected on the basis of their established salient involvement in sleep–wake function and their availability in FreeSurfer's automated subcortical parcellations based on the Desikan–Killiany Atlas [22]. We hypothesized that long sleep duration and poor sleep efficiency at 3-month poststroke would be associated with reduced regional brain volumes of sleep–wake ROI. In a subset of participants with available diffusion magnetic resonance imaging (dMRI) (n = 93), we conducted a whole-brain fixel-based analysis (FBA) to examine long sleep-related differences in fiber-specific white matter pathways [23]. We hypothesized that stroke participants with excessively long sleep duration would exhibit extensive degeneration in key white matter pathways connecting the ABRAS.

Methods

Participants

Data from the prospective, longitudinal Cognition And Neocortical Volume After Stroke (CANVAS) study were analyzed [24]. The CANVAS study includes participants with first-ever or recurrent ischemic stroke within any circulation [25], etiology [26], and no history of dementia or other neurodegenerative condition. The protocol and inclusion criteria for control participants were identical to stroke participants, except that control participants were stroke-free. Participants were recruited from three hospitals in Melbourne, Australia: Austin Health, Eastern Health, and Melbourne Health. The study was approved by each of the hospital's human research ethics committees in line with the Declaration of Helsinki [24, 27]. Data from the 3-month poststroke time-point (stroke n = 112, control n = 40) were used to avoid confounding environmental sleep stressors found in acute intensive care units, such as prolonged or insufficient light exposure, white noise, and overnight clinical interactions [28]. Participants with untreated obstructive sleep apnea were excluded.

The presence of ischemic stroke was a clinical diagnosis, radiologically confirmed on clinical computed tomography (CT) or magnetic resonance imaging (MRI) during the acute hospitalization of the incident event. Stroke participants who were unable to undergo a 3T MRI scan or, because of severe aphasia, were unable to provide informed consent or follow basic instructions were excluded. Participants with transient ischemic attacks and no confirmed dMRI changes on MRI were excluded. As well, those with significant medical comorbidities precluding participation in cognitive-behavioral testing were excluded from participation.

Sleep–wake measurement

Sleep duration and sleep efficiency (the ratio of total sleep time to time in bed) were measured using BodyMedia's SenseWear

armband (SWA) (mean wear time = 6.4 days, range = 1–13). Participants wore the SWA for approximately 1 week immediately following their dMRI sequence assessment (mean: 99 days, range: 44–158 days poststroke). The SWA is worn on the upper left arm and utilizes a combination of accelerometery, near-body ambient skin temperature, heat flux, and galvanic skin response to measure sleep–wake. Validation of the SWA armband against gold-standard polysomnography has been conducted in healthy participants [29, 30], adolescents [31], and in participants with obstructive sleep apnea with an average sleep–wake epoch agreement of 80 ± 1.6% [32]. The accelerometer uses a microelectromechanical sensor which has a scale of ±2 g and a sensitivity of 167 mV/g. With respect to sleep duration, raw data output is binary (i.e. 1 = sleeping, 0 = awake). Physiological data are processed by proprietary algorithms to compute sleep duration and sleep efficiency. Sleep–wake estimations are computed in 1-minute epochs across a single main nighttime sleep period. Averages were extracted using BodyMedia's software (InnerView, BodyMedia, Pittsburgh, PA).

Image acquisition and stroke lesion mapping

Whole-brain images were acquired on a 3T Siemens Tim Trio scanner with a 12-channel head coil (Siemens, Erlangen, Germany). The MR images for the presented analyses were acquired using a T1-weighted three-dimensional (3D) magnetization-prepared rapid gradient (MPRAGE) sequence with the following parameters: 160 sagittal slices, repetition time RT = 1,900 ms, echo time TE = 2.6 ms, inversion time TI = 900 ms, flip angle = 9°, matrix size = 256 × 256, voxel size = 1 × 1 × 1 mm^3 isotropic. High-resolution, 3D sampling perfection with application-optimized contrasts using different flip angle evolutions (SPACE)-fluid-attenuated inversion recovery (FLAIR) images were also acquired for white matter hyperintensity estimation and stroke lesion tracing: 160 sagittal slices, 1 mm thick, RT = 6000 ms, TE = 380 ms, 120° flip angle, and 256 × 256 acquisition matrix. Acquisition of dMRI images was performed using echo-planar imaging (EPI) with the following parameters: repetition time = 8400 ms, echo time = 110ms, voxel size = 2.5 × 2.5 × 2.5mm [3]). Sixty diffusion-weighted images (b = 3,000 s/mm^2) and eight images without a diffusion weighting (b = 0) were acquired. For susceptibility-induced distortion correction, a pair of non-diffusion-weighted images with reverse-phase encoding was also acquired.

Stroke lesion maps were generated in order to visualize the lesion localization topography of the sample. Percentage overlay stroke lesion maps were delineated on FLAIR images for all stroke participants in the study (n = 112) and were not stratified by sleep metrics. Axial slices are displayed in conventional radiological format. Warm colors in yellow and red indicate areas of the highest percentage overlap.

FreeSurfer preprocessing

Cortical reconstruction and volumetric segmentation were performed with the FreeSurfer image analysis suite (version 6.0) (http://surfer.nmr.mgh.harvard.edu/) [33]. FreeSurfer segmentation includes motion correction, removal of non-brain tissue, Talairach transformation, segmentation of subcortical white matter and deep gray matter structures, intensity normalization, tessellation of the gray matter white matter boundary, topology correction, and surface deformation following intensity gradients. Subsequent preprocessing steps are based on the common information from the within-participant template and include skull stripping, Talairach transforms, atlas registration, and creating spherical surface maps and parcellations [34]. Further technical details of FreeSurfer's cortical reconstruction and segmentation procedure have been described previously [35]. The unbiased template was created for each participant using the T1 MPRAGE scans collected each time-point [36]. Tissue segmentations for individual participants were visually inspected and corrected for quality assurance (M.S.K.).

Whole brain FBA

Diffusion-weighted imaging is the gold-standard method to assess white matter architecture in vivo. The vast majority of studies investigating sleep-potentiated white matter brain changes have analyzed dMRI data using the diffusion tensor imaging (DTI) model [37–39]. Briefly, the DTI model posits that the structural integrity of white matter can be estimated by comparing metrics that are derived from a voxel: defined as a single sample, or data point, on a regularly spaced, 3D grid. However, a major limitation of DTI is its limited ability to model and differentiate complex crossing fiber populations. These are present in approximately 90% of all white matter voxels and are likely particularly prevalent in sleep-related white matter tracts [40, 41]. Thus, these voxel-averaged DTI metrics are now regarded as less sensitive in detecting abnormalities in the white matter. Newer methods look at fiber elements—known as fixels—across the whole brain. The term "fixel" refers to fiber bundles or populations with potentially differing orientations that are present within a voxel. In contrast to DTI methods, these whole-brain FBAs are regarded as being more sensitive to differences within the orientation of specific fiber populations and may characterize neurodegenerative differences to fiber populations within voxels more robustly [23, 42, 43]. An FBA can be used to estimate total intra-axonal volume differences in the tissue microstructure (fiber density [FD]) and the fiber-bundle cross-section macrostructure (fiber cross section [FC]). We use a combined FD and bundle cross-section (FD and cross section [FDC]) metric to assess both the micro- and macro-architecture of sleep-related white matter neurodegeneration.

dMRI preprocessing

dMRI data were preprocessed using MRtrix3 (https://www.mrtrix.org) and MRtrix3Tissue (https://3tissue.github.io) [44]. dMRI images were preprocessed by denoizing the data [45], removing Gibbs ringing artifact [46], field map correction of eddy-current distortions [47], motion correction [48], and bias-field correction (N4, http://stnava.github.io/ANTs/). After these initial preprocessing steps, fiber orientation response functions (FODs) were obtained using Single-Shell 3-Tissue Constrained Spherical Deconvolution, with group-averaged response functions for white matter, gray matter, and cerebrospinal fluid tissue compartments. These response functions (+b = 0) were directly estimated from the dMRI data themselves yielding group average anisotropic single fiber white matter response functions ($b \neq 0$) and isotropic gray matter and cerebrospinal fluid response

functions using an unsupervised method [49]. Spatial correspondence for tissue-specific FOD's was achieved by generating a population template using a subset of 30 participants (15 stroke participants and 15 healthy controls) using an optimized nonlinear transformation model [50]. Subsequently, each individual FOD image was nonlinearly registered to the template using an FOD-guided registration method and a bespoke automated method was used to intensity normalize and bias-field correct all FOD images from each tissue compartment [51, 52].

Choice of brain regions for volumetric analyses

Regional volume estimates were generated from FreeSurfer default cortical and subcortical parcellations based on the Desikan–Killiany Atlas [22]. For these ROI analyses, we focused on the following structures given their involvement in sleep–wake function: bilateral (left and right) thalami, bilateral caudate, bilateral putamen, bilateral hippocampi, bilateral amygdala, bilateral accumbens, bilateral pallidum, and brainstem.

Statistical analysis

Statistical analyses were conducted in MATLAB (2018a). All analyses were two-tailed and a critical p-value of 0.05 was used. Differences between groups on demographic and clinical variables were examined using independent samples t-tests (continuous variables, parametrically distributed scores), Mann–Whitney U tests (continuous variables, nonparametrically distributed scores), and Fisher Exact tests (categorical variables).

We analyzed the effect of sleep–wake variables (long sleep duration, n = 24; poor sleep efficiency, n = 29) on ipsilesional (on the same hemisphere as the lesion) and contralesional (opposite hemisphere to the lesion) thalamic, caudate, putamen, hippocampus, amygdala, accumbens, pallidum, and brainstem volumes using a univariate linear regressions model both between- (stroke vs. control) and within- (stroke vs. stroke) group. Healthy controls with optimal sleep characteristics (normal sleep duration: between 6 and 8 h of sleep, n = 25; and optimal sleep efficiency: ≥80%, n = 35) were selected as comparators. Stroke participants with lesions or infarcts in any ROIs were excluded from volumetric analyses in order to reduce the direct effects of peri-infarct involution and atrophy within the infarct site.

For each ROI, we compared groups using a base linear regression model, with age, sex, education, and total intracranial volume (TIV) included as covariates. Body mass index (BMI) and depression were added as covariates in an extended model. The linear regression model was implemented using the MATLAB function, fitlm, with default settings (e.g. "modelspec," "linear"; "RobustOpts," "off"). We did not correct for multiple testing as the analyses were exploratory. We, therefore, provided unadjusted effect sizes for all volumetric comparisons and included only a priori-selected ROI. Age was included to account for loss of brain volume due to normal aging; sex to control for sexual dimorphism; education to adjust for its protective effect on cerebral structures; BMI to correct for risk of undiagnosed obstructive sleep apnea [53]; depression to control for psychiatric hypersomnia mediating long sleep duration; and TIV to control for head size variations.

In stroke participants with available dMRI data (n = 93), a whole-brain FBA was conducted in order to identify tracts with altered white matter fiber integrity. We utilized a combined measure of FDC in the long sleep duration (> 8 h, n = 20) and normal (between > 6 h and < 8 h) sleep duration (n = 59) groups versus controls (n = 40). Herein, we use the term whole-brain FBA to refer to a comparison of all white matter fixels identified within the brain. Statistical comparisons of FDC between groups were performed at each white matter fixel by a General Linear Model, comparing (1) long sleep duration (>8 h) in stroke participants versus healthy controls; (2) long sleep duration versus normal sleep duration (<8 h) in stroke participants; and (iii) normal sleep duration (between >6 and <8 h) in stroke participants versus healthy controls. With respect to nuisance covariates, we undertook a minimalist approach and included age, sex, and TIV in accordance with previously published whole-brain FBA work [43]. Connectivity-based smoothing and statistical inference were performed using connectivity-based fixel enhancement (CFE), using 2 million streamlines from the template tractogram, and with default smoothing parameters (smoothing = 10 mm full-width at half-maximum, C = 0.5, E = 2, H = 3) [23]. Note that in CFE, smoothing is preferentially applied along structurally connected fixels, ensuring that fixel-based metrics are locally smoothed with fixels belonging to the same fiber tract. Family-wise error (FWE)-corrected p-values were then assigned to each fixel using nonparametric permutation testing over 5,000 permutations [54].

Significant fixels (FWE-corrected p-value < 0.05) were then displayed using the mrview tool in MRtrix3. To better appreciate the fiber pathways implicated, significant fixels were displayed on the template-derived tractogram, in which streamlines were cropped to only those fixels that were significant. Significant streamlines were color-coded either by streamline orientation (left-right: red, inferior–superior: blue, anterior–posterior: green) or by the effect size expressed (thresholded from 0 to 40 percent) as a percentage relative to healthy controls or normal sleepers' group. Both whole-brain fixel-based statistical analyses and visualizations were performed in MRtrix3.

Results

Participant demographics

Demographic, cerebrovascular, mood, and stroke characteristics between participants with stroke and healthy controls, and between excessively long versus normal stroke sleepers, are listed in Tables 1–3. Stroke characteristics in participants with poor versus optimal sleep efficiency are listed in Supplementary Table S1. Demographic, cerebrovascular, and sleep characteristics in participants with missing versus available dMRI data are listed in Supplementary Table S2.

Control participants had attained a higher level of education, higher National Adult Reading Test IQ (NART) scores, and a lower prevalence of atrial fibrillation (Table 1).

Participants with stroke had reduced sleep efficiency relative to controls (p = 0.033, mean: 82.92 vs. 85.58). No other sleep–wake variables significantly differed between groups (e.g. mean sleep duration, percentage of long sleepers [>480 min], percentage of short sleepers [<360 min], mean days SWA worn; Table 2).

Stroke characteristics

Long sleepers were more disabled at admission (79% of long sleepers with modified Rankin Scale [mRS] 0–2 at baseline vs.

Table 1. Demographic characteristics of stroke and all control participants

Demographics	Stroke (N = 112)	No.	Control (N = 40)	No.	p
Age in years, M ± SD	68.18 (11.41)	112	68.83 (6.63)	40	0.923†
Sex, male n (%)	79 (71%)	112	25 (63%)	40	0.428‡
Education in years, M ± SD	12.82 (3.80)	112	15.48 (4.53)	40	0.001†
Body mass index, M ± SD	27.91 (4.37)	112	26.58 (3.77)	40	0.091§
NART-FSIQ, M ± SD	111.95 (10.78)	102	118.71 (9.85)	39	0.001†
Hypertension diagnosis, n (%)	71 (63%)	112	17 (43%)	40	0.026‡
Hyperlipidemia diagnosis, n (%)	48 (43%)	112	14 (35%)	40	0.455‡
Atrial fibrillation diagnosis, n (%)	23 (21%)	112	1 (3%)	40	0.005‡
Ischemic heart disease, n (%)	12 (11%)	112	2 (5%)	40	0.357‡
Type 2 diabetes mellitus, n (%)	27 (24%)	112	4 (10%)	40	0.068‡
High alcohol intake (>14 standard drinks per week), n (%)	14 (13%)	112	7 (18%)	40	0.435‡
Depression diagnosis, n (%)	11 (10%)	112	4 (10%)	40	1‡
ApoE_e4 (≥1 allele), n (%)	20 (20%)	98	4 (11%)	38	0.216‡

ApoE, apolipoprotein E allele; NART-FSIQ, National Adult Reading Test-Full Scale; No., number of participants included in each variable without missing data; M, mean; SD, standard deviation.
†Mann Whitney U test.
‡Fisher's exact test.
§Independent samples t-test.

Table 2. Sleep characteristics in stroke and control participants

Sleep variables	Stroke (N = 112)	Control (N = 40)	p
Sleep efficiency ratio, M (SD)	82.92 (7.23)	85.58 (5.14)	0.033†
Average sleep duration in mins, M (SD)	428.80 (75.61)	435.15 (65.05)	0.592†
Long sleepers (≥8 h), n (%)	24 (21%)	9 (23%)	1‡
Short sleepers (≤6 h), n (%)	17 (15%)	6 (15%)	1‡
Days SenseWear worn, mean (SD)	6.32 (1.49)	6.13 (1.55)	0.953†

M, mean; SD, standard deviation.
†Mann Whitney U test.
‡Fisher exact test.

84% non-long sleepers, $p = 0.05$) and at time of diffusion imaging 3 months after stroke (again 79% vs. 92%, $p = 0.038$) (see Table 3).

No significant differences in stroke characteristics were found between stroke participants with poor (<80%) versus optimal (>80%) sleep efficiency (see Supplementary Table S1).

Regional brain volume differences

Stroke participants with long sleep duration ($n = 24$) had lower volumes in the contralesional amygdala (B = –129.56, SE = 60.73, $p = 0.03$) and trending in the ipsilesional thalamus (B = –383.40, SE = 191.95, $p = 0.052$), and larger contralesional pallidum (B = 109.95, SE = 53.72, $p = 0.04$) when compared with controls with normal sleep duration (between >6 and <8 h, $n = 25$) (see Table 4). No significant brain volumetric differences were found in stroke participants with long versus normal sleep duration (see Supplementary Table S3).

Stroke participants with poor sleep efficiency ($n = 29$) had lower volumes in the ipsilesional thalamus (B = –332.73, SE = 112.04, $p = 0.004$) and contralesional hippocampus (B = –186.98, SE = 92.42, $p = 0.04$) when compared with healthy controls with normal sleep efficiency (>80%, $n = 35$). Amygdaloid volumes were numerically smaller but did not reach significance (B = –85.97, SE = 50.76, $p = 0.09$). Larger volumes in stroke participants were found for the bilateral caudate (ipsilesional: B = 301.36, SE = 127.82, $p = 0.02$; contralesional: B = 293.48, SE = 88.87, $p = 0.001$). The contralesional pallidum volumes were numerically larger but did not reach significance (B = 84.55, SE = 48.09, $p = 0.08$) (see Table 5).

Stroke participants with poor sleep efficiency had lower ipsilesional amygdala volumes (B = –123.62.62, SE = 56.32, $p = 0.03$) when compared with stroke participants with optimal sleep efficiency (see Supplementary Table S4).

Whole-brain fiber-specific white matter differences

Figure 1 shows the whole-brain FBA streamline segments associated with significant fiber tract-specific FDC decreases in stroke participants with long sleep duration (>8 h) compared to healthy controls. Streamline segments were cropped from the template tractogram to include only those corresponding to fixels that exhibited a significant (FWE-corrected p-value < 0.05) difference in the FDC metric in the stroke group, colored by effect size (percent decrease) and fiber orientation.

Stroke participants with long sleep duration exhibited FDC reductions within the right thalamocortical tract in regions projecting to the ABRAS when compared with healthy

Table 3. Stroke characteristics in participants with long (≥ 8 h) versus non-long (<8 h) sleep duration

Stroke characteristics	Sleep duration ≥8 h (*n* = 24)	No.	Sleep duration <8 h (*n* = 88)	No.	*p*
Infarct volume, mean (mm^3)	5,957.92	24	7,275.43	88	0.676†
Oxfordshire criteria, *n* (%)		24		88	0.39‡
Lacunar (LACI)	4 (17%)		13 (15%)		
Posterior (POCI)	7 (29%)		31 (35%)		
Partial anterior (PACI)	12 (50%)		44 (50%)		
Total anterior (TACI)	1 (4%)		0 (0%)		
Stroke side, *n* (%)		24		88	0.601‡
Left	7 (29%)		32 (36%)		
Right	17 (71%)		53 (60%)		
Bilateral	0 (0%)		3 (4%)		
Tissue plasminogen activator administered, *n* (%)	3 (13%)	24	11 (13%)	88	1‡
mRS (0–2 vs. 3–4) Baseline, *n* (%)	19 (79%)	24	74 (84%)	88	0.05‡
mRS (0–2 vs. 3–4) 3 months, *n* (%)	19 (79%)	24	81 (92%)	88	0.038‡
NIHSS Baseline, M (SD)	3.38 (3.29)	24	3.05 (2.69)	88	0.655§
NIHSS 3 months, M (SD)	1.08 (1.79)	24	.83 (1.38)	88	0.525§
Days from stroke to 3-month review, M (range)	99.88 (23–158)	24	100.72 (44–460)	82	0.457†

M, mean; No., number of participants included in each variable without missing data; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; SD, standard deviation.
†Mann Whitney *U* test.
‡Fisher's exact test.
§Independent samples *t*-test.

Table 4. Regional brain volumetric differences in stroke participants with long (≥8 h) sleep duration (*n* = 24) versus healthy controls with normal (between >6 and <8 h) sleep duration (*n* = 25)

Region of interest	Est	SE	g (CI)	*p*
Accumbens—Ipsi	−6.68	29	0.18 (−0.38, 0.74)	0.81
Accumbens—Contra	−32.8	30.19	0.46 (−0.1, 1.03)	0.27
Amygdala—Ipsi	83.23	70.11	−0.17 (−0.73, 0.39)	0.23
Amygdala—Contra	−129.56	60.73	0.6 (0.03, 1.18)	0.03†
Brainstem	−511.81	521.91	0.33 (−0.23, 0.9)	0.32
Caudate—Ipsi	−99.9	124.11	0.14 (−0.43, 0.72)	0.42†
Caudate—Contra	152.47	126.44	−0.21 (−0.78, 0.36)	0.23
Hippocampus—Ipsi	−84.65	107.35	0.31 (−0.25, 0.88)	0.43
Hippocampus—Contra	−99.06	92.37	0.41 (−0.16, 0.98)	0.28
Pallidum—Ipsi	27.89	57.84	−0.04 (−0.6, 0.52)	0.63
Pallidum—Contra	109.95	53.72	−0.41 (−0.98, 0.15)	0.04
Putamen—Ipsi	−181.87	220.31	0.28 (−0.3, 0.87)	0.41
Putamen—Contra	167.55	154.82	−0.24 (−0.83, 0.34)	0.28
Thalamus—Ipsi	−383.4	191.95	0.64 (0.06, 1.25)	0.052
Thalamus—Contra	24.98	181.88	0.16 (−0.42, 0.74)	0.89

Stroke participants with lesions in ROIs were excluded (*n* = 3 thalamus, *n* = 1, hippocampus, *n* = 2 caudate, *n* = 3 putamen).
†Signifies use of extended model (including BMI and PHQ-9).

controls. Bilateral degeneration to the corticopontocerebellar tract was extensive, with some fiber regions (e.g. superior cerebellar peduncle) exhibiting FDC reductions of up to 40%. Bilateral pontine degeneration was observed along the cerebellar peduncles, particularly at the decussation of the superior cerebellar peduncle.

Figure 2 shows FDC reductions and orientation in the normal sleep (between >6 and <8 h) stroke group compared with all healthy controls. White matter degeneration was extensive across the whole brain and most apparent along the corpus callosum, inferior fronto-occipital fasciculus, and cingulum. Visually comparing the patterns of white matter degeneration in the "long-sleep stroke versus control" and "normal-sleep stroke versus control" analyses, we observed spatially distinct results, with only some overlap across certain pontine fiber tracts; however, the distribution in the normal-sleeping stroke participants was less extensive (i.e. no cortico-cerebellar projections) and the percentage effect reductions did not exceed 20%. No significant whole-brain FBA differences were found between the long-sleep stroke versus normal-sleep stroke groups.

Table 5. Regional brain volume differences in stroke participants with poor (<80%) sleep efficiency (n = 29) versus healthy controls with optimal (≥80%) sleep efficiency (n = 35)

Region of interest	Est	SE	g (CI)	p
Accumbens—Ipsi	−24.94	25.09	0.21 (−0.29, 0.7)	0.32
Accumbens—Contra	−37.34	26.2	0.33 (−0.17, 0.82)	0.15
Amygdala—Ipsi	−49.86	59.62	0.13 (−0.36, 0.63)	0.4
Amygdala—Contra	−85.97	50.76	0.18 (−0.31, 0.67)	0.09†
Brainstem	−484.7	467.87	0.06 (−0.43, 0.55)	0.3
Caudate—Ipsi	301.36	127.82	−0.53 (−1.05, −0.03)	0.02
Caudate—Contra	293.48	88.87	−0.76 (−1.28, −0.25)	0.001
Hippocampus—Ipsi	−72.25	95.48	0.3 (−0.19, 0.8)	0.45†
Hippocampus—Contra	−186.98	92.42	0.35 (−0.14, 0.85)	0.04
Pallidum—Ipsi	28.51	46.57	−0.18 (−0.68, 0.32)	0.54
Pallidum—Contra	84.55	48.09	−0.41 (−0.91, 0.09)	0.08
Putamen—Ipsi	−105.3	158.29	0.05 (−0.44, 0.55)	0.5
Putamen—Contra	140.21	145.97	−0.34 (−0.84, 0.16)	0.34
Thalamus—Ipsi	−332.73	112.04	0.35 (−0.16, 0.86)	0.004
Thalamus—Contra	−105.49	120.09	0.02 (−0.48, 0.52)	0.38

Stroke participants with lesions to ROIs were excluded (n = 2 thalamus, n = 1 caudate, n = 1 putamen, n = 1 pallidum).
†Signifies use of extended model (including BMI and PHQ-9).

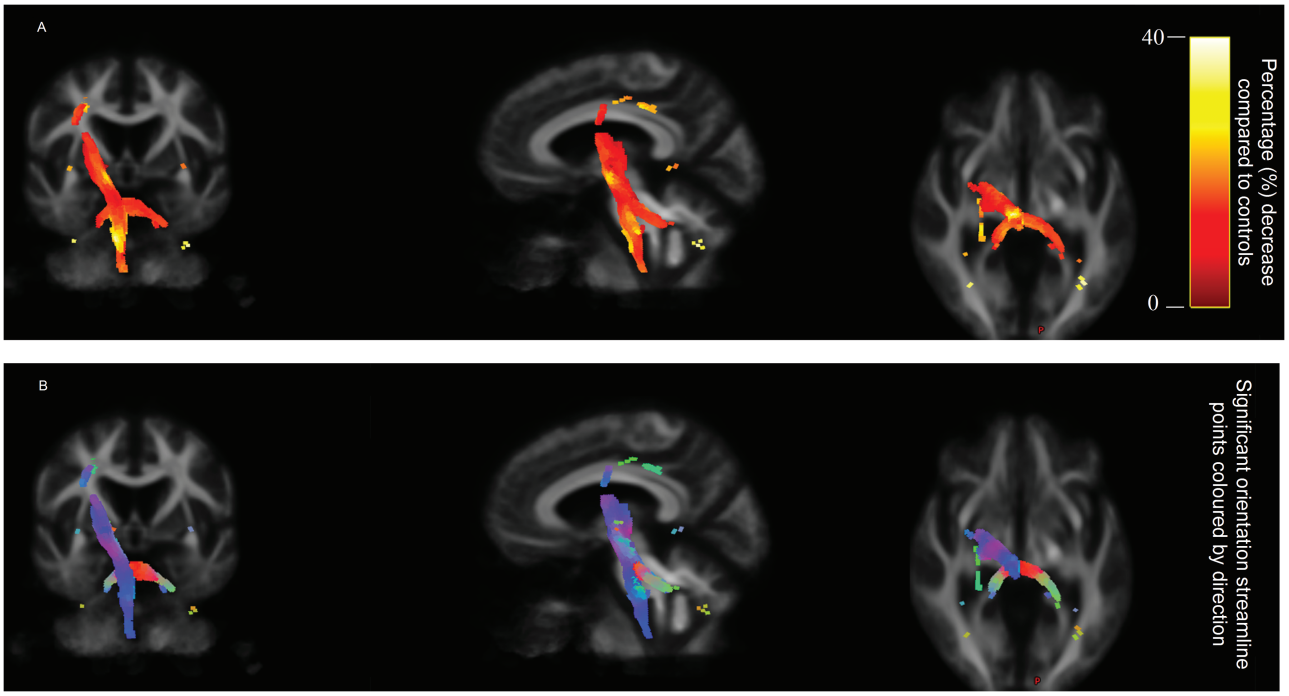

Figure 1. Whole-brain FBA of stroke participants with long sleep duration (>8 h, n = 20) compared with healthy controls (n = 40) revealing significant neurodegeneration to the corticopontocerebellar tract among long sleepers. Streamline segments were cropped from the template tractogram to include only streamline points that correspond to significant fixels (FWE-corrected p-value < 0.05). Streamlines were colored by percentage effect (thresholded from 0% to 40%) decrease in the stroke group compared with the healthy control group for FDC. Significant orientation streamline points are colored by direction (anterior–posterior: green; superior–inferior: blue; left–right: red).

Discussion

The present study identified sleep–wake correlates of regional brain volumetric and white matter degeneration after stroke. The major disease-related findings included the following: (1) stroke participants with long sleep duration and poor sleep efficiency generally exhibited subcortical regional brain volume reductions relative to healthy, optimal sleeping, controls; (2) fiber-specific white matter degeneration to the corticopontocerebellar tract was associated with long sleep duration after stroke compared with controls and was different from white matter degeneration pattern observed in normally sleeping stroke participants compared with controls; and (3) stroke participants with long sleep duration were more disabled at admission and 3-month poststroke compared with non-long sleepers. This exploration of the volumetric and fiber-specific white matter sleep–wake correlates offers valuable insight into the potential neuroanatomical pathogenesis of poststroke sleep disruption. These findings add to the growing literature implicating sleep–wake dysfunction as markers of poor cerebrovascular health.

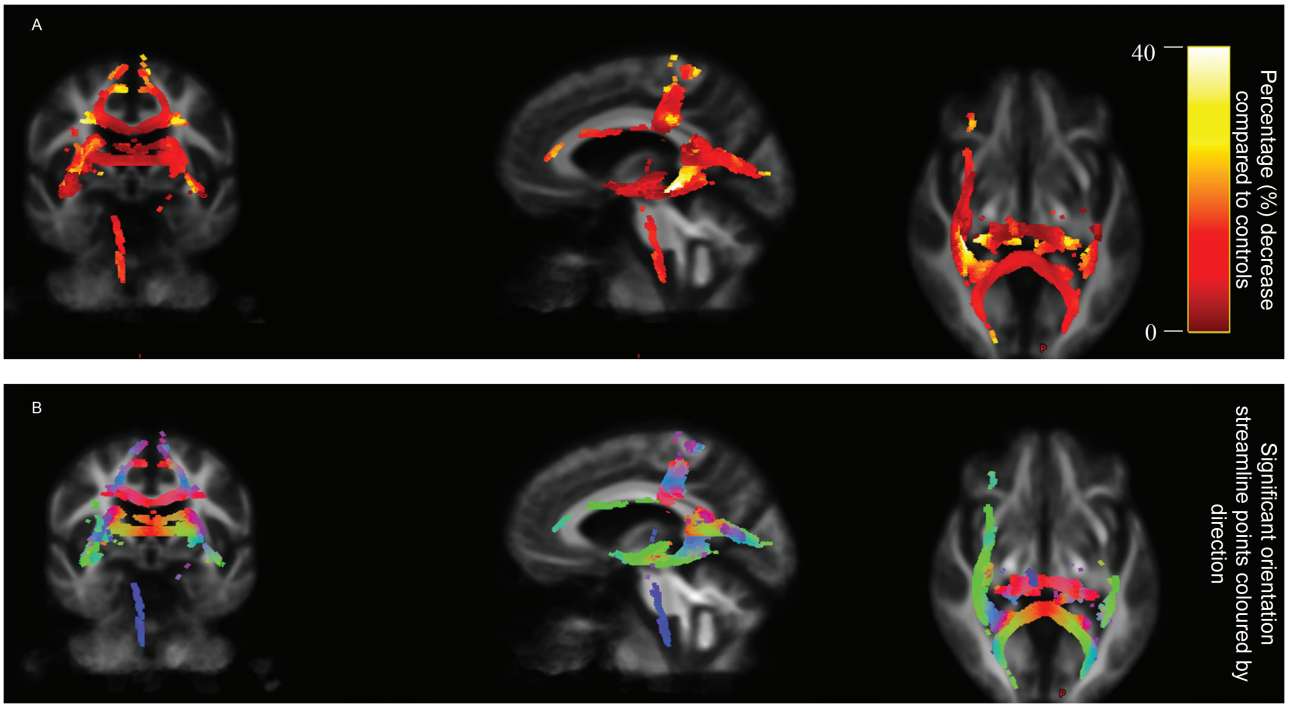

Figure 2. Whole-brain FBA of stroke participants with normal sleep duration (between >6 and <8 h, $n = 59$) compared with healthy controls ($n = 40$) revealing widespread degeneration across the whole brain and most apparent within the corpus callosum, inferior fronto-occipital fasciculus, and cingulum. Streamline segments were cropped from the template tractogram to include only streamline points that correspond to significant fixels (FWE-corrected p-value < 0.05). Streamlines were colored by percentage effect (thresholded from 0% to 40%) decrease in the stroke group compared with the healthy control group for FDC. Significant orientation streamline points are colored by direction (anterior–posterior: green; superior–inferior: blue; left–right: red).

Hereon, we describe the potential clinicopathological implications of sleep-related vascular neurodegeneration and attempt to corroborate experimental and clinical mechanistic, neuroanatomical findings.

The potential for reduced regional brain volumes to drive sleep–wake dysfunction

To explicitly investigate how sleep dysfunction contributes to neurodegeneration beyond the effect of stroke infarction itself, we examined volumetric differences of a priori-selected ROIs in stroke participants with excessively long sleep duration and poor sleep efficiency. Stroke participants with long sleep duration exhibited reduced regional volumes of the contralesional amygdala and trending ipsilesional thalamus when compared with controls. Poor sleep efficiency after stroke was associated with reduced regional volumes of the ipsilesional thalamus and contralesional hippocampus when compared with controls with optimal sleep efficiency. Finally, stroke participants with poor sleep efficiency exhibited reduced ipsilesional amygdala volume when compared with stroke participants with optimal sleep efficiency. Given the cross-sectional design of the present study, we are unable to pinpoint causation or directionality. However, we have previously reported a bidirectional relationship between sleep disruption and stroke [2], and, here, we propose that poststroke sleep dysfunction in the form of excessive sleep duration or poor sleep efficiency is associated with degeneration to sleep–wake ROIs. In addition, we posit that subcortical sleep–wake structures, which appear to be differentially affected and vulnerable to accelerated brain volume loss after stroke, may drive sleep–wake dysfunction after stroke, independent of lesion location (see Figure 3).

Regions in which we found volumetric reductions associated with long sleep duration and poor sleep efficiency, including the thalamus, amygdala, and hippocampus play critical roles in sleep–wake functioning. Several authors have reviewed in detail the neurobiological mechanisms subserving local sleep–wake regulation in animal models and healthy participants [55]. They have established that the sleep–wake system is mediated by a diffuse and complex multi-hierarchical neural network [56, 57]. Interactions between various subcortical structures initiate global changes in neural states via, but not limited to, the dorsal ABRAS, a key hub of neuronal sleep–wake circuitry. Beyond the ABRAS, however, human positron-emission tomography studies also demonstrate the functional neuroanatomical role of amygdalo–cortical interactions for rapid eye movement sleep [58], and hippocampal networks for orchestrating sleep-related oscillatory activities [56, 59, 60]. The ABRAS consists of a myriad of brainstem nuclei that project to the cortex via thalamic and extra-thalamic neurotransmitter-specific pathways [61]. These pathways include pontine serotonergic fiber [62], norepinephrine synthesis from the pontine locus coeruleus [63], dopaminergic fibers from the ventral tegmentum [64], cholinergic fibers from the caudal midbrain and rostral pons [65], and rostral pontine glutamatergic fibers [66]. While not statistically significant, regional brainstem volume was reduced in stroke participants with sleep–wake dysfunction across all experimental conditions.

While neuroanatomical markers of poor sleep efficiency have not been explored poststroke, volumetric correlates of long sleep duration after stroke have been described in small

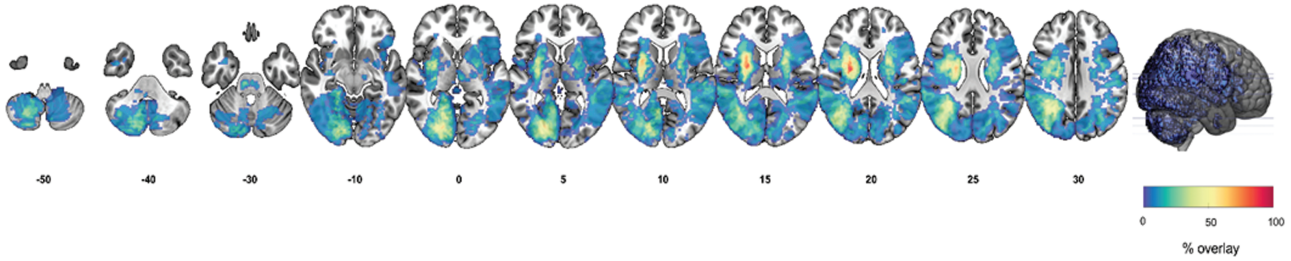

Figure 3. Lesion localization mapping of participants with stroke diagnosis. Percentage overlay stroke lesion maps were delineated on FLAIR images for all stroke participants in the study (*N* = 112). Axial slices are displayed in conventional radiological format. Warm colors in yellow and red indicate areas of the highest percentage overlap.

series case studies involving focal brain lesions and de novo hypersomnia and narcolepsy. These case reports show that focal ischemic brain lesions that affect the ABRAS are associated with arousal inhibition. For example, severe hypersomnia is a presenting symptom of acute paramedian thalamic stroke and accompanied by NREM fragmentation and impaired cognition [67–70]. Hypersomnolence and narcolepsy have also been proposed as the primary manifestation of midbrain strokes that extend into the thalamus or from degenerative pontine lesions [15, 71]. Indeed, focal lesions to the thalamus that extend into the posterior fossa/ABRAS region have an acute effect on sleep–wake activity; however, we excluded participants with infarction in our ROIs (see Figure 3 for lesion localization mapping of all stroke participants). It is important to note that these case reports largely occur in the hyper-acute to acute stages of the stroke where deleterious environmental stressors of acute hospital care may confound sleep and circadian measures—either by inducing overnight sleep deprivation which, in turn, triggers excessive sleep rebound or by altered circadian exposure to Zeitgebers [72]. Here, we show that sleep–wake associated reductions to regional brain volumes of subcortical sleep–wake structures may *not* be transient—occurring in the chronic stages of stroke (approximately 3 months after the incident) in participants with long sleep duration and poor sleep efficiency independent of environmental stressors, confounding comorbidities, and lesion location.

Cerebrovascular disease has been associated with accelerated global brain volume loss, yet subcortical sleep–wake structures appear to be particularly susceptible to vascular neurodegeneration [73]. For example, preliminary findings of subcortical atrophy to the striatum and thalamus have previously been described following cerebral infarction [11, 74–76]. Furthermore, stroke may cause delayed brain atrophy in the ipsilesional hemisphere—degeneration likely related to the area of acute ischemia [75]. Interestingly, we did not observe any discernible difference in the proportion of contralesional or ipsilesional structures affected in poor sleepers. These findings suggest that volumetric reductions identified in poor stroke sleepers are unlikely to be driven directly by stroke lesions and may be driven by vascular risk factors [77]. The direction and cause of this degeneration are difficult to gauge within the current design; pre-morbid sleep dysfunction may exacerbate neurodegeneration in susceptible populations with vascular risk factors [78, 79].

Harris and colleagues report that poststroke hypersomnia is associated with functional independence measure scores 16-points below the mean and a 10-fold increased risk of requiring aged care home [67]. We also identified a functional recovery deficit, as stroke participants with long sleep duration had significantly higher mRS scores at admission and 3-month poststroke when compared with normal sleepers. The proposed pathophysiological mechanisms subserving the observed relationship between long sleep duration and reduced neurological recovery are numerous and may be associated with confounders which were included as covariates (e.g. depression, sleep apnea) and/or true mediators of the effect (e.g. shortened photoperiod/phase advanced circadian rhythms, lethargy, systemic inflammation, degeneration as a proxy/manifestation of poststroke disability) [80]. Alternatively, the demonstrable reductions to sleep efficiency seen in our stroke sample may also be associated with fragmentation to slow-wave sleep, a principle driver of glymphatic clearance function in the brain [81]. Compromised glymphatic activation after stroke may impair extracellular clearance of toxic solutes (e.g. glutamate) and contribute to neuronal excitotoxicity, thereby exacerbating neurological deficits [82].

Less explicable are the significant volumetric *increases* to the contralesional pallidum in stroke participants with long sleep duration, and bilateral caudate in stroke participants with poor sleep efficiency. A possible contributor to these observed increases could be a function of endogenous brain remodeling whereby intense axonal sprouting, dendritic branching, and synaptogenesis occur in the post-acute ischemic phase [83]. In a small sample of 28 participants, Abela and colleagues found gray matter volume expansion within the caudate nucleus [84]. Extensive white matter hyperintensities, common in stroke participants, have also been associated with increased brain volume changes in cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) and may be caused by global increases in cerebral water content [85]. Here, the injured brain exhibits a reemergence of an ontogenetic state: glial, and especially astrocytic, expansion assuages neuronal excitability and enables synaptic plasticity. However, it is unclear why either the pallidum or caudate are exclusively selected; glial cells and neuroblasts provide basic trophic support independent of brain region and have low selectivity for specific neuronal populations [86].

Corticopontocerebellar tract degeneration may mediate long sleep duration

We employed a FBA to characterize white matter fiber density and bundle cross section (i.e. morphological changes) associated with long sleep duration after stroke. In contrast to other DTI modes, such as fractional anisotropy or mean diffusivity, FBAs can resolve crossing fibers which occur in approximately

60%–90% of adult human brain tissue. Crossing fibers may be particularly prevalent in complex multi-hierarchical sleep–wake tracts of interest such as the ABRAS [40]. We found that stroke participants with long sleep duration exhibit bilateral white matter degeneration to the corticopontocerebellar tract when compared with healthy controls. Furthermore, stroke participants with normal sleep duration (between 6 and 8 h) displayed a widespread distribution of white matter reduction, suggesting specificity of the corticopontocerebellar tract for excessive sleep duration after stroke.

Unlike the ABRAS, which contains no cerebellar projections, the corticopontocerebellar tract contains key afferent pontine fibers that synapse in the cerebellar cortex via the cerebellar peduncles. Briefly, thalamocortical fibers project to the dentate nucleus through the superior cerebellar peduncle and cross midline at the level of the midbrain to synapse at the ventrolateral thalamus. Thalamic afferents descend adjacent to the corticospinal tracts and synapse in the medulla [87].

The bilateral pontocerebellar degeneration among our stroke participants with long sleep duration has important sleep–wake implications. Firstly, the pons, and particularly the locus coeruleus located within the rostral pons near the pons-midbrain junction, is a key sleep–wake node [65, 88]. Orexin-1 receptors found in the locus coeruleus promote sleep-state stability [89]. Orexin-receptor knockout mice exhibit behavioral hypersomnolence similar to those of human narcolepsy [90, 91]. In humans, pontine lesions are associated with locked-in syndrome and hypersomnia [92]. In the present study, five participants suffered focal pontine lesions and all exhibited long sleep duration, suggesting that pontine degeneration and focal stroke topography may be associated with the genesis of long sleep duration.

While injury to corticopontocerebellar tract is mainly associated with ataxia and weakness, arousal impairment may also be related to muscular activation, potentially mediated by degeneration to the descending reticular activating system and thalamocortical tracts [93]. Interestingly, while not known to generate endogenous sleep oscillations, the cerebellum contains significant sleep–wake gene expressions in the brain [94], yet has been characterized as "uncharted land" in sleep research [95]. Cell populations known to impact arousal project to the cerebellum, such as cholinergic inputs from the pons and peduncles, and dopaminergic inputs originating in the ventral tegmental area [95]. Our finding of cerebellar degeneration in excessively long sleepers aligns with convincing evidence from investigations of spinocerebellar ataxias such as Machado–Joseph disease and sleep dysfunction [96]. Participants with Machado–Joseph disease, a spinocerebellar ataxia syndrome characterized by neurodegeneration to the cerebellum and its reciprocal thalamocortical fiber projections, exhibit both rapid eye movement sleep and NREM-arousal dysfunction [97]. Moreover, experimental ablation of the superior peduncle, the main cerebellar output pathway, and a region we found associated with extensive degeneration in long sleepers, causes increased drowsiness and decreased wakefulness [19]. An fMRI case study on a patient Kleine–Levin syndrome, a rare idiopathic hypersomnia characterized by exceptionally long sleep duration, identified reduced thalamic and pontine functional connectivity indicative of ABRAS degeneration [98]. Together, these findings substantiate our results and pinpoint a neuroanatomical basis and potential biomarker for excessively long sleep duration, nested within the corticopontocerebellar tract.

Alerting therapies for stroke-related hypersomnolence

Recovery of hypersomnolence after stroke has shown to be concurrent with the recovery of injury to the ABRAS in case reports [99–101]. Pharmacological treatment of hypersomnolence after stroke through eugeroics/wakefulness-promoting agents (i.e. modafinil, amphetamines) or monoamine oxidase inhibitors has not, to our knowledge, been studied. As the etiology and pathophysiology of non-stroke-related hypersomnia remain unclear, treatment may require a combined sleep-behavioral intervention (CBT-i), circadian light therapy, and eugeroic pharmacological intervention [102]. Development of interventions for poststroke-related hypersomnia is warranted and should target the neural substrates of structures that we found were associated with sleep–wake dysfunction.

Limitations

The cross-sectional design of the present study limited our ability to investigate the directionality or causation of sleep-potentiated brain changes. In addition, our sleep measures were limited to sleep duration and sleep efficiency; polysomnographic-EEG measures provide more specific sleep architectural data. Given our exclusive use of accelerometer, we were unable to confirm whether other sleep disorders beyond sleep-apnea were driving our sleep-duration findings (e.g. narcolepsy). We were unable to examine volumetric correlates of the hypothalamus or ventrolateral preoptic nucleus, a key sleep–wake region of interest, due to its exclusion from FreeSurfer's validated atlas which we used to generate our regional volumes. Additional limitations lie in our stroke sample: our cohort included relatively mild strokes; we were unable to obtain pre-stroke or postmortem imaging; and we did not have useable dMRI imaging for all participants.

Conclusions and Future Directions

Our findings suggest that stroke participants with poststroke sleep dysfunction in the form of long sleep duration and poor sleep efficiency exhibit a subcortical pattern of regional brain volume reduction and white matter degeneration to the corticopontocerebellar tract. To further characterize the neuroanatomical pathogenesis of poststroke sleep dysfunction, future work should incorporate longitudinal polysomnography, the gold standard for sleep measurement, to identify sleep architectural signatures or disorders which may, over time, underlie long sleep duration and poor sleep efficiency after stroke. Future work with larger subsamples of stroke participants with sleep–wake dysfunction should also examine the relationship between the dMRI indices and sleep–wake parameters using a correlational methodology to reveal whether there is, for example, a linear decrease in FDC metrics with linearly increasing sleep duration. Studies informed by our exploratory whole-brain findings could further explore FDC differences in specific a priori-defined tracts within the corticopontocerebellar region. In addition, future studies should chart the neuropsychological and psychomotor changes likely subserving sleep-potentiated brain changes after stroke [6]. Finally, longitudinal examination of pharmacological or behavioral treatment of sleep disruption to abate poststroke vascular neurodegeneration and neurological disability is warranted.

Supplementary Material

Supplementary material is available at *SLEEP* online. .

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Appendix B

Supplementary Material (Chapter 3)

Table S3.1. Newcastle-Ottawa quality assessment scale score breakdown for case-control studies

	Selection				Comparability	Exposure		
Citation	Adequacy of case definition	Representativeness of cases	Selection of controls	Definition of controls	Comparability of cases and controls	Ascertainment of exposure	Consistent method of ascertainment	Non-response rate
Adamczak-Ratajczak et al. 2017	A	B	C	A	A, B	A	A	A
Atanassova et al., 2009	A	A	C	A	A	A	A	A
Bassetti & Aldrich, 2001	A	A	B	A	C	A	A	A
Benbir Karadeniz, 2012	A	A	A	A	C	A	A	A
Chen et al., 2015	A	B	B	A	C	A	A	A
Fiorina et al., 1999	A	A	C	B	C	A	A	B
Frauscher et al., 2010	A	A	B	B	A	A	B	B
Gelber et al., 2015	A	A	B	B	A	A	A	A

Giubilei et al., 1992	A	A	C	B	A	A	A	B
Glozier et al., 2017	B	A	B	A	A, B	C	A	B
Gokkaya et al., 2005	A	B	A	B	C	D	A	A
Jiang et al., 2013	A	A	B	A	C	A	A	A
Klobucníková et al. 2015	A	A	B	B	A, B	A	A	A
Muller et al., 2002	A	A	B	A	C	A	A	B
Palomaki et al., 2003	A	A	B	A	A, B	D	A	C
Poryazova et al., 2015	A	B	C	B	C	A	A	A
Ritzenthaler et al., 2009	A	A	A	B	C	A	A	A
Ritzenthaler et al., 2013	A	A	C	B	C	A	A	A
Santamaria et al., 2000	A	B	B	A	C	A	A	A
Siccoli et al., 2008	A	A	B	B	C	C	A	A
Siengsukon & Boyd, 2009	A	B	A	B	A	D	A	A
Siengsukon et al., 2015	A	B	A	B	A	D	A	A
Terzoudi et al., 2009	A	B	B	A	A, B	A	A	A

Wen et al., 2016	A	A	A	A	A	D	A	A
Zhang et al., 2008	A	B	A	A	A	C	A	B
Zhang et al., 2017	A	B	B	A	C	A	A	A

Note: studies can be awarded a maximum of one star (*) for each numbered item within the selection and exposure categories. A maximum of two stars can be given for comparability. Total stars are summed, and studies are rated on a 1-9 scale. Total scores and rating summaries are presented in Tables 1-6.

Selection: 1) *Adequacy of case definition*: A*, case definition is adequate with independent validation; B, case definition is adequate based on self-report or record linkage; C, no description. 2) *Representativeness of cases*: A*, consecutive or obviously representative series of cases; B, potential for selection biases or not stated. 3) *Selection of controls*: A*, community controls; B, hospital controls; C, no description. 4) *Definition of controls: A**, no history of ischaemic stroke (endpoint), B, no description of source

Comparability: 1) *Comparability of cases and controls*: A*, study controls for age; B*, study controls for depression or NIHSS/stroke severity (depending on study outcomes); C, does not control for most important factors.

Exposure: 1) *Ascertainment of exposure*: A*, secure record, B*; structured interview where blind to case/control status; C, interview not blinded to case/control status; D, written self-report or medical record only; E, no description. 2) *Consistent method of ascertainment for cases and controls:* A*, yes; B, no. 3) *Non-response rate: A**, same rate for both groups, B, non-respondents described, C, rate different and no designation.

Table S3.2. Newcastle-Ottawa quality assessment scale score breakdown for cohort studies

	Selection				Comparability	Outcome		
Citation	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Comparability of cohorts	Assessment of outcome	Sufficient follow-up period	Adequacy of follow-up cohorts
Bassetti et al., 1996	B	A	A	NR	C	A	A	C
Boulos et al., 2017a	A	A	A	A	A	B	A	C
Canivet et al., 2014	C	A	C	A	A, B	B	A	A
Chen et al., 2008	B	A	C	A	A, B	B	A	D
Chou et al., 2017	B	A	A	A	A	B	B	A
Eguchi et al., 2010	A	A	C	NR	A	B	B	D
Elwood et al., 2006	B	C	C	B	A	B	A	A
Gianfagna et al., 2016	B	A	C	A	A, B	B	A	B
Hermann et al., 2008	A	A	A	A	A	A	A	C
Huang et al., 2013	B	A	A	A	A	B	A	D
Ikehara et al., 2009	B	A	C	A	A, B	B	A	B

Kakizaki et al., 2013	B	A	C	B	A, B	B	A	B
Katzan et al., 2018	A	A	A	B	A	C	A	B
Kawachi et al., 2016	B	A	C	B	A	A	A	B
Kim et al., 2017	A	A	A	B	C	D	A	A
Lee et al., 2009	A	A	A	A	C	C	A	A
Ma et al., 2017	B	A	C	A	A	B	B	D
Manconi et al., 2014	A	A	A	A	C	A	A	C
Medeiros et al., 2011	A	A	A	B	C	C	B	C
Molnar et al., 2016	B	A	A	A	A, B	D	A	A
Pace et al., 2018	C	A	A	A	A, B	A	A	A
Ponsaing et al., 2017	A	A	A	B	A, B	A	A	A
Takekawa et al., 2007	A	A	A	B	C	A	A	B
Tang et al., 2014	A	A	A	B	C	C	A	B
Vock et al., 2002	C	A	A	A	C	A	A	C
Wang et al., 2016	B	A	A	B	A, B	C	B	A
Wu et al., 2014	C	A	A	A	A, B	B	B	D

Wu et al., 2016	B	C	A	A	C	A	B	C

Note: A study can be awarded a maximum of one star for each numbered item within the selection and outcome categories. A maximum of two stars can be given for comparability. NR: not-reported. Total scores and rating summaries are presented in Tables 1-6.
Selection: 1) *Representativeness of the exposed cohort*: A*, truly representative of the average age, 72, in the community; B*, somewhat representative of the average age (+/- 10 years) in the community; C, selected group of users eg nurses, volunteers; D, no description of the derivation of the cohort. 2) *Selection of the non-exposed cohort*: A*, drawn from the same community as the exposed cohort; B, drawn from a different source; C, no description of the derivation of the non-exposed cohort. 3) *Ascertainment of exposure*: A*, secure record; B*, structured interview; C, written self-report; D, no description. 4) *Demonstration that outcome of interest was not present at start of study:* A*, yes; B, no.
Comparability: 1) *Comparability of cases and controls*: A*, study controls for age; B*, study controls for depression or NIHSS/stroke severity (depending on study outcomes); C, study does not control for most important factors.
Outcome: 1) Assessment of outcome: A*, intendent blind assessment; B*, record linkage; C, self-report; D, no description. 2) *Was follow-up period long enough for outcomes to occur:* A*, yes (5-years for sleep studies, 3 months for stroke studies); B, no. 3) Adequacy of follow-up cohorts: A*, complete follow-up and all subjects accounted for; B, subjects lost to follow up unlikely to introduce bias (≥90% follow up, ≤10% attrition); C, follow-up rate ≤90% and no description of those lost; D, no statement.

Table S3.3. Modified Newcastle-Ottawa quality assessment scale score breakdown for cross-sectional studies

	Selection				Comparability	Outcome	
Citation	Representativeness of the sample	Sample size	Comparability of non-respondents	Ascertainment of exposure	Comparability of groups	Assessment of outcome	Appropriateness of statistical tests
Alvarez-Sabin et al., 2017	A	A	C	A	B	A	A
Benbir Karadeniz, 2013	A	B	C	A	A, B	A	A
Boulos et al., 2017b	A	B	C	A	A, B	A	A

Del Brutto et al., 2015	A	A	A	A	A	A	A
Kantermann et al., 2015	A	A	C	A	C	C	A
Karaca 2016	C	B	C	A	C	C	A
Kim et al., 2017b	A	A	A	A	C	C	A
Leppavuori et al., 2002	A	A	A	A	C	A	A
Rist et al., 2014	A	A	A	A	A	C	A
Rupert et al., 2014	A	B	C	A	C	B	B
Suh et al., 2014	A	A	A	A	A	C	A
Tang et al., 2015	A	A	A	A	A, B	C	A
Zhang et al., 2014	C	A	C	A	C	C	A
Zubier et al., 2014	B	A	A	A	A, B	A	A

Note: A maximum of five stars can be given for Selection. A maximum of two stars can be given for Comparability. A maximum of three stars can be given to Outcome. Total stars are summed, and studies are rated on a 1-10 scale. Total scores and rating summaries are presented in Tables 1-6.

Selection: 1) *Representativeness of the sample*: A*, truly representative of the average in the target population (all subjects or random sampling); B*, somewhat representative of the average in the target population (non-random sampling); C, selected group of users; D, no description of the sampling strategy. 2) *Sample size: A*, justified and satisfactory (n = $\geq$50); B, not justified. 3) *Comparability of non-respondents*: A*, comparability between respondents and non-respondents characteristics is established, and the response rate is satisfactory; B, response rate is unsatisfactory, or the comparability between respondents and non-respondents is unsatisfactory; C, no description of the response rate or the characteristics of the responders and the non-responders. 4) *Ascertainment of exposure*: A**, validated measurement tool; B*, non-validated measurement tool, but tool is available or described; C, no description of measurement tool.

Comparability: 1) *The subjects in different outcome groups are comparable, based on the study design or analysis. Confounding factors are controlled:* A*, study controls for age; B*, study controls for depression or NIHSS/stroke severity (depending on study outcomes); C, study does not control for important confounding factors
Outcome: 1) *Assessment of outcome:* A**, independent blind assessment; B**, record linkage; C*, self-report; D, no description. 2) *Appropriateness of statistical tests*: A*, The statistical test used to analyse the data is clearly described and appropriate, and the measurement of the association is presented, including confidence intervals and the probability level (p value); B, the statistical test is not appropriate, not described or incomplete

Table S3.4. Stroke characteristics and adjusted variables for studies investigating sleep duration on ischaemic stroke risk.

Author, Year	Stroke severity	Stroke topography	Adjustment variables
Chen et al., 2008	-	-	Age, race, smoking, exercise, use of hormone therapy, relevant cerebrovascular disease risk factors (prior cerebrovascular disease, diabetes, hypertension, high cholesterol level requiring pills, body mass index, socioeconomic status (education, family income, and employment status), depression
Eguchi et al., 2010	-	-	Age, sex, BMI, smoking, diabetes, cholesterol, creatinine, 24-hour SBP, riser pattern (vs non-riser), presence of silent cerebral infarction.
Gianfagna et al., 2016	-	-	Age
Ikehara et al., 2009	-	-	Age, body mass index, history of hypertension, history of diabetes, alcohol consumption, smoking, education level, hours of exercise, hours of walking, regular employment, perceived mental stress, depressive symptoms, frequency of fresh fish intake
Kakizaki et al., 2013	-	-	Age, total caloric intake, body mass index, marital status, level of education, job status, history of myocardial infarction, history of cancer, history of stroke, history of hypertension, history of diabetes mellitus, smoking status, alcohol drinking, time spent walking (<1 hour/day, perceived mental stress (low, moderate, or high), self-

			rated health (worse or better), physical function (limited or unlimited)
Kawachi et al., 2016	-	-	Age, education years, marital status, histories of hypertension and diabetes, body mass index, physical activity score, smoking status, and alcohol consumption (g/day)
Wen et al., 2016	-	Ischaemic stroke subtypes: cardioembolism (n= 6, 1.8%), large vessel (n=68, 20.4%), and small vessel (n=133, 9.9%)	Age, sex, sleep duration, daytime napping, snoring, snorting/gasping, education, smoking, alcohol, vegetables, fruits consumption status, history of diabetes, history of hypertension, body-mass index, physical activity, sleep quality, and psychosocial factors
Zhang et al., 2008	-	-	Age, gender, smoking, alcohol drinking, hypertension, diabetes mellitus, coronary heart disease, and hypercholesterolemia

Table S3.5. Stroke characteristics and adjusted variables for studies investigating the impact of non-apnoea sleep disorders on ischaemic stroke risk.

Author, Year	Stroke Severity	Stroke Topography	Adjustment variables
Canivet et al., 2014	-	-	Age, country of origin, marital status, occupational class, psychological stress/pressure, Smoking, gender, alcohol, obsetiy, physical activity, pain, hypertension, diabetes, lipid-lowering drugs
Chou et al., 2017	-	-	Age, sex, hypertension, diabetes, hyperlipidemia, atrial fibrillation, obstructive sleep apnoea

Frauscher et al., 2010	-	pontine infarction (n = 1)	-
Huang et al., 2013	-	-	Age, gender, hypertension, diabetes mellitus, coronary artery disease, congestive heart failure, peripheral artery disease
Ma et al., 2017	-	-	Age, sex, education level, income level, occupation, smoking status, alcohol status, hypertension, diabetes, body mass index, atrial fibrillation, myocardial infarction, plasma concentrations of triglycerides, low and high density pipoprotein cholesterol, urate, sleep duration, daytime sleep, insomnia, hypnotics, snoring
Molnar et al., 2016	-	-	Insomnia
Wang et al., 2016	Non-depressed group: NIHSS = 6.5, Barthel index = 71.5. Depressed group: NIHSS = 9.2, Barthel index = 44.2	Non-depressed group: 53.2% (n=190) cortical infarction, 46.8% (n=168) subcortical. Depressed group: 62% (n=155) cortical infarction, 38% (n=95) subcortical infarction	History of insomnia, adverse life events, living alone, the left carotid artery infarction, the cortical infarction, NIHSS, and Barthel index scores
Wu et al., 2014	-	-	Age, sex, diabetes mellitus, hypertension, hyperlipidaemia, depression, anxiety, atrial fibrillation

Table S3.6. Stroke characteristics and adjusted variables for studies investigating sleep quality, sleep architecture and ischaemic stroke risk.

Author, Year	Stroke severity	Stroke topography	Adjustment variables
Del Brutto et al., 2015	-	WMH in 154 (65%) participants (moderate-to-severe in 52); silent lacunar infarcts in 28 (12%); and deep microbleeds in 17 (7%)	Age, sex, education, smoking status, body mass index, physical activity, diet, blood pressure, fasting glucose, and total cholesterol blood levels
Gelber et al., 2015	-	Microinfarcts, 19.8% (n=33); general atrophy, 29.9% (n=50); lacunar infarcts, 21.0% (n=35); Braak stage 5/6, 18.6% (n=31); neurofibrillary tangles, 15% (n=25); neuritic plaque, 31.1% (n=52); and gliosis and neuron loss in the locus ceruleus, 27.5% (n=46).	Age at death, smoking, body mass index, haemoglobin, high-density lipoprotein cholesterol, diabetes, midlife systolic blood pressure.
Ponsaing et al., 2017	Survivors (n = 54): Scandinavian stroke scale = 51; mRS = 3. Non-survivors (n = 9): Scandinavian stroke scale = 54; mRS = 3.	Survivors: multiple infarctions = 9, cerebral infarction = 40, cerebral haemorrhage = 8, TIA = 6, supratentorial = 44, infratentorial = 5, brainstem = 5. Non-survivors: multiple infarctions = 2, cerebral infarction = 8, cerebral haemorrhage = 1, TIA = 0, supratentorial = 8, infratentorial = 2, brainstem = 0.	Age, lung disease, atrial flutter/fibrillation, modified Barthel index, modified Rankin scale, Scandinavian stroke scale, BMI

Abbreviations: WMH = white matter hyperintensities

Table S3.7. Stroke characteristics and adjusted variables for studies investigating the impact of ischaemic stroke on sleep architecture and sleep quality.

Author, Year	Stroke severity	Stroke topography	Adjustment variables
Alvarez-Sabin et al., 2017	-	Lacunar infarction: n=43, 70.5%	Diabetes mellitus, hyperlipidaemia, smoking habit, ischaemic heart disease, and peripheral artery disease
Bassetti & Aldrich, 2001	-	Laterality: 13 left, 11 right. All supratentorial, extra-thalamic lesions. Stroke volume mean: 20.2 (range: 0.3-122 ml).	-
Chen et al., 2015	Admission NIHSS mean in patients with and without sleep-disorders: 7.93 vs. 4.01	Laterality: 39 left, 34 right. Anterior circulation: 20, posterior circulation: 22, thalamic infarction: 17, non-thalamic infarction: cerebral infarction: 27, subcortical infarction: 32, brainstem infarction: 18, cerebellum infarction: 6	-
Gokkaya et al., 2005	Functional independence measure: all-stroke mean: 92.57	-	-
Giubilei et al., 1992	Admission Canadian neurological scale: mild (score between 6.5-8.5) in 7 pts, and severe (score <6.5) in 11 pts. Six of 8 pts had score of <6.5 at 3-weeks post-stroke.	Four pts had deep MCA; seven pts had superficial MCA; five had complete or partial MCA; one pt with lacunar infarct in lenticulostriate arteries	-
Hermann et al., 2008	Baseline/admission SSS: 47.6 for bilateral infarct, 49.1 for left-sided, and 50.3 for right-sided infarcts. 1-year post-stroke SSS:56.9 for bilateral infarct, 57.4 for left-	Eleven pts had bilateral, 10 left-sided, and 10 right-sided lesions.	-

	sided infarct, 58.0 for right-sided infarct.		
Jiang et al., 2013	NIHSS: VCIND mean = 5.25, simple stroke = 4.63	VCIND vs stroke vs control: Subcortical stroke (basal ganglia and/or thalamus): 29, 35, 0; diffuse white matter hyperintensities: 26, 15, 5; laterality (right/left): 27 (10/24), 13 (6/8), 0	-
Karaca, 2016	Functional independence measure total score mean: 95.4 (range: 43.0-121.0)	Laterality: 9 (39.1%) left, 14 (60.9% right)	-
Katzan et al., 2018	Median modified Rankin Scale (mRS) score at baseline: 1. NIHSS score median at baseline: 0.	-	-
Klobucnikova et al., 2016	No excessive daytime sleepiness: NIHSS = 3.91. Excessive daytime sleepiness: NIHSS = 5.83.	No excessive daytime sleepiness: 85.2% (n=69) supratentorial, 14.8% (n=12) infratentorial. Excessive daytime sleepiness: 76.2% (n=16) supratentorial, 23.8% (n=5) infratentorial.	-
Manconi et al., 2014	Admission NIHSS range: 0-6	Lesion location: 14 infratentorial, 14 supratentorial	-
Muller et al., 2002	Admission NIHSS mean: 9 (range 2–24)	Laterality: 8 right hemisphere, 11 left hemisphere, 1 bilateral	-
Pace et al., 2018	Admission NIHSS mean: 3. Thrombolysis n = 32 (21.1%).	Topography: n = 127 (83%) supratentorial, n = 23 (15%) infratentorial, n = 3 (2%) both. TOAST: n = 18 (11.8%) large-artery atherosclerosis, n = 55 (35.9%) cardioembolism, n = 18 (11.8%) small-vessel occlusion, n = 6 (3.9%) other	Linear regression analysis variables: mRS at discharge or mRS at 3 months. Independent variables: age, sex, diabetes, hypertension, previous stroke/TIA, NIHSS on admission, thrombolysis, infratentorial stroke, large- artery atherosclerosis, cardioembolism, small-vessel occlusion etiology, sleep

			efficiency, apnea–hypopnea index, REM latency, sleep stages, PLMI, and PSG day from stroke.
Poryazova et al., 2015	Admission NIHSS mean: 8.5. Chronic 3-month post-stroke NIHSS mean: 4.3.	Laterality: 6 left hemisphere, 2 right hemispheres. Lesion location: 4 superficial (pial/superficial branches of the MCA), 4 superficial and deep (pial/superficial and deep/perforating branches of MCA). Mean stroke volume (mL): 72.2	-
Santamaria et al., 2000	-	Laterality: 8 left hemisphere, 5 right hemisphere. Thalamic lesion locations: 8 posterolateral, 3 global, 2 anterior. Ischaemic in 8, haemorrhagic in 5.	-
Siccoli et al., 2008	Admission NIHSS mean: 8 (range: 1-16)	Laterality: 5 right hemisphere, 6 left hemisphere. Mean stroke volume: 81 ml (range; 5-200). Lesion location: 8 (73%) superficial (pial/superficial branches of middle, posterior or anterior cerebral artery), 1 (9%) deep (deep/perforating branches of middle cerebral artery), and 2 (18%) superficial deep.	-
Siengsukon & Boyd, 2009	Average Orpington prognostic score: 2.51 (mild)	Laterality: 17 left hemisphere, 23 right hemisphere. Topography: 15 subcortical, 5 cortical, 10 mixed/multiple, 10 unknown.	-
Siengsukon et al., 2015	Average Orpington prognostic score: 1.9 (mild)	Laterality: 7 left hemisphere, 13 right hemisphere.	-
Suh, M., Choi-Kwon, S., & Kim, J.S, 2014	Admission NIHSS mean: 3.88	Laterality: 144 (51.1%) right hemisphere, 124 (44.0%) left hemisphere, 14 (5%) bilateral. Lesion location: 41 (14.5%) anterior cortex, 39 (13.8%) posterior cortex, 35 (12.4%) thalamus, 41 (14.5%) pons and midbrain, 14 (5.0%) medulla, 29 (10.3%) cerebellum	Age, gender, diabetes mellitus, depression, fatigue
Terzoudi et al., 2009	NIHSS mean: 6.1. Barthel index mean: at discharge = 80.4, at 3-months post-stroke = 86.2.	Laterality: 25 (43%) right hemisphere, 21 (37%) left hemisphere, 12 (20%) bilateral. Topography: 7 brainstem, 8 cerebellar, 18 hemisphere cortical, 18 hemisphere deep, 7 multiple.	-

Vock et al., 2002	NIHSS mean: 7. Barthel index mean: at discharge = 95, long-term = 100. Modifided rankin scale: at discharge = 2, long-term = 1.	Laterality: 10 right, 16 left, 1 bilateral. Average lesion volume: 23mL	-
Wu et al., 2016	NIHSS: 0	Laterality: 15 right, 12 left. All thalamic lesions	-
Zhang et al., 2014	Admission NIHSS mean: 7.5	-	-

Abbreviations: NIHSS = National institutes of health stoke scale (score), mRS = Modified rankin scale (score), RBD = rapid-eye-movement behaviour disorder, RLS = restless legs syndrome, VCIND = vascular cognitive impairment no dementia
Note: NIHSS score ratings [435]: 0 = no stroke symptoms, 1-4 = minor stroke, 5-15 = moderate stroke, 16-20 = moderate to severe stroke, 21-42 = severe stroke. mRS score ratings [436]: 0 = no symptoms at all, 1 = no significant disability despite symptoms; able to carry out all usual duties and activities; 2 = slight disability, unable to carry out all previous activities, but able to look after own affairs without assistance; 3 = moderate disability, requiring some help, but able to walk without assistance; 4 moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance; 5 = severe disability; bedridden, incontinent and requiring constant nursing care and attention; 6 = dead.

Table S3.8. Stroke characteristics and adjusted variables for studies investigating the impact of ischaemic stroke on non-apnoea sleep disorders.

Author, Year	Stroke severity	Stroke topography	Adjustment variables
Bassetti et al., 1996	-	All paramedial thalamic stroke	-
Benbir, G. & Karadeniz, D., 2012	-	Laterality: 21 right, 14 left. Stroke topography: 13 MCA, 1 ACA, 1 PCA, 7 corona radiata, 5 basal ganglia, 4 thalamus, 4 centrum semiovale. Stroke subtype: 23 (65.7%) atherothrombotic disease, 12 (34.3%) embolic strokes.	-

Benbir & Karadeniz, 2013	Admission, 3-weeks, and 3-months post-stroke NIHSS mean: 7.9 (range: 3.0-15), 5.6 (range: 0-14), 4.0 (range: 0-7)	-	Age, gender, smoking, body mass index, hypertension and depression.
Boulos et al., 2017	NIHSS median: 0 (range: 0-4)	-	Function outcome (Barthel index) and depressive symptoms
Boulos et al., 2017	NIHSS score ≤ 3	Stroke volumes: median (range): 240 (45-419)"	Age, gender, body mass index, NIHSS, hypertension, hyperlipidemia, diabetes, prior or current smoking history, and coronary artery disease
Chen et al., 2015	Admission NIHSS mean in patients with and without sleep-disorders: 7.93 vs. 4.01	Laterality: 39 left, 34 right. Anterior circlation: 20, posterior circulation: 22, thalamic infarction: 17, non-thalamic infarction: cerebral infarction: 27, subcortical infarction: 32, brainstem infarction: 18, cerebellum infarction: 6	-
Glozier et al., 2017	World Health Organization Disability Assessment Schedule II score: 24.9	83% ischaemic stroke, 13% haemorrhagic stroke, 4% other	Age, sex, depression, anxiety, prior treatment for psychological illness, alcohol use, baseline disability/illness variables, physical comorbidities, World Health Organization Disability Assessment Schedule II score
Kim et al., 2017	Admission NIHSS mean: 3.26, 7-days post-stroke NIHSS mean: 1.72, 3-day post-stroke mRS: 0.21.	Stroke topography: cerebrum 154 (63.9%), brainstem 29 (14.1%), cerebellum 10 (4.8%), multiple 12 (5.0%). Stroke subtypes: large artery atherosclerosis 63 (30.7%),	-

		carioembolism 35 (17.1%), small vessel occlusion 62 (30.2%), undetermined 45 (22.0%)	
Lee et al., 2009	-	Stroke topography of all participants (including hemorrhagic): Multiple subcortical ischaemic lesions: 6, cerebellum: 6, medulla oblongota: 4, pons: 18, medibrain: 1, thalamus: 7, internal capsule 8, basal ganglia and/or corona radiata: 33, cortical lesions with or without subcortical involvement: 54.	-
Leppavuori et al., 2002	Admission Scandinavian stroke scale mean: 50.2	Stroke localis ation: 29.6% right hemisphere and anterior, 13.4% right hemisphere and posterior 45.5%, left hemisphere and anterior, 8.7% left hemisphere and posterior, 2.5% bilateral.	-
Medeiros et al., 2011	Admission mRS scores with restless legs syndrome (RLS): 3.58; without RLS: 2.86.	RLS laterality: 9 right, 2 left, 1 bilateral. Non-RLS laterality: 47 right, 32 left, 5 bilateral.	-
Palomaki et al., 2003	Admission Scandinavian stroke scale mean: 42.8	Laterality: 42 left, 38 right. 20 vertebrobasilar, 80 carotid artery system	Age, gender, living status, Scandinavian stroke scale scores, stroke location, marital status

Rist et al., 2014	-	Volume of white matter hyperintensities (cm3, median and IQR): no RLS = 3.9 (2.7 – 5.8), RLS = 4.0 (2.7-6.0)	Age, sex, smoking status, alcohol consumption, physical activity, body mass index, history of hypertension, history of diabetes, history of cardiovascular disease, history of peripheral artery disease, history of leg operation and history of oedema/swelling of legs and ankles, sleep quality, difficulty sleeping, taking sleep medication
Ruppert et al., 2014	Admission NIHSS mean: 4.93	Topography of three RLS-positive stroke patients: 1) right anteromedial anterolateral pontine lesion, 2) right anteromedial medullary lesion, 3) right anteromedial pontine lesion.	-
Tang et al., 2014	Admission RBD NIHSS mean: 4.9, admission RBD mean: 3.5	RBD vs. non-RBD topography: frontal 0, 12 (0%, 11.3%); temporal 0, 2 (0%, 1.9%) parietal 0, 3 (0%, 2.8%) occipital 0, 1 (0%, 0.9%), basal ganglia 1, 15 (7.7%, 14.2%), thalamus 3, 14 (23.1%, 13.2%), brainstem 6, 20 (46.2%, 19.8%), midbrain 0, 1 (0%, 0.9%), pons 5, 18 (38.5%, 17.0%), pontine base 5, 17 (38.4%, 16.0%), pontine tegmentum 0, 7 (0%, 6.6%), coeruleus/subcoeruleus region 0, 1 (0%, 0.9%), laterodorsal tegmental nuclei 0, 5 (0%, 4.7%), medulla 1, 2 (7.7%, 1.9%), cerebellum 0, 3 (0%,	Stroke location and infarct volume

		2.8%), subcortical white matter 3, 46 (23.1%, 43.4%). Mean infarction volume RBD vs non-RBD (ml): 0.7, 2.2	
Tang et al., 2015	NIHSS mean: all pts = 6.5, insomnia = 3.7, non-insomnia = 3.1. Barthel index mean: all pts = 19.3, insomnia = 19.1, non-insomnia = 19.4.	-	Sex, Barthel index, depression

Abbreviations: NIHSS = National institutes of health stoke scale (score), mRS = Modified rankin scale (score), RBD = rapid-eye-movement behaviour disorder, RLS = restless legs syndrome, MCA = middle cerebral artery, ACA = anterior cerebral artery, PCA = posterior cerebral artery

Note: NIHSS score ratings [435]: 0 = no stroke symptoms, 1-4 = minor stroke, 5-15 = moderate stroke, 16-20 = moderate to severe stroke, 21-42 = severe stroke. Scandinavian stroke scale ratings [437]: the higher the score the better the prognosis; 0 = minimum score, 48 = maximum (long term) score. mRS score ratings [436]: 0 = no symptoms at all, 1 = no significant disability despite symptoms; able to carry out all usual duties and activities; 2 = slight disability, unable to carry out all previous activities, but able to look after own affairs without assistance; 3 = moderate disability, requiring some help, but able to walk without assistance; 4 moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance; 5 = severe disability; bedridden, incontinent and requiring constant nursing care and attention; 6 = dead.

Table S3.9. Stroke characteristics and adjusted variables for studies investigating the impact of ischaemic stroke on circadian rhythms.

Author, Year	Stroke severity	Stroke topography	Adjustment variables
Adamczak-Ratajczak et al., 2017	Admission mean SSS score: 35.0	-	-
Atanassova et al., 2009	-	-	Age, sex, cortisol, melatonin
Fiorina et al., 1999	-	Eight pts with extensive injury to cortex, five pts with minor cortical lesions.	-
Kantermann et al., 2015	Admission NIHSS and mRS mean scores: 4.4, 2.3	-	-
Ritzenthaler et al., 2009	-	-	-

Ritzenthaler et al., 2013	Admission, 1-day post-stroke, and 5-days post-stroke NIHSS scores: 12 (range: 7.25-17), 8 (3-16.75)	Stroke subtypes: 20 cardioembolic, 16 large-atertery atherosclerosis, 1 small-vessel occlusion, 2 rare-cause, 3 crytogenic.	-
Takekawa et al., 2007	Mean mRS scores at 3 months post-stroke: normal: 1.1, separate: 1.4, aberrant: 5.4.	Laterality: 18 left, 24 right, 8 cerebellum or brainstem. Stroke subtypes: 12 small-vessel occlusion, 18 large- artery atherosclerosis, and 20	-
Zhang et al., 2017	-	-	-
Zuubier et al., 2014	-	White matter lesion volumes (ml): 3.8, lacunar infarcts: 43 (4.4%), cerebral microbleeds: 129 (13.3%)	Age, sex, body mass index, activities of daily living, depressive symptoms, sleep apnoea, total cholesterol, systolic blood pressure, blood glucose, antihypertensives, lipid lowering and sleep medication. Analyses with white matter lesions are additionally adjusted for intracranial volume

Abbreviations: NIHSS = National institutes of health stoke scale (score), mRS = Modified rankin scale (score)
Note: NIHSS score ratings [435]: 0 = no stroke symptoms, 1-4 = minor stroke, 5-15 = moderate stroke, 16-20 = moderate to severe stroke, 21-42 = severe stroke. mRS score ratings [436]: 0 = no symptoms at all, 1 = no significant disability despite symptoms; able to carry out all usual duties and activities; 2 = slight disability, unable to carry out all previous activities, but able to look after own affairs without assistance; 3 = moderate disability, requiring some help, but able to walk without assistance; 4 moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance; 5 = severe disability; bedridden, incontinent and requiring constant nursing care and attention; 6 = dead.

Figure S3.1. PsycINFO search strategy and terms.

1. exp sleep/ or exp sleep disorders/ or human biological rhythms/
2. (sleep* or insomnia or insomnias or hypersomnia or hypersomnias or somnolence or restless leg* or periodic limb movement* or rapid eye movement or parasomnia or parasomnias or circadian or polysomnograph* or PSG or melatonin or chronotope).mp.
3. 1 or 2
4. exp cerebrovascular accident/
5. ((cerebral* or cerebro*) adj3 isch*mi*).mp.
6. ((cerebral* or cerebro*) and (thromb* or embol*)).mp.
7. (brain adj (infarct* or lesion*)).mp.
8. (stroke* or cerebrovascular accident* or cerebral* infarct*).mp.
9. or/4-8
10. 3 and 9
11. limit 10 to "therapy (best balance of sensitivity and specificity)"
12. ((case* adj5 control*) or (case adj3 comparison*) or case-comparison or control group*).ti,ab,id. not "Literature Review".md.
13. (cross section* or "prevalence study").ti,ab,id.
14. ((cohort or longitudinal or prospective or retrospective).ti,ab,id. or longitudinal study.md. or prospective study.md. or retrospective study.md.) not "Literature Review".md.
15. 12 or 13 or 14
16. 10 and 15
17. 11 or 16

Figure S3.2. Medline search strategy and terms.

1. exp sleep/ or exp sleep wake disorders/ or circadian rhythm/
2. (sleep* or insomnia or insomnias or hypersomnia or hypersomnias or somnolence or restless leg* or periodic limb movement* or rapid eye movement or parasomnia or parasomnias or circadian or polysomnograph* or PSG or melatonin or chronotype).mp.
3. 1 or 2
4. exp stroke/

5. ((cerebral* or cerebro*) adj3 isch*mi*).mp.
6. ((cerebral* or cerebro*) and (thromb* or embol*)).mp.
7. (brain adj (infarct* or lesion*)).mp.
8. (stroke* or cerebrovascular accident* or cerebral* infarct*).mp.
9. or/4-8
10. 3 and 9
11. limit 10 to "therapy (best balance of sensitivity and specificity)"
12. Epidemiologic studies/ or exp case control studies/ or exp cohort studies/ or Cross-sectional studies/
13. (cohort adj (study or studies)).tw.
14. (case control or cohort analy$).tw.
15. (follow up adj (study or studies)).tw.
16. (observational adj (study or studies)).tw.
17. (longitudinal or retrospective or cross sectional).tw.
18. or/12-17
19. 10 and 18
20. 11 or 19
21. remove duplicates from 20

Figure S3.3.
Embase search strategy and terms.

1. exp sleep/ or exp sleep wake disorders/ or circadian rhythm/
2. (sleep* or insomnia or insomnias or hypersomnia or hypersomnias or somnolence or restless leg* or period limb movement* or rapid eye movement or parasomnia or parasomnias or circadian or polysomnograph* or PSG or melatonin or chronotype).mp.
3. 1 or 2
4. exp cerebrovascular accident/
5. ((cerebral* or cerebro*) adj3 isch*mi*).mp.
6. ((cerebral* or cerebro*) and (thromb* or embol*)).mp.

7. (brain adj (infarct* or lesion*)).mp.
8. (stroke* or cerebrovascular accident* or cerebral* infarct*).mp.
9. or/4-8
10. 3 and 9
11. limit 10 to “therapy (best balance of sensitivity and specificity)”
12. clinical study/ or case control study/ or family study/ or longitudinal study/ or retrospective study/ or cohort analysis/
13. prospective study/ not randomized controlled trials/
14. (Cohort adj (study or studies)).mp.
15. (Case control adj (study or studies)).tw.
16. (follow up adj (study or studies)).tw.
17. (observational adj (study or studies)).tw.
18. (epidiomiologic$ adj (study or studies)).tw.
19. (cross sectional adj (study or studies)).tw.
20. 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19
21. 10 and 20
22. 11 or 21
23. remove duplicates from 22
24. controlled study/
25. 10 and 24
26. 22 or 25
27. remove duplicates from 26

Appendix C

Supplementary Material (Chapter 4)

Table S4.1. Stroke characteristics in participants with poor sleep efficiency (<80%) versus optimal sleep efficiency (≥80%).

Stroke characteristics	**Poor sleep efficiency <80% (n = 29)**	**No.**	**Optimal sleep efficiency ≥80% (n = 83)**	**No.**	**p**
Infarct volume mm^3, M (SD)	6062.49 (8602.95)	29	7447.70 (10787.33)	83	0.767[a]
Oxfordshire Criteria, n (%)		29		83	0.574[b]
Lacunar (LACI)	4 (14%)		13 (16%)		
Posterior (POCI)	13 (45%)		25 (30%)		
Partial anterior (PACI)	12 (41%)		44 (53%)		
Total anterior (TACI)	0 (0%)		1 (1%)		
Stroke Side, n (%)		29		83	0.580[b]
Left	12 (41%)		27 (33%)		
Right	17 (59%)		53 (64%)		
Bilateral	0 (0%)		3 (4%)		
Tissue plasminogen activator administered, n (%)	4 (14%)	29	10 (12%)	83	0.516[b]

mRS (0-2 vs 3-4) Baseline, n (%)	23 (92%)	25	70 (90%)	78	0.545[b]
mRS (0-2 vs 3-4) 3-months, n (%)	26 (90%)	29	74 (91%)	81	0.722[b]
NIHSS Baseline, M (SD)	2.86 (2.81)	29	3.20 (2.83)	83	0.58[c]
NIHSS 3-month, M (SD)	0.97 (1.33)	29	.86 (1.33)	83	0.73[c]
Days from stroke to 3-month review, mean (range)	97.33 (71-155)	24	101.46 (23-460)	82	0.600[a]

M = mean; No.= number of participants included in each variable without missing data; mRS = modified Rankin Scale; NIHSS = National Institutes of Health Stroke Scale; SD = standard deviation; [a] Mann Whitney *U* test, [b] Fisher Exact Test, [c] Independent samples *t*-test Mann Whitney *U* test.

Table S4.2. Demographic, sleep, and stroke characteristics differences in stroke participants with useable DWI imaging versus those with missing DWI data.

Demographic, sleep, and stroke characteristics	**DWI Stroke (n=93)**	**No.**	**Missing DWI Stroke (n=19)**	**No.**	**p**
Age in years, M ± SD	68.22 (11.46)	93	68 (11.52)	19	0.874[a]
Sex, male n (%)	67 (72.04%)	93	12 (63.15)	19	0.424[b]
Education in years, M ± SD	12.70 (12.70)	93	13.42 (3.04)	19	0.332[a]
Body mass index, M ± SD	27.76 (4.18)	93	28.66 (5.27)	19	0.416[c]
NART-FSIQ, M ± SD	111.92 (1.14)	84	112.07 (12.36)	18	0.809[a]
Hypertension diagnosis, n (%)	61 (66%)	93	10 (53%)	19	0.306[b]
Hyperlipidemia diagnosis, n (%)	42 (45%)	93	6 (32%)	19	0.318[b]
Atrial fibrillation diagnosis, n (%)	16 (17%)	93	7 (37%)	19	0.066[b]
Ischaemic heart disease, n (%)	11 (12%)	93	1 (5%)	19	.687[b]
Type 2 diabetes mellitus, n (%)	25 (27%)	93	2 (11%)	19	.153[b]
High alcohol intake (> 14 standard drinks per week), n (%)	11 (12%)	93	3 (16%)	19	.705[b]
Depression diagnosis, n (%)	9 (10%)	93	2 (11%)	19	1[b]
ApoE_e4 (>1 allele), n (%)	19 (24%)	81	1 (6%)	17	0.182[b]

Sleep efficiency ratio, M (SD)	82.54 (7.34)	93	84.79 (6.50)	19	0.143[a]
Average sleep duration in mins, M (SD)	422.77 (69.44)	93	433.84 (102.86)	19	0.991[a]
Long Sleepers (≥ 8 hr), n (%)	20 (22%)	93	4 (21%)	19	1[b]
Short Sleepers (< 6 hr), n (%)	14 (15%)	93	3 (16%)	19	1[b]
Days SenseWear Worn, mean (SD)	6.18 (1.48)	93	5.89 (1.76)	19	.476[a]
Infarct volume, mean (mm^3) (SD)	6304 (9374)	29	9922 (13050)	83	0.384[a]
Oxfordshire Criteria, n (%)		93		19	0.237[b]
Lacunar (LACI)	15 (16.12%)		2 (10.52%)		
Posterior (POCI)	33 (35.48%)		5 (26.31%)		
Partial anterior (PACI)	45 (48.38%)		11 (57.89%)		
Total anterior (TACI)	0 (0%)		1 (5.26%)		
Stroke Side, n (%)		93		19	1[b]
Left	32 (34.40%)		7 (36.84%)		
Right	58 (62.36%)		12 (63.15%)		
Bilateral	3 (3.22%)		0 (0%)		

Tissue plasminogen activator administered, n (%)	9 (9.67%)	93	5 (26.31%)	19	0.067[b]
mRS (0-2 vs 3-4) Baseline, n (%)	78 (91%)	86	15 (88%)	17	0.669[b]
mRS (0-2 vs 3-4) 3-months, n (%)	83 (91%)	91	17 (89%)	19	0.682[b]
NIHSS Baseline, M (SD)	2.98 (2.67)	93	3.79 (3.43)	19	0.255[c]
NIHSS 3-month, M (SD)	.90 (1.39)	93	.79 (1.87)	19	0.761[c]
Days from stroke to 3-month review, mean (range)	99.77 (23-460)	92	105.5 (55-158)	14	0.309[a]

M = mean; No.= number of participants included in each variable without missing data; mRS = modified Rankin Scale; NIHSS = National Institutes of Health Stroke Scale; SD = standard deviation; [a] Mann Whitney *U* test, [b] Fisher Exact Test, [c] Independent samples *t*-test Mann Whitney *U* test.

Table S4.3. Regional brain volume differences in stroke participants with long (≥8 hr) sleep duration (n=24) versus stroke participants with non-long sleep duration (n=88).

Regional brain volume	Est	SE	g (CI)	p
Accumbens - Ipsi	13.55	25.37	0.03 (-0.42, 0.48)	0.59
Accumbens - Contra	8.8	26.21	0.13 (-0.32, 0.58)	0.73
Amygdala - Ipsi	95.67	60.55	-0.18 (-0.63, 0.27)	0.11
Amygdala - Contra	-17.24	49.67	0.3 (-0.16, 0.75)	[a] 0.72
Brainstem	-316.91	427.13	0.25 (-0.2, 0.7)	0.45
Caudate - Ipsi	-176.11	151.11	0.2 (-0.26, 0.66)	0.24
Caudate - Contra	4.41	110.51	0.01 (-0.45, 0.47)	0.96
Hippocampus - Ipsi	51.67	91.41	0.12 (-0.33, 0.57)	0.57

Hippocampus - Contra	-18.81	92.39	0.33 (-0.12, 0.79)	[a] 0.83
Pallidum - Ipsi	-50.39	58.97	0.21 (-0.24, 0.67)	[a] 0.39
Pallidum - Contra	16.98	52.96	0.02 (-0.44, 0.47)	[a] 0.74
Putamen - Ipsi	-101.8	177.27	0.34 (-0.13, 0.8)	0.56
Putamen - Contra	44.99	128.04	0.12 (-0.34, 0.58)	0.72
Thalamus - Ipsi	-40.699	137.8	0.27 (-0.18, 0.73)	[a] 0.76
Thalamus – Contra	39.15	131.44	0.19 (-0.26, 0.65)	0.76

Note: Stroke participants with lesions to ROIs were excluded (n=8 thalamus, n=1, hippocampus, n = 7 caudate, n = 8 putamen, n = 3 pallidum).

[a] signifies use of extended model (including BMI and PHQ-9).

Table S4.4. Regional brain volume differences in stroke participants with poor (<80%) sleep efficiency (n=29) versus stroke participants with non-poor (≥80%) sleep efficiency (n=83).

Region of interest	**Est**	**SE**	**g (CI)**	**p**
Accumbens - Ipsi	-40.22	23.56	0.28 (-0.15, 0.7)	0.09
Accumbens - Contra	-26.84	24.51	0.16 (-0.26, 0.59)	0.27
Amygdala - Ipsi	-123.62	56.32	0.23 (-0.2, 0.65)	0.03
Amygdala - Contra	-3.9	46.16	-0.09 (-0.51, 0.34)	[a] 0.93
Brainstem	-346.51	401.29	-0.14 (-0.56, 0.28)	0.38
Caudate - Ipsi	197.49	138.46	-0.5 (-0.93, -0.07)	0.15
Caudate - Contra	133.64	100.71	-0.4 (-0.84, 0.02)	0.18
Hippocampus - Ipsi	-91.59	84.56	0.03 (-0.39, 0.46)	0.28
Hippocampus - Contra	-114.99	83.94	0.13 (-0.29, 0.56)	[a] 0.17
Pallidum - Ipsi	35.92	55.78	-0.32 (-0.74, 0.11)	[a] 0.52

Pallidum - Contra	56	49.69	-0.39 (-0.82, 0.04)	[a] 0.26
Putamen - Ipsi	100.36	161.28	-0.22 (-0.65, 0.21)	0.53
Putamen - Contra	90.18	116.24	-0.29 (-0.72, 0.14)	0.43
Thalamus – Ipsi	-132.22	121.04	-0.17 (-0.6, 0.25)	[a] 0.22
Thalamus – Contra	-142.66	116.36	-0.04 (-0.47, 0.38)	0.22

Note: Stroke participants with lesions to ROIs were excluded (n=8 thalamus, n=1, hippocampus, n = 7 caudate, n = 8 putamen, n = 3 pallidum).

[a] signifies use of extended model (including BMI and PHQ-9).

Appendix D

Supplementary Material (Chapter 5)

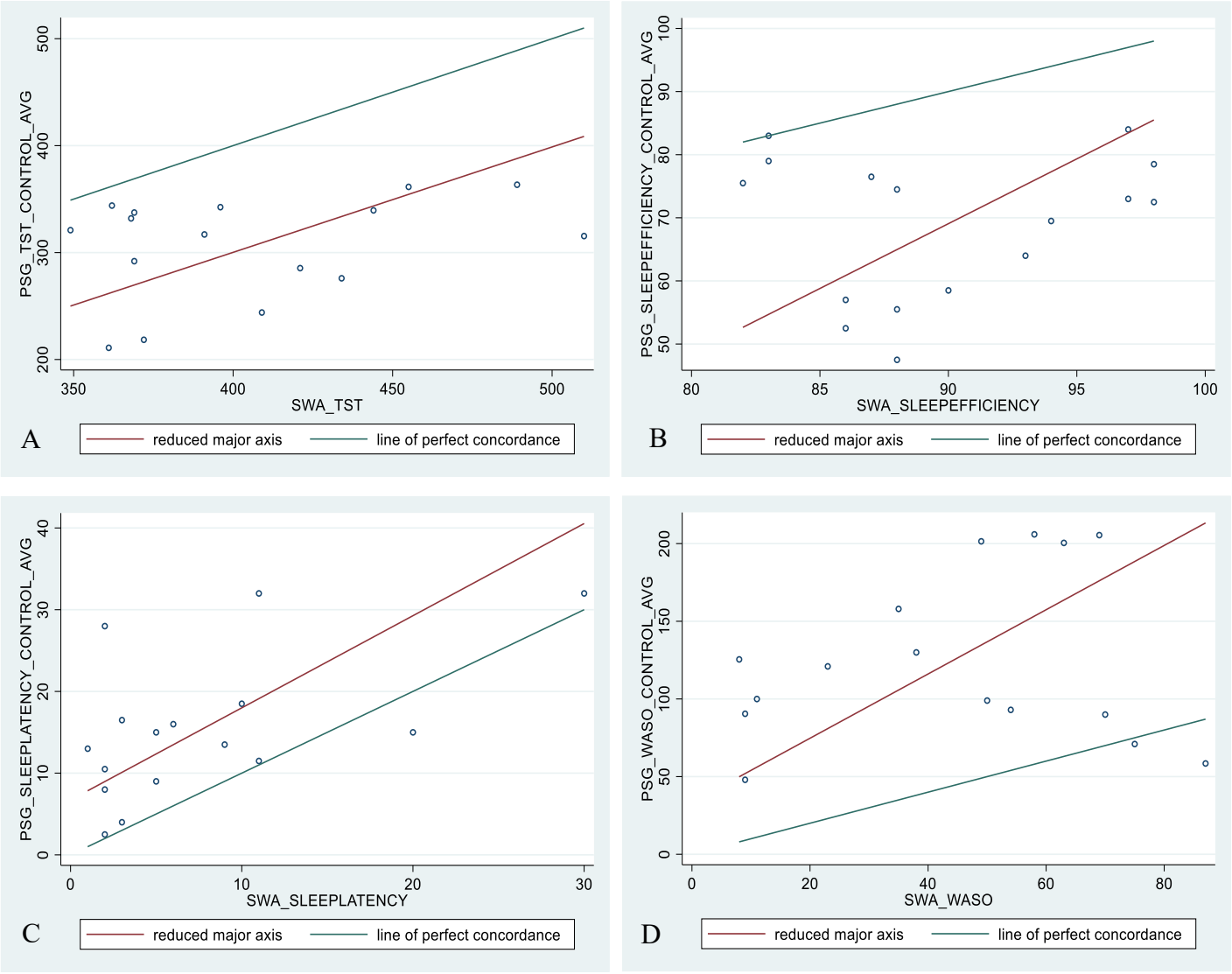

Figure S5.1: Reduced major axis regression plots for healthy controls polysomnographically scored total sleep time (A), sleep efficiency (B), wake after sleep onset (C), and sleep onset latency (D) versus Sensewear Armband scores.