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Greater Preference for Eveningness is Associated with Negative Symptoms in an Ultra-High Risk for Psychosis Sample

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Abstract

Aim

Investigating biological processes in at-risk individuals may help elucidate the aetiological mechanisms underlying psychosis development, refine prediction models and improve intervention strategies. This study examined the associations between sleep disturbances, chronotype, depressive and psychotic symptoms in individuals at ultra-high risk for psychosis.

Methods

A sample of 81 ultra-high risk patients completed clinical interviews and self-report assessments of chronotype and sleep during the Neurapro clinical trial. Mixed regression was used to investigate the cross-sectional associations between symptoms and sleep disturbances/chronotype.

Results

Sleep disturbances were significantly associated with increased depressive and attenuated positive psychotic symptoms. Greater preference for eveningness was significantly associated with increased negative symptoms, but not with depressive or attenuated positive psychotic symptoms.

Conclusion

Sleep disturbances and chronotype may impact the emerging psychopathology experienced by ultra-high risk individuals. Further, the preliminary relationship observed between greater preference for eveningness and negative symptoms offers a unique opportunity to treat negative symptoms through chronobiological approaches.

Keywords: chronotype; negative symptoms; psychosis; sleep; ultra-high risk

Introduction

Growing evidence links sleep and circadian disturbances with the onset and clinical course of psychiatric disorders (Harvey, 2009; Harvey, Murray, Chandler, & Soehner, 2011; Wulff, Gatti, Wettstein, & Foster, 2010). Further, it is now recognised that chronotype, which reflects an individual's circadian preference for daily activity and sleep-wake timings, influences mental health outcomes (Kivelä, Papadopoulos, & Antypa, 2018; Taylor & Hasler, 2018). Specifically, evening chronotypes with delayed sleep-wake schedules and a preference for activity later in the evening, experience increased risk of psychopathology compared to morning chronotypes with advanced sleep-wake schedules and a preference for activity earlier in the day (Kivelä et al., 2018; Taylor & Hasler, 2018). Emerging research suggests that this relationship exists in psychosis, with higher levels of eveningness observed in patients with schizophrenia (Fares et al., 2015; Hofstetter, Mayeda, Happel, & Lysaker, 2003; Mansour et al., 2005), and evening chronotypes endorsing worse psychotic symptom severity in clinical (Hofstetter et al., 2003) and non-clinical samples (Hsu, Gau, Shang, Chiu, & Lee, 2012).

Sleep and circadian disturbances are prevalent in schizophrenia, and are associated with increased psychotic symptomatology, relapse and neurocognitive deficits (Cohrs, 2008; Wulff, Dijk, Middleton, & Foster, 2012). However, less is known about the features and correlates of sleep and circadian abnormalities in the ultra-high risk for psychosis (UHR) population. Existing studies highlight poor sleep quality, delayed sleep timings and irregular sleep-wake cycles (Castro et al., 2015; Lunsford-Avery et al., 2017). Importantly, these characteristics longitudinally predict increased psychotic symptomatology in UHR youth,

implicating sleep and circadian disturbances in the pathogenesis of psychotic disorders (Lunsford-Avery et al., 2017; Lunsford-Avery, LeBourgeois, Gupta, & Mittal, 2015).

Given that a major barrier to improving preventative care is the limited knowledge of biological mechanisms underlying psychosis development (Yung, 2017), investigating sleep and chronotype in UHR individuals may help inform stronger prediction and intervention strategies. Thus, the current study aimed to examine the cross-sectional associations between subjective sleep disturbances, chronotype, positive and negative psychotic symptoms, as well as affective symptomatology in a sample of UHR individuals. It was hypothesised that individuals with (1) increased sleep disturbances and (2) greater preference for eveningness have higher psychotic and depressive symptoms.

Methods

Participants and Procedure

This study used data collected from a side study on sleep conducted during the Neurapro clinical trial (Markulev et al., 2015; McGorry et al., 2017). Individuals referred to treatment services were recruited from 10 international research sites with early psychosis centres. For inclusion, participants had to meet criteria for one of the UHR groups (attenuated psychotic symptoms, brief limited intermittent psychotic symptoms and/or trait vulnerability) and have a recent decrease in or sustained poor functioning. Exclusion criteria included the use of antipsychotic medications.

All participants provided written informed consent; for participants younger than 18 years, parental or guardian consent was obtained. Participants in the sleep study completed, in addition to a clinical interview, a sleep quality and chronotype assessment at baseline, 6 and 12 months. For detailed procedures of the main Neurapro trial, see Markulev et al. (2015) and McGorry et al. (2017).

Measures

Depressive symptoms. The Montgomery-Asberg Depression Rating Scale (MADRS) was used to assess depressive symptoms (Montgomery & Asberg, 1979). Total scores range from 0 to 60, with higher scores indicating more severe depression.

Attenuated positive psychotic symptoms. The Comprehensive Assessment of At Risk Mental States (CAARMS) was used to assess attenuated positive psychotic symptoms (Yung et al., 2005). Following Morrison et al. (2012), symptom severity was operationalised as the summed scores of the product of the global rating scale score (0-6) and the frequency (0-6) of each subscale from the positive symptom dimension: unusual thought content, non-bizarre ideas, perceptual abnormalities and disorganised speech. Scores range from 0 to 144, with higher scores indicating greater symptom severity.

Negative symptoms. The Scale for the Assessment of Negative Symptoms (SANS) was used to assess negative psychotic symptoms (Andreasen, 1982). Total scores range from 0 to 125, with higher scores indicating greater symptom severity.

Sleep disturbances. The Pittsburgh Sleep Quality Index (PSQI) was used to assess subjective sleep disturbances over the previous month (Buysse, Reynolds, Monk, Berman, & Kupfer, 1989). Global scores range from 0 to 21, with higher scores indicating poorer sleep quality.

Chronotype. The Morningness-Eveningness Questionnaire (MEQ) was used to assess preferences for sleep-wake and activity timings (Horne & Östberg, 1976). Total scores range from 0 to 86, with lower scores indicating greater preference for eveningness.

Statistical Analysis

Analyses were performed using IBM SPSS Version 23 (IBM Corp, 2015). Observations were clustered within participants. Therefore, linear mixed-effects models were used to analyse the cross-sectional associations between sleep, chronotype and symptomatology. Each mixed-effects model included a repeated subcommand for three time points, a random intercept for participant and an autocorrelated error covariance structure (AR1), with depressive symptoms, age and sex controlled for. The significance threshold was set at $p < .05$ for all analyses.

Results

Eighty-one UHR individuals consented to the Neurapro sleep study. Participant demographics, sleep disturbances, chronotype and symptomatology at baseline are presented in Table 1.

Sleep Disturbances and Symptomatology

The associations between sleep disturbances and symptomatology are shown in Table 2. PSQI global scores were significantly positively associated with depressive and attenuated positive psychotic symptoms. After controlling for depressive symptoms, PSQI global scores were significantly associated with depressive symptoms, but no longer significantly associated with negative symptoms.

Chronotype and Symptomatology

The associations between chronotype and symptomatology are shown in Table 3.

MEQ total scores were not significantly associated with depressive or attenuated positive psychotic symptoms. However, MEQ total scores were significantly associated with negative symptoms, with lower MEQ total scores (greater eveningness preference) associated with higher negative symptoms, even after depressive symptoms were controlled for.

Discussion

The current study examined the associations between subjective sleep disturbances, chronotype, affective and psychotic symptoms in a UHR sample. As hypothesised, sleep disturbances were associated with increased depressive and attenuated positive psychotic symptoms. However, sleep disturbances were not significantly associated with negative symptoms when depressive symptoms were controlled for, in contrast with a previous study linking self-reported sleep disturbances with negative symptoms (Lunsford-Avery et al., 2013). In partial support of the second hypothesis, greater preference for eveningness was associated specifically with negative symptoms. This association has not previously been described in the literature, although an actigraphy study has shown delayed sleep timings and circadian disruptions to predict psychotic symptom severity in UHR individuals (Lunsford-Avery et al., 2017).

It is possible that individuals with greater preference for eveningness have later sleep timings yet still rise early due to social constraints (e.g. school and work), thereby accumulating sleep debts (Adan et al., 2012). Sleep deficits in vulnerable youth may subsequently contribute to psychosis onset through adverse effects on cognition, neurodevelopment and endocrine function (Lunsford-Avery & Mittal, 2013).

Another plausible explanation is that the relationship observed between eveningness and negative symptoms may be related to altered reward processing. Firstly, dysregulated reward function has been identified as a potential mechanism underlying the increased

psychopathology experienced by evening chronotypes, as variations in the diurnal activity of reward-related neural regions and altered neural responses to reward are observed in individuals with evening preference (Hasler et al., 2012; Hasler, Sitnick, Shaw, & Forbes, 2013; Taylor & Hasler, 2018). Consistent with this, circadian clock genes contribute to the regulation of dopaminergic signalling in the mesocorticolimbic structures centrally involved in reward processing, indicating that the circadian system modulates neural reward pathways (Parekh & McClung, 2016; Webb, Lehman, & Coolen, 2015).

Secondly, negative symptoms in schizophrenia have been associated with abnormal reward function (Bergé et al., 2018; Gold et al., 2013; Gold et al., 2012). Converging evidence indicates that negative symptoms reflect impairments in reward representation and effort-cost calculations (Bergé et al., 2018; Gold et al., 2013; Gold et al., 2012). Based on the literature highlighting circadian-reward interactions and the current finding of an association between eveningness and negative symptoms, we speculate that circadian disturbances may partly underlie negative symptoms for some individuals with psychosis.

Limitations and Future Directions

While only a quarter of the participants from the main study opted to participate in the sleep side study, there were no significant differences between the groups in psychotic symptomatology, general psychopathology and functioning (see Table S1). However, participants in the sleep study had higher depressive symptoms and were younger, implying that the findings are limited in their generalisability to the larger UHR cohort and should be replicated in a more representative sample.

Another limitation is that cross-sectional analyses were used due to low power, making it difficult to derive the direction of the association between eveningness and negative symptoms. It may instead be the case that negative symptoms delay sleep-wake timings, leading to great eveningness preference in UHR individuals. Future research

employing a longitudinal statistical approach and biological measures of circadian rhythmicity would help clarify this relationship.

Low power also limited our ability to investigate specific sleep deficits and interactions between sleep and chronotype. Accordingly, it would be beneficial for larger studies to perform mediation and interaction analyses to further elucidate the mechanisms underlying the links between specific sleep problems, chronotype, symptomatology and cognition in psychosis.

Implications

Negative symptoms are often persistent, contribute significantly to functional impairment and are predictive of conversion to psychosis (Mason et al., 2004; Piskulic et al., 2012). Moreover, treatment options for negative symptoms remain limited, highlighting a critical therapeutic gap (Devoe, Peterson, & Addington, 2018). Therefore, the association observed between greater preference for eveningness and negative symptoms offers a unique opportunity to utilise chronobiological approaches such as bright light therapy, social rhythm therapy and chrono-pharmaceuticals to treat negative symptoms. These interventions aimed at advancing circadian rhythms in evening chronotypes may help ameliorate negative symptoms and improve sleep quality (Corruble et al., 2014; Hasler, Buysse, & Germain, 2016), which could consequently improve functional outcomes and conversion to psychosis.

Conclusion

This study provides preliminary support for a specific association between greater preference for eveningness and negative symptoms, as well as further evidence for sleep disturbance as a relevant factor during the onset of psychotic symptomatology in UHR individuals. Together, these findings contribute to the growing literature highlighting sleep

and circadian-based interventions as promising avenues for psychosis prevention and treatment.

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Conflict of Interest Statement

PDM reports receiving unrestricted research funding from AstraZeneca, Eli Lilly and Company, Janssen-Cilag, Pfizer, and Novartis, as well as honoraria for educational activities with AstraZeneca, Eli Lilly and Company, Janssen-Cilag, Pfizer, Bristol-Myers Squibb, Roche Holding AG, and the Lundbeck Institute. The other authors declare no potential conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available upon reasonable request from the authors. The data are not publicly available due to privacy or ethical restrictions.

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Tables

Table 1

Participant Demographics, Sleep Disturbances, Chronotype and Symptoms at Baseline

	Mean/Frequency	SD/%	Range
Male	31	38.27	-
Age	17.74	3.11	15 - 29
Years of Education	9.84	3.43	2 - 18
MADRS	22.78	9.23	2 - 39
APS	38.53	16.85	0 - 80
SANS	7.05	3.47	0 - 15
PSQI Global	10.20	3.82	2 - 18
MEQ Total	47.30	3.92	38 - 56

Abbreviations: APS, Attenuated Psychotic Symptoms based on the Comprehensive Assessment of At-Risk Mental States; MADRS, Montgomery-Asberg Depression Rating Scale; MEQ, Morningness-Eveningness Questionnaire; PSQI, Pittsburgh Sleep Quality Index; SANS, Scale for the Assessment of Negative Symptoms.

Table 2

Linear Mixed-Effects Model Analyses for Associations between Sleep Disturbances (PSQI Global) and Symptoms

	B	Std. Error	*t*	*95% CI*	*p*
Depressive Symptoms (n=238/N=74)					
PSQI Global	**.84**	**.14**	**6.07**	**0.56, 1.11**	**<.001**
Age	.03	.26	.11	-0.48, 0.54	.91
Sex	-1.95	1.72	-1.13	-5.39, 1.50	.26
Attenuated Positive Psychotic Symptoms (n=239/N=73)					
PSQI Global	**.87**	**.28**	**3.10**	**0.32, 1.42**	**.002**
MADRS	.71	.12	5.90	0.48, 0.95	<.001
Age	-.42	.43	-.99	-1.28, 0.43	.33
Sex	-2.13	2.95	-.72	-8.02, 3.76	.47
Negative Symptoms (n=238/N=74)					
PSQI Global	**-.002**	**.04**	**-.05**	**-0.09, 0.08**	**.96**
MADRS	.22	.02	11.38	0.19, 0.26	<.001
Age	-.18	.09	-1.99	-0.35, 0.001	.05
Sex	1.49	.59	2.50	0.30, 2.67	.02

Abbreviations: MADRS, Montgomery-Asberg Depression Rating Scale; n, number of observations; N, number of participants; PSQI, Pittsburgh Sleep Quality Index.
Note. Participant and observation numbers vary across the analyses due to missing data.

Table 3

Linear Mixed-Effects Model Analyses for Associations between Chronotype (MEQ Total) and Symptoms

	B	Std. Error	*t*	*95% CI*	*p*
Depressive Symptoms (n=113/N=63)					
MEQ Total	**-.13**	**.24**	**-.55**	**-0.62, 0.35**	**.59**
Age	-.02	.37	-.07	-0.76, 0.71	.95
Sex	-1.71	2.54	-.67	-6.78, 3.37	.50
Attenuated Positive Psychotic Symptoms (n=113/N=63)					
MEQ Total	**-.53**	**.41**	**-1.29**	**-1.35, 0.29**	**.20**
MADRS	.89	.16	5.50	0.57, 1.21	<.001
Age	.03	.61	.05	-1.19, 1.25	.96
Sex	-.44	4.26	-.10	-8.96, 8.08	.92
Negative Symptoms (n=113/N=63)					
MEQ Total	**-.15**	**.06**	**-2.36**	**-0.27, -0.02**	**.02**
MADRS	.20	.02	8.03	0.15, 0.25	<.001
Age	-.22	.10	-2.10	-0.42, -0.01	.04
Sex	1.24	.71	1.75	-0.18, 2.66	.09

Abbreviations: MADRS, Montgomery-Asberg Depression Rating Scale; MEQ, Morningness-Eveningness Questionnaire; n, number of observations; N, number of participants.
Note. Participant and observation numbers vary across the analyses due to missing data.