A longitudinal high-resolution exploration into the relationship between sleep disruption and 'in vivo' psychotic symptoms, paranoia, and dissociation in early phase psychosis.

DClinPsy Thesis (Volume 1)

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Thesis declaration form

I confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

Signature: 

Name: Jan Cosgrave

Date: 12.6.21

Overview of the thesis

More than a century of research highlights the omnipresence of sleep and circadian rhythm disruption in psychosis. While earlier understandings focused more on this being a consequence or 'side effect' of psychosis, emergent research has highlighted the potential for a causal pathophysiological link. Clarifying this relationship could pave the way for more targeted treatment programs in early phase psychosis.

This thesis opens with a comprehensive overview of the literature surrounding sleep, circadian rhythms, and psychosis to date (Part 1). This overview closes by highlighting that the nature of the relationship (i.e. which specific psychotic experiences (PE) and sleep or circadian parameters are related), directionality of the relationship and whether there is convincing evidence to infer causality remains unclear. Experimental and clinical studies in both clinical and analogue populations have provided mixed results. This highlights the need for more mechanism-driven research targeting specific experiences within psychosis.

An empirical study follows in Part 2. This study uses experience sampling method in tandem with actigraphy which permits high resolution sampling of daily "in vivo" psychotic experiences with nightly subjective and objective sleep metrics. This is study was designed to address some of the caveats described in Part 1 and takes a mechanism-driven approach to exploring whether nightly sleep or circadian rhythmicity is predictive of next day hallucinations, dissociation, and paranoia in early phase psychosis.

In Part 3, this thesis closes with a critical reflection of the work and what I as a researcher have learned through the process of this study and will take forward into both my clinical and academic career.

Impact Statement

Technological advances have provided widespread opportunities in field of research and practice of clinical psychology alike. It is now possible to remotely monitor the "in-vivo" daily life experiences of a service user's mental health and wellbeing. This allows for a more ecologically valid insight into the difficulties of mental health without the complications of retrospective memory bias and recall. Remote worn technology has now also been further developed to include other biometrics of the patient's lived experience (outside of just reporting their symptoms), allowing for greater insight into the body-mind connection. The work described here details the collection of actigraphy (accelerometery) alongside in-vivo monitoring of the patient's symptoms of early phase psychosis. The actigraphy is used to provide an objective metric of the patient's sleep-wake cycle longitudinally (in this case two weeks). This gives a platform to relate the two phenomena using high resolution data. This allows us to address whether night-time sleep is related to daytime psychotic experiences, and to explore the nature of this relationship using 24-hour sampling of both sleep and psychotic experiences.

The long-term goal of this work is to contribute to the foundations of personalised medicine for people with psychosis. Complexity, comorbidities and heterogeneity are common within mental health treatment, which often makes targeted treatment approaches difficult. However, undergoing high resolution mechanism driven research in serious mental illness may help inform how we can best understand how two phenomena relate to one another, which in turn can inform the understanding of causal relationships. For example, it is not anticipated that poor sleep or circadian arrhythmicity would unilaterally impact all symptoms of psychosis. It is also known that the symptomatic profile of psychosis is notoriously heterogeneous from one individual to the next. Thus, if a patient has a specific symptomatic profile (for example, in their experience of psychosis, they present with a lot of dissociative experiences), and we knew that sleep disruption provokes the onset of dissociative experiences in early psychosis, we would be able to make informed decisions about what targeted sleep interventions a patient with that symptomatic profile would benefit from. This allows for the building of complementary treatments programs to target specific symptoms of the patient's experience as opposed to assuming that a general treatment will suit all people with psychosis (a practice that is commonly employed clinically but has a limited evidence base to support its efficacy).

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Acknowledgments

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I would like to close by dedicating this thesis to my partner Ross whose unwavering support and confidence in my abilities throughout my research and clinical career has provided the backbone needed to survive both my PhD and the DClinPsy. Without him none of this would be possible. Thank you, Ross.

Part 1 - Conceptual Introduction

Sleep and Circadian Rhythmicity in Psychosis: 'Side Effect' or Pathophysiological Mechanism?

This chapter was published in an adapted form as:

Cosgrave, J., Klingaman, E. A., & Gehrman, P. (2020). Chapter 11 - Effectively Assessing Sleep and Circadian Rhythms in Psychosis BT - A Clinical Introduction to Psychosis. In J. C. Badcock & G. Paulik (Eds.), *A Clinical Introduction to Psychosis* (pp. 245–272). Academic Press. http://www.sciencedirect.com/science/article/pii/B9780128150122000110

I have appended this to the end of the thesis (Appendix 2).

Abstract

More than a century of research highlights the omnipresence of sleep and circadian rhythm disruption in psychosis. While earlier understandings focused more on this being a consequence or 'side effect' of psychosis, emergent research has highlighted the potential for a causal pathophysiological link. Clarifying this relationship could pave the way for more targeted treatment programs in early phase psychosis. However, current clinical treatment and experimental studies provide mixed results.

This conceptual review will introduce psychosis as a concept; provide an overview into understanding the mechanics behind sleep and circadian rhythmicity; explore what sleep and circadian rhythm disruption (SCRD) is; and finally provide a critical appraisal of the current literature into the relationship between sleep, circadian rhythms, and psychosis. The review will close with some considerations for future research which provide the backbone of the research study considered in Part 2.

Guiding principles for this conceptual review

This conceptual review is designed to provide the reader with the core concepts relating to three fields of research: sleep, circadian rhythms, and psychosis. The review starts by guiding the reader through what psychosis is and the impact it has on society (**Section 1.1**). This is then followed by the basic principles of sleep, the two-process model, the biological clock and how sleep and circadian rhythmicity is measured in empirical research (**Section 1.2**). This moves the reader onto the third part of this review which explores the wide-ranging impact of impact of sleep and circadian rhythm disruption (SCRD) on mental health (**Section 1.3**), before focusing on its relationship to psychosis (**Section 1.4**). The review closes with some final thoughts on where the gaps are in the current body of literature and what further research could be done to explore the presence of a causal link.

Section 1.1 **Psychosis and its impact to society**

Psychosis describes a loss of contact with reality, usually characterised by false beliefs about what is taking place and who one is (delusions), and by seeing or hearing things that aren't there (hallucinations). The structure of psychosis highlights four different domains: paranoia, grandiosity, hallucinations and thought disorder (Allardyce et al., 2007). Accumulatively, these are referred to as 'positive symptoms', as they are experienced as an addition to everyday life. However, psychosis also includes 'negative symptoms', which present as a wide variety of cognitive and language deficits, and have been shown to manifest before the onset of the illness (Bora & Murray, 2014).

The experience of psychosis can be transient (e.g. substance abuse); characterise the onset of a clinical illness; or exist as a chronic feature of serious psychiatric illnesses (the most well-known of which is schizophrenia - please refer to **Box 1** for the current Diagnostic and Statistical Manual of Mental Disorders 5 criteria (DSM-5; Association Psychiatric Association, 2013). The estimated lifetime prevalence of psychotic disorders varies, with schizophrenia (0.87%) the most common. Other psychotic disorders include major depressive disorder with psychotic features (0.35%), schizoaffective disorder (0.32%), bipolar disorder (0.24%), delusional disorder (0.18%) and schizophreniform disorder (0.07%). Psychosis can also be induced through substance abuse (0.42%) and specific types of general medication (0.21%). The overall lifetime prevalence of all psychotic disorders is estimated to be 3.48% (Perälä et al., 2007). Despite this seemingly low prevalence, the health, social and economic burden of psychotic disorders has been tremendous not only for patients, but also for families, caregivers, and wider society (Chong et al., 2016). The annual cost of these disorders is currently estimated at £14 billion in the UK alone, making psychosis the third most expensive brain condition in the UK (after dementia and mood disorders; Fineberg et al., 2013).

To reduce the liability of these disorders on people and society as-a-whole, a better understanding of what causes psychosis is needed, and in turn, of how best to treat it early on in its course. This has led to the development of Early Intervention Services for psychosis (EIS)

across the UK. Research has supported the development of these services, as intervention during the early phases of psychosis can produce long-term improvements for patient outcomes for up to 10 years later (ten Velden Hegelstad et al., 2012).

Box 1: Schizophrenia DSM 5 – Criteria

Criterion A. *Characteristic Symptoms*: Two (or more) of the following, each present for a significant portion of time during a one-month period (or less if successfully treated). At least one of these should include (1)-(3):
(1) Delusions
(2) Hallucinations
(3) Disorganized speech
(4) Grossly disorganized or catatonic behaviour
(5) Negative symptoms (i.e., diminished emotional expression or avolition)

Criterion B. *Social/occupational dysfunction:* For a significant portion of the time since the onset of the disturbance, one or more major areas of functioning, such as work, interpersonal relations, or self-care, are markedly below the level achieved prior to the onset (or when the onset is in childhood or adolescence, failure to achieve expected level of interpersonal, academic, or occupational achievement).

Criterion C. *Duration of 6 months.* This six-month period must include at least one month of symptoms (or less if successfully treated) that meet Criterion A (i.e., active-phase symptoms) and may include periods of prodromal or residual symptoms. During these prodromal or residual periods, the signs of the disturbance may be manifested by only negative symptoms or by two or more symptoms listed in Criterion A present in an attenuated form (e.g., odd beliefs, unusual perceptual experiences).

Criterion D. *Schizoaffective and major mood disorder exclusion.* Schizoaffective disorder and depressive or bipolar disorder with psychotic features have been ruled out because either (1) no major depressive or manic episodes have occurred concurrently with the active phase symptoms; or (2) if mood episodes have occurred during active-phase symptoms, their total duration has been brief relative to the duration of the active and residual periods.

Criterion E. *Substance/general medical condition exclusion:* The disturbance is not attributed to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or another medical condition.

Criterion F. *Relationship to Global Developmental Delay or Autism Spectrum Disorder:* If there is a history of autism spectrum disorder or other communication disorder of childhood onset, the additional diagnosis of schizophrenia is made only if prominent delusions or hallucinations are also present for at least one month (or less if successfully treated).

Section 1.2 **Understanding Sleep**

Sleep is a neurobiological necessity and is important for many bodily functions, including mood regulation, emotional processing, learning and memory (Walker, 2009). It is a complex, multifaceted behaviour which is the end-product of an interaction between several neural circuits, neurotransmitters, and hormones; none of which are exclusive to sleep's production (Foster et al., 2013).

1.2.1: The Two Process Model

Sleep regulation is governed by two independent (but interrelated) processes: a homeostatic mechanism which is determined by accumulative sleep debt (Process S), and the circadian system that coordinates sleep initiation during the biological night and wakefulness in morning independently of sleep-wake behaviours (Process C). This is known as the Two Process Model of Sleep Regulation and was first championed by Borbély in 1982 (Borbély, 1982). A schematic representation of the Two Process Model is displayed in **Figure 1.1**.

The term "circadian" refers to an endogenous rhythmic biological process that repeats itself approximately every 24 hours, even in the absence of external time cues. The word originates from the Latin "circa diem" or "about a day". The circadian process (Process C) in the Two Process Model represents the temporal configuration, which governs regulatory mechanisms for us to be able to facilitate adaptive behaviours, including feeding, reproduction, and sleep-wake cycles. These precisely coordinated temporal patterns are self-regulating and oscillate with a period of around 24 hours (Crowley et al., 2007). The 'period' of the rhythm refers to the time needed to complete one full oscillation (Grandin et al., 2006). These rhythms originate from the suprachiasmatic nucleus (SCN), which is more commonly known as the 'biological' or 'master' clock and is found in the anterior hypothalamus.

Process S is understood to be reasonably autonomous from circadian timing. Put simply, Process S can be described as sleep pressure increasing as a function of time awake. The

pressure dissipates as one sleeps and restarts the following morning upon wakefulness (Crowley et al., 2007).

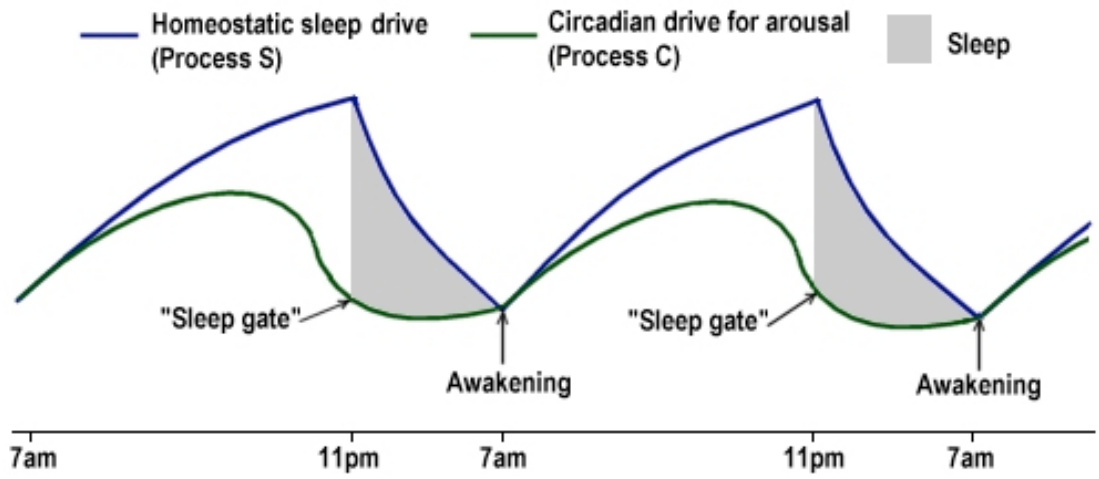

Figure 1.1: A schematic representation of the Two-Process Model of Sleep Regulation (adapted from Daan et al., 1984) The blue line represents Process S or the sleep drive. Sleep pressure is low upon awakening and progressively increases as a function of time awake throughout the day, peaking around bedtime (in this diagram 11pm) and then dissipating during sleep. Process C (the green line) coordinates the timing of sleep and wake. When sleep pressure peaks, Process C initiates sleep; when sleep pressure falls, Process C initiates wake.

1.2.2: The Suprachiasmatic Nucleus

The SCN consists of bilateral nuclei that contain approximately 10,000 neurons each and receives photic information collected by photoreceptor cells in the retina via the retinohypothalamic tract (RHT; Takahashi et al., 2008). The retina is comprised not only of rods and cones but also intrinsically photosensitive retinal ganglion cells (ipRGCs) which possess a photopigment called 'melanopsin', rendering them particularly sensitive to short wavelength blue light. Although rods and cones themselves are thought to also be involved in the communication made to the SCN, the ipRGCs are sufficient, as animals who are visually blind are still able to entrain to the light-dark cycle (Freedman et al., 1999). Thus, light perceived in the retina acts as a neural signal to the SCN and is transmitted via the RHT (**Figure 1.2**). While it is impossible in humans to directly measure the output of the SCN, a measurement by proxy can be obtained via the 24-hour rhythms of physiological processes the SCN governs, including core body temperature, melatonin, and cortisol synthesis.

The term "free running" refers to the SCN's rhythmicity in the absence of external time cues (Box 2). However, most individuals are considered 'entrained' to external cues or "zeitgebers". Light is our most potent zeitgeber, but several nonphotic zeitgebers can also influence the rhythmic signals from the SCN, including mealtimes, clocks, and exercise. A notable downstream projection of the SCN is the pineal gland, which is responsible for melatonin synthesis.

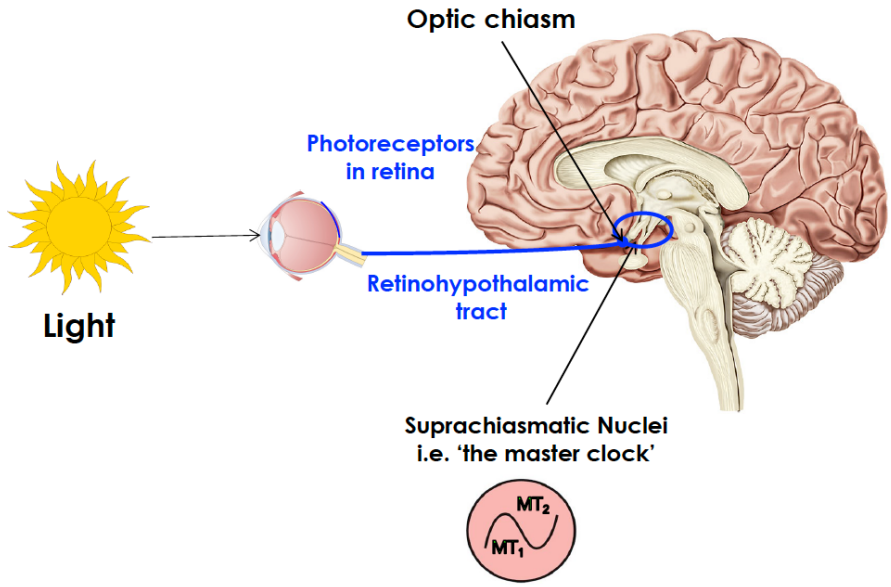

Figure 1.2: How light entrains the biological clock (taken from Cosgrave et al., 2020)

Box 2: Rhythmicity in the Suprachiasmatic Nucleus (SCN)
The term "*free running*" refers to the SCN's rhythmicity in the absence of external time cues. It usually presents as a progressive delay in sleep resulting in someone going "around the clock" i.e. at some points they are going to bed during the day and waking up at night. However, the vast majority of people are considered "entrained" to external cues or "zeitgebers". Light is our most potent zeitgeber, but several nonphotic zeitgebers can also influence the rhythmic signals from the SCN, including mealtimes, clocks and exercise. People tend to be just slightly over 24 hours which is why "free running" most often manifests as progressively delaying the clock each day.

1.2.3: Individual Differences in Circadian Timing

There is evidence to suggest that the period of the biological clock may be subject to interindividual variability. Under laboratory conditions, the clock period has been found to range from 23.89-24.40 hours (Wright et al., 2001). Subtle changes in the period length can give

rise to substantial differences in behaviour, particularly in the timing of the sleep-wake cycle. These differences allow us to discern between individuals who may identify as early ("larks"), late ("owls") and intermediate types. The global term for such categorisations is "chronotype" (Roenneberg et al., 2007).

The self-reported preferred timing of sleep-wake rhythm is one of the most frequently used markers of chronotype (Roenneberg et al., 2007). The misalignment between the endogenous internal timing of the clock (that gives rise to chronotype/preferred sleep timing) and external timing (e.g. shift working patterns, socialising) is thought to impact a number of different variables, including mood and cognitive performance (Biss & Hasher, 2012). Chronotype itself is impacted by a number of different demographic variables, including age, gender and genetic profile (Clarisse et al., 2010). Several genetic polymorphisms are also associated with different chronotypes (Archer et al., 2010), as are different psychiatric disorders (Wulff et al., 2010).

1.2.4: The Architecture of Sleep

The process of sleep itself is both structured and rhythmic. It can be categorised into two genres: rapid-eye movement (REM) sleep, and non-rapid eye movement (NREM) sleep. How humans fluctuate between NREM and REM is under circadian control (Cosgrave et al., 2020; Cosgrave, et al., 2021a). NREM sleep is further divided into four stages based on electroencephalographic (EEG) changes. Typically, NREM and REM sleep occur in alternating cycles, each normally lasting between 90 - 120 minutes. Generally, a healthy young adult should spend approximately 70-90% of their total sleep time (approximately 5-10 hours) in NREM stages; stage 1 accounting for 3-5% of total sleep time, stage 2 for 50-60% and stages 3 and 4 combined for 10-20% (Benbadis, 2006). REM sleep is characterised by rapid eye movements and temporary motor paralysis (Hobson, 2009). It is also considered the most active wake-like sleep stage. Conversely, slow wave sleep (SWS; stages 3 and 4) is considered to be the deepest and most restorative sleep stage, and shows the strongest relationship to how we report subjective sleep quality (Åkerstedt et al., 1997).

Slow wave sleep and slow wave activity (SWA, power in the 0.75 – 4.5 Hz) are considered a physiological hallmark of homeostatic sleep pressure. As such, SWA is high during the first half of the sleep period when sleep pressure is at its peak, and then declines exponentially across the repeated episodes of non-rapid eye movement (NREM) sleep (Crowley et al., 2007). Please refer to **Figure 1.3** below for an overview of sleep architecture.

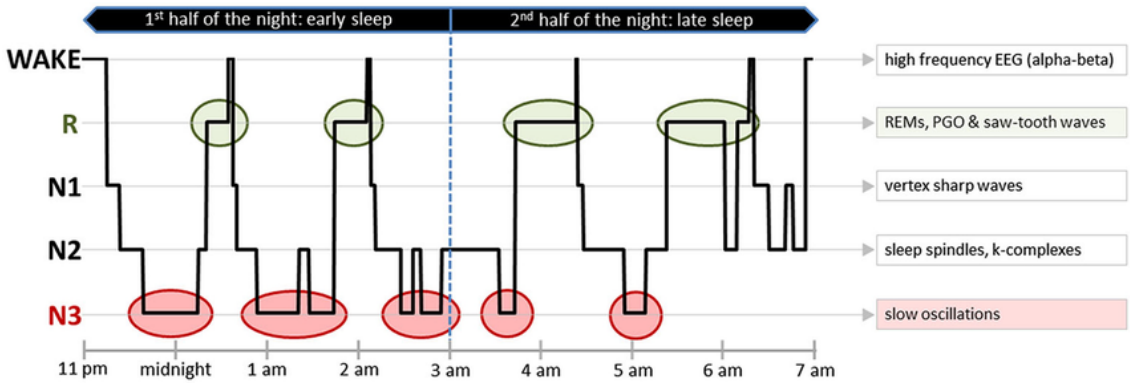

Figure 1.3: A sleep hypnogram depicting a healthy night of sleep across an 8-hour period. The left-hand side of the figure indicates sleep stage and the right-hand side refers to the characteristics found within the EEG signal used to score the sleep stage. Early sleep is predominately characterised by Stage 3 (N3), in contrast to late sleep in the second half of the night that shows greater attachment to REM (R). During wake, high muscle tone and high frequency EEG is observed. Stage 1 (N1), which has slow eye movements (SEM) and vertex sharp waves, follows this. Stage 2 (N2) is denoted by the presence of spindles and K-complexes, and is followed by Stage 3 (N3) upon the presence of six seconds of slow (delta) waves. REM has rapid eye movements as well as Ponto-Geniculo-Occipital Waves (PGO), saw-tooth waves and muscle atonia with co-occurring muscular twitches. Taken from Blume et al., (2015).

1.2.5: The Measurement of Sleep: Actigraphy and Electroencephalography

Polysomnography (PSG) is considered the 'gold standard' of sleep measurement as it is the only approved technology to accurately provide architectural information (sleep stages, depth of sleep, presence of other physiological metrics such as spindles and frequencies; Ancoli-Israel et al., 2003). While classified non-invasive, it involves mounting several electrodes to the participant's scalp, the number and placement of which depends upon the montage used. Set up times, whether it can be ambulatory or done only in lab and the quantity of electrodes required all depend on the PSG density required. This is both laborious and costly. It also only provides detailed information on a 24 to 48 hour period (Ancoli-Israel et al., 2003).

Actigraphy is a non-invasive method of monitoring rest-activity cycles across the entire 24 hour cycle under at home or free-living conditions over several days or weeks (Meyer et al., 2020). This permits the concurrent measurement of sleep and circadian variables and provides the longitudinal information necessary to inform the patterns detailed in **Figure 1.4**. Usually, it's a wrist-worn device that measures wrist movement over several days or weeks. These devices are often fitted with light sensors which provide additional information about the duration and timing of light exposure throughout the day (Cosgrave et al., 2020; Wee et al., 2019).

Actigraphy is considerably more cost-effective, less laborious for both the participant and the research team than PSG and can be used longitudinally but comes at the sacrifice of being a proxy measure for sleep variables. It is used to calculate a number of sleep metrics including sleep onset, sleep offset, sleep period (time between sleep onset and sleep offset, including any wake), sleep fragmentation (an index derived from the frequency and intensity of physical movement during the sleep period), sleep onset latency (SOL; the amount of time between bedtime and sleep onset), wake after sleep onset (WASO; the amount of time spent above a predefined activity threshold), total sleep time (TST; time between sleep onset and final wake time, excluding WASO) and sleep efficiency (% of time in bed spent asleep excluding sleep onset latency). These are proxy measurements based on algorithms developed to compare PSG to actigraphy. Often the actigraphy data are examined in conjunction with the sleep diary to gain a more comprehensive picture of the sleep-wake cycle (Cosgrave et al., 2017, Cosgrave et al., 2020).

More recently, actigraphy has also been used to understand circadian parameters including autocorrelation (measure of rhythm fragmentation), interdaily stability (measure of synchrony between circadian rhythms with the light/dark cycle), intradaily variability (mean of the first derivative of the actigraphy data normalized by the total variance; a measure of rest–activity rhythm fragmentation) and relative amplitude (the relationship between diurnal amplitude and night amplitude; the maximum value of 1 occurs when there is no movement during the night; Castro et al., 2015; McGowan et al., 2019).

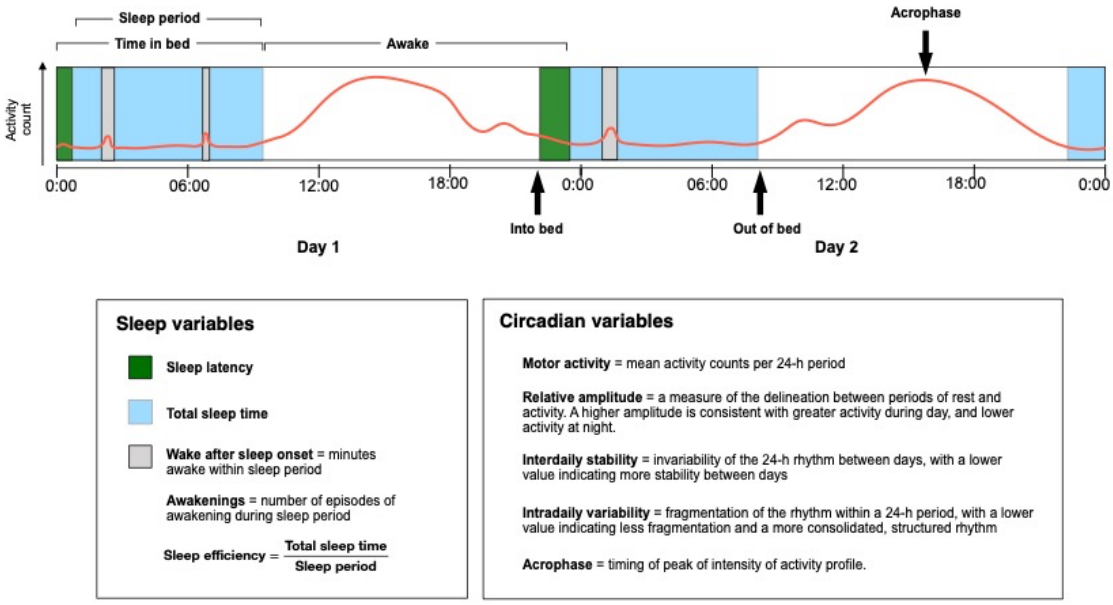

Figure 1.4: Summary of the sleep and circadian rhythm variables provided by actigraphy. Actigraphy measures motor activity using a body-worn accelerometer. Sleep and wake epochs are estimated based on the activity count below and above an algorithmic determined threshold. Sleep diaries are used to help inform how the program calculates this. Taken from Meyer et al., (2020).

1.2.6: Sleep and Circadian Rhythm Disruption

The intricacy of the sleep-wake system makes it vulnerable to disruption, particularly as behaviorally these disruptions can occur as a normal part of everyday life. Sleep and circadian rhythm disruption refers to perturbations placed upon both Process C and Process S. Social timing, as an example, impacts both the availability and duration of sleep (Foster et al., 2013).

The use of alarm clocks to meet work obligations, drinking caffeine to compensate for a truncated sleep period, and then in turn using sleep-promoting medication in the evening to correct for the stimulants taken during the day can easily become a habitual cycle. To consecutively repeat this vicious cycle often means we need to compensate on the weekends by having a 'lie in' in the mornings (Cosgrave et al., 2020; Foster et al., 2013).

This constant misalignment (referred to as 'social jet lag') is one of many ways we can compromise the sleep-wake regulatory systems and experience sleep and circadian rhythm disruption (SCRD; Cosgrave et al., 2020; Foster et al., 2013; Roenneberg et al., 2003).

However, sleep and circadian rhythm disruption also encompasses much further-reaching sleep complaints than those mentioned above. These include more extreme forms of circadian misalignment, such as advanced/delayed cycles, bidian cycles (having a cycle length of 50 hours), non-24 hour cycle lengths, highly irregular and fragmented sleep patterns, hyposomnia or insomnia complaints (see below), shift work disorders and parasomnias (nightmares, sleep paralysis, sleep hallucinations, etc.; Koffel & Watson, 2009) Please refer to **Figure 1.5** for a schematic overview of different sleep patterns.

As such, it is perhaps unsurprising that perturbations to the sleep-wake system can have extensive ramifications on physical and mental health (please refer to **Figure 1.5** for an overview).

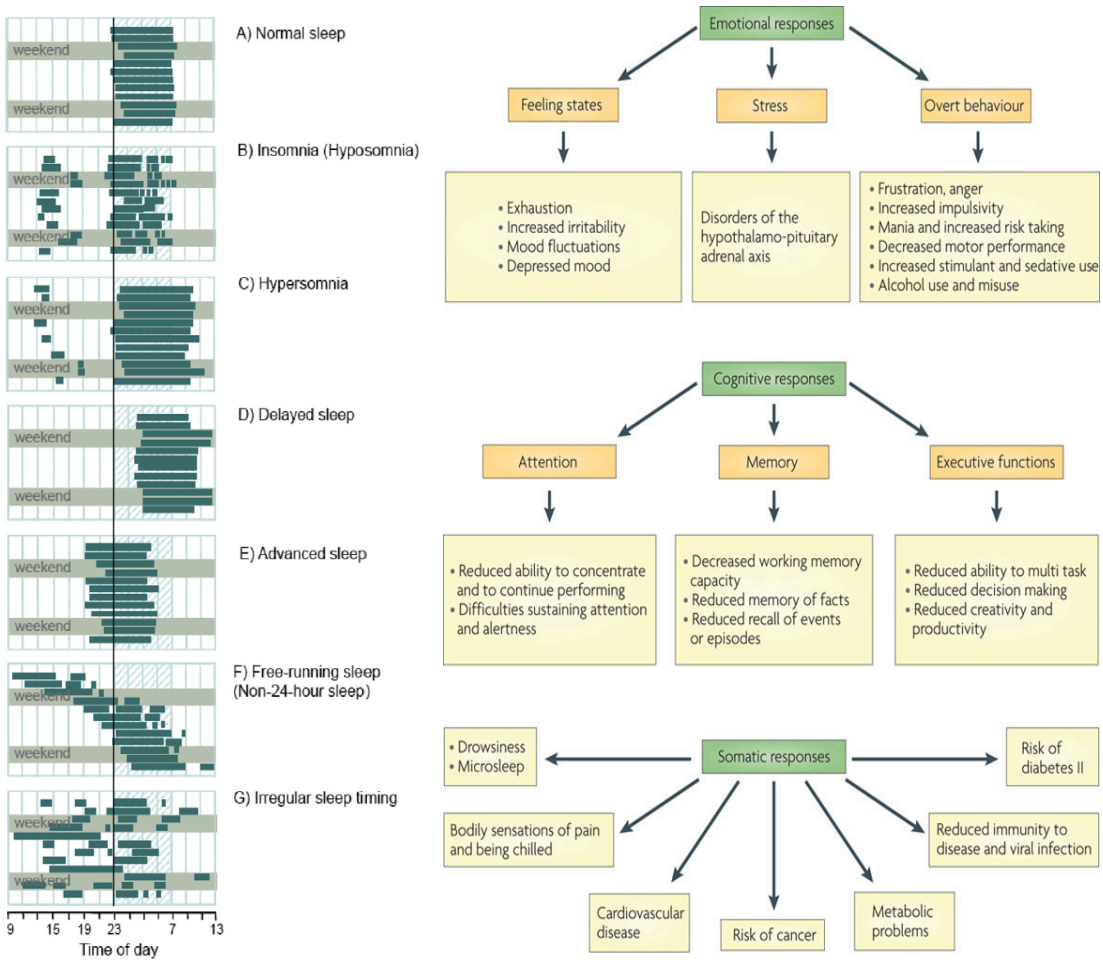

Figure 1.5: On the left-hand side, normal sleep (A) is compared to abnormal sleep patterns (B-G). For a sleep patterning or phenotype to be classified as abnormal, it must be such that the individual reports it as distressing and impactful upon their wellbeing/ability to go about daily obligations. Individuals with insomnia (or hyposomnia) have reduced sleep, as opposed to those with hypersomnia who show excessive sleep. Some SCRD phenotypes can be thought of as pathological extremes of morning or evening chronotypes (e.g. delayed (D), advanced (E) and non-24h-h (or free-running; F) sleep phase types. Irregular sleep-wake cycles (G) lack any kind of clear temporal structure; this is different from insomnia (B), as insomnia is typified by the repeated disruption of nocturnal sleep with excessive daytime sleepiness. Irregular sleep, hyposomnia and hypersomnia are thought to arise from a complex interaction between Processes C and S whereas advanced and delayed cycles primarily arise from Process C related problems. However, all the above phenotypes are fall under the umbrella of SCRD. Taken and adapted from Wulff et al., (2009). On the right-hand side, the ramifications of reduced sleep duration and circadian desynchrony (SCRD) on emotional, cognitive and somatic responses are displayed (taken from Wulff et al., 2010).

Section 1.3 **SCRD and Mental Health**

Emil Kraepelin, one of modern psychiatry's core founders, first documented the relationship between abnormal sleep patterns and mental health in his first textbook in 1883. Previously, recognition of sleep and circadian rhythm disruption (SCRD) in psychiatric disease was limited to the context of secondary factors such as side-effects of medication (Wirz-Justice et al., 2001), abnormal light exposure (Wirz-Justice, 2006), abnormal social timing (Grandin et al., 2006) and pain (Smith et al., 2000; **Figure 1.6**). However, the identification of common mechanistic pathways (including hypothalamic pituitary axis dysregulation; autonomic nervous system dysfunction; overlapping genetic risk & emotional dysregulation) between SCRD and psychiatric disease has led researchers to question whether SCRD could be more causally implemented in mental health problems (Wulff et al., 2010). This evidence has important implications for how we conceptualise and assess SCRD in the context of serious mental illness.

As research into SCRD in mental health has become more prolific, several accounts of SCRD have been cited as comorbidities in a host of psychiatric disorders (**Table 1.1**). Changes in sleep behaviour are now listed as key diagnostic criteria for a number of affective disorders (including seasonal affective disorder, major depressive disorder, bipolar disorder) and are considered a transdiagnostic factor for the development and maintenance of psychiatric disease (Harvey et al., 2011; Wulff et al., 2010). The mechanisms which regulate these relationships are poorly understood. Candidate mechanisms suggested to mediate the relationship between sleep and mental health include (1) association between sleep and emotional disruption, (2) the stress axis (both autonomic and endocrine responses; **Figure 1.6**), and (3) associations between circadian genes and psychiatric disorders. A schematic diagram of this relationship is displayed in **Figure 1.6**. There are numerous additional candidate mechanisms, including social isolation, cognitive deficits, medical health problems, and side effects of medication. All these additional candidate mechanisms contribute to alterations in both psychiatric disease and SCRD. A detailed review of these mechanisms is outside the remit of this review but Wulff et al., (2010) provides a comprehensive overview.

It is important to recognise that while certain psychiatric disorders have stronger associations with specific sleep phenotypes (e.g. post-traumatic stress disorder with fragmented sleep, daytime naps, and hyposomnia – too little sleep), schizophrenia is associated with all of the listed sleep phenotypes.

Psychiatric Disorder	Abnormal sleep/circadian phenotype comorbid with disease	Genetic Associations that may give rise to the SCRD observed
Seasonal Affective Disorder	Hypersomnia in winter Sensitive to bright light therapy	PER2 PER3 BMAL1
Bipolar Disorder (depression)	Hypersomnia and low day-time activity Advanced sleep-wake timing	PER3 BMAL1
Autism	Bedtime resistance, fragmented / disrupted sleep and circadian rhythms Delayed sleep/wake timing Reduced REM onset	PER1
Alcoholism	Insomnia Delayed sleep onset Decreased SWS Decreased REM latency Decreased sleep duration Sleep disturbances promote relapse	PER2
Schizophrenia	SWS deficit Decreased REM latency Defective REM rebound Abnormal circadian sleep/wake cycles (irregular, delayed, free running)	PER1 PER3

Table 1.1: Relationships between clock genes and psychiatric disorders. Adapted from Wulff et al., (2010).

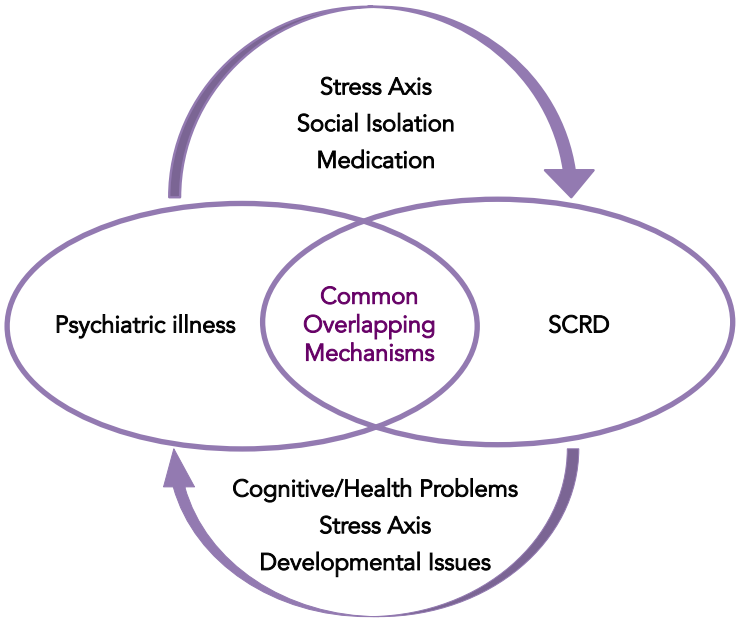

Figure 1.6: Schematic diagram illustrating possible relationships between psychiatric illness and sleep and circadian rhythm disruption (SCRD). It is thought that SCRD and psychiatric illness share common overlapping mechanisms. Atypical functioning of neural circuitry (acting upon several neurotransmitter systems) that renders someone vulnerable to psychiatric illness will have a parallel effect on the sleep and circadian systems. Similarly, disruption of sleep-wake regulation acts upon neural functioning (e.g. the stress axis), which consequently exacerbates or indeed creates a number of health problems (detailed in **Figure 1.5**) and may impact development in younger cohorts. Adapted from Foster et al., (2013).

Section 1.4 **Sleep, Circadian Rhythms and Psychosis**

Up to this point, we have discussed the different processes with sleep (Process S, staging, architecture) and circadian rhythms (Process C, the suprachiasmatic nucleus, CLOCK genes, social jet lag and more profound disruption such as free running) and explored how the complexity of these two systems makes them vulnerable to disruption. We have also explored how disruption to these processes may be integral to the development and maintenance of mental health difficulties (through assorted mechanisms including emotional regulation, genetic overlap and HPA axis functioning). From here, we now examine what happens in SCRD in people with psychosis.

Several studies spanning nearly two decades of research highlight sleep and circadian rhythm disruption (SCRD) to be an important feature of psychosis (Cosgrave et al., 2018). A study by Cohrs, (2008) highlighted that between 30% and 80% of people with a diagnosis of schizophrenia report sleep disturbances. More recent research into the frequency of patients meeting criteria for a variety of different sleep disorders in early psychosis indicated a prevalence of 80% (with insomnia and nightmares highlighted as the most common). Comorbidity amongst sleep disorders is also reported to be high with an average 3.3 disorders per patient. Those who report a sleep disorder also reported significantly higher scores on psychotic experiences (paranoia, hallucinations, and cognitive disorganization), depression, anxiety and lower on wellbeing. Furthermore it is estimated that only 53.1% of the sleep disorders were discussed with a clinician and only a quarter of those reported received treatment (Reeve et al., 2018). As such, SCRD remains both prevalent and under recognized in psychosis.

Outside of symptomatology, SCRD is also associated with several important clinical outcomes, including relapse (Waters & Manoach, 2012), poorer coping (Ritsner et al., 2004), higher distress (Hofstetter et al., 2005), increased frequency of depressive disorders (Palmese et al., 2011) and completed suicide (Pompili et al., 2009). Thus, it remains essential for research to further understand this relationship.

While formerly considered a by-product of psychosis, emergent research suggests sleep and circadian rhythm disruption (SCRD) may be a causally linked to the development and maintenance of the disorder. This is evidenced by the omnipresence of poor sleep across the core phases of the disorder, including the prodrome (with an estimated prevalence of 70-100%; Yung & McGorry, 1997), acute (Kupfer et al., 1970), chronic, and residual phases (Waters et al., 2011). There are now two comprehensive systematic reviews examining the evidence to date in support of this relationship (Davies et al., 2016; Reeve et al., 2015). Furthermore, there is also evidence that there may be a shared genetic and environmental lineage underlying psychotic experiences and SCRD (Taylor et al., 2015).

1.4.1: Sleep and Circadian Rhythms Studies Using Objective Measures in Schizophrenia and Bipolar Disorder

Subjective sleep quality can reflect a number of different sleep related experiences (ex: difficulty falling asleep, difficulty staying asleep) for different people and is correlated with several non-sleep related phenomena (ex: mood and anxiety; Krystal & Edinger, 2008). It has been shown that people with psychosis can self-report their sleep to be better than how it presents objectively (Chung et al., 2020), which is the inverse to how insomnia presents (when subjective sleep is reported to be worse than how it presents when examined with polysomnography). Furthermore, previous work has highlighted that objectively measured sleep interacts with subjective sleep to predict the highest risk of endorsing PE in a healthy sample (Cosgrave et al., 2017). Thus, to explore fundamental questions about the nature and heterogeneity of the disturbance, the level of circadian involvement, as well as informing any underlying mechanisms and causality, objective sleep metrics are essential. The original paper to highlight profound sleep and circadian rhythm disruption with comparison to a healthy control group (that was unemployed to control for the lack of a structured routine) is Wulff and colleagues (2012). This study enrolled 20 people with schizophrenia and reported that half of these individuals showed severe circadian misalignment including phase advances or delays (going to bed very early or very late), non-24 hour periods (the sleep-wake rhythm is not following the light dark cycle) and

abnormal melatonin release (Wulff et al., 2012). The other half showed highly irregular and fragmented sleep.

Since then, a meta-analysis by Meyer et al., (2020) identified 16 studies which explored actigraphic differences in schizophrenia when compared with healthy controls. They reported longer total sleep time and time in bed, greater sleep latency (time to get to sleep) and reduced motor activity. It was also highlighted the heightened prevalence of both insomnia *and* hypersomnia phenotypes (denoted by actigraphy) when compared to controls. Overall, the sleep and circadian presentations in the patient groups compared to controls had heightened heterogeneity. The authors also noted that in the literature to date, comparisons with controls are complex (particularly given the heightened prevalence of unemployment in patient groups), few studies screen for the overrepresented sleep disorders within the patient groups (ex: nightmares, obstructive sleep apnoea and restless leg syndrome) and there are very few that report circadian variables such as chronotype, phase delay or free running patterns. This is in part because the duration of actigraphic recordings are not long enough to support such observations (Meyer et al., 2020).

1.4.2: Sleep and Circadian Rhythms Studies Using Objective Measures: Prodromal Research

For sleep to be considered more than a by-product or reaction to the development of psychosis, exploring whether any sleep disturbance pre-dates the onset of psychosis is pivotal. Given the health service directive in trying to capture psychosis as early as possible in its trajectory, clinical interviews to examine whether someone is at "high risk" of psychosis prior to its onset have been developed (Fusar-Poli et al., 2014). Research in this area remains limited, however preliminary findings indicate the sleep disturbances observed in the prodromal phase equate to what is observed when the person has transitioned to their first episode of psychosis. These include extended sleep onset latency, difficulties with sleep continuity and circadian timing abnormalities (Castro et al., 2015; Zanini et al., 2013). Circadian disruption (lower daily activity, fragmented sleep patterning/desynchronisation from the light-dark cycle) appears to be an

important marker to follow longitudinally. At baseline circadian disturbances predicted increased psychotic symptom severity and psychosocial impairment at a one-year follow-up in a cohort at clinically high-risk for psychosis (when compared to healthy controls; Lunsford-Avery et al., 2017). The authors concluded that circadian rhythm disturbance might signify a potential vulnerability marker for the emergence of psychosis. However, a major limitation of these findings is that the relationships stated are largely reliant on pairwise correlational analyses. Longitudinal research may one day show that interventions to stabilise sleep-wake rhythms offer promise in early intervention services, but this remains an understudied area of research.

1.4.3: Clinical treatment studies exploring sleep and psychosis in both healthy and clinical populations

Much of the research cited to this point has been cross sectional or correlative. Treatment studies can elevate the understanding of a relationship between two phenomena by employing an interventionist-causal approach (Kendler & Campbell, 2009). Under this model, if sleep were causally involved in the development and maintenance of psychosis, one would expect that treating it would improve the experience of psychosis.

To date, there are three treatment studies which explore the impact of treating sleep (specifically using Cognitive Behavioural Therapy for Insomnia; CBT-I) in psychosis (Chiu et al., 2018; Freeman et al., 2015; Hwang et al., 2019). Only one indicated that treating sleep resulted in significant improvements in psychotic symptoms (Chiu et al., 2018). There is a further clinical trial in the treatment of nightmares in patients with psychosis. This demonstrated large effect sizes for the reduction of nightmares and a post-treatment reduction in paranoia and dissociation but no significant differences in hallucinations were reported (Sheaves et al., 2019).

Outside of patients with psychosis, there is a large-scale CBT-I trial with university students as trial participants. Their results indicated a significant reduction in paranoia and hallucinations at each of the timepoints measured (Freeman et al., 2015). This offers more persuasive evidence

that sleep and psychotic experiences may be casually linked but perplexingly, not in a psychosis population.

Using psychotherapy to test for a causal association is complicated by the fact the many of the mechanisms through which change occurs with psychotherapy remain elusive and are subject to therapist and patient effects which are difficult, if not impossible, to control for (Eronen, 2020). Outside of this, the limited current literature in sleep treatment only targets insomnia and nightmares. None of these target the presence of timing, rhythmic abnormalities, or adjacent sleep disorders. As psychotherapy works on several levels (ex: the therapeutic alliance, a compassionate space), it is hard to isolate sleep's impact on specific symptomatology which may also be why certain studies found no significant improvement in psychotic symptoms after treating sleep.

1.4.4: Other sleep phenotypes seen in psychosis: Parasomnias

Sleep and circadian rhythm disruption is an umbrella term for a wide ranging set of difficulties, some of which are specific to what happens at certain points during sleep. Parasomnias are a broad group of sleep disorders that are characterised by undesirable motor, sensory or behavioural experiences that can happen upon entering sleep, during sleep itself or during an arousal from sleep (Medicine, 2005). Common examples include nightmare disorder, sleep terrors, sleep paralysis (where a person when awakening or falling asleep has consciousness but is unable to move or speak yet may hear, see or feel things that are not there), sleep walking, and sleep-related eating disorders (Waters et al., 2017). It has been reported that these experiences are considerably elevated in psychosis and can lead to serious dysfunction due to the sleep disruption incurred, the potential risk to self or others (in cases of sleep walking and REM behavioural disorder) and the emotional burden given that several of these experiences (like sleep paralysis or terrors) can be terrifying (Waters et al., 2017).

Parasomnias are reported to be considerably higher in psychosis compared to the "normal" population. A study by Gangdev et al., (2015) found sleep paralysis to be present in 15% of

outpatients with a diagnosis of a schizophrenia-spectrum disorder (Gangdev et al., 2015). This is approximately double that of those without a psychiatric diagnosis (7.6% lifetime prevalence; Ohayon & Guilleminault, 2006). Sleep paralysis can often be neglected in psychosis, as the hypnagogic and hypnopompic hallucinations commonly experienced during the paralysis are often discounted as psychiatric symptoms (Waters et al., 2017). Outside of sleep paralysis, frequent nightmares occur in 9-55% of people with schizophrenia (Li et al., 2016; Sheaves et al., 2015). While a comprehensive overview of parasomnia related difficulties in psychosis is outside the remit of this review (for further information please refer to Waters et al., 2017), preliminary research indicates that this is another level at which SCRD is more commonly impaired in psychosis yet is infrequently screened for in research studies (Meyer et al., 2020).

1.4.5: What psychotic experiences are related to which sleep and circadian parameters?

Not dissimilar to sleep and circadian rhythm disorders, psychosis is also thought to have a multidimensional structure (Wigman et al., 2011). The number and structure of dimensions of psychotic experiences (PE) varies according to the study and the measures used. Even genetic heritability ranges from 33 to 57% depending on the dimension of PE. This is important because the dimension of PE a patient is reporting will inform their severity, associated distress, clinical risk and long term outcomes (Wigman et al., 2011). In other words, not all psychotic experiences are created equally and emergent research highlights that sleep and circadian rhythm disruption confers risk to only certain types of PE (Cosgrave et al., 2021b). To strive towards the personalised patient-tailored treatment agenda necessary to treat multi-dimensional disorders like psychosis, an intricate research program to understand specifically what kind of sleep and circadian rhythm disruption confers risk to which type of psychotic experience is warranted (Cosgrave et al., 2018; Cosgrave, et al., 2021b).

A recent survey study highlighted that delusional mood, negative symptoms (anhedonia and social anxiety) and dissociative experiences were predicted by circadian phase and sleep quality respectively using cross-sectional regression analyses (Cosgrave et al., 2021b). None of the sleep

variables predicted persecutory ideation, bizarre ideas or perceptual abnormalities indicating that sleep and circadian rhythm disruption may only relate to the occurrence of certain PE. This was, however, a cross-sectional survey study in the normal population that did not include any objective measures of sleep disruption.

To examine which objective or subjective sleep and circadian rhythm parameters are most predictive of which psychotic experiences, longitudinal high-resolution sampling is needed. To date there are two studies with healthy populations both of which indicate that nightly sleep predicts next day dissociation and paranoia respectively (Cosgrave et al., 2021c; Hennig & Lincoln, 2018). Both studies employ both objective and subjective sleep metrics when modelling the data.

There are a further four studies in patients with diagnosed schizophrenia and psychosis (Kammerer et al., 2021; Kasanova et al., 2019; Lee et al., 2019; Mulligan et al., 2016). However, only two of the four studies use objective sleep metrics (Kammerer et al., 2021; Mulligan et al., 2016). Both studies only employed subjective metrics and found no significant relationship between self-reported sleep quality and psychotic symptoms (in both studies they focused on persecutory ideation and subjective sleep quality; Kasanova et al., 2019; Lee et al., 2019).

Mulligan and colleagues found increased (objective) sleep fragmentation and reduced (objective and subjective) sleep efficiency predicted an increase in next day auditory hallucinations. Furthermore, increased fragmentation and decreased subjective sleep quality predicted greater paranoia and delusions of control. This was the first longitudinal study to predict psychotic symptom severity based on objective and subjective measures of nightly sleep in patients with psychosis (Mulligan et al., 2016). More recently a study by Kammerer et al., (2021) found that intradaily stability and relative amplitude (both circadian metrics) predicted persecutory ideation in healthy controls but not in patients with schizophrenia. This again gives an unclear picture of what the nature of the relationship between sleep, circadian rhythm disruption and psychotic experiences is. It does, however, underscore the importance of taking a holistic view to

exploring this relationship. This involves including objective metrics, ensuring the measurement of circadian variables, and exploring adjacent sleep disorders.

Closing Remarks

The findings from the current literature to date can be condensed into three key points. First, subjective sleep is highly correlated with mood and anxiety, can only really capture the presence of insomnia and provides little information on any circadian or timing difficulties and the actual level of disturbance. Most studies which include only subjective metrics report negative results. Thus, the need for objective metrics is essential.

Second, blanket treatment approaches have produced mixed results in clinical populations. This may be because sleep only improves specific dimensions of psychosis, or that sleep improves other outcomes associated with the symptoms of psychosis (ex: negative affect) but is not causally related itself. To clarify this, more studies examining the impact of specific dimensions of sleep and circadian rhythmicity on the specific dimensions of psychosis is needed, ideally in a high-resolution response format captured "in vivo" conditions to understand more of the patient's experience.

Third, there are several pitfalls of the current literature to date (Meyer et al., 2020). These include: (1) the use of cross-sectional designs with healthy control groups in comparison to people with psychosis. This may be misrepresentative given the level of functional impairment people with psychosis can experience; (2) few studies screen for the overrepresented sleep disorders within the patient groups (ex: nightmares, obstructive sleep apnoea and restless leg syndrome) and (3) very few report circadian variables such as chronotype, phase delay or free running patterns.

This calls for longitudinal within-subjects design methods to control for the severity and nature of psychosis, alongside greater reporting of sleep and circadian measures with longer durations of actigraphic recordings to be able to inform the presence of circadian disruption.

Research to date underscores that sleep, circadian rhythmicity, and psychosis are intrinsically linked, but the exact nature of that link remains elusive. One day, sleep could provide the backbone of a novel intervention which treats specific symptoms of psychosis. However, to get to that point the field needs more mechanism-driven research designed to expose sleep and circadian disruption as pathophysiological mechanism in psychosis as opposed to a correlate or mediator of negative affect. In conclusion, we are still missing the silver bullet needed to rethink treatment options in psychosis, but the future outlook is promising.

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Part 2 - Empirical Paper

A longitudinal high-resolution exploration into the relationship between sleep disruption and 'in vivo' psychotic symptoms, paranoia, and dissociation in early phase psychosis.

Abstract

Introduction

There is increasing recognition that sleep and circadian rhythm disruption (SCRD) is an important feature of psychosis. However, it remains unclear what contribution (if any) SCRD plays in the daily fluctuations of the psychotic symptoms, paranoia, and dissociation experienced in early phase psychosis. The aim of this study is to carry out a prospective, high-resolution analysis of the link between nightly SCRD and next-day psychotic symptoms, paranoia, and dissociation in people with early phase psychosis.

Methods

This study joined actigraphy with experience sampling method (ESM) and sleep diaries across a 14-day period in 54 people with early phase psychosis. To observe this relationship over time, participants were then followed up after a minimum of eight weeks (n=35). Momentary assessments of negative affect, psychotic symptoms, dissociation, and paranoia were collected at three timepoints each day at 12pm, 5pm and 10pm. A sleep diary was included in the 12pm time point. Multilevel models with mediation analysis were built to assess the relationships between variables.

Results

Objectively measured increased sleep onset latency predicted higher psychotic symptom severity, dissociation, and paranoia the following day. Subjective sleep quality uniquely predicted next day psychotic symptoms. Mediation analyses highlighted that the relationship between subjective sleep quality and next day psychotic symptoms was fully mediated by negative affect. However, sleep onset latency highlighted a direct and independent effect on next day psychotic symptoms, dissociation, and paranoia.

Discussion

This study highlights sleep disruption to be a predictor of next day psychotic symptoms, dissociation, and paranoia in an early phase psychosis population. Broadly, this study offers preliminary evidence that interventions designed to target sleep disruption (measured objectively) and stabilise sleep-wake patterns could be of benefit in first episode or early phase psychosis.

Section 2.1 **Introduction**

There is increasing recognition that sleep and circadian rhythm disruption is an important feature of psychosis. It is reported to be a salient feature across all of the core phases of the disorder (prodrome, acute, remission and relapse) and is associated with important clinical outcomes including relapse, poorer coping and higher distress (Benson, 2006; Ritsner et al., 2004; Waters & Manoach, 2012; Yung & McGorry, 1997). While formerly considered an epiphenomenon or correlate of psychosis, it is being increasingly regarded as a key psychopathological mechanism (Cosgrave et al., 2018; Waite et al., 2019).

Despite this increased recognition, the nature of the relationship (i.e. which specific psychotic experiences (PE) and sleep or circadian parameters are related), directionality of the relationship and whether there is convincing evidence to infer causality remains unclear (Cosgrave et al., 2018). Experimental and clinical studies in both clinical and analogue populations have provided mixed results (Waite et al., 2019). As mentioned in Part 1, this raises the need for more mechanism-driven research targeting specific experiences within psychosis.

2.1.1: Experience Sampling Method

Experience sampling method is a coordinated diary technique that permits the frequent recurring sampling of thoughts, feelings or experiences in the moment as they happen in daily life (Reininghaus et al., 2016). Being able to capture these moment-to-moment variations of psychological processes as they unfold in the real world allows a detailed exploration of the putative mechanisms which govern them. As ESM studies have a temporal sequencing by nature, this allows for the addition of mediation analyses which can give further insight into the mechanisms behind assorted psychological phenomena (Reininghaus et al., 2016).

Thus, employing an ESM design to explore the role of sleep and circadian rhythm disruption (SCRD) in next day psychotic experiences in early psychosis would permit a more detailed insight into the psychopathological mechanism SCRD plays in next day psychotic experiences.

2.1.2: Previous ESM studies exploring the relationship between Sleep, Circadian Rhythms and Psychosis

To date there are three studies which have attempted this. Mulligan et al., (2016) was the first study to combine an ESM methodology using nightly objective and subjective measurements of sleep. Their sample consisted of patients with chronic schizophrenia (n=22). They found increased (objective) sleep fragmentation and reduced (objective and subjective) sleep efficiency predicted an increase in next day auditory hallucinations. Furthermore, increased fragmentation and decreased subjective sleep quality predicted greater paranoia and delusions of control. This was the first study to predict psychotic symptom severity based on objective and subjective measures of nightly sleep in a clinical sample (Mulligan et al., 2016). Their mediation analyses found partial mediation for objective sleep metrics and full mediation for subjective sleep metrics when predicting next day psychotic experiences.

Kasanova and colleagues (2019) explored the relationship between subjective sleep quality and paranoia across the paranoia continuum (patients with a psychotic disorder and paranoia, patients with a psychotic disorder and no paranoia, and individuals with schizotypal traits). They reported that poor subjective sleep quality predicted subsequent morning paranoia, but that this relationship was not significant when controlling for morning negative affect in the model. They reported that the relationship between sleep disruption and paranoia was fully mediated by negative affect. They also reported no relationship between paranoia and subsequent sleep. Only subjective measures of sleep were used their analysis (Kasanova et al., 2019).

More recently, Kammerer et al., (2021) explored the role of sleep and circadian rhythm disruption in predicting next day persecutory ideation. They recruited individuals with current persecutory delusions (n=67) and compared them to healthy controls (n =39). When the sample was combined, they found that sleep onset latency the night before predicted persecutory

symptoms the following day. However, when isolating the sample to just the people with persecutory delusions this was no longer significant. Circadian disruption was found to predict persecutory symptoms in the healthy controls only. The protocols undertaken by Kammerer and colleagues (2021) and Mulligan and colleagues (2016) were the same (a device which integrated actigraphy and ESM measurements) was used. However, the protocol employed by Kasanova and colleagues (2019) used paper diaries for ESM measurements and no objective sleep measurements were taken.

2.1.3: The Current Study

This study seeks to replicate and extend some of the findings from previous studies while also addressing some of the issues highlighted by Meyer et al., (2020) and Reininghaus et al., (2016). First, the bulk of the literature to date relies on chronic samples. The purpose of this study was to understand the impact of sleep and circadian rhythms in first episode or early phase psychosis. This controls for the confound of illness chronicity in the sample. Second, most of the studies to date use sampling periods of six to seven days, which isn't sufficient to inform circadian disturbances (Meyer et al., 2020). As sleep duration, timing and patterning is notoriously fluctuant and heterogeneous in psychosis (Meyer et al., 2020), we extended our sampling period to 14 days but reduced the number of ESM assessment time points per day to three. Third, none of the studies have managed to capture an element of sleep timing or circadian phase yet the literature suggests this to be an important and understudied area. To address this, we added a mid-sleep point variable as a proxy for circadian phase. This is based on the calculations provided by Roenneberg et al., (2003) which pioneered the use of the mid-sleep point or the time at which sleep duration has reached its halfway mark. This approach to exploring chronotype is now widely employed in sleep and circadian rhythm research.

Comparisons to healthy controls can add complexity to ESM studies as the severity of psychosis and impact it has on functioning can make it difficult to find a comparable control group. As such, we designed this to be a longitudinal repeated measures study so that we could gather data

about the change within each participant over time (and understand how that impacted symptomatology).

Finally, the current literature focuses mostly on persecutory ideation and sleep disruption in psychosis. Our goal was to broaden that focus, as such we included the positive symptoms of psychosis (as reported by Mulligan et al., (2016); hallucinations, thought control and feeling threatened) and dissociation. Dissociation was added as there is growing recognition that dissociative experiences (DEs) have strong ties to sleep disruption and it remains a core and often under recognised element of psychosis (Longden et al., 2020; van der Kloet et al., 2012, 2013). Research into psychotic experiences in healthy or subclinical samples also indicate that dissociation could provide a pathway for the relationship between sleep disruption and psychosis (Cosgrave et al., 2021a; Cosgrave et al., 2021b). Furthermore, it is thought that dissociative experiences mediate the relationship between negative affect and auditory hallucinations in a patient sample (Varese et al., 2011).

Taken together, this study was designed to explore two core research questions which have specific hypotheses attached (**Figure 2.1**):

1. **Do objective or subjective sleep or circadian metrics from the night before predict next day psychotic symptoms, paranoia or dissociation in early phase psychosis (Path A)?**

   Based on previous research, we predict sleep disruption the night before (poorer subjective sleep quality, longer sleep onset latency, lower sleep efficiency, greater wake after sleep onset, shortened total sleep time) will predict dissociation the following day but not psychotic symptoms or paranoia.

2. **To what extent is this mediated by negative affect (Path B and C)?**

Based on the results by Mulligan et al., (2016) and Cosgrave et al., (2021b), we predict that negative affect will act as a partial (but not complete) mediator of relationship between sleep disruption and dissociative experiences.

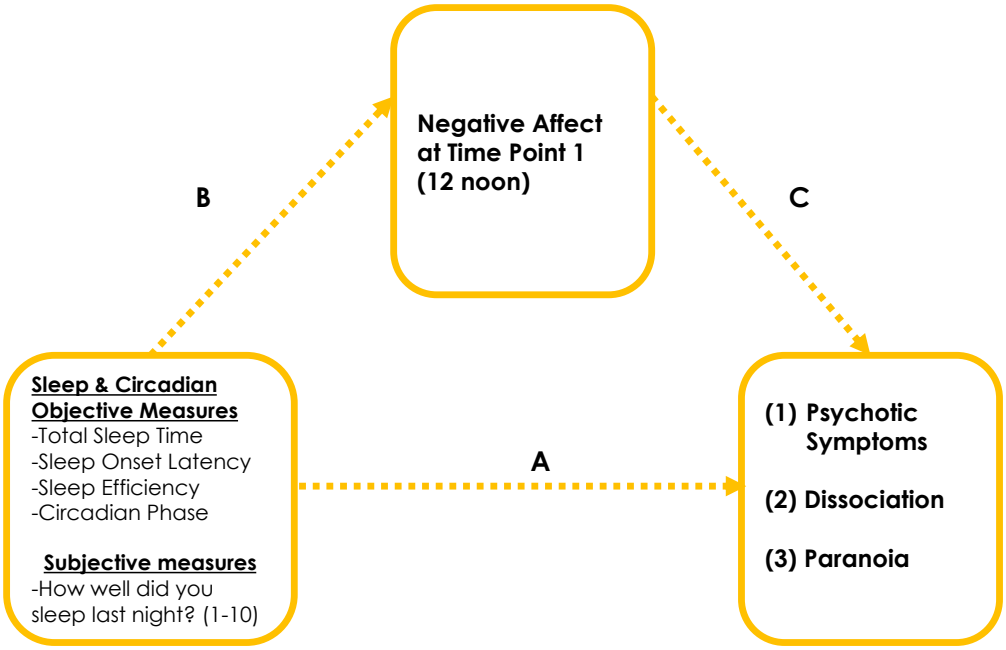

Figure 2.1: Models Examined in the Current Study. Path prediction A is the prediction of psychotic symptoms, dissociation, and paranoia from sleep and circadian parameters. Path prediction B is the prediction of Negative Affect (from Time Point 1) using sleep predictors. Path prediction C is the mediation analysis which combines a model of both sleep measures and negative affect from time point one to predict psychotic symptoms, dissociation, and paranoia later that day. This schematic and approach to mediation analysis is based on the methodology reported by Hennig & Lincoln (2018).

Section 2.2 **Methods**

2.2.1: Participants

The study was reviewed and approved by the London – Bromley UK NHS Research Ethics Committee (REF: 17/LO/1263) and by the Institutional Review Board under the Philadelphia Department of Public Health. Following approval, all participants were recruited from two mental health trusts in UK (London and Oxford) and from the Psychosis Education, Assessment, Care and Empowerment Service (PEACE) in Philadelphia. This study is targeted at early phase or first episode psychosis. Therefore, all participants need to meet criteria to be treated within an Early Intervention for Psychosis team. Outside of this requirement, this study was dedicated to recruiting a "clinically typical" sample which meant keeping the inclusion criteria as unrestrictive as possible to allow the broadest possible participation and to present a sample that resembles service users within clinical services. Inclusion criteria was the same across all three sites. It was noted, however, that differences in clinical provisions across sites did exist, as did the level of socioeconomic deprivation of the service users. This was accounted for in the analysis by including research site as a fixed effect.

If accepted by an early intervention service for psychosis, participants could have any psychiatric diagnosis. In this sample, all had diagnoses of at least one of the following: schizophrenia, paranoid schizophrenia, unspecified non-organic psychosis, psychotic disorder not otherwise specified, schizoaffective disorder, mania with psychotic symptoms, bipolar affective disorder with psychotic symptoms and unspecified schizophrenia spectrum disorder, in line with the International Classification of Diseases-10 (ICD-10; World Health Organization, 1992) and the Diagnostic and Statistical Manual for Mental Disorders, 5th Edition (DSM-V; American Psychiatric Association, 2013). All diagnoses were confirmed by a psychiatrist in their mental health care team. Other inclusion criteria were outpatient status; being 16 to 35 years of age and had a command of the English language to such a level that they could complete the

assessments, questionnaires and give informed consent in English. The presence of sleep disruption or any sleep disorders formed no part of the inclusion criteria for this study.

Exclusion criteria were a diagnosis of an organic, neurological (including epilepsy) or sleep disorder (other than insomnia); pregnancy; moderate to severe learning disabilities; travelling from a time zone greater than two hours from their home time zone in the past two weeks and being currently unstable due to the titrations of medication. Diagnoses and medications were gleaned from their medical team or clinical notes. All participants provided written informed consent to take part in the study.

2.2.2: Baseline Measures

A battery of questionnaires was administered before the ESM phase took place to characterise the sample with regards their mental health and functioning at the beginning of the study. This is common practice in experience sampling method studies (Kammerer et al., 2021; Mulligan et al., 2016). The participant's demographic information and health status was documented at the beginning of the questionnaire. All medical information (medication, diagnoses and comorbidities) was cross-referenced with their medical records.

Positive and Affective Symptoms

Paranoia. Green Paranoid Thoughts Scale (GPTS; Cronbach's α =0.95; Green et al., 2008) The GPTS is a 32 items measure of paranoia that can be divided into two 16-item subscales (examining social reference and persecutory thinking respectively). All items are rated on a 5-point scale, with higher scores indicating greater levels of paranoid thinking. This measure has acceptable psychometrics.

Dissociation. Dissociative Experiences Scale II (DES; Cronbach's α = 0.93). The DES-II (Carlson & Putnam, 1993) is a 28 item self-report scale of dissociation that requires participants

to indicate on a 100 mm visual analogue scales (anchors: 0 = never; 100 = always). This is a widely used metric with good psychometric underpinnings (van Ijzendoorn & Schuengel, 1996).

Hallucinations. The Specialised Psychotic Experiences Questionnaire (SPEQ; Ronald et al., 2013; Cronbach's α = 0.93). The Specific Psychotic Experiences Questionnaire—Hallucinations subscale was used to measure hallucinations. This scale contains nine items scored from 0 (not at all) to 5 (more than once a day), and has good psychometric properties (Ronald et al., 2013).

Negative affect. Depression Anxiety and Stress Scale (DASS; 21 Item Version, Cronbach's α = 0.92 (D); 0.84 (A); 0.87 (S); Henry & Crawford, 2005). The DASS has 3 categories (of 7 items each) targeting depression, anxiety, and stress. Each of the 21 items is scored on a 4-point scale.

Sleep Measures

Sleep Quality. Pittsburgh Sleep Quality Index (PSQI; Buysse et al., 1989). The PSQI measures subjective sleep quality over the preceding month, leading to a score of 0-21, where higher scores indicate poorer sleep quality. The standardised threshold indicating poor sleep quality is 5. The PSQI is commonly used in nonclinical and clinical populations and has also shown appropriate psychometric properties (Backhaus et al., 2002; Carpenter & Andrykowski, 1998).

Circadian Phase. The Munich Chronotype Questionnaire (MCTQ; Roenneberg et al., 2003). The MCTQ evaluates routine sleep-wake timing from bedtime to wake time and is centred on subjects' estimation of their sleep routine over the previous fortnight. These estimations are provided separately for work and free days, and are used to derive a time-based variable (the mid-sleep point on free days; MSF) which is then adjusted for accumulated sleep deficits (MSFsc) from the work-week. The adjusted variable, MSFsc, offers a correlate of circadian phase in local clock time. A later mid-sleep point signifies a later circadian phase (equivalent to late or 'evening chronotype').

Insomnia. The Insomnia Severity Index (Bastien, 2001; Cronbach's α = 0.85) assesses the day-time and night-time components of insomnia, with a score from 0 to 28. Scores of at least 10 are deemed optimal for detecting insomnia in community samples (Morin et al., 2011). It has good psychometric properties for use in both patients and healthy controls (Morin et al., 2011).

Other Sleep Experiences. The Iowa Sleep Experiences Survey (ISES; Cronbach's α = 0.88). The ISES (Koffel & Watson, 2010) contains 18 questions assessing the frequency of a variety of sleep- and dream-related experiences. Each is scored on a 7-point scale (ranging from never (1) to several times a week (7)). There two separate subscales of the ISES measuring general sleep experiences and lucid dreaming respectively. The ISES has an acceptable internal consistency (Koffel & Watson, 2010).

Wellbeing and Functioning

Wellbeing. Warwick Edinburgh Mental Well-Being Scale (WEMWBS; Cronbach's α = 0.93). Tennant et al., (2007) reported this to have good psychometric properties in both patient and health control populations.

Functioning. The Work and Social Adjustment Scale (WSAS; Cronbach's α = 0.86; Mundt et al., 2002) Mundt et al., (2002) reports this to have good psychometric properties in both patient and control populations.

2.2.3: Daily Sleep Measures

Sleep Diary. Participants were asked to completed an abbreviated version of the Consensus Sleep Diary (CSD; Carney et al., 2012) each day on their CamNTech Patient Recorded Outcome-Diary. They were asked to complete their bedtime, wake time and to rate their sleep out of 1-10.

Actigraphy. The sleep-wake cycle was objectively monitored for 14 days and nights using wrist-worn actigraphs (CamNTech Patient Recorded Outcome-Diary, Cambridge, United Kingdom), using a sampling epoch of 60 seconds. Actigraphy delivers a recording of continuous motor activity and has been validated for use on patients with psychosis (Tahmasian et al., 2013). All participants were directed to wear the watch on their non-dominant wrists for the duration of the study.

Actigraphy data was used in conjunction with the sleep diary reporting to define time-in-bed periods for actigraphy monitoring using MotionWare software (Version 15.1.4, CamNtech, Ltd). This program has automated algorithms which enable the generation of the following nightly sleep metrics:

- Sleep Fragmentation: an index derived from the frequency and intensity of physical movement during the sleep period.
- Sleep Onset Latency (SOL): the amount of time between bedtime and sleep onset.
- Wake After Sleep Onset (WASO): the amount of time spent above a predefined activity threshold.
- Total Sleep Time (TST): time between sleep onset and final wake time, excluding WASO.
- Sleep Efficiency (SE): Actual time spent sleeping calculated as a percentage of time in bed.

2.2.4: ESM Protocol and Sampling Procedure

All ESM items were programmed onto the CamNTech PRO-Diary (CamNTech LTD., Cambridge, United Kingdom). Co-production was a key part of designing the ESM layout and protocol of the study. We piloted the use of the watches longitudinally for clinical use prior to opening the study and asked for feedback from service users about what they did or did not like

about the experience and what could be done to improve it. Service users gave the feedback that having a time when they knew the watch would beep and not feeling that it would beep too often was less intrusive and unsettling to their daily schedules. They also noted the importance of explaining what the watch could and could not do and the researcher sitting down with them to explain the data output at the end of the study. This was incorporated into the study design. The watch by default was scheduled to beep three times a day at 12 noon, 5pm and 10pm. However, participants were asked if this schedule suited them, and it was adapted to their needs when this was not possible. We also enquired about the participant's sleep schedule to ensure the beeping of the watch did not interfere with their habitual sleep time. For the 12-noon beep, the sleep diary was also included in the battery of ESM measures. As such, this study has fewer time points and was a more structured ESM schedule compared to similar ESM studies (ex: Kammerer et al., 2021). It was designed this way because of what was discovered during piloting and a recognition that the sample in this study were younger and more vulnerable.

Each beep comprised of eighteen ESM items which included:

Psychosis items included hearing voices ('I am hearing voices'), seeing things ('I am seeing things that are not real'), feeling that thoughts are being influence or suspicious ('My thoughts are suspicious' and 'My thoughts are being influenced') and feeling threatened ('I feel threatened'; Cronbach's $\alpha = 0.89$; Mulligan et al., 2016). Positive symptoms were calculated as the mean across the six items.

Dissociation items used in Cosgrave et al., (2021b) were employed for this study to ensure cross comparison between models and results. These were seven items taken from The Peritraumatic Dissociative Experiences Questionnaire (PDEQ; 'I am losing track of what is going on. I am "blanking or spacing out in some way', 'I feel that I am on "automatic pilot"', 'Things seem to be happening in slow motion', 'The sense of my own body seems distorted or changed', 'I am having difficulty making sense of what is happening' and 'I feel uncertain about what time it is';

Cronbach's α = 0.91; Marmar et al., 1997). This covers depersonalization, derealization, amnesia, out of body experiences, altered time perception and body image. Dissociation was calculated as the mean across the seven items.

Persecutory ideation was measured using three items detailed in Udachina et al., (2014). These were derived from the PaDS-P ('I worry that others are plotting against me', 'I feel that I can trust no-one', 'I believe that some people want to hurt me deliberately'; Cronbach's α = 0.85). Persecutory symptoms were calculated as the mean across the three items.

Negative Affect (NA) was assessed using two items ('I feel low or blue' and 'I feel anxious or worried') based on other ESM protocols (Cronbach's α = 0.83; Reininghaus et al., 2016). NA was calculated as the mean across the three items.

All items were rated on an interval scale from zero to one.

2.2.5: Study Protocol

All participants were recruited from early intervention for psychosis services in London, Oxford and Philadelphia. Each participant was approached by a member of their clinical team to be invited to participate in the study. All participants were then screened for the inclusion and exclusion criteria. Anyone who was excluded at this point was informed of the reasons why and were debriefed accordingly. Eligible participants were then invited into the service to provide consent and complete the online questionnaire (which included all baseline measures) with a member of the research team to take them through. Participants were then briefed about the sleep and ESM component of the study. Time was taken to familiarise them with the PRO-diary watch, with the question-and-answer functionality demonstrated and the abilities of what the watch could and could not measure detailed explicitly.

ESM and sleep phase. After the watch had been with the participant for 24 hours, a member of the research team would call to confirm that the watch was functioning as expected and that the entries were being completed correctly. The researcher also enquired to make sure that they felt comfortable with the watch. A time to come in to collect the watch was also arranged for two weeks in the future.

Post ESM phase. All participants came into the service to return the watch. Their sleep data was examined with them so that they could look at their own data. They were debriefed and invited to come back to repeat the study after an eight-week break. Those who consented to be contacted again, were approached to repeat the ESM and sleep phase. All participants were offered the opportunity to get a personalised sleep report which provided helpful information on their sleep and offered some sleep hygiene tips. These were designed by the lead author on this paper [JC].

Section 2.3 **Analysis**

All analyses were performed in R statistical environment (R Core Team, 2014) with the packages "dplyr" (for data manipulation; Wickham et al., 2014); "magrittr" (for data manipulation; Bache et al., 2016), "lubridate" (for handling of time data; Spinu, 2016), "stringr" (for data cleaning; Wickham & Wickham, 2019), "tidyr" (for data cleaning; Wickham & Wickham, 2017), "psy" (for computing Cronbach's alpha; Falissard & Falissard, 2009) and "lme4" (for modelling analyses; Bates et al., 2007).

As ESM data are characterised by a four-level hierarchical structure (three assessment points nested within days, nested within participants, nested within rounds of the study) and actigraphy present as three-level hierarchical structure (one value per night, nested within participants, nested within rounds), we used linear multi-level models to explore whether night-time sleep was predictive of next day dissociative, paranoid or psychotic symptoms. To ensure reproduction and cross comparability in the field, the authors of the Kammerer et al., (2021)

were contacted for counsel regarding their modelling analyses. The corresponding author provided the script they used for the analysis and we replicated the models that they used.

As such, the analyses presented here were analogous to those from adjacent ESM studies exploring the relationship between sleep and psychosis (Kammerer et al., 2021; Mulligan et al., 2016). Multiple comparisons were corrected for using the Benjamini & Hochberg method which employs a false discovery rate of 5% (Benjamini & Hochberg, 1995). Within each model, we added fixed effects to control for age, gender, the research site where the participant was recruited and their baseline score with the corresponding questionnaire (for example, when paranoia was the outcome measure for the model, we added the baseline GPTS score to the model to account for variation in baseline paranoia across participants). Subject ID and the interaction between subject ID and their day in the study were added as random effects to account for heterogeneity in the sample and in the daily ESM responses.

Due to multicollinearity concerns, it wasn't possible to include fixed effects for all the objective sleep metrics detailed above in the Methods section. We selected total sleep time, sleep onset latency and circadian phase as our objective sleep metrics. These have been reported to be the most influential metrics in previous studies (Cosgrave et al., 2018; Kammerer et al., 2021).
For a participant to be included in the analysis, they needed to have a minimum of 48 consecutive hours of actigraphic recording and a minimum of two ESM time points fully completed on the subsequent days. All participants met these criteria.

In line with the methodologies described by Mulligan et al., (2016), Henning & Lincoln (2018) and Kasanova et al., (2019), mediation by negative affect was determined by adding the negative affect ESM rating at time point 1 (as demonstrated in Figure 2.1) as an additional predictor variable to the model when predicting the psychotic symptoms at time points 2 and 3 during the day. Full mediation was observed when the associated predictors (in this case sleep disruption objective or subjective) are no longer statistically associated with the outcome in the model.

Partial mediation is determined by a reduction in the parameter estimates which indicates that a proportion of the effect size was attributed to negative affect at time point 1.

Section 2.4 **Results**

A full list of the demographics and clinical characteristics of the sample is provided in **Table 2.1** and **Table 2.2**. 54 people were recruited for the study, 34 of whom completed the follow up (62.9%). 48 were taking antipsychotic medication, 15 in augmentation with antidepressants. Antipsychotic medications included: amisulpride, aripiprazole, risperidone, clozapine, paliperidone, olanzapine, quetiapine, paliperidone, haloperidol, lurasidone and risperidone, with a range of doses from 5 to 600mg. Antidepressant medications included duloxetine, trazodone, fluoxetine, sertraline, bupropion, citalopram and mirtazapine with doses ranging from 5 to 200 mg. Eight participants took sedative medications for sleep or anxiety (including diazepam, zopiclone, lorazepam and clonazepam) with doses ranging from 1 to 14 mg. Two participants were prescribed antihistamines for sleep.

The sample was generally considered to be within early phase psychosis with a mean duration of 1.7 years (SD=1.3 years). Most participants held a diagnosis of unspecified nonorganic psychosis (n=22) or unspecified schizophrenia spectrum disorder (n=11).

Completion of ESM metrics in this study was high with an overall response rate of 73% for Round 1 and 75.4% on Round 2. This is in line with other studies in the field (Kammerer et al., 2021; Mulligan et al., 2016).

2.4.1: Baseline measures

Mean scores on the ISI (9.1; cut off for community insomnia = 10) and PSQI (5.1, cut off to indicate poor sleep quality = 5) indicate mild to moderate sleep disturbance below the threshold to indicate insomnia. However, ranges for both the PSQI and ISI were broad. 22 participants scored above 10 on the ISI and 29 scored 5 or above on the PSQI, indicating a broad spread of

sleep reporting in the sample. Problematic alcohol use across the sample was low. 4 participants reported a score of 2 or above on the CAGE (the threshold which indicates clinical significance).

Most participants scored within the average range for wellbeing (between 40-59 points on the WEMWBS; n=30) but indicated significant to severe functional impairment on the WSAS (n=30). Average scores in persecutory ideation, social reference and hallucinations were below what has been reported in other clinical samples with psychosis (ex: Green et al., 2008; Reeve et al., 2021) but similar in level of dissociation experienced (ex: mean= 14.21 in schizophrenia outpatients; Bob et al., 2010).

2.4.2: Do objective/subjective sleep parameters predict next day psychotic symptoms?

Table 2.3 indicates that men endorsed significantly higher psychosis, paranoia, and dissociation than women assuming all other variance is equal. **Table 2.3** also indicates that increased sleep onset latency predicted greater psychotic symptoms, dissociation, and paranoia after accounting for age, gender, site, subject ID and day in the study. Subjective sleep quality of the night before uniquely predicted psychotic symptoms. Circadian phase did not predict any of the three outcomes and there were no significant differences between sites.

Table 2.1: Participant Demographics

Demographic/Variable	Time Point 1			Time Point 2		
	n	***M(SD)***	***Range***	***n***	***M(SD)***	***Range***
Age (Years)	54	23.2(5.3)	16-35			
Gender	54					
Male	31					
Female	22					
Trans (Man)	1					
Diagnosis						
Affective Psychosis	24					
Unspecified Nonorganic Psychosis	22					
Schizoaffective Disorder	2					
Bipolar Affective Disorder with Psychotic Symptoms	6					
Paranoid Schizophrenia	5					
Delusional Psychotic Disorder	1					
Schizophrenia	3					
Unspecified Schizophrenia Spectrum Disorder	14					
Brief Psychotic Disorder	1					
Ethnicity						
White	20					
Black	23					
Asian	5					
Mixed Race	4					
Latino	1					
Smoker	20			12		
Weekly Alcohol Intake (Units)	51	0.9 (2.2)	0 – 10	36	1.2 (2.6)	0 -10
Duration of Psychosis	54	1.7 (1.3)	16 days to 5.3 yrs	-	-	-
ESM Response Rate (%)	52	73.0% (17.4)	33% - 95%	35	75.4% (15.7)	38 % - 97.8%

Note. Participants were only asked the CAGE questionnaire if they endorsed drinking alcohol during the week. For analytic purposes the individual identifying as Trans (Male) was coded as Male.

Table 2.2: Scores on Baseline Measures

Baseline Variable	Time Point 1			Time Point 2		
	n	***M(SD)***	***Range***	***n***	***M(SD)***	***Range***
CAGE	30	0.3 (0.7)	0 - 3	20	0.5 (1.1)	0 - 3
ISI	51	9.1 (6.2)	0 - 26	35	6.7 (5.7)	0 - 24
PSQI	51	5.9 (3.8)	1-18	36	5.1 (3.4)	1 - 14
SPEQ (H)	51	6.6 (10.1)	0 – 41	36	5.9 (8.3)	0 – 43
DES	51	17.3 (16.9)	0 – 70.7	34	17.6 (15.2)	0.2 – 65.6
GPTS (SR)	51	27.2 (12.5)	16 - 68	35	24.8 (10.0)	16 – 48
GPTS (PI)	51	25.7 (14.6)	16- 71	35	20.9 (8.0)	16 – 48
Depression	51	10 (9.1)	0 - 32	35	8.9 (9.1)	0 – 36
Anxiety	51	8.8 (8.3)	0 – 30	35	6.9 (7.3)	0 – 36
Stress	51	10.9 (9.)	0 - 36	35	10.4 (9.1)	0 – 34
MCTQ MSFsc	51	04:12 (48)	02:00 – 07:30	35	04:00 (52)	01:45 – 06:07
WEMWBS	51	46.5 (10.4)	20 – 67	35	47.6 (9.1)	14 – 70
WSAS	51	12.7 (10.2)	0 – 34	35	11.5 (9.3)	0 – 34
ISES	51	1.7 (1.3)	0 – 5.3	35	1.9 (1.3)	0.1 – 5.8

Note. ESM = Experience Sampling Method; CAGE = Screening for Potential Problem Drug and Alcohol Use; ISI= Insomnia Severity Index; PSQI = Pittsburgh Sleep Quality Index; SPEQ = Specific Psychotic Experiences Questionnaire (H; Hallucinations subcategory); DES= Dissociative Experiences Questionnaire; GPTS (SR) = Green Paranoid Thoughts Scale (Social Reference); GPTS (PI) = Green Paranoid Thoughts Scale (Persecutory Ideation); MCTQ = Munich Chronotype Questionnaire Mid Sleep-point (a measure of chronotype). This measures in time and the standard deviation is reported in minutes.

Table 2.3: Effect of Objective and Subjective Sleep Parameters on Next Day Paranoia, Dissociation and Psychotic Symptoms After Adjusting for Age, Gender, Site, Subject ID and Day in Study

Predictor Variable	β Coefficient	SE	df	t	p value
Outcome: Psychotic Symptoms					
SPEQ	0.09	0.09	635.67	1.06	0.29
Age	0.38	0.61	35.09	0.62	0.54
Gender (M)	11.52	5.76	35.19	2.00	0.05
Site (PEACE)	-0.27	6.32	34.93	-0.04	0.97
Site (West London)	-11.00	8.15	36.10	-1.35	0.19
Subjective Sleep Quality	-0.42	0.20	667.66	-2.11	0.03
Total Sleep Time	-0.16	0.21	644.36	-0.75	0.45
Sleep Onset Latency	2.92	0.93	601.67	3.15	<0.01
Circadian Phase	-0.12	0.24	645.24	-0.51	0.61
Outcome: Dissociation					
DES	-0.02	0.07	564.24	-0.32	0.75
Age	0.11	0.62	36.25	0.18	0.86
Gender (M)	12.83	5.79	36.62	2.22	0.03
Site (PEACE)	-2.69	6.34	36.13	-0.42	0.67
Site (West London)	-8.48	8.16	37.14	-1.04	0.31
Subjective Sleep Quality	-0.33	0.20	644.58	-1.62	0.11
Total Sleep Time	-0.04	0.21	634.43	-0.18	0.86
Sleep Onset Latency	2.08	0.92	574.88	2.26	0.02
Circadian Phase	-0.31	0.27	620.85	-1.30	0.19
Outcome: Paranoia					
GPTS (PI)	0.12	0.08	619.40	1.47	0.14
Age	0.12	0.63	34.35	0.20	0.84
Gender (M)	14.57	5.86	34.53	2.49	0.02
Site (PEACE)	-1.45	6.41	33.86	-0.23	0.82
Site (West London)	-10.06	8.30	35.59	-1.21	0.23
Subjective Sleep Quality	-0.51	0.26	662.75	-1.96	0.05
Total Sleep Time	-0.06	0.27	640.82	-0.23	0.82
Sleep Onset Latency	3.20	1.20	580.37	2.67	<0.01
Circadian Phase	0.12	0.08	619.40	1.47	0.14

2.4.3: Does Morning Negative Affect Mediate the Relationship between Objective/Subjective Sleep Parameters and Next Day Psychotic Experiences, Dissociation and Paranoia (Path B & C)?

To address the mediation effect, a model was built using negative affect as the outcome measure (Path B). After controlling for baseline DASS-21 depression scores, only subjective sleep quality (β = -1.21; SE = 0.33; p <0.001) significantly predicted negative affect at time point 1. Total sleep time, sleep onset latency and circadian phase were not significant predictors of negative affect at T1 indicating that negative affect does not mediate the relationship for any of these variables. Full output of this model (with negative affect as the outcome variable) can be found in **Appendix 1**.

Following this, Path C was explored (**Table 2.4**). Negative affect scores upon entry point 1 (T1; at midday) were added as a mediator variable to the models described in **Table 2.3**. Subjective sleep quality was a significant predictor for psychotic symptoms only (**Table 2.3**), but this effect no longer held after negative affect was added to the model. This indicates that negative affect fully mediates the relationship between subjective sleep quality and psychotic symptoms. Sleep onset latency remained a significant predictor of dissociation, paranoia, and psychotic symptoms after the inclusion of negative affect at T1 to the model. This indicates the relationship between sleep onset latency on next day psychotic symptoms to be an independent direct effect.

Table 2.4: Mediation Analysis: Effect of Objective and Subjective Sleep Parameters on Next Day Paranoia, Dissociation and Psychotic Symptoms After Adjusting for Age, Gender, Site, Negative Affect at T1, Subject ID and Day in Study

Predictor Variable	β Coefficient	SE	df	t	p value
Outcome: Psychotic Symptoms					
SPEQ	0.05	0.09	629.79	0.59	0.56
Age	0.38	0.59	34.27	0.65	0.52
Gender (M)	9.96	5.52	34.58	1.81	0.08
Site (PEACE)	0.15	6.05	34.11	0.03	0.98
Site (West London)	-9.72	7.81	35.37	-1.25	0.22
Negative Affect at T1	-0.09	0.02	682.54	4.98	<0.001
Subjective Sleep Quality	-0.29	0.20	665.92	-1.46	0.15
Total Sleep Time	-0.14	0.21	640.42	-0.39	0.69
Sleep Onset Latency	2.98	0.91	596.85	3.27	<0.01
Circadian Phase	-0.09	0.23	641.18	-0.39	0.69
Outcome: Dissociation					
DES	-0.04	0.07	549.37	-0.57	0.57
Age	0.10	0.58	35.56	0.17	0.87
Gender (M)	11.19	5.50	37.15	2.03	0.05
Site (PEACE)	-2.10	6.02	35.47	-0.35	0.73
Site (West London)	-7.19	7.75	36.57	-0.93	0.36
Negative Affect at T1	0.09	0.02	663.93	5.17	<0.001
Subjective Sleep Quality	-0.20	0.20	645.61	-0.99	0.32
Total Sleep Time	-0.02	0.21	634.48	-0.11	0.92
Sleep Onset Latency	2.19	0.91	573.65	2.42	0.02
Circadian Phase	-0.28	0.23	620.37	-1.21	0.22
Outcome: Paranoia					
GPTS (PI)	0.17	0.08	562.16	2.12	0.03
Age	0.15	0.56	32.61	0.26	0.79
Gender (M)	11.13	5.16	33.29	2.16	0.04
Site (PEACE)	-0.45	5.62	32.11	-0.08	0.94
Site (West London)	-8.00	7.30	34.12	-1.10	0.28
Negative Affect at T1	0.16	0.02	670.46	7.01	<0.001
Subjective Sleep Quality	-0.30	0.25	660.42	-1.18	0.24
Total Sleep Time	-0.06	0.26	638.24	-0.21	0.83
Sleep Onset Latency	3.42	1.16	573.98	2.95	<0.01
Circadian Phase	-0.36	0.30	625.72	-1.20	0.23

Section 2.5 **Discussion**

This study was designed to examine whether sleep or circadian disruption from the night before predicts next day dissociation, paranoia, or psychotic symptoms in an early phase psychosis population. The combination of actigraphy alongside subjective sleep reporting and ESM allowed the longitudinal measurement of sleep-wake cycles and ecological assessment of next day symptoms across a 14-day period with a longitudinal follow up. This, to our knowledge, is the first study to use an early phase psychosis population and importantly did not select participants based on their sleep reporting. We believe this to be an important distinction comparative to previous work to ensure the generalisability of the findings in this study to a clinically typical psychosis sample and not just a sub-sample who suffer from assorted sleep or circadian rhythm phenotypes.

There were two core research questions for this study. First, we sought to examine whether objective or subjective sleep or circadian metrics from the night before predicted next day hallucinations, paranoia, or dissociation (Path A). We predicted sleep disruption the night before (poorer subjective sleep quality, longer sleep onset latency, lower sleep efficiency, greater wake after sleep onset, shortened total sleep time) would predict dissociation the following day but not hallucinations or paranoia. This was partially supported by our results. Objectively measured sleep onset latency predicted all three outcomes (paranoia, dissociation, and psychotic experiences). Subjective sleep uniquely predicted next day psychotic symptoms.

Our second research objective was to explore whether this relationship was mediated by negative affect (Path B and C). It was hypothesised that negative affect will act as a partial (but not complete) mediator of relationship between sleep disruption and dissociative experiences. Again, this was partially supported by our results. None of the objective sleep metrics predicted negative affect at T1 indicating that negative affect did not mediate the relationship between objective sleep disruption and next day dissociation, paranoia, or psychotic experiences in this study. This suggests that sleep disruption the night before holds a direct and independent relationship to next day psychotic experiences. The parameter estimates for sleep onset latency

across both sets of models (with and without negative affect at T1) remained broadly consistent which lends further support to a direct and independent relationship between objective sleep disruption and next day psychotic, paranoid, and dissociative experiences.

Negative affect was predicted by subjective sleep quality and subjective sleep quality was no longer significant in predicting psychotic symptoms when negative affect at T1 was added to the model (Path C).

2.5.1: Comparisons with studies using patient populations

This study replicates and extends the findings of previous work in the field. Kammerer et al., (2021) found that of the sleep metrics used in their modelling analyses, sleep onset latency was most predictive of next day persecutory ideation in a combined sample of healthy controls and patients with persecutory ideation. Similarly, the results presented here indicate that next day psychotic, dissociative and paranoid experiences are most sensitive to fluctuations in sleep onset latency the night before. Persecutory ideation was the only outcome measure used in their analyses. The results presented here indicate that this relationship can be generalised to dissociative and psychotic experiences in an early phase psychosis sample. Interestingly, Kammerer et al., (2021) found that this relationship was no longer significant when isolating the sample to just patients with persecutory ideation. Reasons why these results differ may relate to chronicity of illness within the sample, differences in the recruitment and selection of the sample or the addition of alternate parameters to the models.

The results presented here also coincide with Kasanova and colleagues (2019) who similarly reported that subjective sleep quality did not significantly predict next day paranoia when negative affect was included in the model. They concluded that the relationship between subjective sleep quality and next day paranoia was fully mediated by negative affect. Their study only used subjective measures of sleep. In this study, subjective sleep was not a significant predictor for any of the outcome measures after adding negative affect at T1 to the models. The

parameter estimates for subjective sleep quality decreased upon the addition of negative affect at T1 to the model, lending support for the notion that subjective sleep quality works via mechanisms of negative affect whereas objectively measured sleep disruption holds an independent and direct relationship to next day psychotic symptoms in this sample.

Mulligan et al., (2016) used both objective and subjective sleep parameters and reported different outcomes to those in this study. They found that both subjective and objective sleep efficiency predicted auditory hallucinations. Objective sleep fragmentation predicted auditory hallucinations and paranoia and subjective sleep quality predicted all three of their outcomes (auditory hallucinations, paranoia and thought control). They didn't use sleep onset latency as a predictor and this study didn't use sleep efficiency as a predictor due to multicollinearity concerns, so direct comparisons are limited. Neither study found total sleep time to be predictive. Similar to the results described here, subjective sleep quality was no longer significant for paranoia and thought control when accounting for negative affect in their models. The core difference between Mulligan and colleagues and the other studies reported here (including our own) is that the participants were recruited based on meeting the criteria for insomnia. Perhaps unsurprisingly, it also reports the strongest relationship between sleep and psychotic experiences with the highest number of sleep parameters predicting psychosis related outcomes.

Broadly this indicates that studies employing only subjective sleep metrics when predicting psychotic experiences in patient populations find either no or no direct relationship between sleep and psychosis. This underscores the importance of measuring sleep objectively when seeking to clarify this relationship. This may explain why clinical trials have reported mixed results when attempted to reduce the symptom severity of psychosis through the treatment of sleep as the current literature suggests that a shift in the subjective perception of sleep may not be sufficient to get a clinically meaningful improvement in the symptoms of psychosis.

It is also unclear whether the reporting of subject sleep and negative affect can be considered aetiologically distinct phenomena. A study by Gavriloff et al., (2018) found that false positive feedback on sleep efficiency significantly improved positive mood and cognition in an insomnia population which indicates these two variables to be intrinsically linked or governed by overlapping psychological mechanisms.

2.5.2: Studies using analogue or subclinical populations

There are three studies which explore the relationship between sleep and next day psychotic experiences in subclinical or healthy populations. This study was designed to replicate the findings of Cosgrave et al., (2021b) which used a group of good and poor sleepers. In that study, total sleep time and wake after sleep onset (WASO) were the most predictive of next day dissociation. The relationship between WASO and dissociation was moderated by negative affect. There was no relationship between sleep the night before and paranoia the next day. When translated to a clinical population, sleep onset latency was the most predictive sleep variable, and the relationship was seen for all three outcomes (dissociation, psychosis, and paranoia).

A study by Hennig et al., (2020) used actigraphy in conjunction with daily questionnaire sampling of hallucinations and paranoia in individuals with high and low psychosis proneness. They reported that shorter sleep time and negative dream valence predicted next day paranoia whereas feeling less rested (subjective sleep) and dream recall predicted hallucinatory experiences. Furthermore, they found that those relationships were stronger for hallucinatory experiences (but not paranoid) in those with elevated psychosis proneness. They concluded that subjective sleep parameters are more important in predicting psychotic phenomena in their sample.

Another study by Henning & Lincoln (2018) using a healthy adolescent sample (n=61) found that more dreaming and *both* objective and subjective shorter sleep time predicted subsequent

paranoia. They also reported the relationship between paranoia and sleep to be partially mediated by positive and negative affect.

All three studies employed both subjective and objective metrics and find significant relationships between sleep disruption the night before and next day dissociation or paranoia. However, the most predictive sleep variables differ across studies (both in patient and analogue populations), as does the role subjective sleep reporting plays. One explanation of the disparate results may be that self-reporting poorer sleep is more influential in subclinical or premorbid phases of psychosis, but as someone transitions to a first episode of psychosis, more objective parameters of sleep disruption (sleep onset latency and fragmentation) become more influential for sustaining and exacerbating paranoia, psychotic symptoms, and dissociation.

2.5.3: Limitations

This study has many strengths: a longitudinal repeated measures design, high resolution sampling of both subjective and objective sleep metrics alongside circadian parameters, an extended sampling period to 14 days, an early phase psychosis population to control for illness chronicity and the recruitment of a 'clinically typical' population which allowed for a broad participation. It also has a number of important limitations.

First, this protocol does not include a clinical interview to assess psychosis severity (ex: PANSS). The original protocol of study was piloted with an interview, but it elongated the assessment period to a time that was difficult for young people in the early experiences of serious mental illness to complete. It was decided a questionnaire approach was less strenuous, could be done over several time points if necessary and would be less biased to cross site effects. Second, the original sample target for this study was nearly double what was recruited. This study was shut down mid-recruitment due to the Covid-19 pandemic. Given the nature of the study (administering a watch, explaining how it works, etc.), it was deemed unsuitable to conduct remotely with this population and was never able to reopen as a result. Third, there are a

number of variables which sleep and circadian rhythmicity could be impacted by and which could impact symptomatology which are not accounted for within the modelling analyses (medication, functioning, comorbid medical or health problems, baseline psychosis severity). This study only accounts for the mediation of negative affect, however, there may be other pathways by which sleep disturbance provokes psychotic experiences. While the structure of this study allows to inform the psychopathological mechanism between sleep, circadian rhythms and psychosis, as these models assume linear relationships it is not possible to say that sleep and circadian rhythm disruption (SCRD) causes psychosis (using this dataset) but rather that SCRD increases the chances of psychotic, dissociative and paranoia experiences the following day in early phase psychosis.

2.5.4: Clinical Implications

Accumulatively, the literature indicates that sleep and circadian rhythmicity are important parameters to consider in early intervention for psychosis services (EIS). Despite the utility, it isn't realistic to be able to objectively explore sleep and circadian rhythmicity in all service users in busy EI services. However, this does highlight the need for clinicians to ask about sleep and circadian rhythmicity at intake for the service and follow up. This should include questions about sleep duration, quality, timing and rhythmicity, the presence of unusual sleep experiences (ex: nightmares or night terrors) or any sleep disorders (ex: sleep apnoea). Ideally this would be done in conjunction with validated questionnaires.

This would allow for more holistic treatment approaches, for targeted sleep treatments (such as stabilisation, self-help, CBT for insomnia or addressing issues with circadian timing) for those who need it and to identify those who present with more aggressive sleep or circadian presentations that may require signposting or onward referrals to specialist sleep clinics to access the care they need.

2.5.5: Summary & Conclusions

This study shows that sleep disruption is a significant predictor of next day increased symptom severity in early phase psychosis. Specifically, difficulties with the initiation of sleep appear to be most influential for reporting next day dissociation, paranoia, and psychotic symptoms.

Future work should aim to extend and clarify these findings. This research could be taken in several directions. First, our results didn't highlight circadian phase to be a meaningful predictor of next day psychotic symptoms. However, other studies do highlight circadian variables to be important when determining symptom severity in psychosis and in people at ultra-high risk of psychosis (Lunsford-Avery et al., 2017; Wulff et al., 2012). It remains to be discovered which circadian parameters are most influential in this relationship and warrants further exploration. Second, it is likely that the relationship between sleep disruption and psychosis is not the same for everyone. This would imply that some people will have a heightened sensitivity to sleep disruption, which could explain why certain studies report negative results. There is currently no research done to explore this, but it is essential to understand this to design personalised treatment programs for people with psychosis.

Broadly, this study offers preliminary evidence that interventions designed to target sleep disruption (measured objectively) and stabilise sleep-wake patterns could be of benefit in early phase psychosis. Targeted appropriately powered randomised controlled clinical trials with objective metrics could help to clarify this. From a clinical perspective, it is hoped that research studies like this one could be used to help promote awareness around the importance of sleep and circadian rhythmicity in psychosis, which in turn would allow for more holistic treatment approaches to support this clinical population.

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Part 3 - Critical Appraisal

Section 3.1 **Introduction**

This chapter details a critical reflection of the research process and empirical paper presented in Part 2 of the thesis. It opens with some reflections on what brought me into this line of research and why I took the route I have. Reflections on the participants' context and what this study did not manage to capture then follow. The impact of the COVID-19 pandemic on the present research and lessons learned for future research and clinical practice are also presented. The appraisal closes with what I believe the positive impact of this research study to be and what I have taken from this process with a view to informing my career as a qualified clinical psychologist.

Section 3.2 **My own experience with sleep and circadian rhythmicity**

My research doctorate explored the relationship between sleep, circadian rhythms, and psychotic experiences in good and poor sleepers. However, my own personal interests in sleep and circadian rhythmicity long pre-dated the beginnings of my PhD. Both of my parents were shift workers and met while working on a night shift at Cadburys. While their work patterns undoubtedly took a toll on their bodies, I was quite struck by how easily my father could adapt to working throughout the night. As I grew older my eldest brother became a night shift worker as a croupier in a casino.

As I went into my teenage years, I found that it was impossible for me to go to sleep before 1am on school nights. I used to sleep for 14 hours on the weekends to compensate for this. Early into my degree in psychology at the University of Glasgow, I specialised in sleep and circadian rhythms to try to understand this. My undergraduate research project focused on jet lag in mice and we explored techniques to help shift the biological clock earlier or later.

Unknown to my supervisor at the time, I would often try these techniques on myself to see if I could adapt more easily to my 9am lecture schedule.

I noticed how tampering with my sleep wake cycle did lead to drastic changes in my functioning. I also learned that the term "late chronotype" was designed to describe people in my position. This prompted my interest into what sleep-wake rhythms might mean for mental health and functioning and fulfilled the backbone of my PhD thesis proposal which secured funding at the University of Oxford. Working within a sleep lab had the bonus of being able to start work later and finish later without judgement.

My PhD was mostly focused on sleep's relationship with dissociation, which stemmed from an acknowledgment of how much I could disconnect from reality when tired during my undergraduate and secondary school days. At this point, I didn't have a good insight into what serious mental illness or indeed psychosis looked like. As such, I started to work in an early intervention service for psychosis to help understand what was relevant for this population. I managed a caseload focused solely on treating sleep and circadian rhythm disruption, which is what informed the development of this project. I was struck by the extremity and heterogeneity of different presentations and how no two people within this clinic presented in the same way with regards to their sleep.

While this is an empirical quantitative project, my current experience in a psychodynamic placement has taught me that often we are drawn to notions or ideas based on our own life experiences. As such, I think it is important to acknowledge my position and background as a quantitative researcher, as it has almost certainly informed the research questions I have pursued and may in turn provoke bias in the data collection and analysis. Acknowledging this can only serve to help counterbalance this when undergoing empirical research.

Section 3.3 **Impact of the research on the researcher**

I was underprepared for the transition from researching a student population (as I did in my PhD) to a clinical population with first episode psychosis. People within these services were very unwell and often severely traumatised by current or earlier life experiences. I was often in and out of inpatient wards to visit some of the people on my caseload as they grappled with the throes of first episode psychosis.

However, the beginnings of this project provoked my application to the DClinPsy and to in turn become a clinical psychologist. I found that I loved working with people and hearing their stories and that consequently the research took on a new dimension. This research began prior to the beginning of the DClinPsy but my relationship to the project has changed immensely throughout my training. Whilst in research you are trained to isolate specific variables for cause and effect, in clinical practice you are trained to view things holistically and understand an individual within their context.

Section 3.4 **Understanding a participant's context**

This led me to reflect on the disparities between participants recruited in different areas and how this may have impacted their experience of serious mental illness. Prior to starting clinical training, I spent a year researching in America, when I opened Philadelphia as a research site on the study.

Philadelphia is traditionally a poorer city with a majority African American population. This is related to heritage from the American Civil War whereby Philadelphia was one of the first cities deemed free from slavery so naturally became somewhere where many black people from the more southern states decided to settle. It is also traditionally a more industrial city which is considerably less affluent than some of the other major cities along the east coast of America (New York, Washington DC, Boston, etc.).

This gave rise to several differences between to the other sites in the study. First, most service users in PEACE (the service in Philadelphia) were black and the majority of the clinical team supporting them were white. Second, the service was funded by Medicaid which is a government initiative in the USA to provide people with very low incomes (a combined family income of $26,000) free healthcare. PEACE was therefore exclusively for people struggling with poverty in some of the poorest parts of the city. Many of the participants were trapped within the criminal justice system. Indeed, one participant went into prison during their participation in the study for smoking marijuana, another was put on trial for exposure to a minor when he first transitioned to psychosis, and I later discovered that one who presented with an usual sleep pattern was due to the fact that he slept on the streets for three nights a week in order to escape his father at home. Most participants were involved with social services due to difficulties at home and given that they were mostly black, it was hard to see how their race wasn't a determining factor in the treatment they received from the state.

This gave a harrowing first-hand insight into the damage reckoned by poverty and oppression and how this often ran upon racial lines. This is exceptionally difficult to capture numerically and indeed remains uncaptured in the results presented here but will undoubtedly have influenced the participants' experience of both sleep and psychosis. This is an often-unspoken limitation to a lot of clinical research into serious mental illness. Were I to re-run this project, I would try to think more creatively to be able to capture some of these experiences so as to be able to represent participants more as whole objects as opposed to individuals defined by their sleep or severity of psychosis.

Section 3.5 **The Covid-19 pandemic**

This research project was in recruitment in the NHS when COVID-19 first arrived in the U.K. in March 2020. Overnight, the whole study was shut down as the country went into its first

national lockdown on March 23rd 2020. The study was never able to re-open, and this halved the sample size we were hoping to recruit. It was devastating after taking several years to set up the study to have to close it prematurely and not meet target.

This has been a humbling process and difficult year not just from the perspective of research but also for me personally. I battled with low mood and poor motivation at several points over the past year and despite having no personal control over the pandemic, I felt guilty about contacting funders to inform them of how badly the study had been impacted.

However, this has forced me to reassess my values both as a research scientist and a clinician. This has given me an alternate perspective on what is important in empirical research. This study is exceptionally "problem focused" in its orientation, when sleep and circadian rhythmicity could just as easily be used to describe someone's ability to cope or channel resilience within the context of their mental illness. The past year has challenged my ability to cope but, in many ways, bolstered my resilience. I would want my participants to be able not to be defined by what went wrong or what their symptoms were but also what their strengths and capacity for recovery is. This is something I will take with me in all future research projects I design and run.

Section 3.6 **Positive Impact of this Research**

There is a temptation that a critical reflection should focus solely on what went wrong, on what the research missed or could have done more efficiently. But I think there are several facets of this study which I am proud of. First, unusually for a study of this kind, we had waiting lists in every site that we opened. This is because we remained dedicated to a scientist-practitioner approach. All the participants were provided personalised sleep reports to help provide insight and advice into their sleep and circadian rhythmicity. The research team was trained to go through the sleep report with them to explain what the data meant for their sleep pattern. We then uploaded these sleep reports into their clinical notes. At different points during the study, we were contacted by clinicians for support/advice on how to treat poor sleep and for several

of the participants recruited, this study had a direct and meaningful impact on their treatment plans. Seeing the benefits, this resulted in clinicians actively trying to get people from their caseloads into the study and it began to recruit for itself. Our most limiting factor was the very small number of watches we had for the study across sites and the fact that they were used for two weeks at a time.

Second, co-production was a key part in designing the layout of this study. While working in early intervention services during my PhD, I piloted the use of watches with service users and got feedback on what they liked and didn't like about them. It was here that I learned that service users loved seeing their data and getting feedback on what it meant for them which was the beginning of the personalised sleep report. It was also here that I learned that random beep schedules (as are usually implemented in ESM studies) caused unnecessary distress in the participant of worrying about when it might beep and how that would interfere with their schedule or if it would reveal their participation in the study (and in term their use of the service). Finally, I learned the importance of sitting down with a prospective participant to explain what the watch is and what it could and could not do. I learned to ask if there was anything about the watch that made them anxious and whether it would be helpful to take the watch apart. Specifically detailing the watch and calling in to check on the participant led to much better outcomes for ESM completion rates and participant satisfaction.

Third, a goal of this project was to raise awareness around sleep and circadian rhythm disruption in serious mental health. As such, the study team held workshops in each of the sites we opened and in sites where we were invited. This is something I have taken through to clinical training and in each of my placements to date I have held sleep and circadian rhythm workshops and seminars for both service users and clinical teams alike. This is something I look forward to taking into my clinical work and future career as a qualified clinical psychologist.

Finally, this project has taught me immeasurable amounts on what it is to be a leader and to train and lead a team. I personally trained all the research assistants who dedicated their time to this study. I learned how to keep people motivated with targets and goals and how to offer incentives when a certain threshold was met. I learned how to design booklets and training manuals for people who had never studied sleep and circadian rhythms before. I learned a lot around how to consider whether someone was appropriate for this study and how to address disagreement or people doing something that was not in line with the study's outlook or agenda. I learned the importance of acknowledging and praising good work but also how to broach when something wasn't quite at the standard or below target. This will shape and inform my ability to lead in clinical teams going forward.

Section 3.7 **Implications for future research and final conclusions**

I think this study has ignited a passion in me to look at more recovery focused outcomes regarding sleep and circadian rhythms. I have also learned the importance of engaging with the participants and offering them an experience that goes beyond payment to thank them for their time. Finally, I have learned that the only way to really get services to incorporate sleep treatment and assessment into their agenda is by involving them from the ground up in the research and providing live examples of what can be achieved when clinical work and empirical research work seamlessly together. Overall, this project has been exceptionally challenging but immeasurably beneficial to me and to informing the kind of clinician I will be going forward.

Appendices

Appendix 1

Mediation Analysis: Effect of Objective and Subjective Sleep Parameters on Next Day Morning Negative Affect After Adjusting for Age, Gender, Site, Morning Negative Affect, Subject ID and Day in Study

Predictor Variable	β Coefficient	SE	df	t	P - value
Outcome: Morning Negative Affect					
DASS-21 Depression Score	-0.39	0.12	746.41	-3.25	0.001
Age	0.15	0.66	38.66	0.24	0.82
Gender (M)	19.02	6.13	39.20	3.10	<0.01
Site (PEACE)	-8.17	6.71	38.59	-1.22	0.23
Site (West London)	-12.00	8.68	39.65	-1.38	0.17
Subjective Sleep Quality	-1.21	0.33	770.47	-3.66	<0.001
Total Sleep Time	-0.41	0.35	757.41	-1.18	0.24
Sleep Onset Latency	1.94	1.48	737.10	1.31	0.19
Circadian Phase	0.10	0.40	744.69	0.25	0.80

Appendix 2

This appendix contains the published adapted form of Part 1 of this thesis, which is referenced as:

Cosgrave, J., Klingaman, E. A., & Gehrman, P. (2020). Chapter 11 - Effectively Assessing Sleep and Circadian Rhythms in Psychosis BT - A Clinical Introduction to Psychosis. In J. C. Badcock & G. Paulik (Eds.), *A Clinical Introduction to Psychosis* (pp. 245–272). Academic Press. http://www.sciencedirect.com/science/article/pii/B9780128150122000110