UNRAVELLING THE LINKS BETWEEN PSYCHOTIC-LIKE EXPERIENCES, SLEEP AND CIRCADIAN RHYTHMS.

Jan Frances Cosgrave
St John's College
University of Oxford

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Abstract

Psychotic-like experiences (PLEs) are prevalent occurrences deemed comparable with the symptoms of psychosis, but not sufficiently severe to warrant a diagnosis upon clinical presentation. Their presence is associated with several adverse clinical outcomes: the onset of various common mental health disorders (e.g. anxiety, mood, substance abuse), poorer functioning, non-remission and relapse.

Sleep and circadian rhythm disruption (SCRD) is observed in 30-80% of patients with psychosis. The omnipotence of SCRD across all phases of the disorder (including the prodromal, acute, chronic and residual phases) raises the question as to whether SCRD may directly contribute to the development of psychosis.

Assuming that PLEs are along the same continuum to developing psychosis, a logical next step to further disentangle the sleep-psychosis relationship is to examine whether SCRD relates to the experience of PLEs and whether this relationship is bi-directional.

This thesis begins by examining the core predictions made by a continuum model of understanding psychosis and how specific parameters of sleep may influence PLEs. A smaller high-definition cross-sectional study follows, examining biological underpinnings (electroencephalography (EEG), electrocardiography (ECG), endogenous melatonin rhythms and actigraphy) of a complaint of poor sleep and their relation to the occurrence of PLEs. We then refocus on which parameters of sleep are most integral to the sleep-PLE relationship and close with an investigation of how Hypothalamic Pituitary Adrenal (HPA) axis activity may further our knowledge of this relationship.

The findings of this thesis demonstrate specificity in the parameters of sleep shown to impact certain PLEs. The importance of objective sleep and biologically driven measures in this line of research are underscored, with group differences in EEG, ECG and melatonin. This thesis also highlights dissociative symptomatology as a candidate mediator for the sleep-psychosis relationship, and emphasises the ties between paranoia and negative affect. Finally, this thesis also illuminates the challenges of examining the relationship between sleep and PLEs in isolation, and suggests that they must be considered within the broader framework of co-existing mental health problems.

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Abbreviations and Acronyms

AASM	American Academy Sleep Manual
ACTH	Adrenocorticotropin Releasing Hormone
AI	Arousal Index
AIC	Akaike's Information Criterion
AMT6	6-hydroxymelatonin sulphate
ANOVA	Analysis of Variance
ANS	Autonomic Nervous System
ASD	Autism Spectrum Disorder
AUC	Area Under the Curve
AVP	Vasopressin
BDD	Body Dismorphic Disorder
BI	Bizarre Ideas
BIC	Bayesian Information Criterion
BP	Bipolar
BRS	Brief Resilience Scale
CAR	Cortisol Awakening Response
CD	Cognitive Disorganisation
CNS	Central Nervous System
CRH	Corticotropin Releasing Hormone
DASS	Depression Anxiety Stress Scale
DE	Dissociative Experiences
DES	Dissociative Experiences Scale
DLMO	Dim Light Melatonin Onset
DM	Delusional Mood
DSM V	Diagnostic Statistical Manual of Mental Disorders 5th Ed.
ECG	Electrocardiogram
EEG	Electroencephalography
EIS	Early Intervention Service
EMG	Electromyograph
ESM	Experience Sampling Method
FEP	First Episode of Psychosis
FFT	Fast Fourier Transform
GAD	Generalised Anxiety Disorder
GEE	Generalised Estimating Equation
GPTS	Green Paranoid Thought Scale
HF	High Frequency Activity
HPA	Hypothalamic-Pituitary-Adrenal
HR	Heart Rate
HRV	Heart Rate Variability
ipRGCs	Intrinsically Photosensitive Retinal Ganglion Cells
ISI	Insomnia Severity Index
LF	Low Frequency Activity
LF/HF	Low Frequency to High Frequency Ratio
LTE	Traumatic Life Threatening Experiences Scale

MCTQ	Munich Chronotype Questionnaire
MDD	Major Depressive Disorder
MDQ	Mood Disorder Questionnaire
MEQ	Morningness-Eveningness Questionnaire
MLT	Melatonin
MSE	Multiscale Entropy
MSFsc	Mid-Sleep point of Free days, Sleep Corrected
NREM	Non Rapid Eye Movement sleep
NS	Negative Symptoms
OCD	Obsessive Compulsive Disorder
OR	Odds Ratio
OWLS	Oxford Wellbeing and Life Survey
PA	Perceptual Abnormalities
PAD	Phase Angle Difference
PDEQ	Peritraumatic Dissociative Experiences Questionnaire
PE	Psychotic Experiences
PI	Persecutory Ideation
PLE	Psychotic-Like Experience
PNS	Parasympathetic Nervous System
PPPI	Psychosis Proneness Persistence Impairment
PQ16	Prodromal Questionnaire (16 Item Version)
PSG	Polysomnography
PSQI	Pittsburgh Sleep Quality Index
PTSD	Post-Traumatic Stress Disorder
PVN	Paraventricular Nucleus
QIC	Quasi Information Criterion
REM	Rapid Eye Movement sleep
rMSSD	Square root of the mean sum of squared differences between adjacent RR intervals
ROC	Receiver Operating Characteristic
RR	R wave to R wave interval
SCI	Sleep Condition Indicator
SCN	SupraChiasmatic Nucleus
SCRD	Sleep and Circadian Rhythm Disruption
SD	Sleep Disturbance
SDANN	Standard Deviation of the RR interval
SE	Sleep Efficiency
SES	Socio-economic Status
SJL	Social Jet Lag
SNS	Sympathetic Nervous System
SOB	Season of Birth
SOL	Sleep Onset Latency
SPQ BR	Schizotypal Personality Questionnaire –Brief Revised
SREM	Slow Rolling Eye Movements
SSPS	Social State Paranoia Scale
STAI	State Trait Anxiety Index
SWA	Slow Wave Activity
SWS	Slow Wave Sleep
SZ	Schizophrenia
TIB	Time In Bed
TST	Total Sleep Time
VLPO	Ventro-lateral preoptic nucleus
WASO	Wake After Sleep Onset
WHO	World Health Organisation

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Chapter 1:
Introduction

1.1 Schizophrenia, Psychosis and their Burden 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, Suppes, & van Os, 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 1.1 for the current Diagnostic and Statistical Manual of Mental Disorders V criteria (DSM-V; American 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 them the third most expensive brain condition in the UK (after dementia and mood disorders; Fineberg et al., 2013).

In order to reduce the liability of these disorders on people and society as a whole, a better understanding of what causes them is needed, and in turn, of how best to treat them early on in their 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 (Velden Hegelstad et al., 2012).

1.2 The Many Continua of Psychosis

Psychotic-like experiences (PLEs) are prevalent occurrences deemed comparable to the positive symptoms of psychosis, but are not sufficiently severe to warrant a diagnosis upon clinical presentation. What can be defined as a PLE varies, with earlier definitions encompassing just the experience of hallucinations and delusions (which are referred to as psychotic experiences (PEs) as opposed to PLEs; Linscott & van Os, 2013). More recent definitions incorporate a much broader array of experiences. For the purpose of this thesis we have taken a broad definition of PLEs, which encompasses a comprehensive range of positive-like symptoms for psychosis despite the absence of a clinical disorder. **Table 1.1** and **Table 1.2** identify and define the PLEs explored in this thesis. Our primary method of measuring PLEs is the Prodromal Questionnaire (16 item version; please refer to Box 1.2 for an overview of this questionnaire; Ising et al., 2012).

Whilst considered along the same spectrum as psychosis, PLEs may not result in distress, prompt help seeking behaviour, or be bizarre (Linscott & van Os, 2013). These symptoms may be judged as being clinically relevant, or as subclinical due to the nonappearance of adequate consequences of a disorder being present (Linscott & van Os, 2013). PLEs are to some extent undifferentiated from personality traits, which are commonly referred to as schizotypal traits or a schizotypal personality (Linscott & van Os, 2013).

Box 1.1: Schizophrenia DSM V – 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).

PLEs are prevalent in the general population and are endorsed at a rate of approximately 7% (Linscott & van Os, 2013). While approximately 80% of this group will find these experiences to be fleeting, the residual 20% continue to develop enduring psychotic symptoms. From this 20%, approximately 7% will go on to develop their first episode of psychosis (FEP), with a conversion rate of just below 1% per annum (Kaymaz et al., 2012). This suggests that PLEs exist as a continuum within the population and vary with regards to frequency, degree of conviction, preoccupation and the number of different phenomena experienced (Zammit et al., 2013). It also underscores the notion

that 'low grade' or subsyndromal psychotic symptoms are associated with an increased relative risk of later developing a psychotic disorder (Kaymaz et al., 2012).

While earlier work focused on the examination of PLEs as gauges of risk for later developing full psychosis, evidence is accumulating that the risk associated with PLEs extends far beyond psychotic disorders (Kelleher & Cannon, 2011). Indeed, PLEs are associated with the onset of a number of common mental heath disorders including anxiety, mood, substance abuse disorders and suicidality (both ideation and intent; McGrath et al., 2015). Individuals who report PLEs have been shown to have poorer functioning than those without. This effect is exacerbated in the presence of an Axis I diagnosis (Kelleher et al., 2015). When PLEs exist within depression, they predict important clinical outcomes including heightened depressive symptomatology, non-remission and relapse (Wigman et al., 2014). Thus, awareness is growing that PLEs may reflect a susceptibility to a broad spectrum of adverse mental health outcomes, and as such merit their own platform for research to further understand their aetiology and phenomenology (McGrath et al., 2015).

Box 1.2: The Prodromal Questionnaire (16 Item Version; PQ16)

The PQ-16 contains 16 items each with yes/no responses, yielding a score out of 16. A score above 5 warrants further screening for an at risk mental state. Across the 16 items, the Questionnaire assesses several positive symptoms including visual and auditory hallucinations, delusional mood/perplexity, ideas of reference, persecutory thoughts, depersonalisation, derealisation and absorption. Two negative symptoms (excessive social anxiety and avolition) are also evaluated.

This questionnaire has been selected as the main outcome measure for PLEs in this thesis for a number of reasons.

First, it does not have 'hypothetical qualifiers' or describe beliefs of cultural subgroups (e.g. voodoo) which have been highlighted to produce misleading results in the estimated prevalence of PE (Linscott & van Os, 2013).

Second, it covers a broad spectrum of psychotic experiences, not just delusions and hallucinations.

Third, it has good psychometric properties in both healthy and high-risk populations and is quick and easy to score. An overview of different PLEs that can be experienced and how they are examined in the PQ16 can be found in **Table 1.1** and **Table 1.2**.

Factor	PLE	Definition	PQ16 Item(s)
Perceptual Abnormalities	**Visual**	Things appearing different/abnormal (e.g. alterations in colour brightness). Seeing things that other people can't see.	**Item 8:** I have seen things that other people apparently can't see.
	Auditory	Differences in the way things sound (e.g. increased/decreased sensitivity). Hearing things (e.g. voices/sounds) that others cannot hear.	**Item 4:** I often hear unusual sounds like banging, clicking, hissing, clapping or ringing in my ears. **Item 12:** Sometimes I feel suddenly distracted by distant sounds that I am not normally aware of. **Item 13:** I have heard things other people can't hear like voices of people whispering or talking.
	Olfactory	Fluctuations in the ability to smell things (more or less intense). Smelling things that others do not smell.	**Item 3:** I sometimes smell or taste things that other people can't smell or taste.
	Gustatory	Fluctuations in the sense of taste (more or less intense). Experiencing unusual tastes in your mouth .	**Item 3:** I sometimes smell or taste things that other people can't smell or taste.
	Tactile	The experience of strange feelings on or beneath the skin.	*Not examined in PQ16*
	Somatic	Strange feelings in your body (e.g. things are working differently or there is a problem somewhere in the body). Changes in bodily sensations such as heightened or reduced sensitivity.	**Item 16:** I feel that parts of my body have changed in some way, or that parts of my body are working differently than before.
Conceptual Disorganisation (Dissociative Symptoms)	**Depersonalisation**	The repeated experience of feeling detached from one's self and one's own mental processes. This includes experiences of feeling you are standing next to yourself, seeing yourself in the 3rd person or a loss of reality with the immediate environment.	**Item 6:** When I look at a person, or look at myself in a mirror, I have seen the face change right before my eyes.
	Derealisation	The experience of losing touch or a sense of reality with the immediate environment. Examples are feeling that other people or objects around them are not real.	**Item 5:** I have been confused at times whether something I experienced was real or imaginary.
	Absorption	The sense of being so preoccupied or absorbed by something that you become inattentive to what is happening around you. Examples include: realising you did not hear part of a conversation you are having with another person, reliving an experience when you are uncertain as to whether the event actually happened or was conjured in a dream.	**Item 2:** I often seem to live through events exactly as they happened before (déjà vu).

Table 1.1: Part I of overview of different psychotic-like experiences examined in the PQ16 and the respective psychotic symptom category they are associated with. Definitions of PLEs are based upon those provided by the Comprehensive Assessment of At Risk Mental States (CAARMS; Yung, Phillips, McGorry, Ward, Donovan, & Thompson, 2002). Cognitive Disorganisation in this context overlaps perfectly with the three main categories of dissociative symptoms according to the Dissociative Experiences Scale (Bernstein et al., 1993), which is further discussed in Sections 2.6.1.1 and 2.6.1.2.

Factor	PLE	Definition	PQ16 Item(s)
Bizarre Ideas	**Ideas of Reference**	Having the experience that something around you has special meaning or people trying to pass on messages.	**Item 10:** I sometimes see special meanings in advertisements, shop windows, or in the way things are arranged around me.
	Thought Broadcasting	Feeling as though your thoughts are broadcast so that others know what you are thinking.	**Item 9:** My thoughts are sometimes so strong that I can almost hear them.
	Thought Insertion	The feeling of having thoughts that are not your own being inserted into your head.	**Item 11:** Sometimes I have felt that I'm not in control of my own ideas or thoughts.
	Made Thoughts	The feeling that something outside yourself is controlling your thoughts/feelings/actions.	*Not examined in the PQ16*
	Somatic Passivity	Experiencing strange sensations in the body due to forces outside yourself.	**Item 16:** I feel that parts of my body have changed in some way, or that parts of my body are working differently than before.
Paranoia	**Persecutory Ideation**	Feelings of being watched, followed, talked about or laughed at.	**Item 14:** I often feel that others have it in for me.
Delusional Mood		Feeling puzzled by reality or surroundings, or the experience that familiar surroundings feel strange.	**Item 15:** I have had the sense that some person or force is around me, even though I could not see anyone.
Negative Symptoms*	**Avolition**	An extreme lack of motivation (also commonly found in depression)	**Item 1:** I feel uninterested in the things I used to enjoy.
	Social Anxiety	An overwhelming fear or anxiety of social situations.	**Item 7:** I get extremely anxious when meeting people for the first time.

Table 1.2: Part II of overview of different psychotic-like experiences examined in the PQ16 and the respective psychotic symptom category they are associated with. *Cognitive deficits are also considered a core part of the negative symptoms of psychosis but are not examined in this thesis (Bora & Murray, 2014).

1.3 The Basic Principles of Sleep – Introducing the Two Process Model

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). 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; Borbély, 1982). This is known as the Two Process Model of Sleep Regulation and was first championed by Borbely 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 (circa diem – 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, Acebo, & Carskadon, 2007). The term "period" of the rhythm refers to the time needed to complete one full oscillation (Grandin, Alloy, & Abramson, 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).

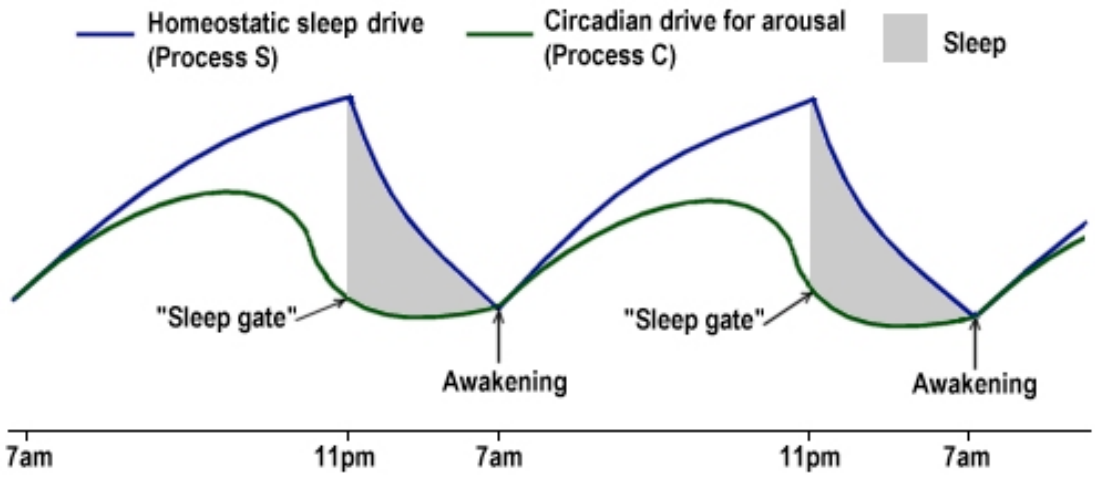

Figure 1.1: A schematic representation of the Two-Process Model of Sleep Regulation (adapted from Daan, Beersma, & Borbély, 1984). The blue line represents Process S or the sleep drive. Sleep pressure is low upon awakening and progressively increases as a function of time awake throughout the day, peaking 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.

1.4 The Suprachiasmatic Nucleus

The SCN consists of bilateral nuclei that contain approximately 10,000 neurons each (Takahashi, Hong, Ko, & McDearmon, 2008) and receives photic information collected by photoreceptor cells in the retina via the retinohypothalamic tract (RHT). 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. 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. These processes are further discussed in Chapter 4 and Chapter 7.

The SCN contains cells with intrinsic rhythmicity that can generate a self-sustained rhythmicity (even in the absence of light) via an auto-regulatory transcription-translation feedback loop, which regulates the expression of Period (Per1, Per2, Per3), Cryptochrome (Cry1, Cry2), TIM, DEC1 and DEC2

genes. The functioning of the clock on a molecular level is beyond the scope of this thesis, but Takahashi et al. (2008) provides a comprehensive overview.

The term "free running" refers to the SCN's rhythmicity in the absence of external time cues. 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 meal-times, clocks and exercise. A notable downstream projection of the SCN is the pineal gland, which is responsible for melatonin synthesis. This process is further described in Chapter 4.

1.5 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, Hughes, Kronauer, Dijk, & Czeisler, 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 (or "larks"), late (or "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 click (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, Le Floc'h, Kindelberger, & Feunteun, 2010). Several genetic polymorphisms are also associated with different chronotypes (Archer et al., 2010), as are different psychiatric disorders (Wulff, Gatti, Wettstein, & Foster, 2010a). Chronotype is further discussed in Chapter 4.

1.6 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. NREM sleep is further divided into four stages on the basis of 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). Stage 1 is observed immediately after the onset of sleep and is categorised by slow rolling eye movements (SREM). Stage 2 sleep is determined by the presence of specific wave types called sleep spindles (short bursts of high frequency between 12-14 Hz) and K-complexes and predominantly lies in the theta band (6-7 Hz). Stages 3 and 4, or slow wave sleep (SWS), is characterised by delta activity (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, SWS is considered to be the deepest and most restorative sleep stage, and shows the strongest relationship to how we report subjective sleep quality (Akerstedt, Hume, Minors & Waterhouse, 1997).

Slow wave sleep (SWS; stages 3 and 4) 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 1.2** below for an overview of sleep architecture.

1.7 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).

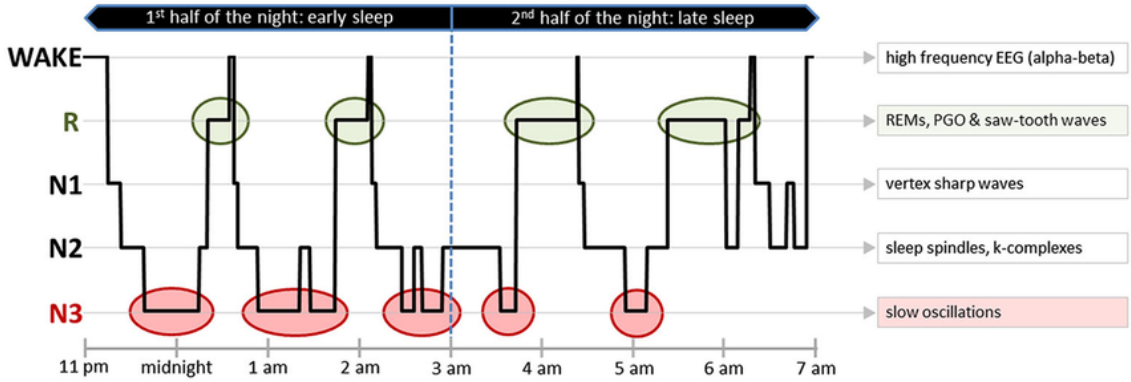

Figure 1.2: A sleep hypnogram depicting a healthy night of sleep across an 8-hour period. The left-hand side of the figure indicates sleep stage and the right-hand side refers to the characteristics found within the EEG signal used to score the sleep stage. Early sleep is predominately characterised 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, del Giudice, Wislowska, Lechinger, & Schabus, 2015).

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

Sleep and circadian rhythm disruption 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 1.3** for a schematic overview of different sleep phenotypes.

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 1.3** for an overview; taken from Wulff, Gatti, Wettstein, & Foster, 2010a).

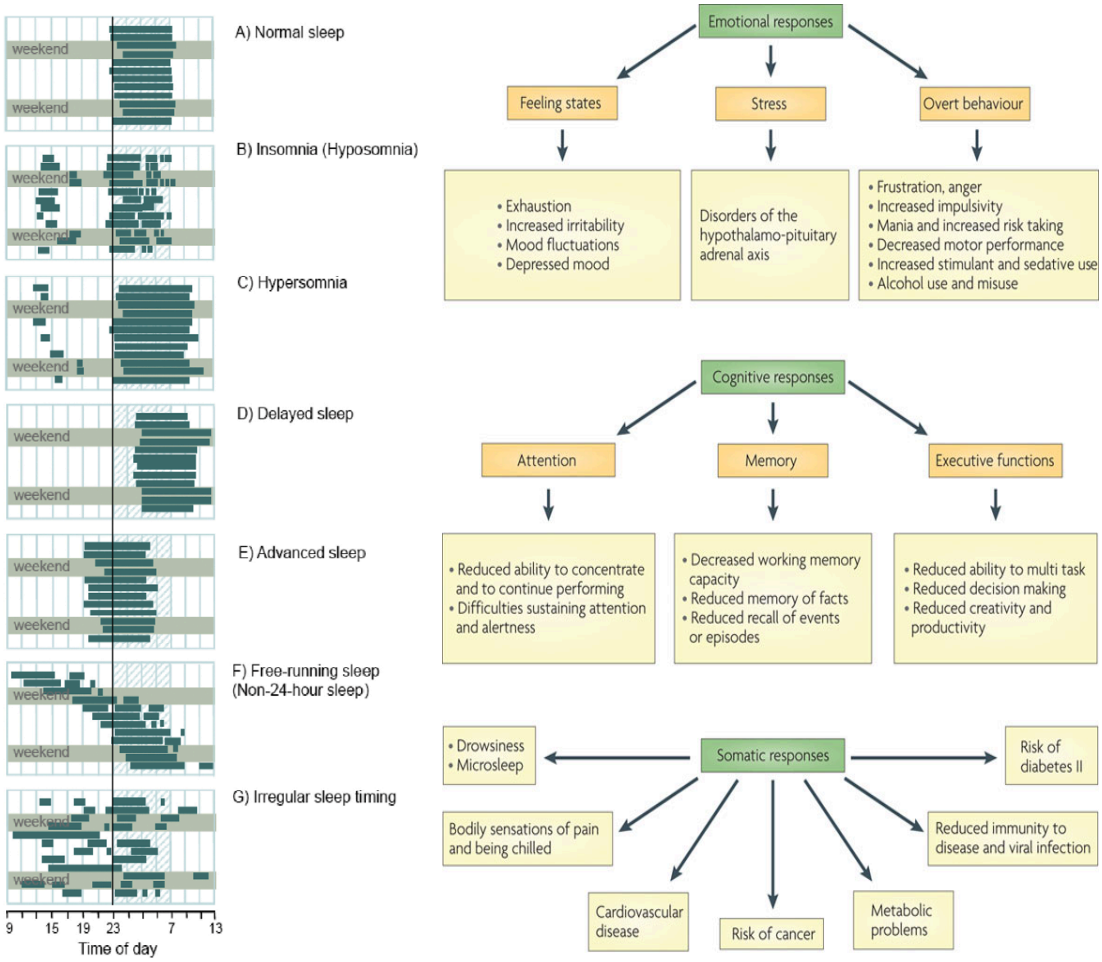

Figure 1.3: On the left-hand side, normal sleep (A) is compared to abnormal sleep patterns (B-G). In order for a sleep patterning or phenotype to be classified as abnormal, it must be such that the individual reports it as distressing and impactful upon their wellbeing/ability to go about daily obligations. 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) 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 are primarily arise from Process C related problems. However, all of the above phenotypes are fall under the umbrella of SCRD. Taken and adapted from Wulff, Porcheret, Cussans, & Foster (2009b).
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, Gatti, Wettstein, & Foster (2010a).

1.8 Insomnia Disorder

Insomnia is the most prevalent sleep disorder. An estimated 25% of adults report dissatisfaction with their sleep, and of these, approximately 10-15% report insomnia symptoms that are allied with daytime functioning and impairment, with 6-10% meeting the criteria for insomnia disorder (Buysse, 2008). This renders insomnia one of the most common complaints in primary care (Aikens & Rouse, 2005). At a chronic level, the burden of insomnia to the individual is great, with reduced quality of

life, cognitive impairments, and an increased risk of accidents occurring at home, work and while driving, as well as an increased risk of other psychiatric and medical health disorders (Morin & Benca, 2012).

Insomnia is characterised as either the complaint of persistent discontent with subjective quality or duration of sleep, difficulties initiating or maintaining sleep, or the impression that the sleep obtained is non-restorative. In order to meet the definition of insomnia, these subjective complaints of sleep must be married with reports of daytime dysfunction and must be present for at least three nights per week for a minimum period of three months (Dodds, Miller, Kyle, Marshall, & Gordon, 2016; Morin & Benca, 2012).

Insomnia has been found to be associated with a number of medical conditions, including chronic pain, coronary heart disease, Parkinson's disease and gastrointestinal disorder (Thase, 2005). Insomnia merits its own mention in this chapter (separately from other sleep disorders), due to its high prevalence and omnipotence across numerous psychiatric disorders (Harvey, Murray, Chandler, & Soehner, 2011). Insomnia's co-occurrence with mental health problems is staggering, with insomnia diagnoses found to be comorbid in depression and anxiety in 69-73% of cases (Johnson, Roth, & Breslau, 2006).

1.9 SCRD and Mental Health

The notion that sleep disruption and atypical brain functioning may be intertwined has predated modern psychiatry. 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 (Kraepelin, 2007).

Previously, recognition of sleep and circadian rhythm disruption in psychiatric disease was limited to the context of secondary factors such as side-effects of medication (Wirz-Justice, Haug, & Cajochen, 2001), abnormal light exposure (Wirz-Justice, 2006), abnormal social timing (Grandin et al., 2006) and pain (Smith, Perlis, Smith, Giles, & Carmody, 2000). However, the identification of common mechanistic pathways between SCRD and psychiatric disease has permitted more dynamic

interpretations of the relationship (Wulff, Gatti, Wettstein, & Foster, 2010a). Assigning simple 'cause and effect' interpretations to abnormal sleep phenotypes and SCRD in mental health is not likely to be fruitful. Assuming neurotransmitter systems on some level are impacted in psychiatric disease, this impact is also likely to impact Processes C and S. These processes also impact on a broad array of neural and neuroendocrine functioning that are likely to impact mental health status. SCRD itself impacts on social behaviours, such as light exposure, which is likely to further destabilize our internal rhythms and physiology. Many of these abnormalities will also impact upon the stress axis. When these disruptions are combined with the use of medication, substance abuse or other forms of self-medication, an interaction with all of these processes is likely, further complicating the processes to which SCRD and mental health are directly linked (as well as adjacent; Wulff, Gatti, Wettstein, & Foster, 2010a).

Despite these complications, numerous aberrations in the timing and architecture of sleep are frequently cited as comorbidities in a plethora of psychiatric disorders (**Table 1.3**). Changes in sleep behavior 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, Gatti, Wettstein, & Foster, 2010a). The mechanisms which regulate these relationships are poorly understood (Wulff, Gatti, Wettstein, & Foster, 2010a). 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; see below), and (3) associations between circadian genes and psychiatric disorders. A schematic diagram of this relationship is displayed in **Figure 1.4**. There are numerous additional candidate mechanisms, including social isolation, cognitive deficits, medical health problems, and side effects of medication. All of these additional candidate mechanisms contribute to alterations in both psychiatric disease and SCRD, but for the purposes of this thesis, we limit our exploration to the three listed above.

Sleep Phenotype	Related Disorder
Delayed Sleep Phase	Schizophrenia Obsessive Compulsive Disorders Seasonal Affective Disorder Bipolar Disorder
Non-24h Sleep phase	Schizophrenia
Irregular sleep-wake cycle	Schizophrenia (48h cycle)
Fragmented sleep with daytime naps	Schizophrenia Post-traumatic stress disorder Unipolar Depression
Hypersomnia	Bipolar Disorder (depressive phase) Unipolar depression Schizophrenia
Hyposomnia	Schizophrenia Chronic Insomnia Post-traumatic stress syndrome Alcoholism Bipolar disorder (both depressive and manic phases) Unipolar depression Autism Generalised Anxiety Disorder

Table 1.3: Sleep wake phenotypes found to be associated with different psychiatric disorders. Adapted from Wulff et al. (2009b).

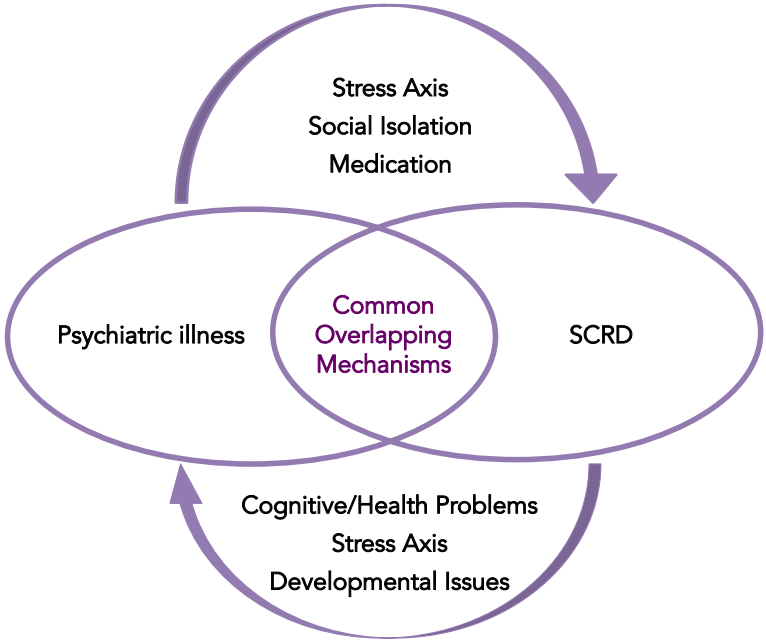

Figure 1.4: Schematic diagram illustrating possible relationships between psychiatric illness and sleep and circadian rhythm disruption (SCRD). It is thought that SCRD and psychiatric illness share common overlapping mechanisms. Atypical functioning of neural circuitry (acting upon several neurotransmitter 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 1.3**) and may impact development in younger cohorts. Adapted from Foster et al. (2013).

1.9.1 Sleep Disturbance and Emotional Dysregulation

Extensive amounts of behavioural data now support what is often anecdotally reported: sleep disturbances powerfully intensify negative mood, including anxiety, confusion, depressive symptoms, distress and catastrophising (e.g. Dinges et al., 1997; Fairholme & Manber, 2015; Franzen, Siegle, & Buysse, 2008; Novati et al., 2008; Talbot, McGlinchey, Kaplan, Dahl, & Harvey, 2010; Kahn-Greene, Killgore, Kamimori, Balkin, & Killgore, 2007). Experimentally-induced sleep deprivation research has shown positive mood to be attenuated in both intensity and frequency in sleep-deprived subjects (Paterson et al., 2011). Sleep disturbances also exaggerate negative emotional responses to goal-thwarting events, but equally blunt the positive emotional response to goal-enhancing events (Zohar, Tzischinsky, Epstein, & Lavie, 2005). Neurologically, sleep deprivation has also been shown to attenuate medial prefrontal cortical activity and heighten amygdala activation, which are known drivers of emotion in the brain (Yoo, Gujar, Hu, Jolesz, & Walker, 2007).

Furthermore, there is good evidence to suggest this relationship is bidirectional. First, a number of emotional states including stress (Galambos, Vargas Lascano, Howard, & Maggs, 2013), anxiety (LeBlanc et al., 2009) and pre-sleep negative emotion (e.g. Vandekerckhove et al., 2011) have been reported to have a negative impact on both sleep duration (longer time spent getting to sleep and more time awake after sleep onset) and architecture (decreases in slow wave sleep and REM counts across the night; for a review please refer to Kahn, Sheppes, & Sadeh (2013)). Furthermore, from a molecular standpoint, orexin neurons located in the hypothalamus receive afferents from areas known to regulate emotion (such as the amgydala), which are known drivers of sleep-wake behaviour (Yoshida, McCormack, España, Crocker, & Scammell, 2006). However, longitudinal observational studies employing high-resolution techniques are still lacking in this field. This is further addressed in Chapter 6.

1.9.2 The Stress Axis

The experience of stress occurs when somebody observes the pressures of their environment to be "…as taxing or exceeding his or her resources and endangering his or her well-being" (p.19, Folkman, 2013). In response, the physiological consequences of stress are activated. These consist of both top-down central nervous system processes (which constitute the cognitive component of

stress, e.g. 'I feel I can't cope with the situation') and sub-cortical processes located within the limbic system (constituting the emotional stress component, e.g. anxiety). Together, these areas forward their signals (e.g. 'I am in danger!') via efferent neuronal pathways towards the hypothalamus, which colloquially is considered the 'control centre' of the brain for the stress axis (Tsigos & Chrousos, 2002). It earns this reputation because it is linked to two of the core systems responsible for the physiological response to stress: the hypothalamus-pituitary-adrenal (HPA) axis, and the autonomic nervous system (ANS), which are referred to as endocrine and autonomous responses respectively. Collectively, the HPA axis and the ANS coordinate numerous psychological (e.g. emotional processing) and physiological (e.g. endocrine and cardiovascular activation) processes to safeguard physiological homeostasis of the individual being challenged by their environment (Del Rey, Chrousos, & Besedovsky, 2008; Sapolsky, Romero, & Munck, 2000). The primary output of the HPA axis is the 'stress hormone' cortisol. The ANS has two branches labelled the sympathetic (SNS) and parasympathetic nervous system (PNS). Together, they control a wide range of bodily systems, including cardiovascular, respiratory, gastrointestinal, renal and endocrine functioning. The sympathetic nervous system is considered responsible for the 'fight or flight' response to the environment (Beauchaine & Thayer, 2015). Chemically, this is regulated by the release of noradrenaline (norepinephrine) from the sympathetic nerve terminals throughout the body, as well as the secretion of adrenaline (epinephrine) from the adrenal medulla (Meerlo, Sgoifo, & Suchecki, 2008). In opposition, the parasympathetic nervous system is the 'rest and digest' system. These systems are considered to have conflicting responses, where one system initiates a physiological response, and the other inhibits it (Meerlo et al., 2008).

1.9.2.1 The Stress Axis: Autonomic Functioning

A core theory underlying the formation of psychopathology is the dysregulation of the stress axis (in both endocrine and autonomic responses). Physiological hallmarks of the ANS frequently employed in psychopathology research are heart rate (HR) and heart rate variability (HRV). HRV is an objective measure used to describe the variation in time that occurs between consecutive heartbeats. HRV is generally derived from the analysis of inter-beat timings, which are referred to as the RR (R wave to R wave) intervals. Descriptive measures of the RR interval over certain time epochs, such as the standard deviation (SDANN) or the square root of the mean of the sum of squares of differences between adjacent RR intervals (rMSSD), are examples of time domain measures used in the

examination of HRV (Dodds et al., 2016).

High resting HR and low HRV are considered physiological indicators of hyperarousal, both indicating inflexibility in cardiovascular control. It is approximately two decades since the first studies emerged that linked HR and HRV to psychopathology. Earlier studies examined the relationship between tonic HRV and psychological adjustment outcomes in children, adolescents and adults (Fabes, Eisenberg, & Eisenbud, 1993; Liew et al., 2011), temperamental complaisance (Huffman et al., 1998), and attachment security and positive social interactions with partners (Diamond, Fagundes, & Butterworth, 2012). Conversely, low HRV has been associated with a plethora of internalising and externalising psychopathology (e.g. Beauchaine, 2012; 2015) and psychiatric disorders including anxiety (e.g. Kemp et al., 2014), phobias (e.g. Åhs, Sollers, Furmark, Fredrikson, & Thayer, 2009), autism (e.g. Neuhaus, Bernier, & Beauchaine, 2014), depression (e.g. Rottenberg, 2007), panic disorder (e.g. Asmundson & Stein, 1994) and schizophrenia (Montaquila, Trachik, & Bedwell, 2015), amongst others (please see Beauchaine & Thayer (2015) & Pittig, Arch, Lam, & Craske (2013) for reviews).

In the reverse direction, sleep is known to have a profound effect on cardiovascular functioning. This effect is impacted by both sleep architecture (sleep stage) and quality (amount of slow wave sleep and wake after sleep onset, etc.; Burgess, Trinder, Kim, & Luke, 1997). More recently, it has been suggested that differences in HR and HRV in different psychiatric disorders may also manifest as heightened arousal during sleep. The research in this area is still in its infancy, but evidence can be found in spectral analyses of EEG displaying heightened amounts of alpha and beta frequencies during sleep (e.g. Armitage & Hoffmann, 2001; Jurysta et al., 2010), and also via increased nocturnal HR and decreased nocturnal HRV during sleep (Brosschot, Van Dijk, & Thayer, 2007; Spiegelhalder et al., 2011; Yang et al., 2011). This succinctly demonstrates a viable pathway by which psychopathology (via stress axis dysregulation in the ANS) may incur SCRD.

Furthermore, we know both noradrenaline and norepinephrine (products of SNS activation) have been shown to vary according to the time of day. Adrenaline in particular shows a pronounced daily rhythm, which is a consequence of the sleep-wake rhythm but also subject to circadian regulation via the master clock, independently of sleep-wake regulation. Equally, we know that transitions from

wake to sleep have been characterised as the autonomic balance of cardiovascular regulation shifts to parasympathetic dominance (Meerlo et al., 2008). Increased SNS activation has been shown to occur following both sleep deprivation and also interrupted/fragmented sleep. Moreover, when recovery sleep is inadequate, both heart rate and blood pressure remain elevated, indicating greater sympathetic activity (please see Meerlo et al., 2008 for a review). Thus, prolonged SCRD could result in chronic dysregulation of the ANS, rendering an individual more susceptible to psychiatric disease. HR and HRV, and their relationship to sleep, are discussed in further detail in Chapter 3.

1.9.2.2 The Stress Axis: HPA Axis Functioning

As described in Section 1.9.2, cortisol is the primary effector of the HPA axis and is commonly labelled as the 'stress hormone' (Chida & Steptoe, 2009). Full details of cortisol synthesis and its relationship to sleep-wake regulation are discussed in Chapter 7. As such, we provide here only a brief overview of cortisol's relationship to sleep and mental health.

Cortisol synthesis and secretion are established to have strong ties to sleep-wake regulation, based on research studies whose findings can be summarised into three key points. First, the rhythmic patterns of daily cortisol secretion are under the circadian control of the master clock. Second, sleep deprivation results in mild increments in cortisol levels, although this has been contested (please see Meerlo et al., 2008 for a review). Third, if recovery sleep (post-deprivation) is insufficient, cortisol levels have been shown to remain elevated the following day. Whilst these relationships have been shown to be small, it is anticipated that chronic or repeated elevation of cortisol may result in a significant 'cortisol load' which could be instrumental in shifting the brain from adaptation to disease, particularly in vulnerable individuals (De Kloet, Joëls, & Holsboer, 2005). Chronic elevation of glucorticoids (cortisol) have been found to be associated with decreased neuronal plasticity and neurogenesis, which in turn have been deemed as potential candidates for pathophysiological mechanisms of mood disorders (Dranovsky & Hen, 2006; Elbejjani et al., 2015; Sapolsky et al., 2000).

Thus, it has been suggested that cortisol may become dysregulated due to SCRD, which in turn makes an individual more vulnerable to psychiatric disease (Wulff, Gatti, Wettstein, & Foster, 2010a). In opposition, daily cortisol rhythms and the cortisol awakening response are also thought to be a physiological hallmark of a number of psychiatric disorders (Fries, Dettenborn, & Kirschbaum, 2009;

Kudielka & Kirschbaum, 2003). This highlights the bi-directional nature of the relationship: SCRD dysregulates HPA axis activity and impacts cortisol synthesis, rendering persistent sufferers of SCRD more vulnerable to psychiatric disease (potentially via mechanisms of neural plasticity). Conversely, sufferers of psychiatric disease display anomalous cortisol secretion patterns compared to healthy controls, which may impact the internal synchrony of the circadian pacemaker and equally result in poorer quality sleep, resulting in a vicious cycle. The relationship between cortisol, sleep and psychiatric disease is explored in more detail in Chapter 7.

1.9.3 Association between Circadian Genes and Mental Health Disorders

The production of circadian rhythms at a subcellular level is believed to rest upon the activity of a core group of clock genes. Central to this process is an auto-regulatory series of feedback loops that regulate the transcription of these core clock genes. Transcriptional regulators BMAL1 and CLOCK drive the expression of the Per (PER1/PER2/PER3), TIMELESS (Tim) and Cry (CRY1/CRY2) genes. These genes produce and repeat a molecular cycle of gene expression, protein synthesis and protein degradation that takes approximately 24 hours to complete (Wulff, Gatti, Wettstein, & Foster, 2010a). This molecular clock is found in most cells around the body and helps synchronise other bodily functions and structures (such as organs); we refer to these as 'peripheral clocks'. The peripheral clocks are synchronised by the master clock, which keeps the whole body running on the same timing (Reppert & Weaver, 2002).

Recently, there have been a few notable developments in this line of research. First, the 24-h sinusoidal expression patterns of the clock genes have been found to be significantly dysregulated in patients suffering from major depressive disorder (MDD) when compared to healthy controls (and accounting for time of death). Furthermore, interventions established to have potent anti-depressant effects in MDD (namely ketamine and sleep deprivation) have been hypothesised to partly act to reset abnormal clock genes. It has also been suggested that relapse may be in part conceptualised as a reoccurrence of desynchrony in the clock genes (please see Bunney, Li, Walsh, Vawter, Cartagena, Barchas et al., 2015, for a review). In bipolar disorder, CLOCK and TIM genes have been found to be associated with violent suicide attempts, multiple suicide attempts and a family history of suicide attempts (Pawlak, Dmitrzak-Weglarz, Maciukiewicz, Wilkosc, Leszczynska-Rodziewicz, Zaremba et

al., 2015), and it is also believed that patient response to lithium treatment is in part regulated by clock gene expression (Rybakowski, Dmitrzak-Weglarz, Dembinska-Krajewska, Hauser, Akiskal, Akiskal, 2014). Finally, fibroblast analysis based on skin samples from patients with chronic schizophrenia highlighted a loss of rhythmic expression in CRY1 and PER2 when compared to healthy controls (Johansson, Larsson, Hetta, Lunkdvist, 2016). **Table 1.4** provides an overview of some of the established relationships between clock genes and psychiatric disorders.

1.10 Sleep and Psychosis

Evidence is now accruing that sleep and circadian rhythm disruption (SCRD) is a feature of psychosis. A study by Cohrs (2008) highlighted that between 30% and 80% of patients with a diagnosis of schizophrenia report sleep disturbances (SD). This frequently manifests as patients exhibiting extended sleep onset latency (time to get to sleep) and difficulties with sleep continuity and insomnia (with a prevalence of 50-70%; Benson, 2006; Tandon, Keshavan, & Nasrallah, 2008; Waters & Manoach, 2012). These disturbances are also associated with important clinical outcomes, including relapse (Waters & Manoach, 2012), poorer coping (Ritsner et al., 2004) higher distress (Hofstetter, Lysaker, & Mayeda, 2005), increased frequency of depression (Palmese et al., 2011) and completed suicide (Pompili et al., 2009).

More recently, it has been debated that SCRD may represent a risk factor or may in fact directly contribute to the development of psychosis. This is evidenced by the omnipotence of poor sleep across all of the core phases of the disorder, including the prodrome[1] (with an estimated prevalence of 70-100%; Yung & McGorry, 1997), acute (Kupfer, Wyatt, Scott & Snyder, 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 (Gabriel Davies, Haddock, Yung, Mulligan, & Kyle, 2016; Reeve, Sheaves, & Freeman, 2015). Furthermore, there is also evidence that there may be a shared genetic and environmental lineage underlying psychotic experiences and SCRD (Taylor, Gregory, Freeman, & Ronald, 2015).

[1] Those considered en route to develop the disorder but upon presentation did not show symptoms severe enough to warrant a clinical diagnosis (Zanini et al., 2013).

Psychiatric Disease	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 1.4: Relationships between clock genes and psychiatric diseases. Adapted from Wulff, Gatti, Wettstein, & Foster (2010a).

Interestingly, the differences observed in the prodromal phase equate to what is observed when the patient has transitioned to psychosis: extended sleep onset latency, difficulties with sleep continuity and circadian timing abnormalities (Castro et al., 2015; Zanini et al., 2013). Most recently, it has also been noted circadian disruption (lower daily activity, fragmented sleep patterning/desynchronisation from the light-dark cycle) at baseline predicted increased psychotic symptom severity and psychosocial impairment at a one-year follow-up in a clinically high-risk for psychosis cohort (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. As such, identification and interventions to stabilise sleep-wake rhythms may offer promise in early intervention services. However, a major limitation of these findings is that the relationships stated are largely reliant solely on pairwise correlational analyses.

1.11 Sleep Disturbances, Insomnia and PLEs

The logical next step to further disentangle the nature of the relationship between sleep and psychosis is to examine if SCRD relates to the experience of PLEs. Unfortunately, markedly less work has explored this relationship, despite this being imperative for understanding the temporal nature of the relationship between sleep and psychosis. One such study, an international survey study undertaken by the World Health Organisation (WHO), reported an association between sleep disturbances and PLEs. The authors reported that endorsing a sleep problem resulted in a significant increased risk for endorsing at least one psychotic symptom (OR=2.41). This relationship, while reduced in magnitude, remained significant when adjusting for anxiety and depression (OR=1.59). Though commendable for its large sample size and broad geographic dispersal, this study had particularly low resolution measurements for psychotic experiences (four items) and even lower resolution for sleep problems (one item; Koyanagi & Stickley, 2015). A similar study by Oh et al., (2016) expanded upon these findings with a higher-resolution sleep measure derived from DSM-I criteria (assessing four different sleep parameters) and a psychosis screen including six specific PLE experiences. The authors found that difficulty falling asleep and early morning awakenings significantly increase the risk of endorsing one or more PLEs (Oh et al., 2016). Similar studies report comparable relationships with insomnia and PLEs in adolescent and student samples (Lee, Cho, Cho, Jang, & Kim, 2012; Sheaves, Porcheret, Phil, Tsanas, & Espie, 2016; Taylor et al., 2015). Taylor et al. (2015) suggest that the overlap between these experiences also have common genetic underpinnings. However, these studies lack specificity in the sleep parameters they examine. Most recently, Andorko et al., (2017) combated this issue with a large sample (n=420) and the use of the Iowa Sleep Disturbances Inventory (Koffel & Watson, 2010) alongside the Prodromal Questionnaire (brief version) for the examination of PLEs. The authors reported significant main effects of fragmented sleep, night anxiety, sleep hallucinations and depressive symptoms. Furthermore, the authors underscore the importance of gaining a more comprehensive understanding of the relationship between sleep disturbances and PLEs: that is, of gaining insight as to whether there are sleep-specific disturbances (e.g. an insomnia complaint, daytime lethargy or parasomnias, etc.), accounting for potential confounds, enabling more nuanced interpretations of the sleep-PLE relationship (Andorko et al., 2017).

All of the studies listed above employ survey-based methodologies. An alternate approach to understanding the relationship between sleep and PLEs is to take an experimental approach with the

use of sleep deprivation in healthy participants. Kahn-Greene, Killgore, Kamimori, Balkin, & Killgore (2007) found that a night of sleep deprivation in a group of healthy human participants resulted in significant increases in anxiety, depression and paranoia. More recently, Petrovsky et al., (2014) examined the effects of sleep deprivation on PLEs specifically, and found that sleep deprivation significantly increased perceptual distortion, cognitive disorganisation and anhedonia.

1.12 Bringing Everything Together

Overall, there is now a substantive body of research investigating the relationship between sleep and PLEs, which unanimously suggests these two phenomena are interlinked. However, there are currently four core areas in which this literature could be expanded and improved upon.

First, the majority of the studies cited above are premised upon survey designs. The employment of survey designs permits highly powered regression analyses but often the resolution of the measures used is sacrificed as a result (Andorko et al., 2017). Thus, sleep measures collected so far are primarily subjective (often based on one or two questions) and do not offer any insight into an individual's objective sleep. Self-report entries reflect the observer's individual sleep-related experiences and perceptions (e.g. difficulty falling asleep, difficulty staying asleep), which are correlated with non-sleep related phenomena (e.g. state of mood; Krystal & Edinger, 2008). As such, objective sleep measurements are imperative to further understand the sleep–PLE relationship.

Second, a major limitation of survey data collected at one time point is that it is unclear which symptomatology manifested first: the sleep disturbances, or the PLEs (Andorko et al., 2017). As objective sleep differences have already been noted in individuals at risk of psychosis when compared to healthy controls (e.g. Castro et al., 2015), it may then be more pertinent to note whether the signal can be seen in the opposite direction: i.e. does a cohort with a complaint of poor sleep (insomnia) endorse a greater number of PLEs, and if so, what parameters of their sleep dictate this?

Third, there is currently a dearth of biologically driven research tackling which physiological parameters relate to or mediate this relationship on a more fundamental level (Foster et al., 2013).

Fourth, experimental studies (with sleep deprivation, as an example) offer tightly controlled environments that permit intricate manipulations and can give greater insight into causality and

potential mechanisms at play. However, such experiments lack ecological validity, which is what happens naturally in an individual's environment that may give rise to the relationship between sleep and PLEs (Agostini, Carskadon, Dorrian, Coussens, & Short, 2016). Short term ecological methodologies are often restricted in their interpretations due to numerous confound variables. However, longitudinal observations offer both the ecological validity and the power to help bolster the potential confounds of using naturalistic or 'at-home' settings.

This thesis is designed to tackle these four core pitfalls found in the current literature on sleep and PLEs. To address pitfalls one, two and three, we have recruited a healthy student group (free from confounding medical health problems) with an attenuated insomnia complaint for psychological, sleep (objective and subjective) and physiological phenotyping, and compared them to a good sleeping group. For this design, each participant undergoes three weeks of sleep monitoring, which gives the study a longitudinal dynamic.

A student sample was chosen as research on PLEs in this population may hold greater clinical relevance and may incur greater distress as compared to younger children and adolescents (Kelleher, Keeley, et al., 2012b; Zammit et al., 2013). Furthermore, understanding sleep's role in PLEs is particularly pertinent in university students as they are a cohort particularly susceptible to disrupted sleep scheduling and patterns (Brown, Buboltz, & Soper, 2002).

There are six core threads to this thesis. Chapter 2 examines the main predictions made by the psychosis continuum model to understand whether PLEs behave in similar ways to psychotic disorders, as well as examining how SCRD may influence this relationship through high-resolution PLE and sleep questionnaires in a large community survey sample. To address the lack of biologically driven research, Chapter 3 and Chapter 4 examine objective sleep measures and physiological differences (in electrocardiography, electroencephalography, melatonin synthesis or acrophase, and actigraphy) between a good sleeping and a group with a complaint of poor sleep (attenuated insomnia), as well as examining how these differences may relate to PLEs. Chapter 5 seeks more specifically to describe which objective or subjective sleep parameters best predict PLEs. Chapter 6 aims to see if the relationship between sleep and PLEs can be seen on a daily basis. Finally, Chapter 7 targets how HPA axis functioning relates to the relationships between sleep and psychotic-like experiences (that are described in Chapter 5 and Chapter 6).

Chapter 2:
Do Risk Factors for the Development of Psychosis Confer Risk to Subsyndromal Psychotic Features?

The construction of the OWLS survey was done in collaboration with another doctoral student in the research group, Ross Purple. Ross and I collaboratively reviewed the literature for the risk factors to be included in the survey. We also collaboratively advertised the survey. Furthermore, Dr. Ross Haines from the Department of Statistics offered considerable advice on how to manage and conduct the analyses presented here.

2.1 Introduction

An editorial by Kelleher & Cannon (2011) highlighted accumulating evidence that a wide range of risk factors for schizophrenia also present as risk factors for individuals to endorse psychotic experiences (PEs). These risk factors include obstetric complications, family history, identifying as a migrant/belonging to an ethnic minority group, unemployment, lower SES, relationship status, urbanicity, childhood abuse, traumatic events, bullying, cannabis use, tobacco and alcohol use, cognition, neuroanatomy and comorbid psychopathology. This continuity of risk factors from symptoms to the disorder succinctly demonstrates the construct validity between clinical and non-clinical phenotypes (Kelleher & Cannon, 2011).

A systematic review and meta analysis by Linscott & van Os (2013) was conducted to examine predictions made by the *psychosis-proneness-persistence-impairment model (PPPI model).* The PPPI model suggests that PEs have phenomenological continuity, i.e. they arise from the same 'pathogenic

mechanisms' that also result in a psychotic disorder. This would suggest that PEs behave as if they are on the trajectory to the disorder. A core prediction of phenomenological continuity would be that PEs relate to key risk factors for psychosis as they would the disorder itself, i.e. the likelihood of PEs is increased upon exposure to risk factors recognised to predict psychotic disorders. Thus it would be expected that risk factors for psychosis that discern subgroups in the general population should also account for variability in PEs across cohorts. It would also be expected that those lying further upon the psychosis-proneness continuum possess greater numbers of risk factors or certain risk factors in greater severity (Linscott & van Os, 2013).

The first of these predictions was tested by means of meta-analysis by Linscott and colleagues (2013), who found that (younger) age, belonging to an ethnic minority, having a lower income, not being married, family history of mental health, alcohol use, cannabis use, recreational drug use and traumatic experiences were all associated with an increased risk of PEs (Linscott & van Os, 2013). Furthering the work of Linscott & van Os (2013), we designed the Oxford Wellbeing Life and Sleep Survey (OWLS) survey to examine the prevalence of *all* established risk factors for psychosis and their efficacy in predicting the occurrence of PEs. To ensure that only established risk factors were included - that is, risk factors with a consensus in research that they heighten the risk of psychosis - we conducted a systematic review of the meta-analyses and systematic reviews of the risk factors in psychosis research. This survey, to our knowledge, is the first to methodically examine all of the potential risk factors for psychosis in their ability to predict the occurrence of PEs.

Referring back to Section 1.10, evidence is now accruing that sleep and circadian rhythm disruption (SCRD) may also confer risk for psychosis. This is evidenced by the omnipotence of poor sleep across all of the core phases of the disorder, including the prodrome, acute, chronic, and residual phases (Yung & McGorry, 1997; Kupfer et al., 1970; Waters et al., 2011). However, considerably less is known about sleep's relationship with the risk factors for psychosis, and this knowledge could considerably help inform the nature and role of sleep in psychosis. It yet remains to be discovered what parameters of a sleep complaint are most informative in the prediction of PEs, and whether there are certain parameters of sleep that are more relevant for certain types of PEs.

This study is designed to examine the preliminary results from the OWLS survey. For this, seven hypotheses have been developed based on the literature. Initially, the five core predictions of the PPPI model as laid out by van Os, Linscott, Myin-Germeys, Delespaul, & Krabbendam (2009) will be examined. Based on these core predictions, (1) it is predicted that the distributional properties of the PQ16 will replicate that simulated by van Os and colleagues (2009), i.e. distributed 'half-normally' with the majority of the population endorsing very low values but with a considerable section of the population endorsing increasingly higher values; (2) it is anticipated that the PEs will possess psychopathological continuity, i.e. that PEs will more frequently exist within common comorbidities (depression and anxiety disorders); (3) it is expected that those at the higher end of the continuum will have demonstrated the greatest need for care; and (4) in line with demographic validity, it is predicted that demographic associations with psychotic disorders will also extend to individuals with PEs (e.g. ethnicity). However, certain demographic phenomena - urbanicity, season of birth and level of education - are predicted to only be observable cross-sectionally and as such will not directly predict the occurrence of PEs. A number of risk factors have only been reported epidemiologically in the literature (e.g. obstetric complications), therefore it is exploratory as to whether these will exist cross-sectionally only or will also be predictive of the occurrence of PEs. (5) In line with aetiological validity, some of the known genetic and non-genetic causes that are known contributors to the most severe forms of psychosis are also predicted to impact PEs or attenuated versions of psychosis (e.g. family history and severe child abuse).

Referring to the relationship between sleep and psychosis, it is further hypothesised that (6) based on the previous literature on sleep and schizophrenia, and assuming a continuum approach, that insomnia (which focuses on sleep related anxiety) and self reported sleep quality (which is related to a low self reported sleep efficiency) will independently predict an increased risk of PEs; and (7) based on previous literature indicating circadian misalignment in schizophrenia (Wulff, Dijk, Middleton, Foster, & Joyce, 2012), it will be examined whether chronotype predicts risk of PEs. It is anticipated that later chronotypes (denoted by a later mid-sleep point; MSFsc; Section 2.2.2.2) will predict increased risk of PEs based on melatonin and actigraphy studies in schizophrenia and bipolar phenotypes (Robillard, Naismith, Rogers, Ip, et al., 2013a; Wulff et al., 2012).

For the analysis of PEs, it was not possible to use the combined total PEs score due to the heterogeneity in the response (this is further explained below in Section 2.2.4). As such, clustering the psychotic symptoms within the PQ16 questionnaire was considered, as detailed in **Table 1.1** and **Table 1.2**. These clusters are negative symptoms, perceptual abnormalities, bizarre ideas, delusional mood, paranoia and cognitive disorganisation (dissociation). This approach permits the exploration of risk factors specific to certain symptoms, as well as those shared across different psychotic symptoms.

2.2 Methodology

The survey was targeted at the general population (aged 18-65 years) in the Oxford area. As such, advertisements were placed in a diverse number of venues and locations in Oxford (including schools, churches, university departments, community centres, hospitals, etc.), as well as online. Psychosis in later life has been shown to have a different risk profile when compared to psychosis developed earlier in life (Linscott & van Os, 2013). As such, while elderly participants were not excluded from the analysis, advertising was focused to target younger cohorts. The survey was hosted online via LimeSurvey (Schmitz, 2012) on the Oxford University network. The survey protocol and contents were approved by the Medical Sciences Interdivisional Research Ethics Committee (MSD-IDREC-C1-2014-054), and all participants gave informed consent online when agreeing to complete the survey.

2.2.1 Survey Development

2.2.1.1 Risk Factor Selection

The selection of risk factors presented in the survey was premised upon a systematic 'meta' review of the literature, i.e. a review of the available meta-analyses and systematic reviews that globally account for the published data on a specified risk factor for the development of psychosis. Full details of the methodology employed and the risk factors identified in this process can be found in Appendix A. Parental communication is the only risk factor highlighted by the systematic review of the literature that could not be included, as it is evaluated by the means of video recordings and there was therefore no feasible way to replicate this accurately in a survey format.

2.2.1.2 Question Selection and Design

Where possible, established questionnaires were employed to evaluate the presence of the risk factor of interest. When this was not possible, or the established questions did not target the risk factor as desired, questions were edited from established questionnaires. In remaining cases, we designed questions based upon previous questionnaire measures that adequately investigated the risk factor of interest. For example, when asking about the use of cannabis, it was important to ascertain the frequency and duration of use to adequately assess if the consumption presented as a risk for psychotic symptoms. An overview of each of the risk factors, sociodemographic characteristics and questionnaires evaluated in the OWLS survey is presented in **Table B.1** and **Table B.2** in Appendix B. For further information regarding how each of the risk factors and sociodemographic variables were scored and evaluated, please refer to Appendix C.

2.2.2 Survey Structure

2.2.2.1 Sociodemographic Characteristics

Data were gathered on sex, age, ethnicity, level of education, diagnoses of psychiatric disorders, and help-seeking behaviour for any psychiatric disorders listed.

2.2.2.2 Sleep Questionnaires

Our secondary objective for the study was to understand how sleep and circadian rhythm differences might relate to different risk factors for psychosis. As such, three different sleep-related questionnaires were included in the survey, covering sleep quality, chronotype and an insomnia complaint. These questionnaires are described below.

Pittsburgh Sleep Quality Index (PSQI; Buysse, Reynolds, Monk, Berman, & Kupfer, 1989).

The PSQI measures subjective sleep quality over the previous month, yielding a score ranging from 0-21, with higher scores representing poorer quality sleep. The standardised cut-off score for poor sleep quality is 5. The PSQI is a widely used in both clinical and nonclinical populations and has demonstrated good psychometric properties (Backhaus, Junghanns, Broocks, Riemann, & Hohagen, 2002; Carpenter & Andrykowski, 1998).

Short Form Sleep Condition Indicator (SCI; Espie et al., 2014).

The SCI is comprised of just two items: (1) `thinking about a typical night in the last month, how many nights a week do you have a problem with your sleep?'; and (2) `thinking about the past month, to what extent has poor sleep troubled you in general?'. Possible responses to the first question are '0-1', '2', '3', '4', and '5-7'; these are scored 4, 3, 2, 1 and 0 respectively. Possible responses to the second question are 'not at all', 'a little', 'somewhat', 'much', and 'very much'; these are also scored 4, 3, 2, 1 and 0 respectively. The scores from these two questions are added to give the SCI score: the lower the score, the more aggressive the insomnia complaint. The SCI has demonstrated good psychometric properties (Espie et al., 2014).

The Munich Chronotype Questionnaire (MCTQ; Roenneberg et al., 2003) was used to assess chronotype. The MCTQ contains simple questions about sleep timing, such as bedtime, time to get ready for sleep, sleep latency, time of wake-up, and time to get up (or time in bed after wake-up). These are asked separately for work and free days, and subjects are asked to judge their sleep habits over the last two weeks. The questionnaire response produces a time-based variable, the mid-sleep phase on free days (MSF), which correlates well with entrained circadian acrophase. The MSF is then corrected for sleep deficits accumulated during the work-week (Roenneberg et al., 2007). MSFsc (Mid-Sleep Phase on Free days Corrected for the Sleep Deficit accumulated during the work week) provides a quantitative measure of chronotype as a continuous, time-based variable (Allebrandt & Roenneberg, 2008), with larger values indicating a later mid-sleep point. The continuous distribution of MSFsc, with extreme early and late types on either end, is population specific. The MCTQ-assessed information allows the calculation of "social jetlag," defined as the discrepancy between social and endogenous time (absolute difference in hours between the uncorrected MSF and mid-sleep on work days; Wittmann, Dinich, Merrow, & Roenneberg, 2009).

The other most commonly used assessment of chronotype is the Horne-Östberg Morningness-Eveningness Questionnaire (MEQ; Horne & Östberg, 1976). The MEQ assesses subjective daily preferences and results in a score along a Morningness-Eveningness axis, with the lowest score (16) being extreme Eveningness type, and the highest score (86) being extreme Morningness type. These preferences are based on when people prefer to be active or to rest. The calculated mid-sleep time on free days (MSF) of the MCTQ correlates well with the MEQ (Zavada, Gordijn, Beersma, Daan, &

Roenneberg, 2009). The MEQ does not differentiate between workdays and work-free days, and the questions emphasise subjects' activities within their rest-activity behaviour in comparison to other people, rather than based on their own sleep timings. As such, the MCTQ was employed for this study rather than the MEQ.

2.2.2.3 Other Questionnaires

Outcome measure: Psychotic-like experiences: Prodromal Questionnaire 16 Item Version (PQ16; Ising et al., 2012). The PQ16 contains 16 items, each with yes/no responses, yielding scores out of 16. A score of 6 or above warrants further screening for an at risk mental state. Across the 16 items, the Questionnaire assesses positive symptoms (visual and auditory hallucination, delusional mood/perplexity, ideas of reference and persecutory thoughts), negative symptoms (excessive social anxiety) and avolition. This questionnaire was selected as it does not have 'hypothetical qualifiers' or describe beliefs of cultural subgroups (e.g. voodoo) which have been highlighted to produce misleading results in the estimated prevalence of PE (Linscott & van Os, 2013). It has acceptable psychometric properties in both healthy and high-risk populations (Ising et al., 2012).

Axis I Symptomatology: Depression Anxiety and Stress Scale (21 Item Version; Henry & Crawford, 2005). This scale was selected as it takes a dimensional view of depression, anxiety and stress, which often co-present with both sleep disturbances and PEs. It can be subdivided into three categories (of 7 items each) targeting depression (e.g., 'I couldn't seem to experience positive feeling at all'), anxiety (e.g., 'I was aware of dryness of my mouth') and stress (e.g., 'I found it hard to wind down'). Each of the 21 items and is scored on a 4 point scale from 0 ('did not apply to me at all - NEVER') to 3 ('applied to me very much, or most of the time – ALMOST ALWAYS'). It has displayed good psychometric properties (internal consistency; α=0.82-0.93; Henry & Crawford, 2005).

Traumatic Events: Life-Threatening Experiences Scale (LTE; Brugha & Cragg, 1990). The LTE is a 12-item self-report questionnaire assessing different categories of traumatic life events, selected for their established long-term consequences (Brugha & Cragg, 1990). The LTE used here is adjusted for the age at which the trauma took place. As such there are six response categories: never, 0–12, 13–18, older than 18, past year and past 6 months. The total score is the number of items endorsed (maximum score=12). Participants were then asked to rate their level of stress associated with each

event endorsed, choosing the one of four options (not stressful, slightly stressful, moderately stressful and very stressful).

2.2.2.4 Other Risk Factors

Further to the psychometric measures, we evaluated a number of risk factors based upon the results of the systematic review. These included infections of the brain; brain injury; cannabis use; childhood abuse (questions taken from Cuijpers et al., 2011); childhood bullying; childhood social withdrawal (social withdrawal subscale items 42, 65, 88 & 111 from the Child Behavioural Checklist edited to make appropriate for retrospective report; Achenbach & Edelbrock, 1983); family history of psychiatric disorders; migrant status; help-seeking behaviours in relation to the PEs; latitude position at birth; diagnosis of epilepsy; obstetric complications at birth (taken from Lumbiganon et al., 2010; Souza et al., 2000); paternal age; season of birth; presence of 22q11.2 deletion syndrome diagnosis; and urbanicity. See Appendix B and Appendix C for further details.

2.2.3 Data Cleaning

A stringent duplicate removal process was employed to ensure the data set was free from duplicate respondents. Primary matching for duplicates was done based upon email address (fuzzy matching was used on prefix of the email address to account for the same individual using different email providers). Possible matches were further verified by date of birth comparison as well as gender and ethnicity. There were a total of 3,477 responses in the raw data. 1,420 incomplete responses were removed and a further 177 duplicates were removed from the dataset prior to analysis.

Furthermore, respondents who reported their age to be below 16 years (n=8), above 65 years (n=8) or reported a DOB that was implausible (n=3) at the time of completing the survey were also removed.

143 respondents either confused Bedtime and Lights Off (n=64) or AM/PM timings (n=78) for the PSQI and MCTQ. These were corrected if the time between bedtime and lights off was less than two hours. Responses with over an hour between bedtime and lights off were examined to see if the respondent was reporting a sleep problem. Each correction was performed in the context of the participants' responses: nothing was altered if the data looked implausible or the answers were

incongruent (n=3) – instead, these respondents were discarded. Furthermore, 146 respondents reported distress for items on the PQ16 that they did not endorse as experiencing. Respondents who did this for more than one item on the PQ16 were discarded (n=46).

Respondents reporting a psychotic disorder (n=23) were also excluded from the analysis. This left a total of 1789 survey responses available for analysis.

2.2.4 Statistical Analyses

Statistical analyses were performed within the R statistical environment (R Core Team, 2012). Cross-sectional differences were conducted using chi-square frequency analyses across four pre-defined PEs risk categories. These categories were: (i) a PQ16 score of 0, indicating a very low risk; (ii) a PQI6 score between 1 and 5, indicating minimal risk; (iii) a PQ16 score above 5 (the established cut off for the PQ16), indicating a moderate or 'at-risk' group; and (iv) a PQ16 score above 5 *and* having sought help *and* with distress associated with these symptoms, indicating the highest risk group. These groups were designed to examine psychopathological continuity (hypothesis 2), increased need for care for those further upon the continuum (hypothesis 3) and the presence of cross-sectional differences in demographic variables (hypothesis 4). The Benjamini and Hochberg correction was used to adjust p-values for multiple comparisons. This correction controls for the false discovery rate, as opposed to the family-wise error rate which the more conservative Bonferroni method employs (Benjamini & Hochberg, 1995).

To address hypotheses (3) – (7), we performed multivariate statistical modeling to predict PQ16. However, the overall internal consistency of the PQ16 was quite low (Cronbach's α=0.79), as were the correlations between each pair of PQ16 items (please refer to Appendix D for the correlation matrix), and the items themselves were endorsed at very different rates. With these considerations in mind, rather than modelling with the combined PQ16 score as the outcome variable, we decided a more appropriate approach was to build a model for each subcategory of the PQ16 defined in **Table 1.1** and **Table 1.2**: (1) perceptual abnormalities, (2) bizarre ideas, (3) delusional mood, (4) persecutory ideation, (5) cognitive disorganization (dissociative symptoms) and (6) negative symptoms (social anxiety & avolition).

This approach offers the advantages of providing understanding of whether there was specificity in risk factors for certain psychotic experiences, as well as of which risk factors were shared different PE categories. This coincides with the clinical literature on schizophrenia, which has long been considered a very heterogeneous disorder with certain patient groups presenting no overlapping symptomatology (Tandon, Nasrallah, & Keshavan, 2009).

For each subcategory of the PQ16 listed above, we built a multivariate logistic regression model, using the set of predictor variables (risk factors, demographics, sleep variables and psychopathology measures) to predict the binary response of whether any of the questions on that subcategory had been endorsed.

The estimated regression coefficients from the resulting models can be exponentially transformed into odds ratios, thus giving a measure of risk associated with each predictor variable. Further, for each survey respondent, we can use the estimated regression coefficients to derive the estimated probability of endorsing at least one question within the PQ16 subcategory. These predicted probabilities can be compared to the known responses to gauge the quality of the model.

The negative symptoms PQ16 subcategory was modelled first as a proof of concept, as many of the predictor variables relate to the presence of a mood disorder or depressive/anxious symptomatology. As anticipated, this model had high predictive power, and we therefore extended this approach to the other subcategories.

Given the large number of possible combinations of the predictor variables for inclusion in each model, we used model selection based upon the Akaike Information Criterion (AIC) to objectively provide a set of candidate models for further consideration. The AIC is used to measure the relative quality of a collection of models, and features a penalty for model complexity, thus discouraging overfitting. Both forward selection and backward elimination (standard model selection procedures) were used to propose candidate models. Beginning with a simple intercept-only model (with no predictor variables), forward selection iteratively adds the predictors offering maximal reduction to the AIC, until no further reduction is possible. Backward elimination instead iteratively removes predictor variables from a complex model until no further reduction in AIC is possible.

To assess model quality, and to further discourage overfitting, we built our models using only 70% of the data. This `training' data was randomly selected. When the models were finalised, they were then also fit to the remaining 30% of the data (the 'test' data), thus allowing us to assess their generalisability, based on the quality of model fit to data the models had not seen.

To assess the accuracy of our models, we calculated the classification success rate on both the training and test datasets (i.e. the ability of the model to predict the known response), and computed Receiver Operating Charateristic (ROC) curves. The ROC curves plot the true positive rate (sensitivity) against the false positive rate (1-specificity) for varying classification thresholds, and provide a visual representation of the model's ability to reliably discriminate between those endorsing and not endorsing at least one item on the relevant PQ16 subscale.

The area under the ROC curve (AUC) was also calculated. This area can be interpreted as the probability that a randomly chosen participant who endorsed the psychotic symptom and a randomly chosen participant without the psychotic symptom could be reliably distinguished based on their responses to the main effects in the model.

Migrant status (1st and 2nd generation), 22Q11.2 deletion syndrome, epilepsy, latitude, brain injury and brain infection were excluded from the set of potential predictor variables, as they were infrequently endorsed in our sample. Furthermore, the majority of this sample (69%) possesses high levels of education (already holding a bachelors, masters or PhD, or currently studying towards a tertiary qualification). As such, it was deemed that the level of education would simply act as a proxy for age as opposed to a descriptive variable of education level, and for this reason, it was excluded from the analysis. Finally, stress (from the DASS questionnaire) was very highly correlated with both anxiety ($r=0.74$) and depression ($r=0.71$), and was accordingly excluded from the analysis due to concerns of collinearity. Whilst still relatively high ($r=0.63$), the correlation between anxiety and depression was lower, and these were both included in the set of potential predictor variables.

2.3 Results

2.3.1 Survey Demographics

A total of 1789 (27.2% women; mean age=27.6; SD=10.9) survey responses were included in these analyses. Over half of the sample examined (n=1000; 55.9%) possessed an undergraduate degree (n=473; 26.4%) or a postgraduate higher qualification (MA or PhD (n=527; 29.5%)) with a substantial subsection studying towards a higher level of education (n=1234; 69.0%), indicating this to be a highly educated survey cohort.

2.3.2 Distributional Validity

Of the 1789 participants who completed the survey, 1417 respondents endorsed at least one PE (79.2% of sample). Of these respondents, 364 endorsed a PQ16 above 5 (20.3%). 144 respondents were categorised as high-risk (8.1%), having endorsed a PQ16 above 5 with associated distress and help seeking behaviour specific to the PEs.

Figure 2.1 displays the distribution of the PQ16 in the sample, and **Figure 2.2** demonstrates the relative prevalence of endorsement for individual items on the PQ16. The most common experience endorsed was avolition (akin to depression; 36.8%). This was closely followed by social anxiety (33.2%), absorption (33.0%), thought insertion (29.8%) and thought broadcasting (27.6%).

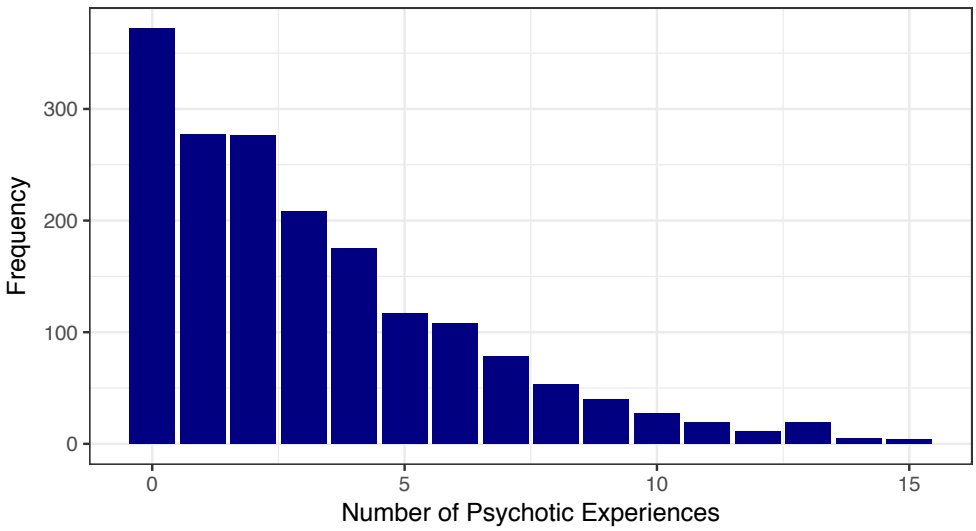

Figure 2.1: Bar chart of PEs endorsed in OWLS survey respondents (n=1789). A 'half-normal' distribution can be observed, with the majority of the population endorsing very low numbers of PEs, but a considerable section endorsing higher values (even at rates above 5, the clinical cut off of the PQ16).

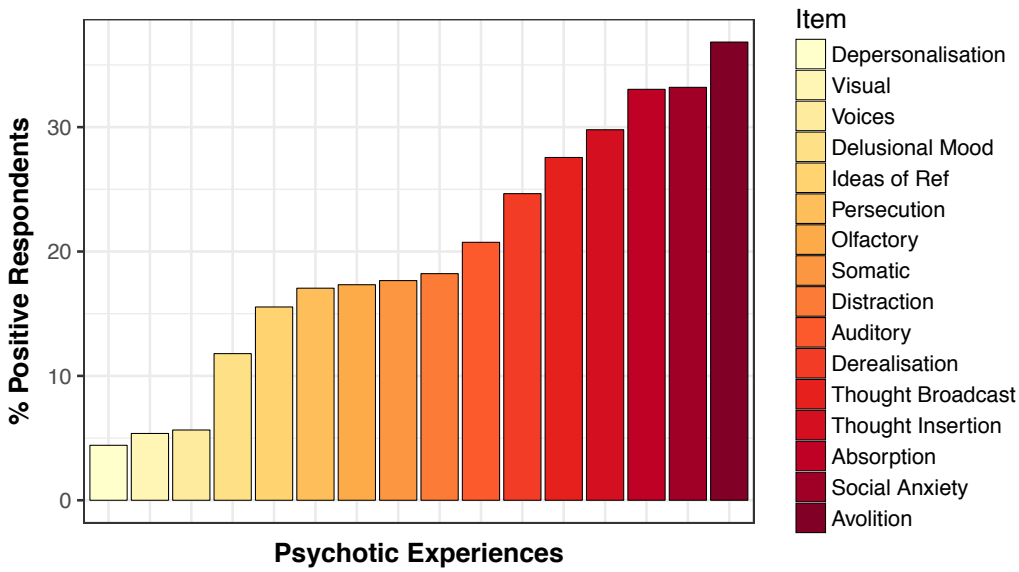

Figure 2.2: Breakdown of endorsement of each PQ16 item (n=1789).

2.4 Assessment of the PPPI model Cross-Sectionally Using Discrete Categories

2.4.1 Psychopathological Continuity

Table 2.1 highlights the number of respondents who report a mental health diagnosis in each of the four risk categories, and the relative proportions of these diagnoses are highlighted in **Figure 2.3**. The proportion of respondents with psychiatric comorbidities goes up as a function of risk category (no PLEs=8.3%, 1-5 PLEs=24.6%, at risk=30.0%, high risk=71.5%). A chi-square test examining equality of proportions highlighted that mental health diagnoses are not equally distributed across categories, x^2(3, n=1789)=220.18, p<0.0001 (**Table 2.3**).

Similar results were found for the number of respondents with a significant insomnia problem according to the SCI (no PLEs=18.0%, 1-5 PLEs=27.4%, at risk=43.6% and high risk=66.7%), x^2(3, n=1789)=138.87, p<0.0001 (**Table 2.3**). This was also found for poor sleep quality as measured by a significant PSQI score (no PLEs=22.8%, 1-5 PLEs=48.2%, at risk=71.8% and high risk=84.0%), x^2(3, n=1789)=218.58, p<0.0001.

	1: None	2: 1-5	3: At Risk	4: High Risk	Overall
n	372	1053	220	144	1789
Age	29.9 (11.6)	27.7 (11)	24.8 (9.2)	24.9 (9)	27.6 (10.9)
% Female	30.9	27.8	25.9	15.3	27.2
Level of Education					
Low	2 (0.5%)	20 (1.9%)	19 (8.6%)	7 (4.9%)	48 (2.7%)
Med	106 (28.5%)	437 (41.5%)	121 (55%)	77 (53.5%)	741 (41.4%)
High	126 (33.9%)	281 (26.7%)	39 (17.7%)	27 (18.8%)	473 (26.4%)
Very High	138 (37.1%)	315 (29.9%)	41 (18.6%)	33 (22.9%)	527 (29.5%)
Studying	244 (65.6%)	721 (68.5%)	167 (75.9%)	102 (70.8%)	1234 (69%)
Studying BA/BSc	95 (25.5%)	379 (36%)	96 (43.6%)	58 (40.3%)	628 (35.1%)
Diagnoses					
Depression	22 (5.9%)	191 (18.1%)	50 (22.7%)	85 (59%)	348 (19.5%)
MDD	3 (0.8%)	22 (2.1%)	4 (1.8%)	14 (9.7%)	43 (2.4%)
Social Anxiety	1 (0.3%)	19 (1.8%)	12 (5.5%)	20 (13.9%)	52 (2.9%)
Health Anxiety	1 (0.3%)	6 (0.6%)	0 (0%)	3 (2.1%)	10 (0.6%)
OCD	0 (0%)	18 (1.7%)	3 (1.4%)	8 (5.6%)	29 (1.6%)
BDD	0 (0%)	9 (0.9%)	8 (3.6%)	5 (3.5%)	22 (1.2%)
GAD	7 (1.9%)	62 (5.9%)	16 (7.3%)	35 (24.3%)	120 (6.7%)
Panic	3 (0.8%)	13 (1.2%)	5 (2.3%)	9 (6.2%)	30 (1.7%)
Alcohol/Sub.	1 (0.3%)	1 (0.1%)	0 (0%)	3 (2.1%)	5 (0.3%)
Phobia	0 (0%)	2 (0.2%)	2 (0.9%)	4 (2.8%)	8 (0.4%)
Other	5 (1.3%)	51 (4.8%)	19 (8.6%)	30 (20.8%)	105 (5.9%)
Treatment					
Counselling	28 (7.5%)	206 (19.6%)	55 (25%)	94 (65.3%)	383 (21.4%)
Medication	23 (6.2%)	187 (17.8%)	46 (20.9%)	83 (57.6%)	339 (18.9%)
Hospitalisation	1 (0.3%)	20 (1.9%)	7 (3.2%)	17 (11.8%)	45 (2.5%)
Untreated	2 (0.5%)	12 (1.1%)	3 (1.4%)	4 (2.8%)	21 (1.2%)
Psychometric Profile					
Psychotic Exp¶	0	2	7	7	2
PE - Distress¶	0	2	8	12	2
Depression¶	4	10	18	26	10
Anxiety¶	2	6	12	18	6
Stress¶	8	12	20	26	14
Help Seek	0 (0%)	197 (18.7%)	0 (0%)	144 (100%)	341 (19.1%)
Ethnicity					
White	311 (83.6%)	910 (86.4%)	178 (80.9%)	130 (90.3%)	1529 (85.5%)
Asian	36 (9.7%)	72 (6.8%)	23 (10.5%)	5 (3.5%)	136 (7.6%)
Arabic	2 (0.5%)	2 (0.2%)	1 (0.5%)	3 (2.1%)	8 (0.4%)
Black	5 (1.3%)	5 (0.5%)	1 (0.5%)	1 (0.7%)	12 (0.7%)
Mixed	13 (3.5%)	46 (4.4%)	15 (6.8%)	4 (2.8%)	78 (4.4%)
Other	5 (1.3%)	18 (1.7%)	2 (0.9%)	1 (0.7%)	26 (1.5%)

Table 2.1: Demographic overview of survey respondents (n=1789). Treatment respondents can put down more than one response. The outcome variables marked ¶ presented with a skewed distribution, as such, the median was used as a measure of central tendency.

	1: None	2: 1-5	3: At Risk	4: High Risk	Overall
n	372	1053	220	144	1789
Age	29.9 (11.6)	27.7 (11)	24.8 (9.2)	24.9 (9)	27.6 (10.9)
% Female	30.9	27.8	25.9	15.3	27.2
Genetic and Developmental Risks					
Family History (Schiz/BP)	10 (2.7%)	30 (2.8%)	8 (3.6%)	9 (6.2%)	57 (3.2%)
Family History (Other)	80 (21.5%)	230 (21.8%)	65 (29.5%)	64 (44.4%)	439 (24.5%)
Paternal Age	45 (12.1%)	120 (11.4%)	39 (17.7%)	16 (11.1%)	220 (12.3%)
Obstetric Comp	50 (13.4%)	175 (16.6%)	36 (16.4%)	42 (29.2%)	303 (16.9%)
SOB	185 (49.7%)	532 (50.5%)	103 (46.8%)	74 (51.4%)	894 (50%)
Latitude (North)	13 (3.5%)	25 (2.4%)	4 (1.8%)	3 (2.1%)	45 (2.5%)
22Q11.2	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Migrant	96 (25.8%)	229 (21.7%)	44 (20%)	30 (20.8%)	399 (22.3%)
Migrant 1st	5 (1.3%)	13 (1.2%)	2 (0.9%)	0 (0%)	20 (1.1%)
Migrant 2nd	7 (1.9%)	40 (3.8%)	6 (2.7%)	5 (3.5%)	58 (3.2%)
Sleep Risks					
PSQI¶	4	5	7	8	5
PSQI > 5	85 (22.8%)	508 (48.2%)	158 (71.8%)	121 (84%)	872 (48.7%)
SCI¶	7	6	4	2	5
SCI < 4	67 (18%)	288 (27.4%)	96 (43.6%)	96 (66.7%)	547 (30.6%)
MSFsc	4.08	4.36	4.66	4.5	4.34
SJL	1.125	1.125	1.25	1.25	1.125
Childhood Risks					
Bully	71 (19.1%)	305 (29%)	84 (38.2%)	76 (52.8%)	536 (30%)
Social WithD	1	2	4	4	2
Prop^{N} SocialW	268 (72%)	882 (83.8%)	206 (93.6%)	137 (95.1%)	1493 (83.5%)
Physical Abuse	49 (13.2%)	208 (19.8%)	75 (34.1%)	62 (43.1%)	394 (22%)
Sexual Abuse	28 (7.5%)	109 (10.4%)	38 (17.3%)	36 (25%)	211 (11.8%)
Psych. Abuse	62 (16.7%)	255 (24.2%)	95 (43.2%)	83 (57.6%)	495 (27.7%)
Emot. Abuse	57 (15.3%)	283 (26.9%)	115 (52.3%)	83 (57.6%)	538 (30.1%)
Trauma					
Prop^{N} Trauma	324 (87.1%)	982 (93.3%)	218 (99.1%)	141 (97.9%)	1665 (93.1%)
Trauma Event	3	3	4	4	3
Trauma Distress	2	2	3	3	2
Adolescent/Adult Risk					
Urbanicity	100 (26.9%)	264 (25.1%)	52 (23.6%)	27 (18.8%)	443 (24.8%)
Brain Injury	6 (1.6%)	17 (1.6%)	3 (1.4%)	3 (2.1%)	29 (1.6%)
Brain Infection	3 (0.8%)	4 (0.4%)	1 (0.5%)	1 (0.7%)	9 (0.5%)
Cannabis Ever	111 (29.8%)	406 (38.6%)	95 (43.2%)	69 (47.9%)	681 (38.1%)
Cannabis Now	29 (7.8%)	123 (11.7%)	37 (16.8%)	29 (20.1%)	218 (12.2%)
Epilepsy	0 (0%)	10 (0.9%)	4 (1.8%)	3 (2.1%)	17 (1%)

Table 2.2: Proportional distribution of risk factors across groups (n=1789). Family history was counted using First Degree Relatives only, and cannabis (now) refers to participants endorsing using cannabis in the past three months at a frequency of once a month or more. The outcome variables marked ¶ presented with a skewed distribution, as such, the median was used as a measure of central tendency.

PPPI prediction	Category	Variable	x^2	df	p	Adj. p
(2) Psychopathological Continuity	Diagnoses	All Diagnoses	220.2	3	<.001	<.001
	Psychometrics	Sleep Quality	218.6	3	<.001	<.001
		Insomnia	138.9	3	<.001	<.001
(3) Need for Care	Treatment	Counselling	211.1	3	<.001	<.001
		Medication	181.4	3	<.001	<.001
		Hospitalisation	60.4	3	<.001	<.001
(4) Demographic Validity*	Urbanicity		3.89	3	0.27	0.29
	Ethnicity	Non-white	8.17	3	0.043	0.053
	SOB		1.13	3	0.771	0.771
	Migrant		3.68	3	0.300	0.314
	Paternal Age		7.01	3	0.072	0.083
(5) Aetiological Validity	Family History**		37.1	3	<.001	<.001
	Obstetric C.		18.7	3	0.003	0.004
	Bullying		64.3	3	<.001	<.001
	Social Withdrawal		65.9	3	<.001	<.001
	Child Abuse	Physical	75.9	3	<.001	<.001
		Sexual	39.1	3	<.001	<.001
		Psychological	119.9	3	<.001	<.001
		Emotional	147.2	3	<.001	<.001
	Cannabis Use	Ever	19.2	3	<.001	<.001
		Now	19.9	3	<.001	<.001
	Trauma	Ever	38.2	3	<.001	<.001

Table 2.3: An assessment of the PPPI model examining risk cross-sectionally along the continuum (n=1789). As the sample was uniformly highly educated, we did not investigate educational differences between groups. *There were not a sufficient number of endorsements of 22Q11.2 syndrome, latitude, epilepsy, brain injury, and brain infection to examine these proportionally across groups.
**Family history of schizophrenia/bipolar disorder and other disorders needed to be combined, as it was otherwise underpowered to detect differences. Only 1st degree relatives with a mental health disorder were considered.

2.4.2 Need for Care

To assess need for care, we considered the relative proportion of respondents who required counselling, medication and hospitalisation for the diagnoses they endorsed. Counselling was reported by 7.5%, 19.6%, 25.0% and 65.3% of respondents in the no PLEs, 1-5 PLEs, at-risk and high-risk groups respectively. Similar trends were found for both medication (6.2%, 17.8%, 20.9% and 57.6% respectively) and hospitalisation (0.3%, 1.9%, 3.2% and 11.8% respectively). Chi-square tests (see **Table 2.3**) highlighted these proportions to differ significantly between groups for each treatment. **Figure 2.3** highlights the relative distribution of treatment outcomes across groups.

2.4.3 Demographic and Aetiological Validity

None of the demographic variables assessed demonstrated significant differences in their distribution across the four groups. **Table 2.3** shows that no differences were found for urbanicity (p=0.27),

ethnicity (p=0.053), season of birth (p=0.77), migrant status (p=0.30) or paternal age (p=0.072). It was not possible to assess 22Q11.2 deletion syndrome, latitude, epilepsy, brain and infection due to the low incidence rates of these risk factors in our sample.

Aetiological validity variables included family history, obstetric complications, bullying, social withdrawal, child abuse, cannabis use and trauma. Based on chi-square tests for equality of proportions, **Table 2.3** shows that a family history of mental health disorders distributes unequally across groups (p<0.0001), as do the endorsement of obstetric complications, (p=0.003), childhood risks including bullying (p<0.0001), social withdrawal (p<0.0001), physical abuse (p<0.0001), sexual abuse (p<0.0001) psychological abuse (p<0.0001) and emotional abuse (p<0.0001). **Table 2.2** shows the proportions at which each of these variables are endorsed.

Adolescent and adult risks such as trauma (p<0.0001), ever using (p=0.0003) and current cannabis use (p<0.0002) were also found to distribute unequally between groups (**Table 2.3**).

Figure 2.3 and **Figure 2.4** highlight the differences in the relative distribution of risk factors and psychometric scores across the four groups. **Figure 2.5** highlights the distribution of the PSQI, social withdrawal and traumatic events scores across the four groups.

2.5 Predicting the Occurrence of PLEs

2.5.1 Model Summaries for the Categories of Psychotic Symptoms

Table 2.4 shows the models of best fit for the negative symptoms and perceptual abnormalities subcategories. For negative symptoms, this table highlights depression (OR=1.13, 1.11-1.16, p<0.0001), anxiety (OR=1.06, 1.03-1.10, p=0.0001), social withdrawal (OR=1.21, 1.12-1.30, p<0.0001) and PSQI (OR=1.10, 1.02-1.19, p=0.017) as significant predictor variables. The odds ratios would suggest that a one point increase in depression, anxiety, social withdrawal or PSQI would predict a 13%, 6%, 21% and 10% increase in the probability of endorsing negative symptoms respectively, assuming all other variables are kept constant.

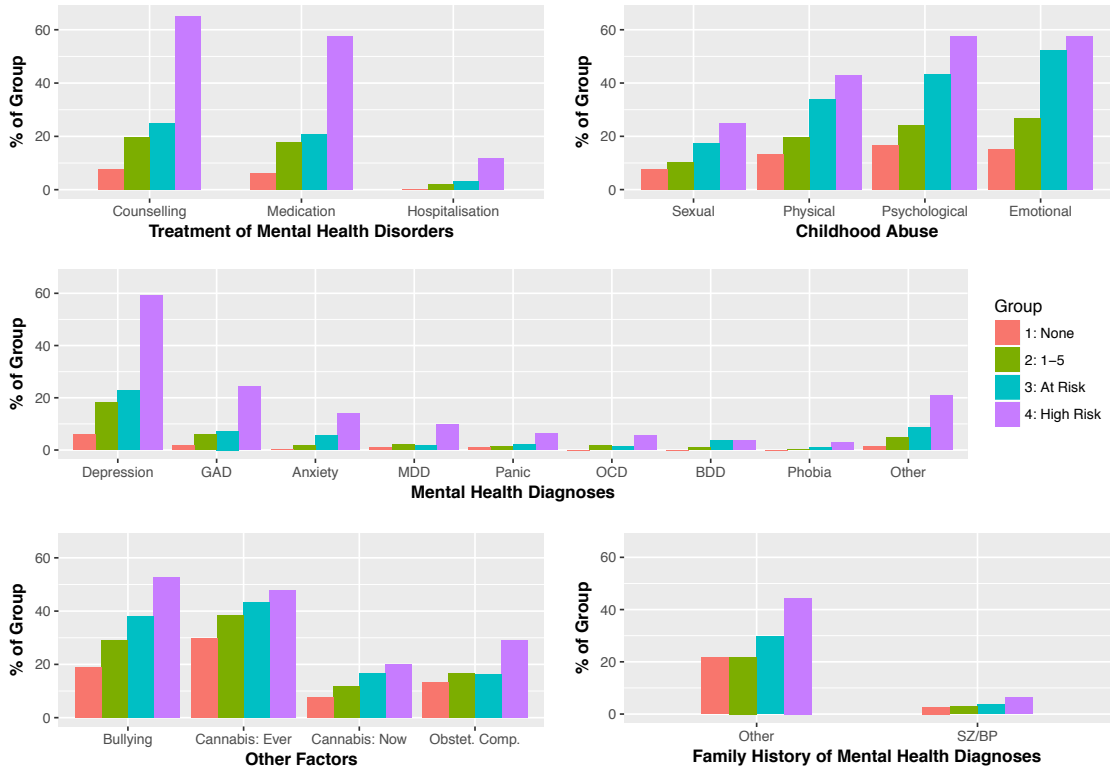

Figure 2.3: Proportional distributions of risk factors across the four groups (n=1789). *Top left*: the proportions of the treatment reported across the four groups, highlighting how need for care increases with respect to the number of psychotic symptoms endorsed and the level of distress incurred. *Top right, bottom left*: the distribution of child abuse, bullying, cannabis use and obstetric complications across the four groups, which is in support of aetiological validity. *Bottom right:* the distribution of family history across groups, demonstrating an upward trend across groups, which is again in support of demographic and aetiological validity.

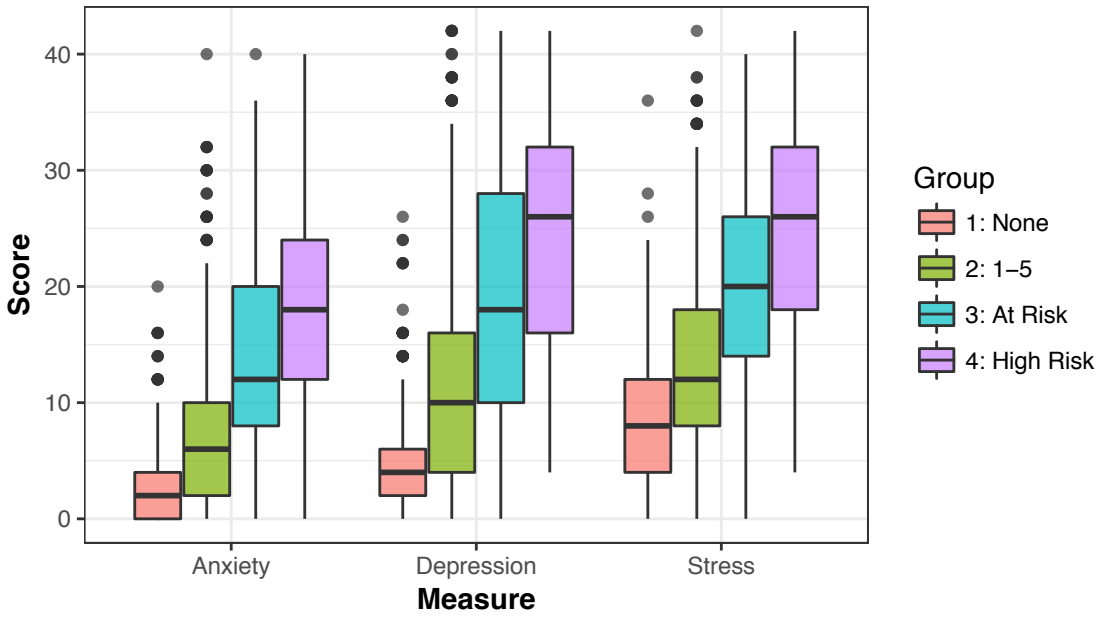

Figure 2.4: Boxplots highlighting the anxiety, depression and stress scores across the four groups (n=1789). The thick horizontal black line within each box represents the median and the boxes represent the interquartile range. An upward trend on each psychometric is observed with respect to group. This supports the psychopathological validity assumption of the PPPI model.

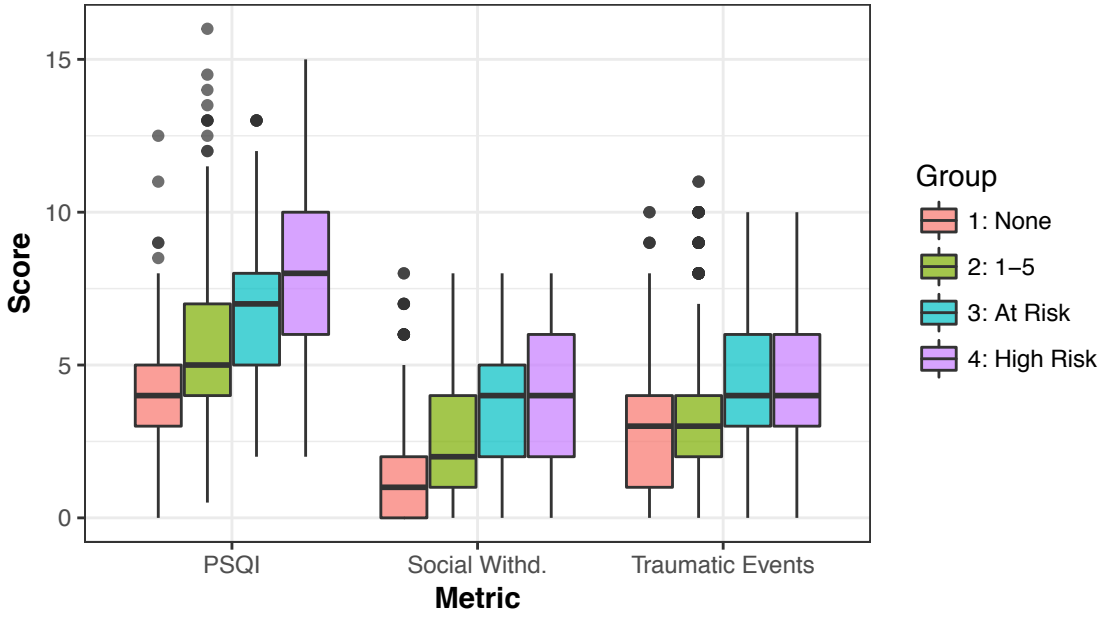

Figure 2.5: Boxplots highlighting PSQI, social withdrawal scores and the number of traumatic events experienced across the four groups (n=1789). An upward trend on each measure is observed across groups, supporting the aetiological validity assumption. The number of traumatic events is slightly different as the medians are the same for the low and no risk groups, as well as for the at-risk and high-risk groups, indicating the threshold of above 5 on the PQ16 may be meaningful with respect to traumatic events.

Perceptual abnormalities were also best predicted by anxiety (OR=1.08, 1.06-1.10, p<0.0001), Traumatic Events (OR=1.13, 1.11-1.16, p<0.0001), social withdrawal (OR=1.07, 1.01-1.14, p=0.030). A one-point increase in anxiety, traumatic events endorsed, or social withdrawal predicted an 8%, 13% and 7% increase in the probability of endorsing perceptual abnormalities. A small effect of age was observed (p=0.0634), with a one-year increase predicting a 1% decreased probability of endorsing perceptual abnormalities.

Table 2.5 shows the models of best fit for the persecutory ideation (paranoia) and bizarre ideas subcategories. Persecutory ideation was also predicted by depression (OR=1.04, 1.02-1.06, p<0.0001), anxiety (OR=1.07, 1.04-1.09, p<0.0001) and social withdrawal (OR=1.11, 1.02-1.20, p=0.019), with one-point increases predicting 4%, 7% and 11% (respectively) increased risk of endorsing paranoia. Furthermore, psychological abuse (OR=1.45, 1.00-2.09, p=0.0479), having used cannabis (OR=1.46, 1.04-2.06, p=0.0302) and bullying (OR=1.44, 1.01-2.06, p=0.0448) were all found to significantly increase the risk of endorsing paranoia (by 45%, 46% and 44% respectively, assuming all other variables are kept constant). Participants identifying as male had a reduced risk (OR=0.60, 0.41-0.88, p=0.0094) with men 40% less likely to endorse paranoia than women.

Negative Symptoms					
	OR (95% CI)	**Estimate**	**SE**	**Z**	**p**
Intercept	-	-2.15	0.32	-6.73	<0.0001
Gender (Male)	0.79(0.57-1.08)	-0.24	0.16	-1.48	0.1389
Depression	1.13(1.11-1.16)	0.12	0.01	10.22	<0.0001
Anxiety	1.06(1.03-1.10)	0.06	0.01	3.88	0.0001
Social Withdrawal	1.21(1.12-1.30)	0.19	0.04	4.90	<0.0001
Comorbidities	1.23(1.00-1.54)	0.21	0.11	1.90	0.0580
PSQI	1.10(1.02-1.19)	0.09	0.04	2.40	0.0165
MSFsc	0.91(0.82-1.01)	-0.09	0.05	-1.725	0.0845
Perceptual Abnormalities					
	OR (95% CI)	**Estimate**	**SE**	**Z**	**p**
Intercept	-	-1.46	0.22	-6.68	<0.0001
Anxiety	1.08(1.06-1.10)	0.08	0.01	8.18	<0.0001
Traumatic Events	1.13(1.06-1.20)	0.12	0.03	3.70	0.0002
Social Withdrawal	1.07(1.01-1.14)	0.07	0.03	2.17	0.0302
Physical Abuse	1.30(0.95-1.76)	0.26	0.16	1.66	0.0963
Comorbidities	1.14(0.98-1.33)	0.13	0.08	-1.64	0.1013
Age	0.99(0.97-1.00)	-0.01	0.01	-1.86	0.0634
Sexual Abuse	1.34(0.90-1.99)	0.30	0.20	1.43	0.1538

Table 2.4: Model summaries for Negative Symptoms and Perceptual Abnormalities.

Comorbidities and distress from traumatic events did not significantly impact the probability of endorsing paranoia (p=0.06 and 0.08 respectively).

Similar to negative symptoms and paranoia, bizarre ideas (BI) were also predicted by depression (OR=1.05, 1.03-1.07, p<0.0001), anxiety (OR=1.08, 1.05-1.10, p<0.0001), traumatic events (OR=1.13, 1.06-1.21, p<0.0001) and social withdrawal (OR=1.16, 1.08-1.23, p<0.0001), with 5%, 8%, 13% and 16% increases in the risk in endorsing BI for a one-point increment in each of the respective predictors (holding all other variables constant). Furthermore, both physical abuse during childhood (OR=1.43, 1.02-2.00, p=0.0391) and cannabis use (OR=1.52, 1.17-1.98, p=0.0018) were found to be significant predictors, with a 43% and 52% increased risk in endorsing BI for those who have smoked cannabis and experienced physical abuse respectively (holding all other variables constant). Both insomnia (SCI) (OR=1.06, 1.00-1.13, p=0.0554) and emotional neglect (OR=1.35, 0.99-1.84, p=0.0571) were just above the p-value threshold of 0.05.

Persecutory Ideation					
	OR (95% CI)	**Estimate**	**SE**	**Z**	**p**
Intercept	-	-3.23	0.36	-8.93	<0.0001
Depression	1.04(1.02-1.06)	0.04	0.02	4.50	<0.0001
Anxiety	1.07(1.04-1.09)	0.06	0.01	5.13	<0.0001
Psychological Abuse	1.45(1.00-2.09)	0.37	0.20	1.98	0.0479
Social Withdrawal	1.11(1.02-1.20)	0.10	0.04	2.34	0.0194
Cannabis (ever)	1.46(1.04-2.06)	0.38	0.17	2.17	0.0302
Bullying	1.44(1.01-2.06)	0.37	0.18	2.01	0.0448
Gender (male)	0.60(0.41-0.88)	-0.51	0.20	-2.60	0.0094
Comorbidities	1.18(1.00-1.41)	0.17	0.09	1.91	0.0559
Trauma (Distress)	1.08(0.99-1.17)	0.08	0.04	1.73	0.0796
SCI	0.94(0.87-1.02)	-0.06	0.04	-1.52	0.1285
Bizarre Ideas					
	OR (95% CI)	**Estimate**	**SE**	**Z**	**p**
Intercept	-	-2.20	0.34	-6.42	<0.0001
Age	0.99(0.97-1.00)	-0.013	0.01	-1.94	0.0530
Depression	1.05(1.03-1.07)	0.046	0.01	5.29	<0.0001
Anxiety	1.08(1.05-1.10)	0.073	0.01	5.88	<0.0001
Traumatic Events	1.13(1.06-1.21)	0.124	0.03	3.64	<0.0001
Social Withdrawal	1.16(1.08-1.23)	0.145	0.04	4.151	<0.0001
Insomnia (SCI)	1.06(1.00-1.13)	0.062	0.03	1.92	0.0554
Physical Abuse	1.43(1.02-2.00)	0.355	0.17	2.06	0.0391
Emotional Neglect	1.35(0.99-1.84)	0.301	0.16	1.90	0.0571
Cannabis (Ever)	1.52(1.17-1.98)	0.418	0.13	3.12	0.0018

Table 2.5: Model summaries for Persecutory Ideation and Bizarre Ideas.

The final two models, presented in **Table 2.6**, were for delusional mood and cognitive disorganisation. Delusional mood (DM) was also predicted by anxiety (OR=1.04, 1.02-1.07, p=0.0002) and traumatic events (OR=1.19, 1.02-1.22, p=0.0118) and social withdrawal (OR=1.10, 1.00-1.20, p=0.00438), with 4%, 19% and 10% increases in the probability of endorsing DM respectively for corresponding one-unit increases in the predictor variables (holding all others constant). Other significant predictors for delusional mood were psychological abuse (OR=2.24, 1.49-3.34, p<0.0001) and MSFsc (OR=1.24, 1.10-1.40, p=0.0003). Sexual abuse failed to reach significance (p=0.1190).

Finally, cognitive disorganisation (CD) was also predicted by anxiety (OR=1.07, 1.05-1.10, p<0.0001), social withdrawal (OR=1.10, 1.03-1.17, p=0.0058) and traumatic events (OR=1.07, 1.00-1.14, p=0.0375). Having smoked cannabis also predicted cognitive disorganisation (OR=1.32, 1.03-1.70, p=0.0314), with cannabis users having an estimated 32% increase in the probability of endorsing cognitive disorganisation (with all other variables held constant). Further to this, CD was the only

category to be predicted by the PSQI (OR=1.10, 1.03-1.16, p<0.0050) and age (OR=0.97, 0.96-0.98, p<0.0001), with a one-point increase in PSQI predicted to increase the risk of endorsing CD by 10%, and being a year older predicted to give a 3% decrease in the risk of endorsing CD. Emotional neglect failed to reach significance (p=0.0658).

Of the risk factors considered, ethnicity, season of birth, paternal age, urbanicity, 1st degree relatives with a family history, presence of comorbidities and the treatment for comorbid mental health problems did not significantly predict an increased risk of any of the above psychotic symptom categories.

Delusional Mood					
	OR (95% CI)	**Estimate**	**SE**	**Z**	**p**
Intercept	-	-4.59	0.38	-12.20	<0.0001
Psychological Abuse	2.24(1.49-3.34)	0.80	0.20	3.93	<0.0001
Anxiety	1.04(1.02-1.07)	0.04	0.11	3.68	0.0002
MSFsc	1.24(1.10-1.40)	0.22	0.06	3.60	0.0003
Traumatic Events	1.19(1.02-1.22)	0.11	0.04	2.52	0.0118
Social Withdrawal	1.10(1.00-1.20)	0.09	0.05	2.02	0.0438
Sexual Abuse	1.46(0.90-2.35)	0.38	0.25	1.56	0.1190
Cognitive Disorganisation (Dissociation)					
	OR (95% CI)	**Estimate**	**SE**	**Z**	**p**
Intercept	-	-0.98	0.24	-4.08	<0.0001
Anxiety	1.07(1.05-1.10)	0.07	0.01	6.42	<0.0001
Social Withdrawal	1.10(1.03-1.17)	0.09	0.03	2.76	0.0058
Age	0.97(0.96-0.98)	-0.03	0.01	-4.61	<0.0001
PSQI	1.10(1.03-1.16)	0.09	0.03	2.81	0.0050
Traumatic Events	1.07(1.00-1.14)	0.07	0.03	2.10	0.0375
Cannabis (Ever)	1.32(1.03-1.70)	0.28	0.13	2.15	0.0314
Emotional Neglect	1.31(0.98-1.75)	0.27	0.15	1.84	0.0658

Table 2.6: Model summaries for Delusional Mood and Cognitive Disorganisation.

2.5.2 Evaluation of Model Quality

The boxplots in **Figure 2.6** provide a visualisation of the models' discrimination abilities – i.e. how effective each model is at correctly predicting whether an individual endorsed a psychotic symptom or not - for the individuals in the randomly selected training dataset (consisting of 70% of the data).

In such plots, instances with large amounts of overlap denote that the predicted probability of endorsing the outcome is similar for those who actually do and those who do not endorse a psychotic

symptom; thus highlighting that the model is doing a poor job of discriminating between these groups. Instances with good separation between the boxes indicate the model is successfully allocating a much higher probability of endorsing a psychotic symptom to those who actually did endorse them, than to those who actually did not. In such cases, the model is discriminating successfully between the groups.

The boxplots presented here show some of the models outperform the others. The logistic regression model for negative symptoms (a model which is primarily a proof of concept) demonstrates excellent discrimination ability between participants who did/did not endorse negative symptoms. Similarly, the models for paranoia, bizarre ideas, perceptual abnormalities and cognitive disorganisation show clearly distinguishable differences in the predicted probabilities for those who did/did not endorse the outcome. The model for delusional mood appears to have the most limited discrimination ability between groups, with a large number of outlying observations within those who did not endorse delusional mood.

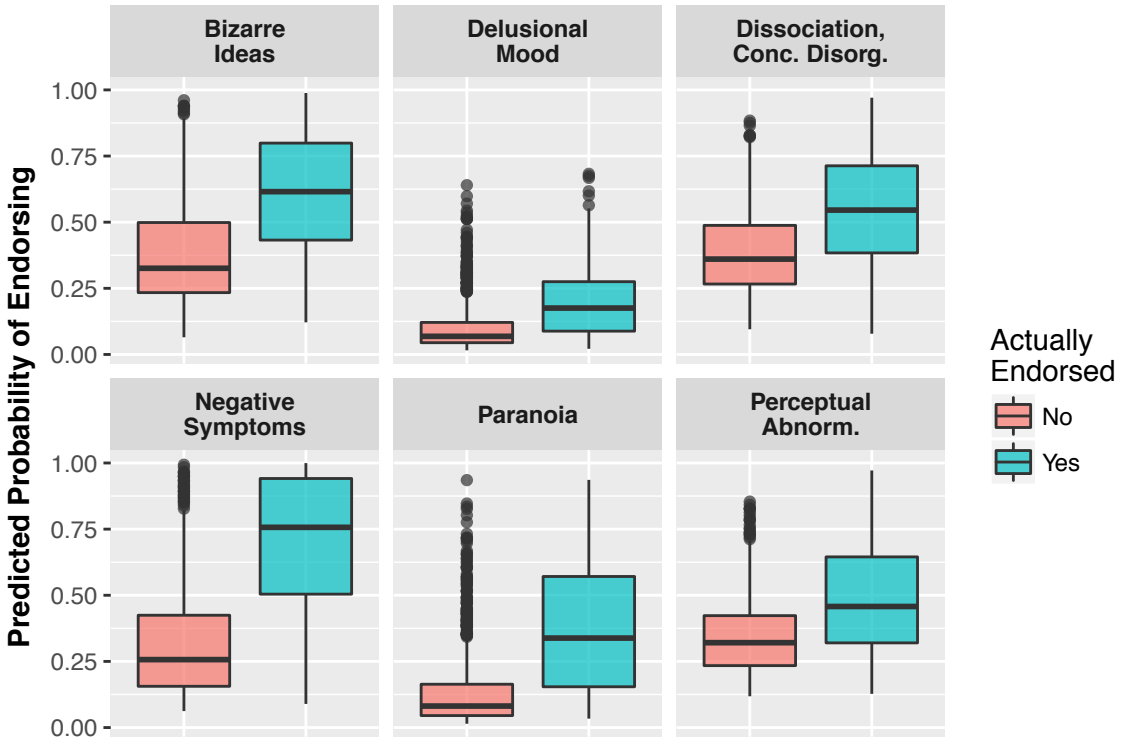

Figure 2.6: Boxplots of predicted probabilities from each of the six logistic regression models for survey respondents in the training dataset. The predicted probabilities for those respondents who endorsed each subcategory are compared to those who did not.

To further explore the ability of the logistic regression models to discriminate between individuals who did and didn't endorse subcategories of the PQ16, **Figure 2.7** presents the ROC curves for the fit of each model to the training dataset. Logistic regression models can be used for classification by splitting individuals based on their predicted probabilities of endorsing the outcome: those above a given threshold are predicted to endorse the outcome, the rest are predicted to not. Each plot in **Figure 2.7** shows how the true positive rate (sensitivity) and the false positive rate (1-specificity) vary as this threshold for classification is varied.

A model with high discrimination ability will simultaneously have a high true positive rate and a low false positive rate (i.e. high sensitivity and specificity), leading to an ROC curve that approaches the top-left corner of the plot. A model with poor discrimination ability will lead to an ROC curve that approaches the 45-degree diagonal line (the 'line of no discrimination, which is equivalent to a coin-toss). As with the boxplots, it can be observed that some of our models have stronger discrimination ability than others, with the models for negative symptoms, paranoia and bizarre ideas having the greatest separation from the line of no discrimination.

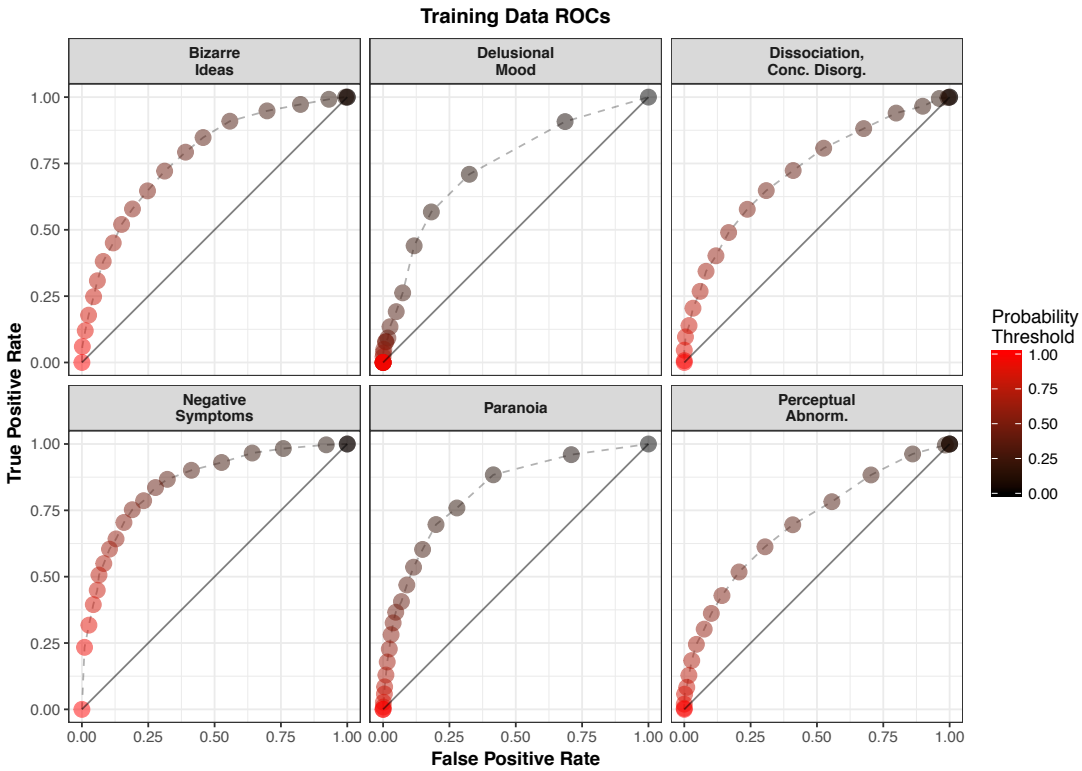

Figure 2.7: Receiver Operating Characteristic (ROC) curves for each of the six logistic regression models for survey respondents in the training dataset. For each plot, the points show how the true positive rate (sensitivity) and the false positive rate (1-specificity) vary as the threshold for classification is varied.

A useful summary statistic that quantifies this is the area under the ROC curve: a value of 1 corresponds to a model offering perfect discrimination, and 0.5 corresponds to a model with no discrimination ability. As mentioned earlier, this statistic (also referred to as the c-statistic) can be interpreted as the probability that a randomly chosen participant who endorsed the psychotic symptom and a randomly chosen participant without the psychotic symptom could be reliably distinguished, based on the predictor variables of the model. The area under the ROC curve for each of our models is presented in **Table 2.7** for both the training and test datasets.

Finally, **Table 2.8** presents another related metric of model quality. For each model, the optimal classification threshold (based on the training data) is detailed, alongside the resulting percentage of correctly classified individuals in the training data. The percentage of correctly classified individuals in the test data is also provided, based upon the same classification threshold. It can be observed that the correct classification rate varies between 66 and 78% across the six models, and significantly, that the models perform similarly well on the training data (on which they were built) and the test data (which they had not previously seen). In some cases, the models even perform better on the test dataset, lending weight to the argument that the models are not overfitted to the training data.

	Training Data (70%)	Test Data (30%)
Negative Symptoms	0.86	0.87
Perceptual Abnormalities	0.71	0.70
Bizarre Ideas	0.78	0.73
Paranoia	0.82	0.82
Delusional Mood	0.75	0.73
Dissociation	0.73	0.74

Table 2.7: The Area Under the ROC Curve for the training and the test data.

	Threshold	Training Data	Test Data
Negative Symptoms	0.44	78.3	78.8
Perceptual Abnormalities	0.39	66.5	67.6
Bizarre Ideas	0.46	71.3	67.2
Paranoia	0.20	78.3	76.2
Delusional Mood	0.10	68.6	69.1
Dissociation	0.46	68.3	68.3

Table 2.8: Classification success rate for each PLE category.

2.6 Discussion

This study was designed to allow for in-depth examinations of the predictions made by the PPPI model as proposed by Linscott & van Os (2013) and van Os et al., (2009). Our first hypothesis related to the distributional properties of PLEs. We found the distribution of PLEs in this population to have a 'half-normal' distribution, with the majority of the population endorsing very low values but with a considerable section of the population endorsing increasingly higher values, as suggested by van Os et al., (2009). Second, based on our group formulations to identify subgroups that may be deemed to be further along the psychosis-proneness continuum, we found that cross-sectionally increased PLEs were associated with increased common psychopathological comorbidities (e.g. depression and anxiety disorders), as is observed in the disorder itself. This lends further support for the notion of psychopathological continuity (Linscott & van Os, 2013; van Os et al., 2009). This was further supported by the distributions of psychometric scores on depression, anxiety and stress, which demonstrated progressive increases by group. Finally, complaints of poor sleep quality and insomnia were also found to distribute differently across groups, supporting the role of sleep disruption of in the psychosis-proneness continuum model.

Third, it was predicted that those at the higher end of the continuum would also demonstrate the greatest need for care. Again, this was supported cross-sectionally by chi-square tests for our three treatment outcomes (counselling, medication and hospitalisation), and the highest levels of endorsement being in the at-risk and high-risk groups. Fourth, it was predicted that demographic associations with psychotic disorders would also extend to individuals with PLEs (e.g. ethnicity). It was also assumed that certain demographic phenomena would only be observable cross-sectionally and as such would not predict the occurrence of PLEs themselves. Cross-sectionally, none of the demographic variables (urbanicity, ethnicity, SOB, migrancy, paternal age) assessed in the OWLS survey highlighted any differences across the four groups. Fifth, in line with aetiological validity, it was anticipated that some of the genetic and non-genetic factors that are known contributors to the most severe forms of psychosis would also impact more attenuated forms or PEs (e.g. family history and severe child abuse). All of the aetiological risks examined (family history, bullying, social withdrawal, all forms of child abuse, past and current cannabis use, and experiencing a trauma) displayed progressive increases across the four groups. Interestingly, the self-report of obstetric

complications at birth also varied across the groups, lending further support to the notion of aetiological continuity in the PPPI model.

2.6.1 Modelling Analyses

2.6.1.1 SCRD and Psychotic Symptoms

Our SCRD hypotheses specific to the modelling outcomes were that sleep variables - an insomnia complaint, poor sleep quality (with regards to low sleep efficiency, denoted by the PSQI) and aberrant timing - would predict an increased risk in PLEs. This was only partially supported by the results obtained. SCRD as a risk factor displayed remarkable specificity in its prediction of different categories of PLEs. The PSQI was found to be significant for cognitive disorganisation only.

2.6.1.2 SCRD, Dissociation and Cognitive Disorganisation

Cognitive disorganisation in this survey is a direct replica of the core categories of dissociative experiences (DEs), which have now been repeatedly argued to have strong ties to sleep and sleep disruption, despite being formerly thought of as a consequence of trauma (Koffel & Watson, 2009; Murray, 2002).

Evidence for this relationship can be gleamed from correlative data which shows DEs to be related to longer REM periods, insomnia and unusual sleep experiences (van der Kloet et al., 2013), and also from experimental sleep deprivation paradigms that have demonstrated an increment in dissociative experiences in healthy volunteers (Giesbrecht, Smeets, Leppink, Jelicic & Merckelbach, 2007). Furthermore, sleep normalisation predicted a decrement in dissociative experiences in an inpatient sample (van der Kloet, Giesbrecht, Lynn, Merckelback & de Zutter, 2012a), and the presence of dissociation was found to be predicted by unusual sleep experiences (based on structural equation modelling; van Heugten-van der Kloet, Merckelback, Giesbrecht & Broers, 2014). For a general overview of the sleep-dissociation relationship, please see van der Kloet, Merckelbach, Giesbrecht & Lynn (2012b).

Globally, DEs can be defined as disruption to the routine integration of beliefs, emotions and everyday life experiences into our consciousness and memory (van der Kloet et al., 2014). This disruption can range from the relatively benign absentmindedness of everyday life to profound

amnesia for life events and to severe disturbances to our sense of self, identity and the experience of every day reality (van der Kloet et al., 2012a). A hallmark ESM study by Varese and colleagues (2011) examined the role of dissociation in auditory hallucinations in 42 patients with a schizophrenia diagnosis. They found that patients who had hallucinated (n=21) during the six-day assessment period endorsed greater levels of dissociation compared to both non-hallucinating patients and controls. Furthermore, the presence of auditory hallucinations was predicted by dissociation, particularly under high stress. Hallucinating patients also endorsed higher dissociation when reacting to minor daily stress. Overall, the authors concluded dissociative experiences could be considered a precipitating or mediating factor for auditory hallucinations (Varese, Udachina, Myin Germeys, Oorschot, & Bentall, 2011).

There now exist several studies and one review discussing the relationship dissociative experiences have to auditory hallucinations (Allen, Coyne, & Console, 1997; Černis et al., 2014; Freeman et al., 2013; please refer to Pilton, Varese, Berry, & Bucci, 2015 for a review). DEs are also very common in healthy individuals (van der Kloet, Merckelbach, Giesbrecht, & Lynn, 2012b). As such, they represent an interesting category of symptoms for understanding the role of SCRD in psychotic experiences.

2.6.1.3 The SCI and MSFsc

Beyond the PSQI, the SCI (which is more specific to an insomnia complaint or a worry of poor sleep) significantly predicted bizarre ideas, and sleep timing (denoted by a later mid-sleep point) significantly predicted delusional mood. This succinctly highlights the point made in the introduction that SCRD is an exceptionally broad concept; as such, it is necessary to specify which strains of SCRD may have greater ties to different symptoms of psychosis. The analysis of this survey (to our knowledge) is the first attempt to do this in such detail.

Understanding which parameters of sleep could have ties to certain symptoms of psychosis is crucial for furthering our understanding of the role in SCRD in psychosis. Both constructs are broad and heterogeneous. As such, it is not anticipated that all sleep parameters would impact unilaterally in all patients with psychosis. Determining these specificities could help explain why results of a clinical trail examining the impact of cognitive behavioural therapy for insomnia on psychotic symptoms failed to produce significant results (as the effect would be lost in a summary score of psychotic

symptoms; Freeman et al., 2015), and why heterogeneity in terms of the different SCRD observed in schizophrenia has been noted in the literature (as, like SCRD, schizophrenia presents with many different phenotypes which could represent differences in different symptomatic profiles; Wulff et al., 2012).

2.6.2 Broader Interpretations of the Modelling Analyses

This study provides a unique insight not only into the shared risk factors for psychotic symptoms, but those that are specific to a specific genre of psychotic symptom. **Figure 2.8** summarises our results, highlighting anxiety, social withdrawal during childhood and trauma (with the exception of paranoia) to all be commonly held risk factors across the five domains. This is unsurprising, as both trauma and anxiety have long been hailed as important triggers for psychosis (Evans, Reid, Preston, Palmier-Claus, & Sellwood, 2015; van Os, Linscott, Myin-Germeys, Delespaul, & Krabbendam, 2008). The second most commonly shared risk factor was having ever used cannabis, which was shared by paranoia, bizarre ideas and cognitive disorganisation. Importantly, while generally considered a risk factor for psychosis (Moore et al., 2007), cannabis was not found to predict perceptual abnormalities, which are commonly regarded as the most discernable symptoms of psychosis. This may relate to why the consideration of cannabis as a risk factor is still very much a subject of debate in the psychosis literature (Arseneault, 2004).

Interestingly, depressive symptoms were shared only by paranoia and bizarre ideas. This may relate to more affective psychoses, but this is purely speculative at this point. Psychological abuse was shared by both delusional mood and paranoia. Risk factors unique to specific categories were bullying and gender for paranoia, physical abuse for bizarre ideas and age for cognitive disorganisation. Age was however trending for significance for both bizarre ideas and perceptual abnormalities in the same direction (with youth considered to increase risk). An analysis to this level of detail with psychotic symptoms has yet to be reported in the literature. As such, discussion of the underlying mechanisms leading to certain risk factors relating to certain psychotic symptoms would be purely speculative.

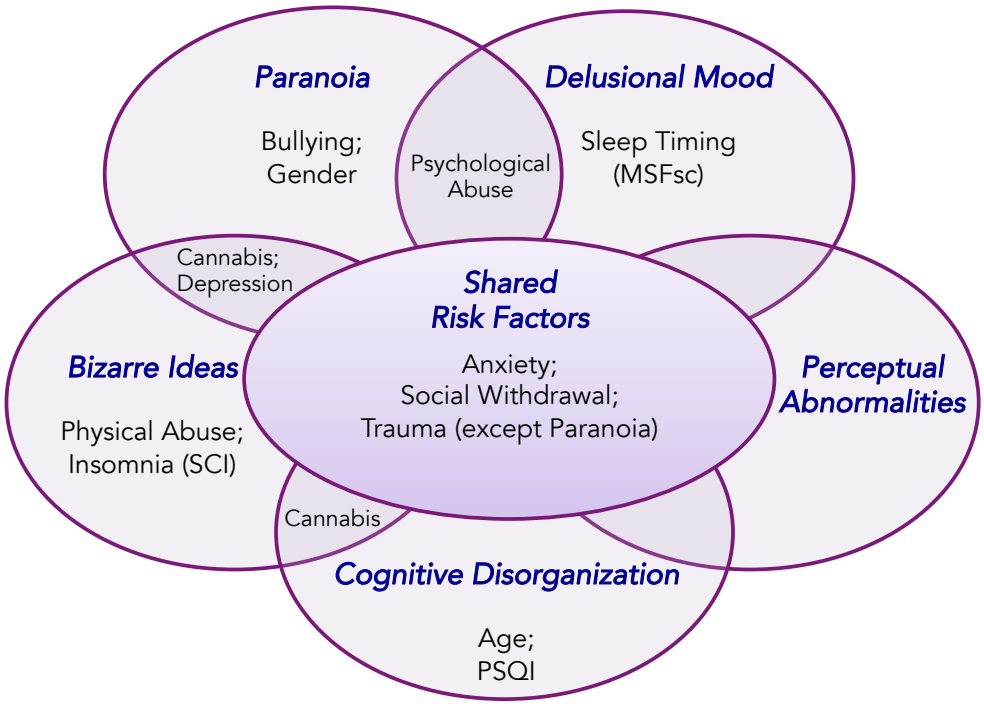

Figure 2.8: The overlapping and distinct risk factors for the five categories of psychotic symptoms.

2.6.3 Disparity between Modelling and Cross-sectional Observations

The analyses presented here also present broader implications for the disparity in outcomes between cross-sectional group and regression analyses. On a cross-sectional basis, differences in group prevalence (according to the number of psychotic symptoms an individual presents and/or help seeking behaviour) are seen for the majority of risk factors examined, with the exception of urbanicity, ethnicity, SOB, migrant status and paternal age. However, the only risk factors to translate to the models (aside from anxiety and depression scores) are bullying, physical and psychological abuse, cannabis, trauma, social withdrawal and sleep related variables. Taken together it would appear that childhood risk factors as a category are overrepresented with only sexual abuse and emotional neglect missing (both of which featured in models but failed to reach significance). Psychiatric diagnoses, which presented stark differences cross-sectionally, did not significantly predict the occurrence of any category (although it was trending for paranoia). Equally, family history (which distributed differently across groups and is a widely held risk for psychosis) did not individually predict any specific category of psychotic symptoms. Similar disparities have been reported before in the literature. Cannon et al., (2016) reported that despite being established risk factors for psychosis,

family history, stressful life events, traumas and age did not predict actual transition to a psychotic episode using their individualised risk calculator.

Another study found urbanicity and parental education level to not be predictive of the onset of schizophrenia and non-affective psychosis, but a family history of psychosis was found to have a very pronounced effect (OR=3.06, 1.58-5.94; Linscott & van Os, 2013).

Both positive and negative results have been presented for urbanicity (Linscott & van Os, 2013; Johns et al., 2004). Despite a meta-analysis highlighting the impact of a winter/spring birth on the prevalence of schizophrenia (Geoffrey Davies, Welham, Chant, Torrey, & McGrath, 2003), negative results have been reported for the detection of PLEs (Kelleher & Cannon, 2011).

Given the considerable amount of disparity in what predicts risk across studies, the results presented here suggest that disparity may be (in part) triggered by a difference in affinity for different risk factors for different psychotic symptoms. Future research could investigate if this is the case. This could certainly help explain why psychotic disorders like schizophrenia are so heterogeneous in their clinical presentation (Tandon et al., 2009), as different risk factors may manifest as different symptomatologies or indeed highlight different pathways to the disease. This is purely speculative at this point and warrants considerable research before these notions could be substantiated.

2.6.4 Limitations

A number of caveats merit mention. First, the survey did not examine relationship status, yet we know this to be associated with the endorsement of PEs (McGrath et al., 2015). Student status has been show to be associated with lower PE occurrence (McGrath et al., 2015). As students are overrepresented in this sample this may bias the results.

The questionnaires employed don't address the number of times a certain PE was experienced but rather whether that experience occurred during the last year. Psychotic experiences can vary in terms of the degree of conviction, intensity, impact on functioning, frequency and pre-occupation (Zammit et al., 2013). More fine-grained analyses informing what risk factors may increase these parameters of PEs were not possible given the nature of the PQ16 questionnaire.

Self-report measures (such as those employed here) have been shown to over-estimate the occurrence of psychotic experiences when compared to semi-structured clinical interviews, as they do not permit the cross-examination of the subject to ensure that the experiences endorsed are indeed psychotic (Zammit et al., 2013).

This survey has a low geographical dispersal as recruitment only took place around Oxford. Location and the level of income of the country does considerably impact the prevalence of PEs (Linscott & van Os, 2013; McGrath et al., 2015). There was a very low ethnic dispersal in this survey, yet ethnicity has been repeatedly shown to impact the prevalence of PLEs (Johns et al., 2004; Linscott & van Os, 2013; van Os et al., 2009). Furthermore, socio-economic status may impact PLE prevalence, however, considering the education levels in this sample it is unlikely to have had a huge impact on these results (Hudson, 2005).

Cognitive decline in adolescence is considered a very potent risk factor for psychosis, specifically between the ages of 13-18 years, and this could not be evaluated in this format (MacCabe et al., 2013). Exposure to alcohol and other psychoactive drugs (outside cannabis) have been found to increase risk of PEs, but these were not examined in this survey (van Os et al., 2009). There are an extensive number of genetic risk factors (outside family history) which have been shown to increase the risk of psychosis and PEs which could not be examined in survey format (van Os et al., 2009).

Finally, the rates of PEs presented here are substantially above what has been previously reported in the literature (7-12%; Johns et al., 2004; Kelleher, Connor, et al., 2012a). This may reflect a sampling bias, as the survey was advertised as relating to wellbeing; could be reflective of the structure/wording of the PQ16 (which encourages a more liberal response style/lower threshold for endorsement); or indeed, could reflect both of these.

2.6.5 Wider Implications

More broadly, the advantages and clinical implications of supporting the PPPI model are clear. First, poor prognosis (measured by clinical need) is predicted by environmental exposure networking with genetic risk (van Os et al., 2009). Second, the logical conclusion of the PPPI model would be to

conceptualise psychosis as an infrequent consequence of a relatively common phenotype that can be measured. Psychosis in this scenario is described as enduring measurable subsyndromal PEs. As such, the underlying causes of psychosis can be traced to the exposure of risk factors which make common/transient PEs persist (van Os et al., 2009).

The OWLS survey is the first of its kind: a survey designed to tackle the question of whether empirically robust risk factors can predict the occurrence of PLEs, or whether it remains that the majority of these risks are only observable using cross-sectional comparisons. Previous studies have used larger samples but lower resolution measures, or have reanalysed national survey data, but the OWLS survey is the first to specifically target risk factors for psychosis and examine in detail what their relationship holds to PLEs. It is also the first survey to examine what the role of SCRD may play in the specific categories of psychotic symptoms using high-resolution measures and modelling analyses.

Future work should consider longitudinal follow-ups of samples using the OWLS survey to understand the role of risk factors in the transition: not just to a clinical diagnosis of psychosis, but also to a significant increase in the number of PLEs endorsed and the distress attached to them, as our grouping categories highlight this to be of great relevance for important treatment outcomes for both the individual and the healthcare service (e.g. hospitalisation).

Furthermore, our analyses of certain risk factors (e.g. ethnicity) were limited due to the low geographic dispersal of the survey. Future research would ideally use this survey multi-nationally to understand the impact of geographic dispersal on risk factor prevalence and rates of PLE endorsement. Finally, further research aimed at replicating the specificity of risk factors (particularly SCRD) to certain categories of psychotic symptoms may be of real benefit to understanding the heterogeneity of the disorder itself.

Chapter 3:
A Novel Analysis of Nocturnal Heart Rate and Heart Rate Variability in Insomnia Sufferers and Good Sleepers

The work presented here was done in collaboration with Jessica Phillips and Prof. David Steinsaltz of the Department of Statistics. Some of the analyses presented here were conducted as part of a Masters' project designed for Jessica Phillips, which I co-supervised with my supervisor, Dr. Katharina Wulff.

3.1 Background

Chapter 2 focused on a large survey cohort and found associations between specific sleep parameters and sub-categories of psychotic symptoms. Two subjective sleep questionnaires, the SCI (examining an insomnia complaint) and the PSQI (examining a complaint of subjective poor sleep quality) were found to predict the endorsement of bizarre ideas and cognitive disorganization respectively. Both of these questionnaires are strongly predictive of the presence of an insomnia disorder (Carpenter & Andrykowski, 1998; Morin, Belleville, Bélanger, & Ivers, 2011). Insomnia's burden is not just what is costs the individual and the state in and of itself, but also the costs it incurs as a feature of numerous comorbid psychiatric disorders, including psychosis and schizophrenia (Cohrs, 2008; Johnson et al., 2006; Waters & Manoach, 2012; Wulff et al., 2012).

In Section 1.9.2, the stress axis was highlighted as a potential mediator of the relationship between sleep and mental health, with specific reference to the ANS. It was also noted that there is currently a dearth of biologically driven research into the sleep-PLE relationship. As such, this chapter focuses

on the biological underpinnings of a complaint of poor sleep. Specifically, this chapter is designed to help elucidate the role of hyperarousal in an insomnia complaint.

3.2 Introduction

There are numerous neurobiological idiosyncrasies associated with insomnia disorder that would accumulatively indicate insomnia to be at least partially pathophysiologically driven by mechanisms of hyperarousal of the autonomic nervous system (ANS; Sateia & Nowell, 2004), which we also know to be affected in psychiatric disease. Examples include an increased activation of the autonomic nervous system demarcated by increased metabolic rate, body temperature, activation of the hypothalamic-pituitary adrenal axis activity, brain glucose metabolism and reduced heart rate variability during sleep (Morin & Benca, 2012).

Referring back to Section 1.9.2.1, one such form of hyperarousal (alongside numerous psychopathologies) that has gained extensive attention in the insomnia literature is nocturnal heart rate (HR) and heart rate variability (HRV; Dodds et al., 2016).

Nocturnal HR and HRV are time domain measures of an electrocardiogram (ECG) signal. However, spectral analysis of HRV is thought to permit further insight into the workings of the autonomic nervous system by differentiating between its two subcategories: the sympathetic and the parasympathetic nervous systems. It is understood that spectral analysis highlighting low frequency (LF) activity is associated with both parasympathetic activity and sympathetic activity. High frequency (HF) activity is correlated with parasympathetic activity only. Taken together, the ratio between these (the LF/HF ratio) offers an estimated sympathovagal balance that is the assumed symmetry between both the sympathetic and parasympathetic systems (Dodds et al., 2016). The utility and scientific interpretation of spectral analyses of HRV remains contentious (Billman, 2007; Burr, 2007; Reyes del Paso, Langewitz, Mulder, Roon, & Duschek, 2013); as such, they are not a core focus of the analysis in this chapter.

The appeal of examining HR and HRV in insomnia is twofold. First, insomnia is related to cardiovascular mortality (Spiegelhalder et al., 2011). However, it remains uncertain whether

cardiovascular measures can be directly related to the risk of someone developing the symptoms of insomnia. Thus, the investigation of HR and HRV can help elucidate the potential health risks associated with the presence of insomnia disorder. Second, high HRV is a signal of healthy cardiovascular autonomic function, whereas low HRV is found in those with cardiovascular morbidity and mortality in clinical and nonclinical samples. It is thought that a low nocturnal HRV indicates decreased cardiovascular adaptability. Consequently, it confers risk to the initiation and progression of cardiovascular disease (Jarrin et al., 2016), and has also been linked with the development of numerous psychiatric disorders (Gorman & Sloan, 2000; Moon, Lee, Kim, & Hwang, 2013). Decreased cardiovascular adaptability and increased nocturnal heart rate are frequently cited as examples of physiological hyperarousal in insomnia; as such, their presence could help inform the pathophysiology of insomnia disorder.

A recent systematic review by Dodds et al. (2016) provided an overview of 22 studies comparing HRV between insomnia patients and controls, and concluded that it was not possible to confirm that HRV is "reliably impaired in insomnia patients" (p.2, Dodds et al., 2016), due to the high risk of bias in a majority of the studies reviewed, as well as the lack of consistency in the HRV findings in insomnia patients. The authors also highlighted numerous issues with the current body of literature on HRV and insomnia, and we have aimed to directly combat some of the issues in this study. First, we have conducted 'ambulatory' or at home EEG as opposed to using a laboratory setting, as this has been known to impact sleep in insomnia sufferers (McCall, Erwin, Edinger, Krystal, & Marsh, 1992). There are currently only four studies that have done this (Dodds et al., 2016). Our controls are taken from the same population as the insomnia group and were age and gender matched where possible. We have selected a 'subclinical' insomnia group, and as such, we have eroded complications with medication or comorbid medical disorders. All participants were aged between 18-30 years and were screened for medical health disorders, rendering the population in our sample to be ostensibly 'healthy'. Furthermore, few studies to date control for or examine the impact of arousals on nocturnal HR and HRV, yet we know arousals are frequently allied to, or potentially induced, by cardiac fluctuations throughout the night (Bonnet & Arand, 1997). By contrast, this study provides a structural examination of arousals with respect to sleep architecture.

This study was designed to explore the pathophysiology of insomnia through analysis of nocturnal

HR and HRV. We aimed to expand upon the current knowledge and analysis of nocturnal HR and HRV in insomnia sufferers by employing multiscale entropy (MSE) analyses on nocturnal heart rate across each of the sleep stages (measured with ambulatory PSG) throughout the night. This is the first time MSE, in unison with polysomnography, has been applied as an analytic technique in an insomnia cohort. This allows for more fine-grained analyses of nocturnal HR with respect to sleep staging. Numerous physiological systems in humans are inherently complex, with complexity in this context referring to the occurrence of non-random oscillations on multiple time scales in what appear to be erratic physiological outputs (Costa, Goldberger, & Peng, 2002; Lipsitz & Goldberger, 1992). Incrementally more evidence suggests that aging and disease is associated with a reduction in biological complexity. Reductions of this kind have been reported upon in heart rate (Chaves et al., 2008), respiration (Peng et al., 2002), gait (Hausdorff, Rios, & Edelberg, 2001), posture (Duarte & Sternad, 2008), motor activity (Hu, Van Someren, Shea, & Scheer, 2009) and red blood cell flickering (Costa, Ghiran, Peng, Nicholson-Weller, & Goldberger, 2008b), and have been thought to be associated with adverse clinical outcomes (Chaves et al., 2008; Hausdorff et al., 2001). To our knowledge, there is only one study to date that investigates the utility of MSE on nocturnal HR in insomnia. Yang et al. (2011) analysed 24 hour ECG data and reported a summary MSE value for nocturnal heart rate in patients with major depression, primary insomnia, and healthy controls, and found that reduced physiological complexity was observed exclusively during the night time period in both the insomnia and depressed patients. The authors concluded that this indicates a pivotal role of sleep disturbances in the pathophysiology of cardiac autonomic controls.

We aim to expand upon these findings in a number of ways. Yang et al. (2011) used only subjective measures of sleep, and it is therefore impossible to conclude whether these pathophysiological differences relate to objectively measured sleep rather than just self-reported poor sleep. To help clarify this issue, we employ MSE with PSG to understand whether varying levels of physiological complexity were present across the sleep architecture of good and poor sleepers, employing separate MSE analyses for each of the stages. We also examine physiological complexity in a younger, more homogeneous sample than Yang and colleagues, as aging itself is known to reduce the complexity of biological signals (Manor et al., 2010).

Taken together, it is predicted that: (1) the insomnia sufferers will display objectively poorer sleep,

based on previous literature (Spiegelhalder et al., 2015), specifically in the domain of sleep efficiency and sleep onset latency obtained; (2) that insomnia sufferers will display a greater number of arousals and a significantly greater arousal index across the night; (3) that insomnia sufferers will display increased nocturnal heart rate and decreased HRV across different stages of sleep throughout the night, demarcating increased hyperarousal during sleep; (4) that it will be possible to replicate the findings of Spiegelhalder et al. (2011) with a significant interaction between group and sleep stage with nocturnal heart rate as the outcome variable; (5) that, in line with previous research in insomnia, there will be a significant difference in HRV between groups, with the insomnia group showing decreased variability; and finally, (6) that good sleepers will display higher biological complexity in their nocturnal heart rate throughout the night when compared to the insomnia group.

3.3 Methodology

3.3.1 Participants and Recruitment

The sample consisted of 47 university students aged 18-30 years from Oxford. The final sample consisted of 43 students, with 23 in the insomnia group (mean age=23.7 years, SD=3.5, 14 women), and 20 controls (mean age=22.7 years, SD=3.2, 11 women). Four recordings were excluded from the analysis, due to drop-out prior to EEG set up (n=2), non-compliance with the protocol (n=1) and a suspected circadian rhythm disorder (n=1). For the ECG analyses, a further participant was excluded due to the detection of a cardiac arrhythmia. This subject was included for the PSG group comparisons.

Students were recruited via poster advertisements and email. Email addresses were sourced from a secure database comprised of individuals who consented to be contacted about opportunities to participate in research conducted by the Sleep and Circadian Neuroscience Institute in the University of Oxford. The study protocol was approved by the NRES Committee North West-Liverpool Central (REC: 14/NW/1142) and all participants gave written informed consent.

Eligibility for the study was based upon subjective reporting of sleep quality and insomnia, using the Pittsburgh Sleep Quality Index (PSQI; please refer to Section 2.2.2.2) and the Insomnia Severity

Index (ISI). The ISI is a brief questionnaire devised to measure both the night-time and day-time elements of insomnia. The ISI ranges from 0-28, with scores of 10 and above considered optimal for detecting insomnia in community samples (Morin et al., 2011). Both measures have shown good psychometric properties for use in both patients and healthy controls (Backhaus, Junghanns, & Hohagen, 2004; Carpenter & Andrykowski, 1998; Morin et al., 2011).

For this study, controls were required to have a Pittsburgh Sleep Quality Index (PSQI) score of 3 or below and an Insomnia Severity Index (ISI) score of 6 and below. The insomnia group were required to have a PSQI of 8 or above (three points higher than the standard cut off of 5) and an ISI of 10 or above, creating a degree of separation in the subjective reporting of sleep quality between the groups. Exclusion criteria included a diagnosis of a psychotic disorder (past or present), taking medication known to affect sleep, taking any psychotropic medication, brain injury, epilepsy, shift work, hospitalisation in the previous six months and travelling through two or more time zones in the previous two weeks.

3.3.2 Ambulatory Polysomnography (PSG)

All participants underwent two consecutive nights of ambulatory PSG sleep monitoring. The first night served as an adaptation night, and the second night was used for the present analyses. Both nights were set up in the participants' home environment. Recordings were set to run 14 hours, with the start time occurring based on the participant's estimation of the earliest possible time they could go to bed. Participants were asked to be extra vigilant when completing their sleep diaries to determine lights off and lights on. Actiwatch data was also used to aid this (described later in Section 4.3.2). The montage included 19 electrodes mounted bilaterally: ten on the scalp according to the international 10–20 system - Fp1, Fp2, F3, F4, C3, C4, P3, P4, O1, O2; as well as A1 and A2 (for offline referencing); two EOGs (for eye movements); three EMGs (for musculus mentalis movements); ground (at FPz) and a reference electrode at position FCz. The *Somnomedics* signal was recorded with a 24-channel Somnoscreen plus EEG amplifier (*Somnomedics Inc.*); all electrodes were referenced to contralateral mastoids and digitized with 128 Hz sampling rate.

EEG recordings were manually scored by an experienced rater at 30 second epochs according to the criteria of the American Academy of Sleep Medicine Manual (AASM; 2015), with the addition of

stage 4 scoring to highlight over 50% of slow waves present in a 30 second epoch. Five recordings (12%) were second scored with a 90% concordance rate to ensure a high standard of both scoring and inter-rater reliability. All arousals were manually scored by visual inspection following the AASM guidelines. Briefly, an arousal was defined as an abrupt shift of EEG frequency including alpha, theta and/or frequencies greater than 16 Hz (but not spindles), lasting at least three seconds in duration and preceded by at least 10 seconds of stable sleep (Berry et al., 2012).

Sleep recordings were evaluated for the following parameters of sleep continuity: *Total Sleep Time* (TST, defined as time between sleep onset and final awakening, including arousals but excluding periods defined as movement or awake); *sleep efficiency* (ratio of TST to time in bed × 100 %); *wake after sleep onset* (WASO, defined as the difference between TST and sleep period time (time from sleep onset until final awakening, including movement and time awake)); *sleep onset latency* (time from lights out until sleep onset (defined as first epoch of Stage 1)); *number of awakenings*; *arousal count*; and *arousal index* (number of arousals per hour of TST; Sleep Disorders Atlas Task Force of the American Sleep Disorders Association, 1992). Sleep architecture parameters were amounts of Stages 1, 2 and slow wave sleep (marked as either stages 3 or 4), or rapid eye movement sleep (REM) as a duration and percentage of TST and REM latency (the amount of time taken before the first bout of REM sleep).

3.3.3 ECG Recording and Analysis

During polysomnographic recordings, the heart rate (HR) signal was obtained by two surface disposable electrodes that were placed just below the right clavicle and on the anterior axillary line on the costal arch. Participants were instructed to do this before bed. The ECG sampling rate was 256 Hz. All epochs were inspected visually for artefacts or inaccurate detections. Arousals during the EEG recording are frequently married with fluctuations in HR. Given arousals tend to be more prevalent in insomnia sufferers, five consecutive heartbeats of ECG recording pre- and post-arousal were removed to prevent arousals biasing the HR. Heart rate throughout the sleep period was determined using timestamps of the QRS complex from lights off to lights on throughout the recording. Furthermore, all wake arousals or artefacts were discarded from analysis. For each epoch, mean HR was calculated from RRI time series. For evaluating HRV, both time and frequency domain methods were applied. In the time domain, the standard deviation of RRIs (SDNN) were analysed for each epoch. SDNN reflects overall HRV. Frequency domain measures based on the fast-Fourier

transform (FFT) algorithm were applied on the regularly sampled interpolation of the RRI time-series (10.24 Hz). Spectral power was calculated for three frequency bands: low frequency (LF; 0.04–0.15 Hz), high frequency (HF; 0.15–0.4 Hz) and total power (0.04–0.4 Hz). The LF/HF ratio was computed as a marker for sympathovagal balance.

3.3.4 Analyses of Biological Complexity: Multiscale Entropy (MSE)

Longer time series are able to provide important information that enable the separation of physiological conditions, and are important in assessing control mechanisms for the long-term regulation of biological systems. Previous research has explored the utility of MSE in ECG measures as a marker of complexity of cardiac system controls and found it to be a useful determinant of cardiac functioning (Costa, Peng, & Goldberger, 2008a).

Multiscale Entropy (MSE) is a novel method of evaluating complexity in a finite time series. Traditional entropy measures quantify the predictability of a time series, such that maximum entropy is awarded to completely unpredictable signals and minimum entropy to predictable or periodic signals (neither of which are truly complex as they can be simply described). Although there is no agreed definition of complexity, we regard it as being associated with 'meaningful structural richness' and therefore, in physiological signals, incorporating correlations over many time scales. MSE demonstrates the complexity of the original time series by revealing the dependence of the entropy on this time scale. This method offers promise as this could give an indication of adaptability in HR by looking at 'complexity', which in this context refers to a sense of non-random fluctuations in the HR signal.

Each uninterrupted period was taken (after arousals were removed) from the RR interval data. Subsequently, each participant had its sample entropy (a type of entropy measure commonly used on physiological data) evaluated at the scales that were reasonable given each period's length. In order to estimate sample entropy accurately, recordings of just 10^m to 20^m points were needed, where m is the run length that must be fixed to compute this embedding entropy. Thus, this family of statistics is much better suited for EEG analysis than traditional non-linear techniques (Abásolo, Hornero, Espino, Álvarez, & Poza, 2006). Typically, one respiratory cycle is approximately five cardiac beats in length. Scales less than one respiratory cycle are referred to as "small" time scales and larger scales are

referred to as "large" time scales.

In order to clarify the differences in the trends of the MSE curves for each group, the entropy values were modeled as a quadratic function of scale. The coefficients of these linear models were estimated using the weighted least squares method. Weighting was based on the number of observations contributing to the group mean entropy at each scale accounts for fluctuations in the variance, due to the decreasing sample size. These models were then used to make predictions based on the scale factor.

3.3.5 Statistical Analysis

In order to test the null hypothesis that two categorical variables are independent from one another against the alternative that they are dependent, we performed chi-square tests of independence.

Statistical analyses were performed within the R statistical environment (R Core Team, 2014), with the packages nlme, chron, pracma, and lubridate being used in particular. The package nlme is concerned with the analysis of mixed effect models; pracma enables the calculation of sample entropy; and lubridate and chron allow superior handling of times within the data.

3.4 Results

There were no significant differences in the mean ages of the two groups ($t=1.078$; $p=0.287$).

The mean self-reported sleep quality (PSQI) of the control group was 2.3 (SD=0.9) as opposed to 10.1 (SD=2.2) in the insomnia group. The mean insomnia scores (ISI) were 14.4 (SD=3.3) for the insomnia group and 1.5 (SD=1.5) for the controls. Taken together, these highlight a substantial difference in subjective sleep quality and insomnia between groups. Polysomnographic data show the insomnia group had significantly lower sleep efficiency, spent longer in bed, and had significantly longer SOL and WASO. However, when correcting for multiple comparisons, only sleep efficiency and WASO remained significant **(Table 3.1)**.

	Good Sleepers	Insomnia Group	Group Differences		
Measurement	**Mean (SD)**	**Mean (SD)**	**t**	**p**	**p_{adj}**
Sleep Efficiency %	94.55% (4.2%)	88.43% (7.1%)	3.46	0.002	0.009
TIB (Hr)	7:57 (0:48)	8:43 (1:08)	-2.59	0.013	0.063
TST (Hr)	7:30 (0:42)	7:41 (1:08)	-0.66	0.512	0.652
SOL (Hr)	0:14:(0:24)	0:36 (0:32)	-2.46	0.018	0.064
REM Latency (Hr)	1:26 (0:44)	1:30 (0:36)	-0.35	0.733	0.733
WASO (Hr)	0:27 (0:25)	1:02 (0:40)	-3.49	0.001	0.009
REM (Hr)	1:52 (0:33)	1:43 (0:33)	0.83	0.411	0.575
Stage 1 (Hr)	0:23 (0:14)	0:21 (0:15)	0.40	0.695	0.733
Stage 2 (Hr)	3:42 (0:33)	3:56 (0:51)	-1.07	0.291	0.475
Stage 3 (Hr)	0:24 (0:10)	0:30 (0:09)	-1.79	0.081	0.188
Stage 4 (Hr)	1:09 (0:21)	1:11 (0:19)	-0.35	0.726	0.733
Arousal Index	8.70 (2.20)	9.87 (4.27)	-1.10	0.258	0.458

Table 3.1: Polysomnography (PSG) parameters of the insomnia and good sleeping group (n=43). Note that TIB=Time in Bed; TST=Total Sleep Time; SOL=Sleep Onset Latency; and WASO=Wake After Sleep Onset. p-values reported here were corrected for multiple testing using the Benjamini & Hochberg correction method (Benjamini & Hochberg, 1995), which controls for false discovery rate as opposed to the more commonly employed Bonferroni method, which controls for the family-wise error rate.

3.4.1 Arousals

The two-way contingency table displayed in **Table 3.2** highlights the total arousal count by sleep stage. A chi-square test of independence showed the insomnia group differed significantly in the way the arousals are distributed across the stages of sleep when compared to the good sleeping group ($\chi^2(4)=18.629$, $p<0.001$). This highlights a group and stage association with respect to arousal count. The insomnia group experiences approximately 37% more arousals than the good sleeping group, but it is worth noting that the insomnia group includes approximately 21% more subjects. The total arousal count for each subject and the count across each of the sleep stages highlight the vast inter-individual differences in the number of arousals across the night (**Figure 3.1**).

Figure 3.2 illustrates the mean arousal counts from all subjects in each group, further categorised by the stage in which they occurred. The highest proportion of arousals occur in stage 2 of the sleep cycle but the mean difference in stage 2 arousals between good and insomnia sufferers was not significant ($t=1.87$; $p=0.0713$).

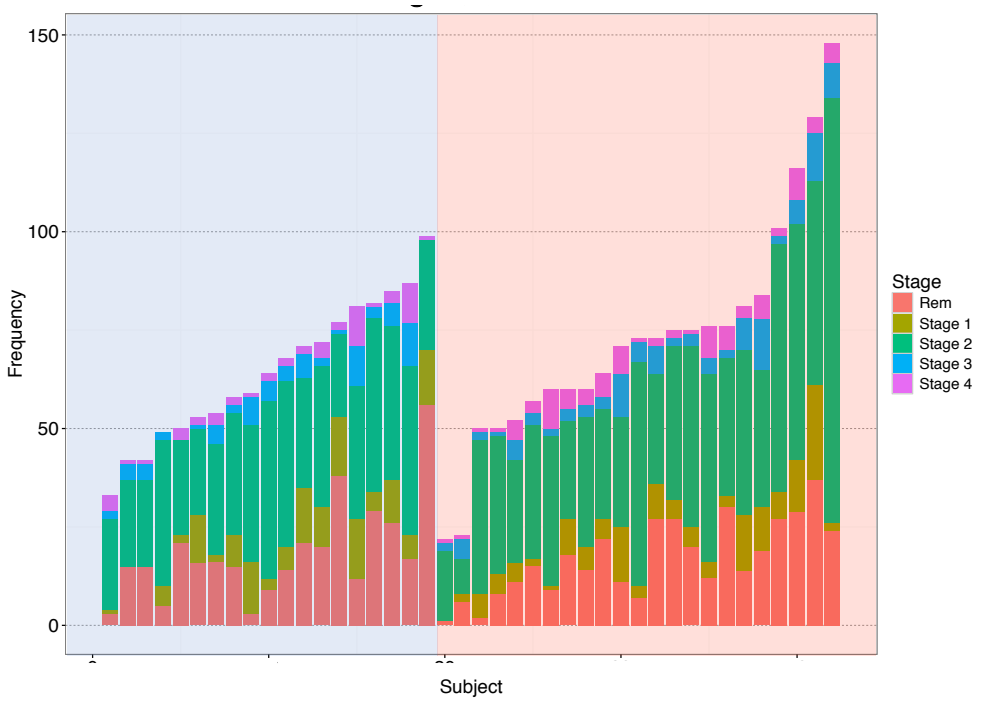

Figure 3.1: Inter-individual variability in arousal counts across sleep architecture for good sleepers and insomnia sufferers. The highest scorers belong to the poor sleeping group, although clear group differences do not appear to be present. A chi-square test of independence showed the insomnia group differ significantly in the way the arousals are distributed across the stages of sleep compared to the good sleeping group ($\chi^2(4)=18.629$, $p<0.001$), highlighting a group and stage association with respect to arousal count.

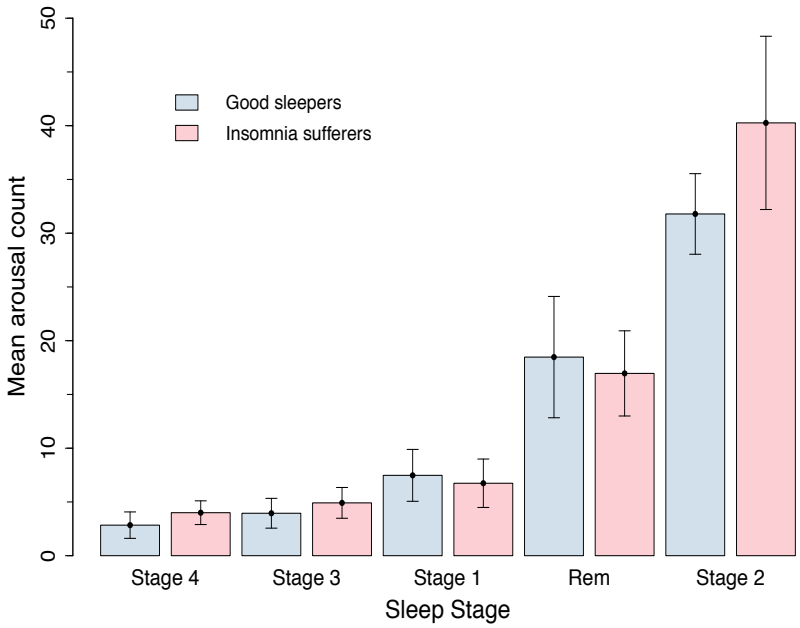

Figure 3.2: Mean differences in arousal counts across sleep architecture for good sleepers and insomnia sufferers. We see that stage two presents both the highest number of arousals and the most pronounced difference between groups, although this difference failed to reach significance ($t=1.87$; $p=0.07$). Error bars represent 95% confidence intervals for the mean value.

	Good Sleepers		Insomnia Group	
Sleep Stage	**Total**	**Mean (SD)**	**Total**	**Mean (SD)**
REM	351	18.47(12.55)	390	17.04(9.56)
Stage 1	142	7.47(5.37)	155	6.74(5.51)
Stage 2	604	31.79(8.34)	926	40.26(19.72)
Stage 3	75	3.95(3.08)	113	4.91(3.50)
Stage 4	54	2.84(2.73)	92	4.00(2.70)

Table 3.2: Arousal counts across each sleep stage for good sleepers, compared to the insomnia group (n=43).

There were no significant differences in arousal index between groups (t=-1.10; p=0.277).

To further understand how arousals may be allied with impacts on sleep architecture, we investigated group differences in the number of arousals that were followed by an epoch of wake, a stage change or that maintained the same stage. Using Welch's t-test, we found no significant differences between groups (please refer to **Table 3.3**).

	Good Sleepers		Insomnia Sufferers			
Architecture Following Arousal:	**Count**	**Mean (SD)**	**Count**	**Mean (SD)**	**t**	**p**
Epoch of wake	87	4.58 (2.52)	121	5.26 (3.93)	-0.68	0.501
Epoch of alternative stage	350	18.42 (6.52)	488	21.22 (9.53)	-1.12	0.268
Maintained stage	884	46.53 (15.0)	1187	51.61 (23.24)	-0.86	0.398

Table 3.3: Summary statistics for arousals that follow a change in sleep architecture in the following epoch (n=43).

3.4.2 Nocturnal Heart Rate

The trajectory of heart rate (averaged for every 30 second epoch) across the night with respect to the sleep stages is shown in **Figure 3.3**. Heart rate declines from sleep start towards mid-sleep across Stages 2, 3 and 4, while waking-up, stages 1 and REM tend to be affiliated with an increase in HR. How the trajectories can differ between groups is also illustrated in **Figure 3.3**.

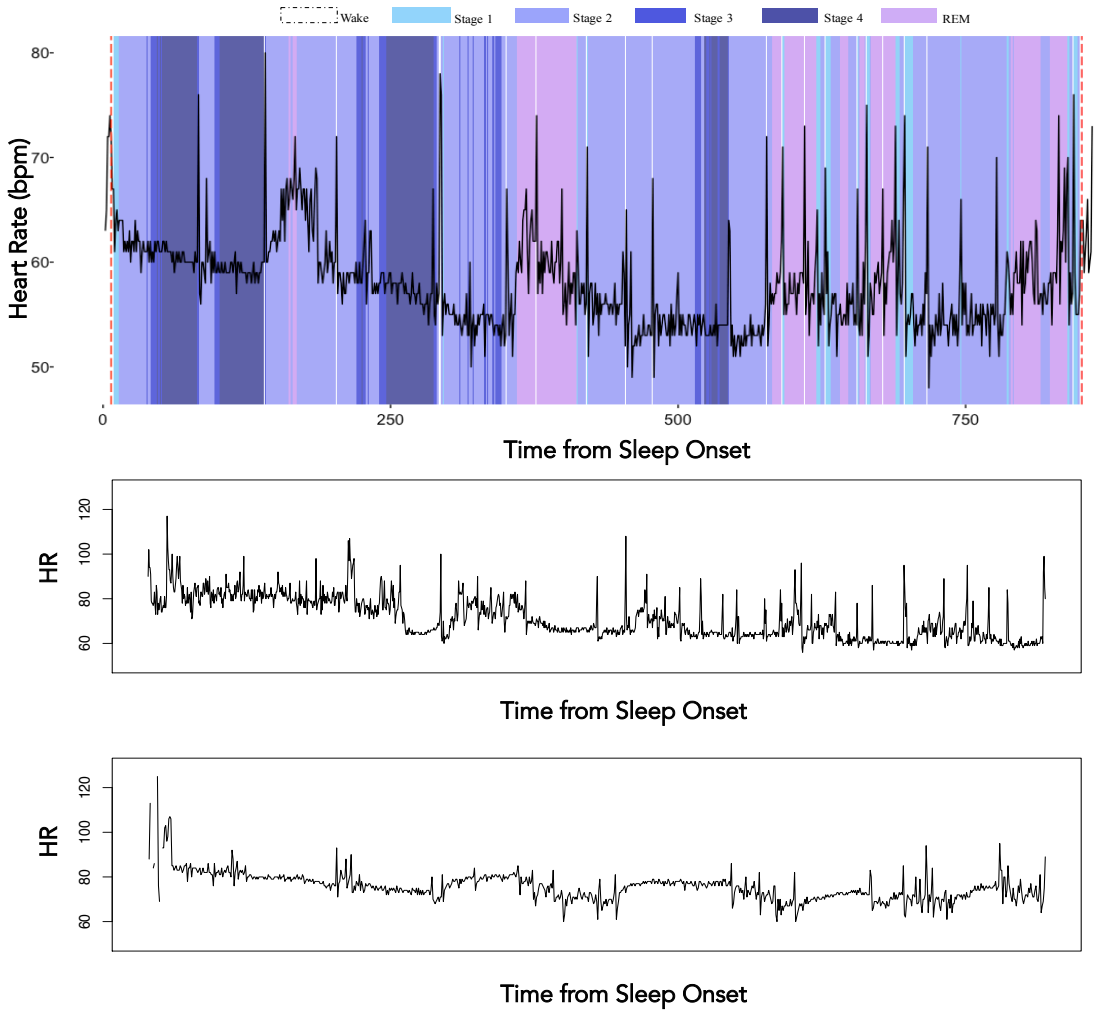

Figure 3.3: Trajectories of nocturnal HR. *Top panel:* The trajectory of nocturnal HR across the stages of sleep throughout the night. The nocturnal HR of a good sleeper averaged over 30 second epochs is displayed throughout the sleeping period. Sleep stages are overlaid with different colours to highlight the fluctuations in HR attached to different sleep stages throughout the night. *Middle panel:* The nocturnal HR of a good sleeper averaged over 30 second epochs throughout the sleeping period. *Bottom panel:* The same information for a person with insomnia.

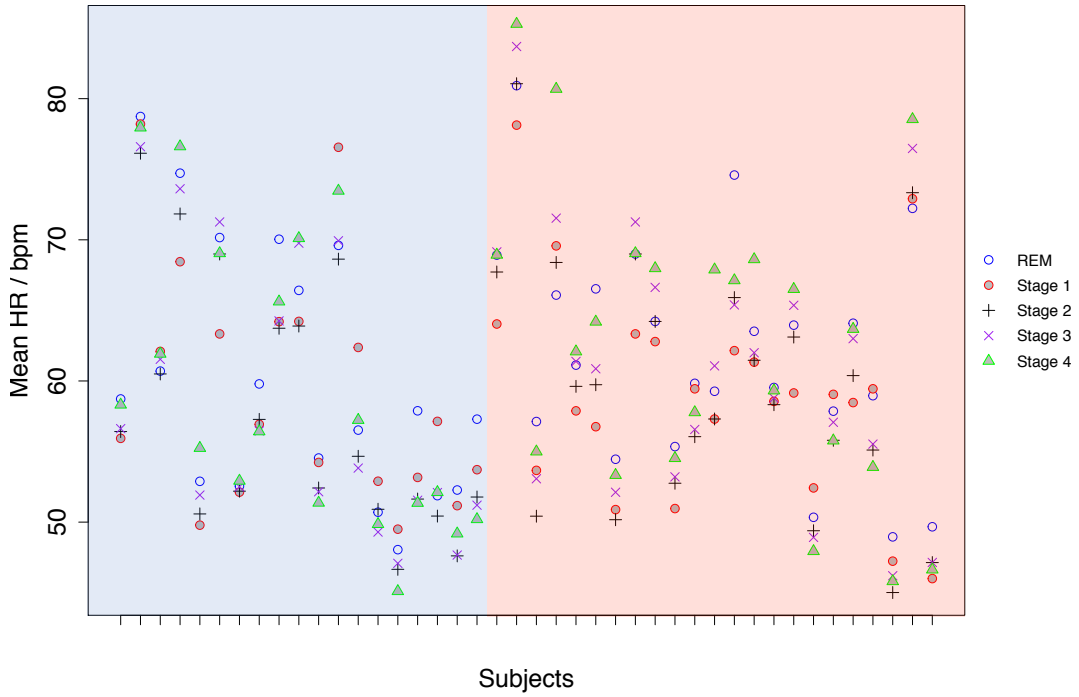

Figure 3.4: Mean Nocturnal Heart Rate at different sleep stages (symbols and colour-coded) for each subject (n=42). The good sleepers are displayed in the blue shaded region, and the insomnia group in the pink region.

Figure 3.4 demonstrates the mean HR for each person, categorised by sleep stage, and averaged across all sleep cycles. This illustrates the large amount of variability between individual subjects, ranging from mean HR below 50 bpm to above 80 bpm in two extreme cases. When tested using Welch's t-test, there were no significant differences between the two groups in mean HR in stage 1. There was, however, a significant difference in the means during stage 4 (μ_0=59.11, μ_1=62.79, t=-13.31, p<0.0001), with the insomnia group demonstrating a significantly higher HR than the good sleepers. Significant differences were also observed between the mean HR in stage 4 and that in stage 1, with group means μ_0=-2.58 for good sleepers and μ_1=1.32 for the insomnia group (t=-2.62; p=0.012; **Figure 3.5**). Therefore, the good sleepers on average had a heart rate approximately two and a half beats lower per minute in stage 4 than in stage 1. Comparatively, the insomnia group had a HR approximately one beat higher in stage 4 than in stage 1. These results are summarized in **Table 3.4**.

Stage Comparisons		μ_0	μ_1	t	p	p_{adj}
Stage 1	Stage 2	-3.85	-1.48	-2.36	0.024	0.060
	Stage 3	-3.27	0.27	-3.05	0.005	0.030
	Stage 4	-2.58	1.32	-2.62	0.012	0.040
	REM	-0.97	1.33	-2.01	0.050	0.100
Stage 2	Stage 3	0.59	1.81	-2.97	0.006	0.030
	Stage 4	2.97	1.27	1.91	0.060	0.100
	REM	2.88	2.83	0.08	0.940	0.940
Stage 3	Stage 4	1.15	0.68	0.64	0.530	0.588
	REM	2.30	1.01	1.47	0.150	0.213
Stage 4	REM	1.62	-0.14	1.39	0.170	0.213

Table 3.4: Comparisons of mean nocturnal HR across sleep stages for good sleepers and the insomnia group.

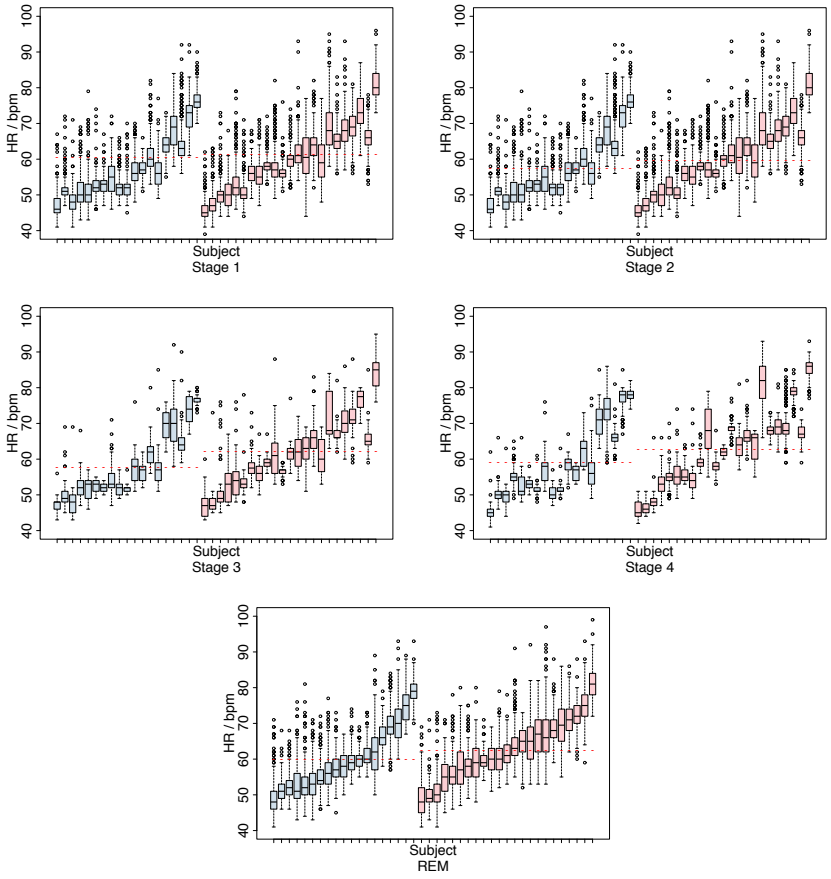

Figure 3.5: Boxplots highlighting, for each sleep stage, the variability in nocturnal HR between and within individuals (n=42). The dashed red line indicates mean HR for each group. Blue boxes denote individuals in the good sleeping group, while pink shading denotes individuals in the insomnia group. While the mean HR of the two groups is closely matched at sleep stage 1, the difference becomes increasingly more apparent towards deeper stages of sleep. Considerable inter-individual variability between participants is also demonstrated.

To further explore the effect of group and stage on HR, we built mixed effects models to predict Nocturnal Heart Rate and the Nocturnal LF/HF ratio, with stage and group as fixed effects, and a varying intercept for each subject. Age and gender were also included as fixed effect covariates in these models. An overview of the models is given in **Table 3.5**. There was no significant effect of group ($F_{(38,1)}$=0.501, p=0.48) or age ($F_{(38,1)}$=0.983, p=0.33) evident. Gender was a significant predictor ($F_{(38,1)}$=0.518, p=0.004), as were both stage ($F_{(41343,5)}$=4028, p<0.0001) and the interaction between group and stage ($F_{(41343,5)}$=159.7, p<0.0001). This interaction is illustrated in **Figure 3.6** highlighting the insomnia group to have a lower sleep to wake reduction.

Age ($F_{(38,1)}$=7.241, p=0.011), sleep stage ($F_{(41343,5)}$=1798, p<0.0001) and the group by stage interaction ($F_{(41343,5)}$=48.63, p<0.0001) were all significant predictors of the frequency domain measure of low frequency over high frequency (LF/HF ratio).

	DF_n	DF_d	F	p
Outcome Variable: HR				
Intercept	1	41343	2592	<0.0001
Age	1	38	0.983	0.330
Gender	1	38	0.518	0.004
Group	1	38	0.501	0.480
Stage	5	41343	4028	<0.0001
Group:Stage	5	41343	159.7	<0.0001
Outcome Variable: LFHF				
Intercept	1	41343	286.30	<0.0001
Age	1	38	7.241	0.011
Gender	1	38	0.444	0.509
Group	1	38	0.230	0.634
Stage	5	41343	1798	<0.0001
Group:Stage	5	41343	48.63	<0.0001

Table 3.5: Mixed effects models with nocturnal heart rate and nocturnal LF/HF ratio as primary outcome variables. DF_n and DF_d denote the numerator and denominator degrees of freedom respectively.

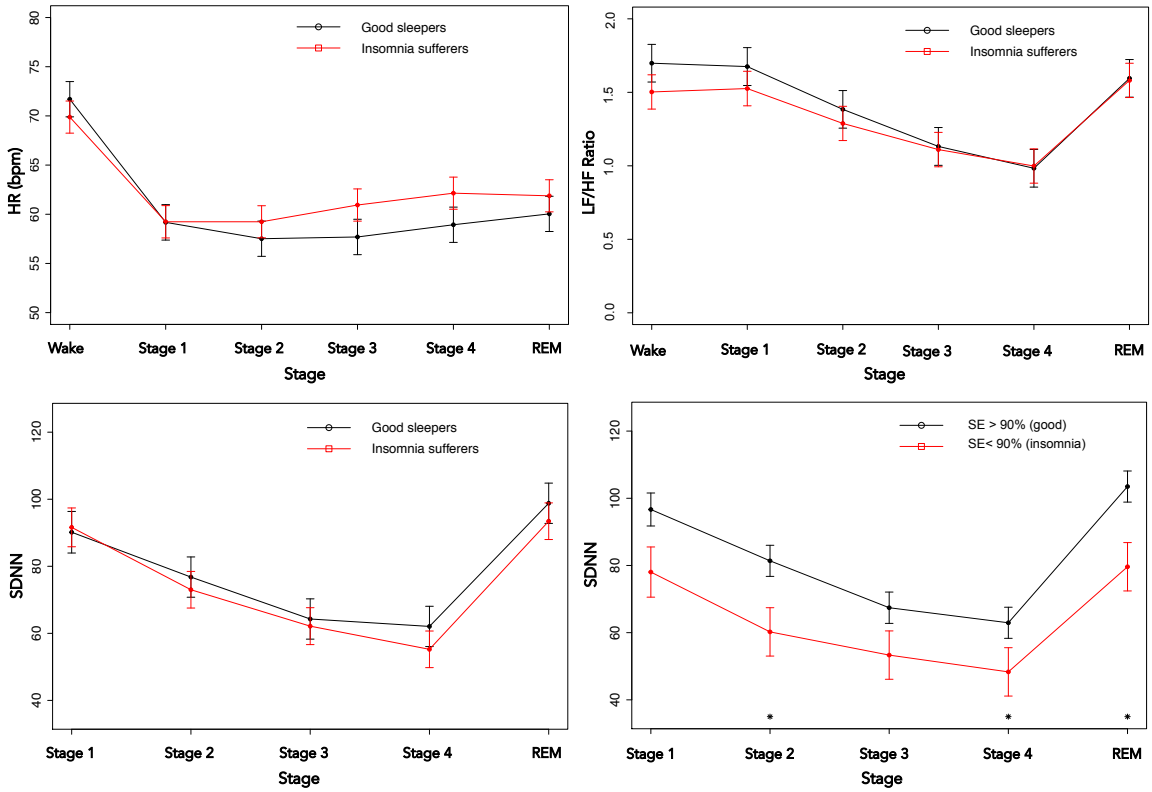

Figure 3.6: Interaction plots for HR and LF/HF ratio. *Top left*: the difference in nocturnal HR between sleep stages and groups is highlighted, with the reduction in HR for the insomnia group attenuated across all stages of sleep (with the exception of stage 1) when compared to the good sleepers. Values are mean ± standard error. *Top right*: the difference in LF/HF ratio is highlighted between sleep stages and groups. The inverse of HR is observed, with the most pronounced differences in wake, Stage 1 and Stage 2. *Bottom left*: group differences in SDNN across sleep stages, with groups defined by subjective sleep. The variability is consistently, but non-significantly, less in those with poor sleep, except for sleep stage 1. *Bottom right*: group differences in SDNN across sleep stages, with groups defined by objectively measured sleep (above and below 90% SE). Similarly to the subjective groupings, a noticeable decline in SDNN is observable from stage 1 to stage 4, with significant differences between groups at stages 2, 4 and REM.

3.4.3 Heart Rate Variability

SDNN was calculated over the uninterrupted periods of sleep that fell within one sleep stage for each individual. No significant differences were found at any stage between the groups determined by PSQI and ISI scores (p=0.98; 0.59; 0.61; 0.30; 0.60 for stages 1, 2, 3, 4 and REM respectively). Neither group ($F_{(40,1)}$=0.28, p=0.60) nor the group by stage interaction ($F_{(150,4)}$=0.47, p=0.76) showed significant main effects on heart rate variability (**Figure 3.6**). However, there was a significant main effect of stage ($F_{(150,4)}$=55.64, p<0.0001), noticeable as a decline in SDNN from stage 1 to stage 4.

Regrouping the individuals based on objectively measured sleep efficiency (SE) derived from polysomnography, the SDNN values were again assessed between the two. The groups were split

based on having a SE of either above or below 90%. The same mixed effects model now highlighted a significant main effect of group ($F_{(39,1)}$=6.13, p=0.02; **Figure 3.6**).

The group effect was found to be significant at stages 2, 4 and REM (p=0.051; 0.003; 0.080; 0.036; 0.024 for stages 1, 2, 3, 4 and REM respectively).

Predictor	DF_n	DF_d	F	*p*
Subjective Sleep Grouping				
(Intercept)	1	150	454.51	<0.0001
Group	1	40	0.28	0.60
Stage	4	150	55.64	<0.0001
Group:Stage	4	150	0.47	0.76
Objective Sleep Grouping				
(Intercept)	1	146	512.67	<0.0001
Group	1	39	6.13	0.02
Stage	4	146	54.30	<0.0001
Group:Stage	4	146	0.75	0.56

Table 3.6: ANOVA table for the fixed effects of linear mixed model with SDNN as the primary outcome variable, and using 'Group' defined both subjectively and objectively based on sleep measures (n=42). The degrees of freedom used to calculate the F statistic, and the corresponding p-value, were produced in R with the package nlme. The subjective grouping was based upon the recruitment criteria for this study, and the objective grouping was based on scoring above or below 90% SE using the polysomnographic data.

3.4.4 Analyses of Biological Complexity: Multiscale Entropy (MSE)

The same periods used for SDNN throughout the night were also used for the MSE. Using Welch's t-test, which allows for unequal variance between samples, there was a significant difference in entropy between the groups. The separation between groups increases as a function of time scale (**Figure 3.7**). In all plots, the black lines denote the good sleeping group, the red lines denote the insomnia group, and the error bars represent the standard error. Scales marked with × are those at which the two groups are significantly different at the α=0.05 significance level and those marked with + are significant at the α=0.10 significance level. These curves display little or no separation at small time scales, with profiles starting to separate at scale 10, except for Stage 1, which had only

scales up to 4. No differences between groups were observed in Stage 1 sleep at any scale factor (p=0.37, 0.92, 0.78, 0.97 for scales 1, 2, 3 and 4 respectively). Significant differences in entropy were observed at scale 18 for stage 2 sleep; in scales 9, 10, 12, 13, 14 and 18 in SWS (p=0.023); and at scales 10 and 12 (p=0.011) in REM sleep. The averages of the two groups were then plotted to give the MSE curves illustrated in **Figure 3.7**.

Figure 3.8 illustrates these fitted models for each stage by plotting the curves based on the predictions made by the model using quadratic functions of scale (with 95% confidence intervals). The regression lines demonstrate the differences between the two groups in the trends over the larger time scales in stage 2, SWS and REM. An overview of the random effect of subject ID can be found in **Table 3.7**. The coefficients of the fixed effects models for scale and scale^2 can be found in **Table 3.8**.

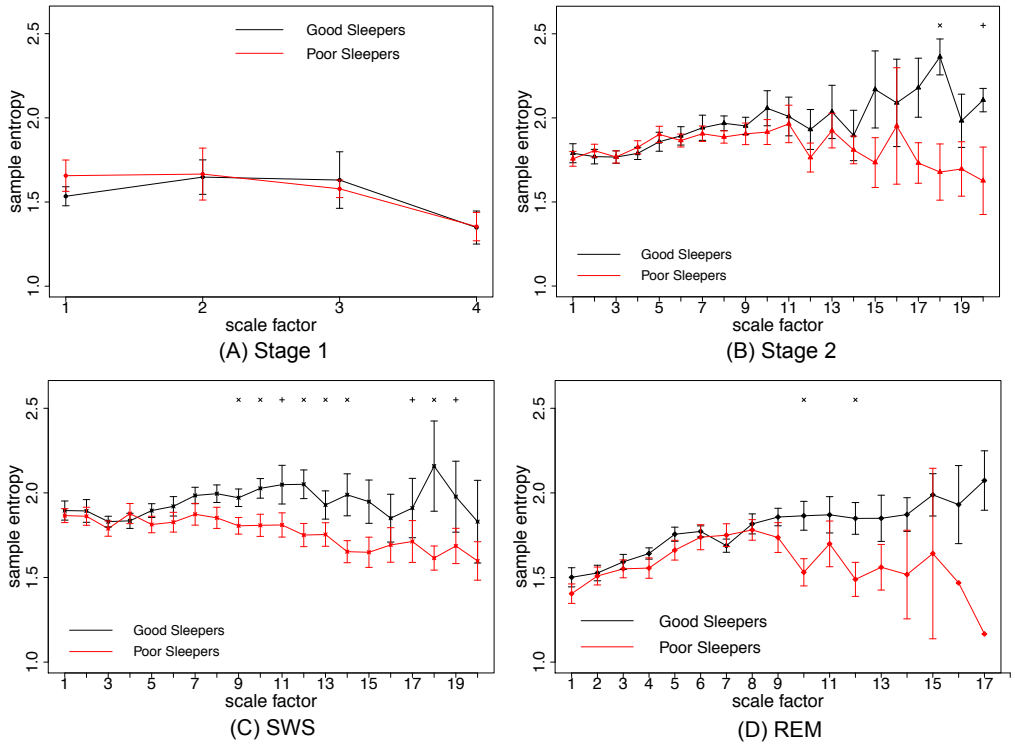

Figure 3.7: Multiscale entropy analyses for all four sleep stages and varying scales. Stage 3 and 4 are collapsed into slow-wave sleep (SWS). Scale factors marked above with × indicate a significant difference at the α=0.05 significance level, and those marked with + a significant difference at the α=0.10 significance level. Error bars represent the standard errors. The good sleep group are plotted in black, and the insomnia group in red.

	Good Sleepers		Poor Sleepers	
Stage	**σ**	**σ_b**	**σ**	**σ_b**
Stage 1	0.3364	0.2460	0.3689	0.2292
Stage 2	0.1621	0.2134	0.1716	0.1702
SWS	0.1842	0.2350	0.1966	0.1941
REM	0.1350	0.1786	0.1965	0.1721

Table 3.7: Random effects estimates of subject on entropy measures for each stage and group from the mixed model analyses. σ_b denotes the variation in entropy accounted for by within individual differences and σ denotes the variability accounted for by differences between individuals in the group. Values are given as standard deviations.

		Good Sleepers		Insomnia Group	
Fixed Effect	**Stage**	**β**	**SE**	**β**	**SE**
Intercept	Stage 1	1.628	(0.109)	1.610	(0.117)
	Stage 2	1.906	(0.043)	1.833	(0.039)
	SWS	1.972	(0.045)	1.806	(0.043)
	REM	1.758	(0.038)	1.577	(0.049)
Scale	Stage 1	0.604	(0.625)	-0.259	(0.707)
	Stage 2	2.567	(0.445)	1.682	(0.374)
	SWS	1.210	(0.324)	-0.554	(0.248)
	REM	3.140	(0.422)	0.841	(0.565)
$Scale^2$	Stage 1	-0.264	(0.466)	-0.814	(0.480)
	Stage 2	-1.454	(0.347)	-2.059	(0.273)
	SWS	-0.826	(0.293)	-0.750	(0.228)
	REM	-2.090	(0.317)	-3.182	(0.371)

Table 3.8: Estimated coefficients of the fixed effects of the intercept, scale and $scale^2$ for the good sleeping and insomnia groups from the mixed model analyses. The difference in trends is apparent between groups, with a decrease in sample entropy for the insomnia sufferers as the scale factor is increased. Conversely, the good sleepers gradually increase in sample entropy as the scale increases.

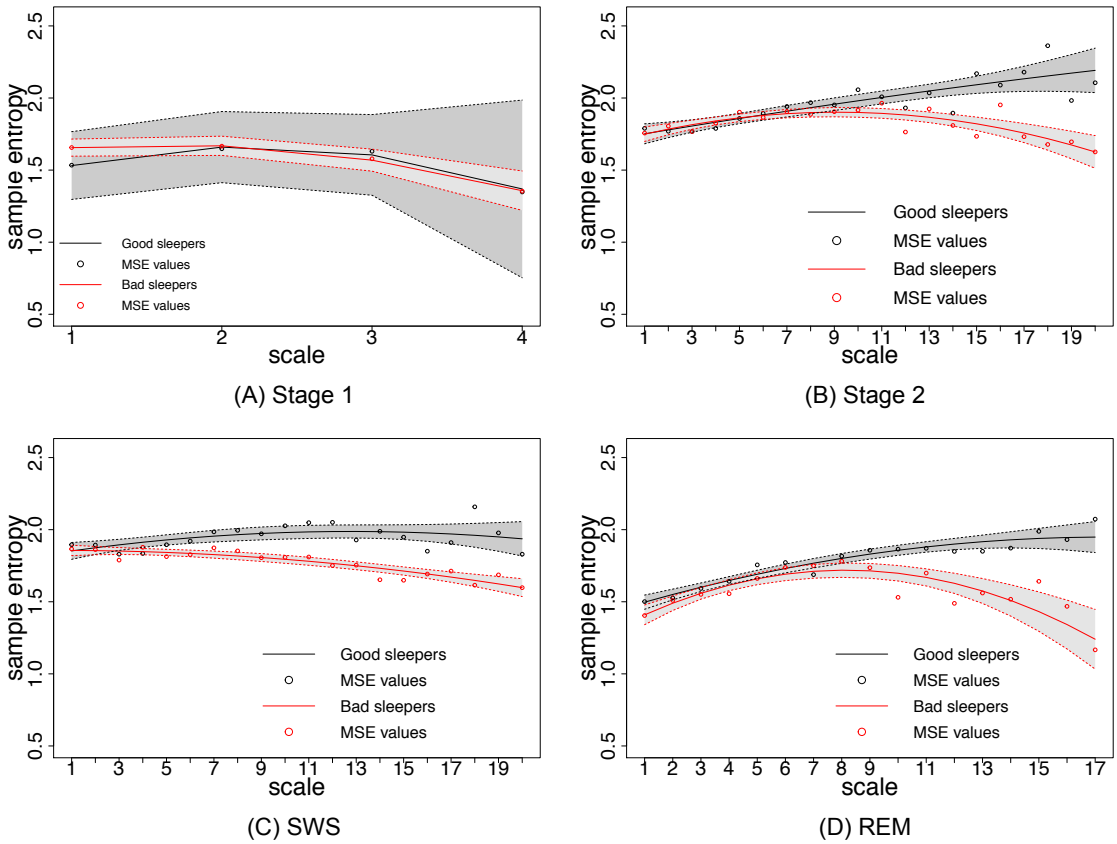

Figure 3.8: Multiscale entropy analyses for all sleep stages using quadratic functions of scale.

Analogous to **Figure 3.7**, these graphs indicate that as the scale factor increases the sample entropy decreases for the insomnia group. The good sleeping group displays an inverse pattern with an increase of sample entropy as a function of scale factor. As before, there were no differences between groups in Stage 1 sleep. Parameters used for both models (with and without the quadratic scale predictor) were pattern length m=2 and similarity threshold r=0.2(SD[$y(\tau)$]), based on previous literature investigating physiological time series data and HR (Richman & Moorman, 2000).

3.5 Discussion

The combined analysis of ambulatory polysomnography and ECG data in a sample of 43 university students aged 18-30 revealed five main findings. First, we investigated whether polysomnographic measurements of sleep were significantly different in our good sleeping and insomnia groups. We predicted that the insomnia sufferers would display objectively poorer sleep, based on previous literature specifically in the domain of sleep efficiency and sleep onset latency obtained (Spiegelhalder

et al., 2015). Insomnia is frequently considered a disorder of the perception of sleep (Harvey & Tang, 2012), thus significant differences in polysomnographic measures between controls and insomnia patients are scarce (Spiegelhalder et al., 2015). This study is unique in that it uses a medication free and age and gender controlled population. Furthermore, it utilises at-home polysomnography, and members of the insomnia group were also recruited on the basis of attenuated insomnia symptoms as opposed to presenting a chronic insomnia disorder. Group differences highlighted significant differences in sleep efficiency and wake after sleep onset, demonstrating that the perception of sleep appears to be influenced most by these measures. Sleep onset latency was trending towards significance, but was over the α=0.05 threshold when controlling for multiple comparisons. Total sleep time, time spent in each sleep stage and the time taken for the first episode of REM to onset (REM latency) showed no significant differences between groups.

Second, we predicted that insomnia sufferers would display a greater number of arousals and a significantly greater arousal index across the night, demarcating increased hyperarousal during sleep. Arousals in sleep are frequently married with fluctuations in HR, thus understanding group differences would also help inform ECG analyses. Currently, there is a dearth in the literature surrounding the distribution of arousals across stages and the distinction between arousals that impact on sleep architecture and those that don't. A chi-square test highlighted that the total count of arousals was distributed differently across the stages for each group. However, there were no distinct differences in the structure of arousals, i.e. there was no evidence to suggest that arousals differed based on duration, the mean frequency relative to stage, or in total frequency count when comparing the insomnia and good sleeping groups. A trend towards a greater frequency of arousals was observed in stage 2, but this failed to reach significance. Assessing arousals that generated an impact on sleep architecture, we investigated those that were followed by a change in sleep stage or an epoch of wake. No significant differences were found in the number of arousals that impact sleep architecture between groups. Interestingly, there does appear to be a considerable amount of heterogeneity in the number of arousals experienced by each participant in this study. While this difference may not relate to the subjective perception of sleep, this may relate to other neurophysiological underpinnings of sleep that are not accounted for in this study and warrant further research.

Third, we predicted that insomnia sufferers would display increased nocturnal HR and decreased HRV across different stages of sleep throughout the night. Based on the exploratory plots, it seems that heart rate is inherently related to the sleep stage, which has been extensively reported upon in the literature on heart rate and sleep (Jarrin et al., 2016). Furthermore, in line with previous literature on HR and HRV and insomnia, gender was a significant predictor, with women having a higher mean HR than men, when all other variables are constant (group, sleep stage and age; Spiegelhalder et al., 2011). Using linear mixed models, we found a significant interaction indicating the insomnia group to have a lower wake to sleep reduction in their HR compared to that seen in the good sleeping group. This is a replication and furthering of the results of Spiegelhalder et al. (2011) who reported a similar pattern in nocturnal heart rate when comparing chronic insomnia patients to healthy controls. In their dataset, the authors were unable to model with stages 3 and 4 due to the relative scarcity of deep sleep in the polysomnography recordings. Here we have demonstrated that this blunted reduction in HR is also pronounced in slow wave sleep when comparing good sleepers and the insomnia group.

Fourth, in line with previous research in insomnia, we predicted there would be a significant difference in HRV between groups, with the insomnia group showing decreased variability. This could not be supported by our findings. Analyses on the standard deviation of the RR-interval (SDNN), a summary measure of heart rate variability, highlighted no significant differences between the groups based on subjective measures. This finding was contrary to our hypothesis, but in support of previous literature which also produced negative findings (please refer to Dodds et al., 2016). Interestingly, when recategorising the groups based on objective measurement of sleep efficiency (those who display above or below a sleep efficiency of 90%), a significant difference was found between the high sleep efficiency and the low sleep efficiency group. This conflict between objective and subjective categorisations of sleep quality may hint at the greater utility of nocturnal heart rate across the stages of sleep, as opposed to HRV, for observing the presence of neurophysiological hyperarousal in insomnia patients. Conversely, HRV measures may be a better indicator of objective disturbances in sleep.

Spectral analyses of HRV highlighted a significant main effect of stage and an interaction effect of group and stage. However, group was not independently a significant main effect in the model, and there were no significant differences in the values of LF/HF between the two groups in any stage.

Our results partially support those of Spiegelhalder et al., (2011), who also reported no group differences, but a significant main effect of stage in the LF/HF ratio. Our results differ in that we found a significant interaction between group and stage, whereas Spiegelhalder and colleagues (2011) found this to be non-significant. Results regarding LF/HF ratio should be interpreted with caution as suitability of this ratio as a measurement of sympathetic cardiac control has (justifiably) come under considerable scrutiny (Reyes del Paso et al., 2013).

The final hypothesis and objective for this study was to examine the utility of multiscale entropy (MSE) in the analysis of cardiac time series data, in conjunction with polysomnography data, as a novel analysis technique to explore the differences in nocturnal HR across different stages of sleep in insomnia sufferers when compared to good sleepers. We predicted that good sleepers would display higher biological complexity in their nocturnal heart rate throughout the night when compared to the insomnia group. MSE analyses suggest that the profiles of the MSE curves are very similar between groups over small time scales. However, as the time scales increase, the profiles gradually separate, with the healthy control group consistently assigned to higher entropy values denoting higher complexity in the system. These results support the findings of previous research using MSE to explore heart conditions: under free running conditions, the cardiac dynamics of healthy, young subjects are evaluated as the most complex (Richman & Moorman, 2000; Valencia, Porta, & Vallverdú, 2009). Similarly, the dynamics of the RR intervals of healthy controls were evaluated as most complex when assessing the severity of sleep disordered breathing (W.-Y. Pan et al., 2015). In stage 1, none of the scales showed a significant difference in the value of entropy. The curves take on significantly different values at scale 10 in slow wave sleep and REM, and at higher scales in these stages, as well as in stage 2.

These trends are further highlighted by the use of the linear regression models as a quadratic function of scale. The decrease in the entropy as a function of scale for the insomnia group suggests that the coarse-grained time series become progressively more regular and less complex, which could be a signal of a degradation of the control mechanisms over long time scales and a reduction in long-range correlations within the series. This pattern differs from the literature on studies concerning heart disease and sleep disordered breathing, where the biggest differences in entropy are seen in smaller time scales. This could suggest that the complexity of the signal in relation to insomnia is not of the

same nature as that seen in cardiac disease. The difference in smaller scales is attributed to the higher amplitude of the respiratory modulation of heart rate in healthy subjects (Pan et al., 2015; Valencia et al., 2009). This distinction is not present in our study, so may suggest that the reduction in complexity observed in an insomnia group may have greater ties with the neurophysiological arousal experienced in insomnia (and psychiatric disorders), encompassing psychological factors as well as physiological. This is purely speculative at this point and it would require further research to substantiate these claims.

A number of caveats to the MSE analysis merit mention. First, nocturnal HR data is naturally split into separate stages, and once arousals are removed the signal is inevitably split into a large number of individual, uninterrupted time series, most of which are too short to use to calculate sample entropy with a reliable degree of accuracy. Few are long enough to use to calculate entropy at higher scales, leading to a decreasing sample size as scale increases. This leads to group difference testing being underpowered and thus susceptible to false negatives as they have a high type-2 error rate. This may explain why SWS exhibited more positive results and a greater distinction between groups, as more subjects were able to be used to evaluate higher scales (due to fewer interruptions), thus increasing the power of the tests. Second, MSE for stage 1 was not studied to a suitable number of scales due to difficulty in adequate data harvesting from subjects across both groups: this stage lacked in both duration and frequency. Third, the choice of parameters may be limiting in the use of MSE; it is speculated that using $m > 2$ might increase the information present in the pattern, improving the distinction between the two groups. However, the sample entropy algorithm would then need a substantially higher number of data points in a time series (ideally $> 10^m$). This would mean using time series in which the stationarity assumptions are usually violated by living biological systems (Costa, Goldberger, & Peng, 2005; Thuraisingham & Gottwald, 2006).

Despite the fact that there are only a few statistically distinct values of entropy for the two groups, t-tests of many of the other larger scales produced p-values in the region of 0.1-0.2. Although not statistically significant at the level of α=0.05, in a subclinical group of individuals and with low powered tests especially at the larger scales, these values could represent emerging differences between the two groups which may become more apparent with higher powered tests and a clinical level of division between the groups.

In summary, objective measures of sleep do differ between the insomnia and good sleeping group. Given the insomnia group are recruited on the basis of having attenuated insomnia symptoms, these two groups remain relatively close, and as such it is not anticipated that group differences would be substantial. Despite this, we have presented a number of emerging differences that warrant further research. Our results indicate a poor perception of sleep quality may have a stronger relationship with the patterns seen in nocturnal heart rate across sleep stages, as opposed to heart rate variability, which has a stronger affiliation to categorisations based on objective measures of sleep quality and thus is not as heavily influenced by subjective perception.

The complexity of the signal in the RR intervals does appear to be concomitant with subjective perception of sleep, which may become more pronounced with a clinical population. Future research could explore an entropy value that is less dependent on data length to increase the reliability of the entropy values in short time series, allowing more scales to be evaluated with shorter data sets, leading to increased power in tests. Another possibility is to use the analysis laid out in this report with a clinical population (and across psychopathological disorders) to see if the positive results are replicated with greater power and if further scale values demonstrate differences.

Chapter 4:
An Investigation into Endogenous Melatonin Rhythms

Chapter 3 was dedicated to investigating the ECG and EEG signals between the two groups to understand the physiology of a complaint of poor sleep. Furthering this theme, we focus in this chapter upon the melatonin production and timing as an endogenous output of the master clock.

4.1 Introduction

Melatonin (MLT) is a highly evolutionarily conserved hormone which has been reported in a wide spectrum of organisms, including (but not limited to) bacteria, fungi, invertebrates and vertebrates (Zawilska, Skene, & Arendt, 2009). Its remarkable consistency across species speaks to its physiological importance (Zawilska et al., 2009). In vertebrates, melatonin is predominantly produced in the pineal gland (Srinivasan, Smits, et al., 2009b).

Melatonin production is greater at night than during the day in all animal species, irrespective of whether they are nocturnal, diurnal or crepuscular species (Srinivasan, Pandi-Perumal, et al., 2009a). In humans, the secretion of melatonin follows a distinct endogenous circadian rhythm which is driven by the SCN (Srinivasan, Smits, et al., 2009b). This rhythm is synchronised to the environmental 24-hour light-dark cycle, which is projected to the biological clock via the RHT that originates from photo-sensitive cells in the retina (Section 1.4; Berson, Dunn, & Takao, 2002). A schematic diagram demonstrating this process can be found in **Figure 4.1**.

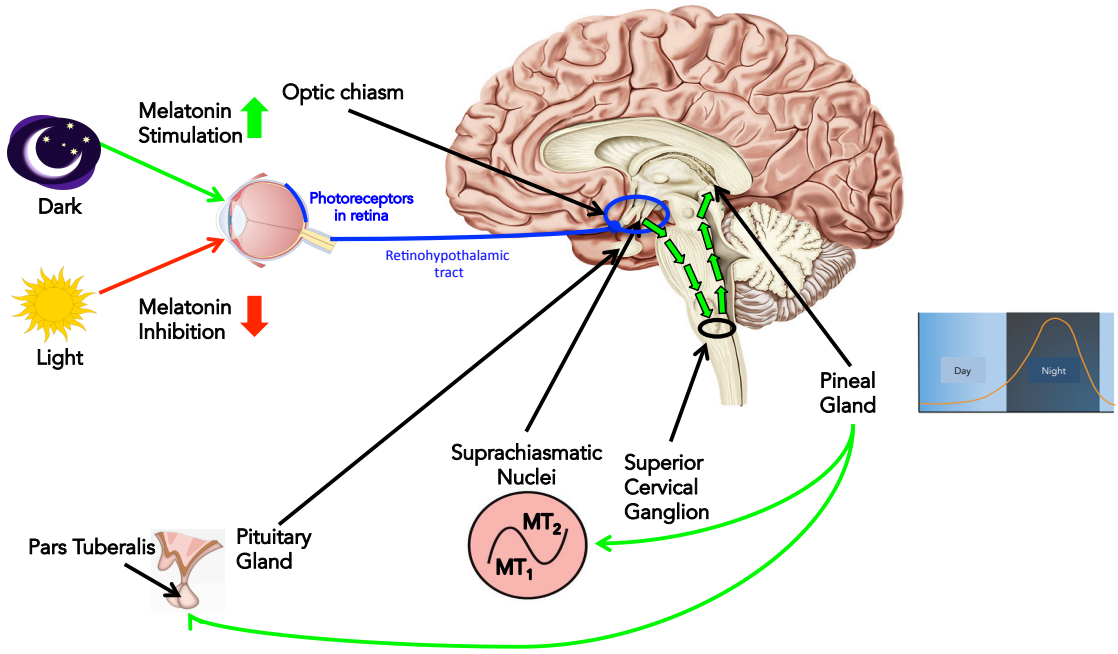

Figure 4.1: A schematic overview of the production of melatonin. Melatonin (MLT) is synthesised primarily in the pineal gland but also in the retina. MLT synthesis is driven by a rhythm that originates from the Suprachiasmatic Nucleus (SCN) or the 'biological clock'. Neural signals initiated at the SCN follow a multisynaptic pathway to the superior cervical ganglia. Norepinephrine released from the postganglionic fibers activates adrenoceptors in the pinealocyte, which results in melatonin synthesis. This system is radically supressed by light exposure - our primary synchronising agent or 'zeitgeber' - that permits entrainment to the light/dark cycle. Light is received by the retina and is projected directly to the SCN via the retinohypothalamic tract (RHT). Melatonin produced in the pineal also functions as an internal signal to the SCN that relays day length, permitting the regulation of the circadian rhythms with melatonin receptors MT_1 and MT_2. The pars tuberalis of the pituitary gland also receives and interprets the rhythmic melatonin signal produced by the pineal. This rhythmic signal generates a precise sequence of expression of circadian genes through the activation of MT_1 receptors. This informs the diurnal rhythm of cortisol production which is further discussed in chapter 6. This is diagram is adapted from Dubocovich et al., (2010).

Melatonin increases approximately two hours before an individual's bedtime (Shochat, Luboshitzky, & Lavie, 1997). This coincides with the onset of evening sleepiness (Srinivasan, Pandi-Perumal, et al., 2009a). It then stays high during the night, decreases rapidly at sleep offset, and is virtually untraceable during the day due to environmental light exposure that inhibits melatonin secretion (Etain, Milhiet, Bellivier, & Leboyer, 2011).

Melatonin is a marker of the time of the day, but equally as a time of the year, due to its seasonal variation (Etain et al., 2011). The peak of melatonin during the night is closely associated with the nadir in core body temperature, alertness and performance, as well as peak self-reported tiredness and fatigue (Åkerstedt, Gillberg, & Wetterberg, 1982). Interestingly, melatonin has been described as a 'hormonal fingerprint' (p394, Zawilska et al., 2009), as it is present with remarkably high stability within healthy individuals but varies considerably with respect to its amplitude across individuals

(Zawilska et al., 2009). This 'hormonal fingerprint' correlates well with inter-individual variation in sleep timing and chronotype (Section 1.5; Zavada et al., 2009).

There is now a growing body of evidence to suggest that melatonin may be a biomarker or hallmark for a number of psychiatric diseases, highlighting circadian misalignment or disruption as a potential contributor to psychopathology (Wulff, Gatti, Wettstein, & Foster, 2010a; Zawilska et al., 2009). Traditionally, the investigation of melatonin relies upon five core parameters: the amplitude (the highest level of melatonin secretion reported during the night), the MLT acrophase (the time at which this peak occurs), the Dim Light Melatonin Onset or DLMO (the time at which the first rise in melatonin in the evening is observed), the phase angle difference (PAD) for sleep onset and offset (the time between sleep onset and offset and the MLT acrophase respectively; Lewy, Lefler, Emens, & Bauer, 2006) and the Mesor or C (the average melatonin amplitude in a 24 hour period; Wulff, Joyce, Middleton, Dijk, & Foster, 2009a; Wulff et al., 2012; Zawilska et al., 2009).

A number of studies have reported `low melatonin syndrome', a notion that suggests low melatonin secretion to be a biomarker for psychiatric disease. This has found to be the case in Major Depressive Disorder (MDD; e.g. Miles & Philbrick, 1988), bipolar disorder (e.g. Beck-Friis et al., 1985); schizophrenia (Anderson & Maes, 2012; Monteleone, Maj, Fusco, Kemali, & Reiter, 1992; Wulff et al., 2012) and suicidality (Wetterberg, 1983; for a review please see Srinivasan, Smits, et al., 2009b). However, it would appear that the presence of low melatonin secretion in bipolar disorder is contingent upon whether the individual is manic, euthymic or dysthymic at the point of measurement (Srinivasan, Smits, et al., 2009b). These results must be interpreted with caution, as a number of both contradictory and negative results have also been reported, and often these studies suffer from very limited sample sizes (e.g. Little, Ranc, Gilmore, Patel, & Clark, 1997; for a review please refer to Srinivasan, Pandi-Perumal, et al., 2009a and Pacchierotti, Iapichino, Bossini, Pieraccini, & Castrogiovanni, 2001). It is also unclear whether the differences in melatonin across different disorders are due to differences in psychotropic medication (which are known to impact MLT synthesis), to atypical light exposure, or to variability found in the general population at baseline. Furthermore, other disorders such as anorexia (Ferrari et al., 1989) and panic disorder (McIntyre, Judd, Burrows, Armstrong, & Norman, 1990) have been reported to show increased melatonin levels when compared to controls.

Acrophase advances and delays in melatonin rhythms have also been reported in a number of different psychiatric disorders. Schizophrenia has been reported to have both (Anderson & Maes, 2012; Wulff et al., 2012), as has depression (Srinivasan, Pandi-Perumal, et al., 2009a; Srinivasan, Smits, et al., 2009b). Bipolar patients advance or delay depending on the manic or depressive MLT acrophase of the disorder (Srinivasan, Smits, et al., 2009b), and seasonal affective disorder presents with a delayed MLT acrophase allied to the winter season (Zawilska et al., 2009). Taken together, a number of psychiatric disorders have been reported to present with differences in melatonin when compared to healthy controls. As such, it has been proposed that misalignment of the master clock with the external environment could underpin a number of different psychiatric disorders (Wulff, Gatti, Wettstein, & Foster, 2010b). However, the differences observed are undeniably heterogeneous between studies and disorders, and as such should be interpreted with caution.

A wide variety of studies have been conducted on psychopathology and melatonin, yet relatively few have investigated whether an insomnia complaint may have an underpinning in circadian misalignment. A study by Riemann et al., (2002) measured nocturnal serum melatonin in 10 drug-free insomnia patients. Results highlighted that the insomnia patients had a blunted melatonin peak when compared to healthy controls. The authors emphasise that these findings should be interpreted with caution due to the very small sample size employed (10 patients and 10 age- and gender-matched controls). A more recent study by Leger, Laudon, & Zisapel (2004) investigated urinary melatonin at home in elderly insomnia patients (aged above 54 years). They replicated the blunted melatonin response in insomnia patients when compared to young volunteers or age-matched controls with a substantially larger sample (n=517), and concluded that low melatonin secretion is associated with more severe insomnia in elderly patients and that more generally melatonin production declined with age.

While few studies have examined melatonin rhythms in insomnia, there have been a number of melatonin supplement trials in insomnia cohorts with promising results. A systematic review by Rikkert & Rigaud (2001) reported that melatonin supplements resulted in decreased sleep latency in four out of six randomised control trials studied. Furthermore, three studies saw improvements in total sleep time, wake after sleep onset and sleep efficiency. The authors concluded that there is sufficient evidence to suggest melatonin supplements as an effective treatment in elderly insomnia

sufferers. A randomised placebo-controlled trial highlighted similar benefits for chronic sleep onset insomnia in children (aged 6-12 years). The melatonin group displayed an advanced sleep onset and longer sleep duration when compared to controls (Smits, Nagtegaal, van der Heijden, Coenen, & Kerkhof, 2001). A meta-analysis comprising of 17 studies and participant cohorts that included healthy subjects, artificially induced insomnia subjects and insomnia patients found that exogenous melatonin advanced sleep onset by an average 3.9 minutes, and increased both sleep efficiency and duration by 3.1% and 13.7 minutes respectively (Brzezinski et al., 2005). It is unclear at this point what the underlying therapeutic mechanisms for these results are. Potential possibilities are that melatonin acts as a 'pseudo-hypnotic' as it increases drowsiness (which is poorly regarded in the field of chronobiology as the pathways have been shown to be different for hypnotics and melatonin; please refer to Scheer & Czeisler (2005) for a review), or that it acts as a chronobiotic/timing agent (Scheer & Czeisler, 2005) which impacts or enhances clock signalling (yet it is unclear in these studies whether any of the participants are phase delayed/have a late type chronotype/have very low melatonin levels). Another possibility is that melatonin acts as an inducer of sleep onset and maintenance via an alternate mechanism, such as thermoregulation (which may act alongside its efficacy as a timing agent; please refer to Kräuchi, Cajochen, Pache, Flammer, & Justice, 2009 for a review).

In the last decade, the development of melatonin agonist drugs has led to a revival of the melatonin and insomnia debate, with an explosion of randomised controlled trials to investigate the efficacy of these drugs on sleep disturbances. A multicentre placebo controlled randomised control trial of Tasimelteon (a purely synthesised melatonin receptor agonist) showed improvements in sleep onset latency, sleep efficiency and wake after sleep onset in experimentally induced 'transient insomnia' in a very large healthy sample (n=411). Phase II of the trial (n=39) noted that Tasimelteon also successfully shifted plasma melatonin most potently with a 100mg dose. The authors concluded that this would be more appropriate for transient insomnia experienced in relation to shift work or jet lag, but do not mention its direct relevance to insomnia disorder itself (Rajaratnam et al., 2009). However, an alternate (but chemically almost identical) melatonin agonist labelled Ramelteon has been trialled for its efficacy in chronic insomnia. Results highlighted Ramelteon to produce a significant reduction in sleep onset latency and an increment in total sleep time (n=107; Erman, Seiden, Zammit, Sainati, & Zhang, 2006).

There is extensive research on the efficacy of melatonin agonists in sleep disorders, the review of which is beyond the scope of this thesis (please refer to: Srinivasan et al., 2012 & Pandi-Perumal, Srinivasan, Poeggeler, Hardeland, & Cardinali, 2007). Globally, it would appear melatonin agonists are indeed effective for treating insomnia disorder.

Despite the extensive number of studies investigating the efficacy of exogenous melatonin and melatonin agonist medications, there is a relative dearth of studies examining whether endogenous melatonin (rhythm or amplitude) is indeed impacted in insomnia, yet this could hold real promise for the therapeutic mechanisms that these drugs possess. The largest study of endogenous melatonin to date is restricted to insomnia sufferers over the age of 54 years, which is at the upper limit or indeed beyond the limit of most of the drug studies mentioned. Furthermore, elderly insomnia cohorts are more likely to suffer from confounds, complications and comorbidities.

Thus, the aim of this chapter is to examine whether an insomnia complaint in a healthy, young, medication-free population is associated with differences in melatonin acrophase and/or amplitude when compared to age- and gender-matched good sleepers. We predict, based on the previous literature in insomnia, that the insomnia group will have significantly lower mean melatonin amplitude when compared to the good sleeping group (1). MLT acrophase has never been examined in an insomnia cohort, so this is an exploratory analysis in nature. However, based on the efficacy of melatonin agonists in insomnia cohorts, we would also predict the insomnia group to have a delayed MLT acrophase when compared to the good sleeping group, which would help inform their efficacy (2). Given the comorbidity of insomnia with schizophrenia, depression and bipolar disorder (Harvey et al., 2011), and the wide number of studies reporting relationships between these disorders and melatonin, we investigated the depression, mania and psychotic-like experiences reported by each group as an exploratory secondary outcome with a view to understanding how these variables relate to our primary melatonin outcomes (acrophase and amplitude).

4.2 Methodology

For the participants' demographics and recruitment protocol, please refer to Section 3.3.1. Each participant was asked to complete the *'Melatonin Rhythm Procedure'* detailed below in Section 4.2.1 and the three psychometric questionnaires detailed in Section 4.2.2.

Self-report sleep entries reflect the observer's individual sleep related experiences and perceptions, such as difficulty falling asleep and difficulty staying asleep: both of which are correlated with non-sleep related phenomena (e.g. state of mood; Krystal & Edinger, 2008). Thus, the sleep-wake patterns were objectively monitored long-term for three weeks using wrist-worn actigraphs with an integrated light sensor (MotionWatch 8, CamNtech Ltd.). The quantitative actigraphy data were annotated in conjunction with standardised diary entries of sleep timings and daily activities. Actigraphy data were sampled at one-minute epochs, and MotionWare software (version 1.1.15, CamNtech, Ltd.) was used to calculate sleep onset, sleep offset, sleep period (SP; time between sleep onset and sleep offset, including WASO), 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 (% of time in bed spent asleep excluding sleep onset latency) and variability in sleep onset and sleep duration (measured by their standard deviations).

4.2.1 Melatonin Rhythm Procedures

Melatonin is most commonly collected via saliva, serum or urine. Serum melatonin holds an advantage as it accurately estimates real pineal hormonal secretion, but it is invasive and difficult to obtain for clinical purposes and research studies (Wetterberg et al., 1999). Urine collection is comparatively more convenient, can be done at home (offering more ecological validity) and is a non-invasive alternative (Wetterberg et al., 1999). Furthermore, both saliva and serum tend to be 'point' collections while urine is more suitable for measuring the entire period. This prevents missing the measurement of the MLT acrophase, which point sampling could if it were too widely spaced (Arendt, 1982). Melatonin levels are detected in urine via the melatonin metabolite 6-hydroxymelatonin sulphate (aMT6; Wetterberg et al., 1999). Urinary melatonin highly correlates with

plasma melatonin levels (Fellenberg, Phillipou, & Seamark, 2009), is consistent with serum levels (Arendt et al., 1982) and correlates strongly with the early morning peak of melatonin production (the acrophase; Almay, Knorring, & Wetterberg, 1987). Thus, urinary melatonin was collected for this study.

To estimate the circadian acrophase of the participant's circadian pacemaker, a 48-hour profile of aMT6 was employed using an established and published protocol (please refer to Wulff et al., 2009a; Wulff et al., 2012). The protocol required the participants to comply with several instructions. First, the participants were instructed to remain hydrated and to avoid drinking alcohol during the 48-hour period. Prior to starting the collection of the first sample, the participants were asked to note down the time that they last went to the bathroom.

For collection, each participant was asked to pass a full volume of urine into a bottle approximately every four hours (approximately eight hours when asleep). Furthermore, they were told that although going to the bathroom more frequently than every four hours was acceptable (and urine collection was still to take place), going to the bathroom less than every four hours would produce unreliable results. The participants were instructed to note down the date, time of collection and approximate volume in the bottle every time they went to the bathroom (the large urine bottle had measurement marks on it to allow for more accurate volume estimations). Participants were then instructed to pipette 5ml from the large urine bottle into two small 5ml aliquots. The large urine bottle, disposable pipettes and aliquots were all provided to the participants prior to starting sampling. Finally, the participants were asked to seal and label the aliquots (with handwritten labels provided by the experimenter) and note down the labels used on the collection sheet. In the event that a sample was missed, participants were asked to note down the time of the sample on the sampling sheet.

Participants were also provided with sample bags to store the samples in and were instructed to keep all samples in the refrigerator until the researcher collected them. Upon collection, all samples were stored in laboratory freezers at -20°C. The melatonin assay was outsourced with Surrey Assays Ltd. Melatonin sulphate concentrations were determined in duplicate for each urine sample by radioimmunoassay (Aldhous & Arendt, 1988). The raw data were sent back to our lab for further analysis.

4.2.2 Questionnaires

The Munich Chronotype Questionnaire (MCTQ; please refer to Section 2.2.2.2; Roenneberg et al., 2003).

Depression Anxiety and Stress Scale (21 Item Version, Cronbach's α=0.94; please refer to Section 2.2.2.3; Henry & Crawford, 2005).

Prodromal Questionnaire 16 Item Version (PQ16; Cronbach's α=0.77; please refer to Section 2.2.2.3; Ising et al., 2012).

Mood Disorder Questionnaire (MDQ; α=0.87; Hirschfeld et al., 2000) The MDQ is a five-part questionnaire. The first portion comprises 13 brief yes-or-no statements related to manic symptoms, all of which begin with the precursor "has there ever been a period of time when you were not your usual self and…". These questions assess various bipolar symptoms, such as hypersexuality ("...were you much more interested in sex than usual?") and racing thoughts ("...thoughts raced through your head or you couldn't slow your mind down?"). The second portion of the questionnaire is one yes-or-no question asking whether the manic symptoms occurred simultaneously. The third portion has the subject evaluate the problems caused by those manic behaviours along a four-point scale, ranging from "no problem" to "serious problem". The fourth and fifth portions of the MDQ assess bipolar disorder in the subject's relatives and previous bipolar diagnoses respectively. These portions of the MDQ do not relate directly to receiving a positive screen, and therefore were not used in our analysis. The MDQ has demonstrated satisfactory psychometric properties previously (please refer to Miller, 2004).

4.2.3 Melatonin Analysis

To determine rhythms in melatonin sulphate from our unequally spaced collection times, we applied the following non-linear regression model to our data:

$$MT = c + (Amp \times Cos\left(\frac{2\pi \times (t-tc)}{T}\right)),$$

where *MT* represents the aMT6 secretion rate (ng/h) and *t* represents time. Model parameters are *c,* representing mesor (rhythm adjusted daily mean); *Amp*, representing amplitude; *tc*, representing acrophase angle; and *T*, representing period.

This model was then fit to the sequentially sampled aMT6 concentrations over 48 hours using the PROC NLIN procedure in SAS software for Windows, Version 7 (version 9.1.1; SAS Institute, Cary, NC, USA). The model was run separately for each individual. The results were then collated and group analyses were performed in R (R Core Team, 2014).

4.3 Results

4.3.1 Melatonin Data Cleaning

Of the 47 participants who took part in the study, 45 completed the melatonin sampling. Reasons for non-completion related to time commitments.

Of these 45 participants, a further six participants needed to be excluded from the analysis. Reasons for exclusion were suspected protocol noncompliance (n=2), unreliable sampling due to too few samples provided (n=2), and completing the sheets incorrectly or misunderstanding the instructions (n=2). This resulted in 39 participants (n=20 good sleepers; n=19 insomnia group) who were used for the modelling analyses.

For two subjects, one data point was excluded from the model due to being highly incongruent with the data pattern; due to a mis-estimation of total volume of urine in the bottle. For another subject, two data points needed to be excluded for the same reason.

For 12 participants, the baseline model parameters were unsuitable; this is usually an indicator that the individual's MLT acrophase/amplitude or period were outside what the model can reasonably account for. When this arose, an iterative series of solutions were employed after the data was checked for suspected non-compliance/participant error, data errors with regards to timing, and the conversion of data formats from time to decimalised numbers.

The first process was to make minor alterations to the period *T* in the model. The default parameter is 24 hours, as such this would be shifted starting at 23.5 (with increments of 0.10) to 24.5 based on observations of the model fit and predicted peak. Second, the graphical parameters of the projected model fit were altered as these often obscure the model fit. Third, the data points were examined for anomalous or highly incongruent samples. If an incongruent sample was discovered, the model was re-run with the anomalous sample removed. In a small number of participants, the above procedures did not improve the fit of the model. In those cases, a final model alteration was done, whereby the predicted peak of melatonin (4 am based on the default model parameters) was altered based on the projections of the model fit. This was only employed if the baseline model suggested that the participants' peak was much later than what the model could account for.

Using these four alterations, all 12 models resulted in a significant fit, indicating that the model aptly described the data provided (this is based upon the protocol used by Wulff et al., 2009a & Wulff et al., 2012) .

4.3.2 Actigraphy

Table 4.1 highlights the subjective and objective differences in sleep between groups. As a marker of variability of sleep timing and duration, the standard deviations of Total Sleep Time (TST) and sleep onset were also calculated. Actigraphic parameters were approximately normally distributed; as such, mean differences were tested using Welch's two-sample t-test (an adaptation of Student's t-test to account for unequal variance between groups). Prior to correcting for multiple testing, both the sleep period ($t(38.3)=-3.02$, $p=0.0004$) and Wake After Sleep Onset (WASO; $t(42)=-2.10$, $p=0.042$) were found to be significantly higher in the insomnia group than in the good sleepers group. This indicates that while the insomnia group spent a significantly longer time in bed, they did not get significantly more TST and experienced more WASO. Sleep offset also appears to be trending to significance, with the insomnia group getting up on average 33 minutes later than the good sleepers ($t(41.7)=-1.98$, $p=0.054$). However, after correcting for multiple comparisons using the Benjamini Hochberg method (Benjamini & Hochberg, 1995), only sleep period remained significant. **Figure 4.2** provides a graphical overview of each of the actigraphic measures between groups.

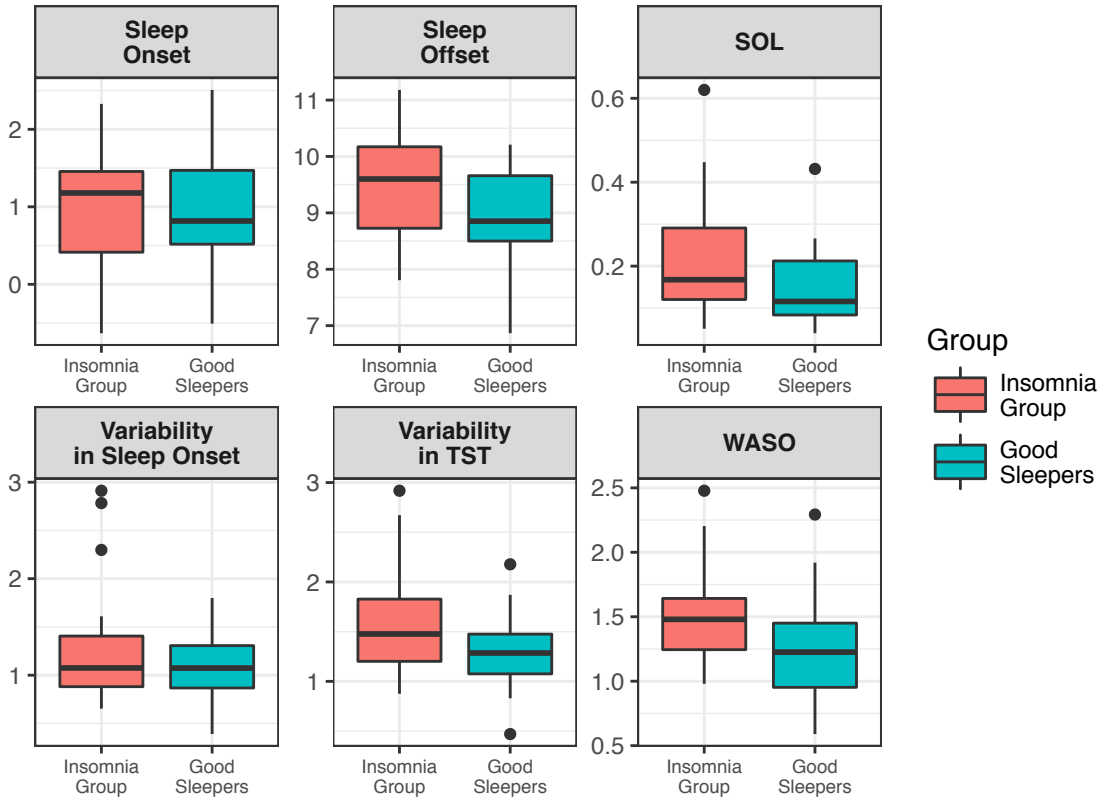

Figure 4.2: Boxplots of the actigraphic measures between groups, highlighting group differences. Of note is the difference between groups in WASO and the trending difference in sleep offset. The solid black line in each box represents the median. The box heights represent the interquartile range.

4.3.3 Melatonin and Chronotype

Table 4.2 highlights the group differences in age, season of recruitment, chronotype, circadian acrophase, melatonin amplitude, the mesor and the phase angle for sleep onset and offset. There were no significant differences in age (t(41.65)=-1.13, p=0.26) or the season of recruitment between groups (χ^2(3)=2.56, p=0.46). Only two participants did not fall into the neutral category for chronotype (morning, n=1; and evening, n=1). As such, there were no significant differences between groups (χ^2(2)=2.00, p=0.37). Furthermore, there were no significant differences in MSFsc (t(43.81)=-0.95, p=0.35) or social jet lag (t(42)=0.21, p=0.84). Analyses of group differences in melatonin production using Welch's t-test highlighted a significant difference in MLT acrophase (t(31.22)=-2.12, p=0.04) but not in amplitude (t(33.99)=1.07, p=0.29), mesor (t(32.52)=1.28, p=0.21), phase angle onset (t(34.95)=-1.81, p=0.07) or offset (W=187, p=0.69). Group differences in MLT acrophase are highlighted in **Figure 4.3** and **Figure 4.4**.

	Good Sleepers		Insomnia Group		Group Differences			
	Mean	(95% CI)	Mean	(95% CI)	t	df	p	p_{adj}
Subjective Sleep								
PSQI	2.36	(1.99-2.74)	10.23	(9.23-11.22)	-	-	-	-
ISI	1.32	(0.75-1.89)	14.59	(13.13-16.16)	-	-	-	-
Objective Sleep (measured actigraphically over three weeks)[a]								
Sleep Onset (h:m)	00:58	(00:36-01:19)	00:59	(00:38-01:22)	-0.14	42.0	0.892	0.892
Sleep Offset (h:m)	08:55	(08:32-09:18)	09:28	(09:02-09:53)	-1.98	41.7	0.054	0.153
Sleep Period (hr)*	7.96	(7.68-8.24)	8.47	(8.26-8.67)	-3.02	38.3	0.004	0.040
TST (hr)	6.69	(6.43-6.96)	6.95	(6.70-7.21)	-1.48	42.0	0.147	0.184
SOL (min)	9.0	(6.6-11.4)	12.6	(9-16.8)	-1.73	35.9	0.092	0.153
Fragmentation Index	27.58	(24.39-30.78)	31.33	(28.61-34.04)	-1.86	40.9	0.071	0.153
WASO (hr)	1.27	(1.09-1.44)	1.51	(1.34-1.67)	-2.10	42.0	0.042	0.153
Standard Deviation in Sleep Onset (hr)	1:05	(0:55-1:14)	1:16	(0:59-1:33)	-1.22	32.1	0.233	0.259
Standard Deviation in Sleep Offset (hr)	01:18	(01:08-01:28)	01:33	(01:19-01:47)	-1.79	38.2	0.081	0.153
Sleep Efficiency (%)	84.16	(82.11-86.21)	82.09	(80.04-84.14)	1.48	42.0	0.146	0.184

Table 4.1: Descriptive statistics of the objective (n=44) and subjective (n=47) measures of sleep. Adjusted p-values were calculated using the Benjamini Hochberg method.
[a] Three individuals were excluded due to non-compliance (n=1) and malfunctioning watches (n=1) and suspected circadian rhythm disorder.
*Sleep Period is the time spent in bed excluding SOL.

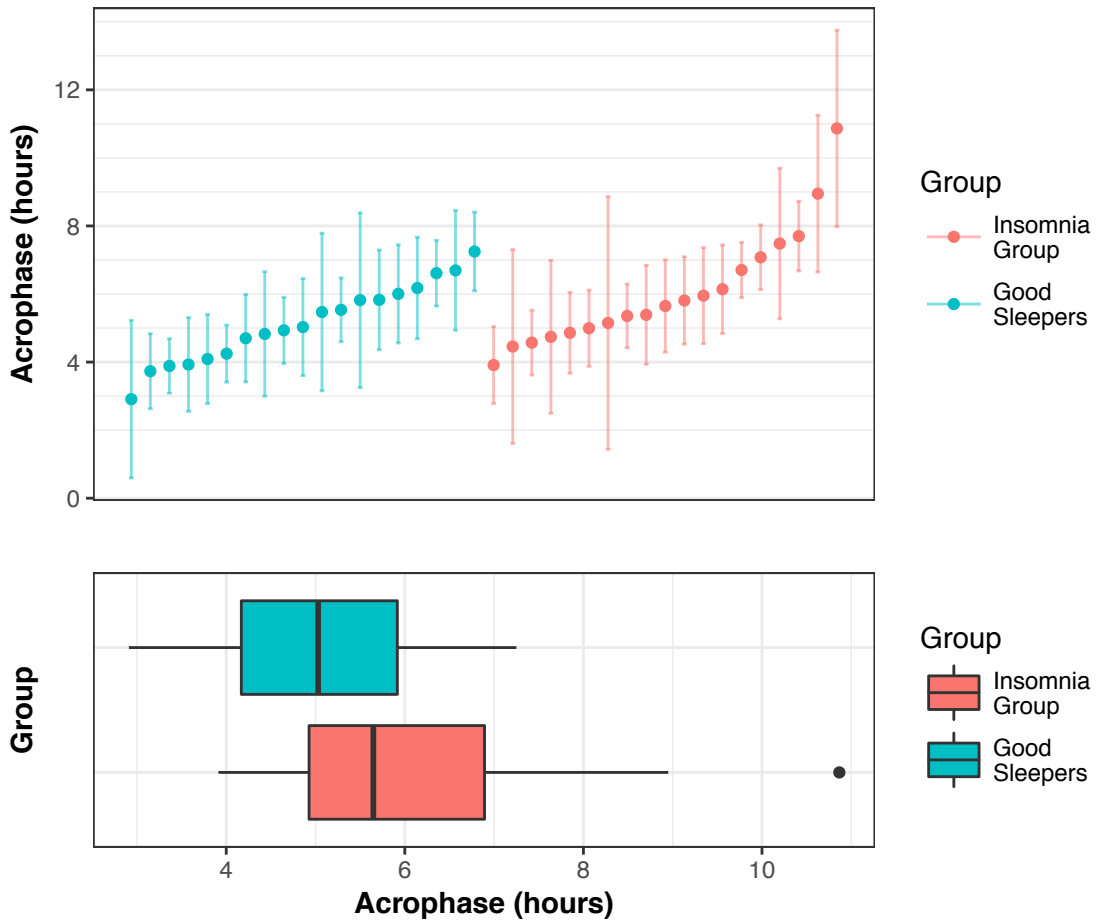

Figure 4.3: Plots highlighting group differences in melatonin acrophase. *Top:* The individual differences in melatonin acrophase are highlighted, with a dot for each individual representing the acrophase estimate, and error bars representing a standard error either side of the estimated acrophase. *Bottom:* The group differences in melatonin acrophase are highlighted. The thick black lines highlight the group medians, and the box widths represent the interquartile range. A slight trend towards a delay in in the insomnia group is visible.

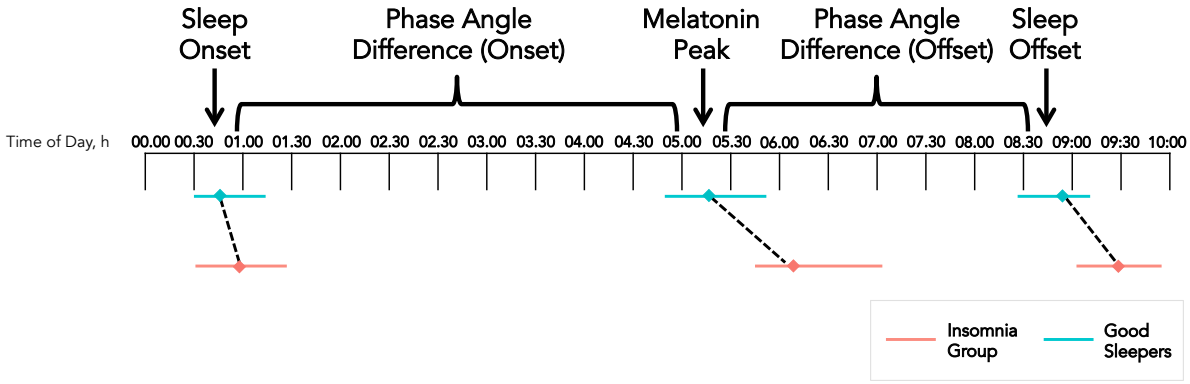

Figure 4.4: The relationship between acrophase (melatonin peak), sleep onset, and sleep offset for the good sleeping and insomnia groups**.** Diamonds represent the group means, and the lines represent a standard error either side of the mean. These are mapped against a timeline of the biological night. The insomnia and good sleeping group overlap at sleep onset, yet we see delays in the melatonin peak coinciding with a slightly extended delayed sleep offset for the insomnia group. This indicates the time in bed (excluding sleep onset latency) to be slightly elongated for the insomnia group when compared to the good sleeping group.

	Good Sleepers	Insomnia Group	Group Differences				
	Mean (95% CI)	Mean (95% CI)	x^2	t	df	p	p_{adj}
Age	22.7 (21.5-24.0)	23.8 (23.6-24)		-1.13	41.65	0.26	-
Season			2.56		3	0.46	-
Spring	12 (25.55%)	11 (23.40%)					
Summer	2 (4.25%)	3 (6.38%)					
Autumn	6 (12.77%)	2 (4.25%)					
Winter	4 (8.51%)	6 (12.77%)					
Chronotype			2.00		2	0.37	-
Morning Type	1 (2.12%)	0					
Neutral	23 (48.9%)	21 (44.68%)					
Late Type	0	1 (2.12%)					
MSFsc	4.69 (4.18- 5.19)	5.00 (4.54-5.45)		-0.95	43.81	0.35	0.70
SJL‡	1.11 (0.86-1.36)	1.08 (0.86-1.29)		0.21	42	0.84	0.84
Depression*	1.50	7.00		79	-	<0.001	<0.001
Mania*	1.50	7.00		107.5	-	<0.001	<0.001
Psychotic Exp*	1.00	3.00		70.5	-	<0.001	<0.001
Acrophase (h:m)†	05:08 (04:33-05:38)	06:06 (05:16-06:55)		-2.12	31.22	0.04	0.12
Amplitude, ng	1120.0 (726.3-1513.8)	872.4 (590.2-1154.6)		1.07	33.99	0.29	0.29
Mesor, ng	969.1 (657.8-1280.5)	740.6 (535.6-945.6)		1.28	32.52	0.21	0.29
Phase A. (On)#	4.31 (3.7-5.0)	5.14 (4.5-5.8)		-1.81	34.95	0.07	0.18
Phase A. (Off)*♦	3.64 (2.9-4.3)	3.44 (2.6-3.9)**		185	-	0.69	0.69

Table 4.2: Descriptive statistics for season, chronotype, melatonin and age.

‡ Two people were excluded from this comparison as they presented with a negative social jet lag, i.e. their mid-sleep point was earlier on weekends when compared to work days.

† A total of six people were excluded from the melatonin analysis.

* Mania, depression, phase angle offset and psychotic experiences were not normally distributed; hence Wilcoxon rank sum tests with continuity corrections were employed. The values in the 't' column here represent the test statistic 'W' and the medians are reported as opposed to the mean.

Phase A. (On) represents the phase angle difference at sleep onset, i.e. the difference in time between the sleep onset and the MLT acrophase.

♦ Phase A. (Off) represents the phase angle difference at sleep offset, i.e. the difference in time between the sleep offset and the MLT acrophase.

** There was one negative value in the insomnia group for phase offset. As such, a Wilcoxon rank sum test with continuity correction was employed. The value in the 't' column here represents the test statistic 'W' and the median was reported as opposed to the mean.

4.3.4 Melatonin in Relation to Psychometric Measures and both Objective and Subjective Sleep Parameters

The Wilcoxon rank sum test with continuity correction was employed for analyses of group differences in the psychometric measures, as the distributions for all three measures were skewed. For these measures, the median and test statistic 'W' were reported. The insomnia group displayed significantly higher scores in depression ($W=79$, $p<0.001$), mania ($W=107.5$, $p<0.001$) and psychotic-like experiences ($W=70.5$, $p<0.001$).

Table 4.3 highlights the correlations between objective and subjective sleep with the main parameters of the melatonin analysis (acrophase, peak and mesor) and psychotic like experiences (PQ16), mania (MDQ) or depression (DASS-21). We can see strong correlations between the timings of sleep (sleep onset and offset) and the MLT acrophase, amplitude and mesor. Objective sleep offset was also correlated with the subjective measure PSQI ($r=0.45$). The MLT acrophase was also moderately correlated with PSQI ($r=0.41$). Interestingly, there is a moderate correlation also between the MLT acrophase and psychotic-like experiences, which, when tested, was trending on significance ($r=0.30$, $p=0.066$).

	PSQI	MDQ	Dep	PQ16	Onset	Offset	TST	WASO	MSFsc	Acro.
PSQI	-									
MDQ	0.53	-								
Depression	0.54	0.60	-							
PQ16	0.62	0.71	0.77	-						
S. Onset	0.23	0.21	0.14	0.25	-					
S. Offset	0.45	0.32	0.16	0.25	-0.78	-				
TST	0.30	-0.01	0.01	-0.13	0.01	0.49	-			
WASO	0.14	0.31	0.08	0.25	-0.12	0.09	0.38	-		
MSFsc	-0.03	0.26	0.19	0.31	0.35	0.25	-0.16	0.14	-	
Acrophase	0.41	0.22	0.06	0.30	0.52	0.50	0.20	-0.14	0.29	-
Amplitude	-0.17	-0.16	-0.14	-0.16	-0.48	-0.52	-0.15	-0.06	-0.16	-0.16

Table 4.3: Serial pairwise correlations between melatonin, MLT acrophase, amplitude, psychometric measures, and subjective and objective sleep parameters. Due to the limited sample size (n=39), and thus limited power, significance testing was not carried out. Had it been performed, shaded backgrounds indicate correlations above the significance threshold.

4.4 Discussion

Taken together, this cohort (a young student population with a moderate insomnia complaint) seems to display small but reliable differences in the acrophase of their melatonin rhythms. This is evidenced by the insomnia group displaying a significantly longer sleep period (time in bed excluding SOL) when compared with the good sleeping group, in addition to a later sleep offset (nearing significance, $p=0.054$).

Despite this later MLT acrophase and sleep offset, there were no differences in chronotype (measured via habitual mid-sleep point) between the two groups. Furthermore, there were no significant differences between groups in melatonin amplitude or phase angle difference for sleep onset or offset. Thus, these analyses may offer preliminary evidence that an insomnia complaint in this population may in part be mediated by either a late endogenous rhythm or masking from the environment (e.g. light at night or studying late at night).

These findings do not align with the results presented by Riemann et al., (2002) and Leger et al., (2004), who found that there was a dampening or reduced amplitude of the melatonin rhythm in an insomnia cohort, but did not report a difference in acrophase. Leger et al., (2004) used an aging cohort and demonstrated that melatonin concentration decreases with age. Hence, the disparity in amplitude findings is likely to be caused by the disparity in age between the cohort reported here and Leger's cohort. Neither Riemann et al. (2002) nor Leger et al. (2004) reported on phase angle differences between groups, so it is unclear if this could have been affected also. In Riemann et al. (2002), the authors highlight that disconcordance between insomnia groups (with regards to the presence of objective measures of sleep) may reflect underlying subcategories of insomnia disorder; namely psychophysiological insomnia, sleep state misperception and idiopathic insomnia. In the previous chapter, we did find an objective sleep disturbance in the insomnia group (as measured by polysomnography, see Chapter 3), thus the discrepancy between our results and those of Riemann's may be in part due to the recruitment of different subcategories of insomnia. It could also be that objective disturbances in sleep highlight a more 'biologically aggressive' insomnia phenotype, as has been suggested by Vgtonzas and colleagues (Vgontzas, Fernandez-Mendoza, Liao, & Bixler, 2013). Taken together, the results from this cohort may in part help explain why melatonin agonists have

presented with such success in insomnia disorder, as MLT acrophase delays are present but under-recognised in insomnia complaints. Trials have shown melatonin agonists to advance the melatonin acrophase in experimentally induced insomnia, which would offer support for this explanation (Rajaratnam et al., 2009).

Given the age of this cohort relative to those investigated in previous insomnia studies, it could be that an insomnia complaint in this cohort has a stronger underpinning in a delayed sleep MLT acrophase or later chronotype. This interpretation would be in line with the observed actigraphic differences between groups. Such differences have also been reported in adolescent and young adult unipolar and bipolar phenotypes (Robillard, Naismith, Rogers, Ip, et al., 2013a; Robillard, Naismith, Rogers, Scott, et al., 2013b). Interestingly, the mania scores had the strongest correlation with the sleep offset ($r=0.32$) when compared to depression ($r=0.16$) and psychotic-like experiences ($r=0.25$), again potentially representing a subgroup in this insomnia cohort.

Furthermore, this insomnia cohort also score higher on depression, mania and psychotic-like experiences compared to the good sleeping group. Thus, the MLT acrophase delay described here may relate to an underlying vulnerability to psychopathology to any (or all) of the above disorders. Major Depressive Disorder, bipolar disorder and schizophrenia have all been reported to present with both acrophase advances and delays in melatonin rhythms. Again, the heterogeneity in results may also be indicative of subcategories within these disorders, a possibility that has been repeatedly noted in the literature. The heterogeneity of these disorders' clinical presentation is considerable (Srinivasan, Smits, et al., 2009b; Wulff et al., 2012). Further support for this explanation is provided by the efficacy of melatonin agonists in depressive disorders (for a review please see Hickie & Rogers, 2011), schizophrenia patients with insomnia (Shamir, Laudon, Barak, & Anis, 2000) and in bipolar disorder (Alexis Geoffroy, Etain, Micoulaud Franchi, Bellivier, & Ritter, 2015). Additionally, referring back to Section 1.9.3, several circadian gene variants have been noted to play a role in susceptibility to psychotic and mood disorders (Etain et al., 2011; Monti et al., 2013; Wulff, Gatti, Wettstein, & Foster, 2010a). However, it is interesting that the correlation between melatonin acrophase has stronger affinities with both mania ($r=0.22$) and psychotic experiences ($r=0.30$; $p=0.066$), as compared to depressive symptoms ($r=0.06$). While not reaching statistical significance, this difference

could potentially represent emerging differences. Further research with a similar cohort and larger sample size is warranted to support these speculations.

A number of caveats merit mention. First, as this was an 'at-home' protocol, the melatonin collection could have been subject to noncompliance. When this was obvious due to incongruent sampling or implausible volumes, the data points or indeed the whole participant were excluded from the analysis. Nonetheless, this may have impacted the results. Second, we had no control over the participants' light exposure which, as mentioned in the introduction, heavily suppresses melatonin secretion (Zawilska et al., 2009). Again, this may have impacted our results. However, monitoring participants longitudinally across a three-week period in naturalistic settings does support the ecological validity of these findings, which is often lost when using a laboratory environment.

These caveats notwithstanding, we believe that this study offers a novel contribution to the field and highlights a potentially underexploited area of biologically driven research into insomnia that may help inform its pathophysiology. The heterogeneity observed in melatonin findings between different insomnia or other psychopathology cohorts could further indicate subtypes and potentially help define them. Future research should aim to replicate these findings both at-home and in a more controlled laboratory environment to see if similar results are produced in the same cohort. Furthermore, future research should investigate whether, if replicated, these differences demonstrate specificity to certain psychometric measures.

Chapter 5:
The Interaction Between Subclinical Psychotic Experiences, Insomnia and Objective Measures of Sleep

Moving away from group differences in physiology, this chapter is refocuses on the sleep-PLE relationship discussed in the introduction. The aim here is to describe which objective or subjective sleep parameters best predict PLEs.
This chapter is currently under review at Schizophrenia Research.

5.1 Introduction

Schizophrenia is accompanied by changes in sleep and the circadian sleep-wake cycle (Wulff, Gatti, Wettstein, & Foster, 2010a), ranging from extreme circadian misalignment (sleep phase advances/delays, bidian cycles and non-24 hour periods) to highly irregular and fragmented sleep patterns, and these changes are observed across all phases of the disorder (Section 1.10; Wulff et al., 2012). Furthermore, there are now a number of studies examining the relationship between poor sleep and PLEs (Section 1.11).

With the shift in psychiatry research towards transdiagnostic, multi-domain approaches (van Os & Reininghaus, 2016), the dimensional concept allows variance extending into sub-threshold psychosis in healthy human samples. Furthering the research described in Section 1.11, it was tested whether the relationship between schizophrenia and sleep is bi-directional, hypothesising that healthy young adults with self-reported insomnia endorse a greater number of psychotic-like experiences than those

with self-reported good sleep. Statistical models are applied to examine whether parameters of sleep predict this relationship, and if so, which parameters: subjective, objective, or both.

5.2 Methodology

5.2.1 Participants

The eligibility for the study including the inclusion and exclusion criteria and demographics of the cohort are described in Section 3.3.1. The final sample consisted of 44 students: 22 in the insomnia group (mean age=23.7 years, SD=3.5, 14 women), and 22 controls (mean age=22.8 years, SD=3.2, 11 women). Three participants were excluded from the analysis, due to having a malfunctioning wrist-worn actigraph (n=1), non-compliance with the protocol (n=1) and a suspected circadian rhythm disorder (n=1). Slight differences in group means and SD in the ISI and PSQI between chapters are a result of different exclusions from different analyses.

The mean subjective self-reported sleep quality (PSQI) of the control group was 2.3 (SD=0.9), as opposed to 10.1 (SD=2.2) in the insomnia group. The mean insomnia scores (ISI) were 14.4 (SD=3.3) for the insomnia group and 1.5 (SD=1.5) for the controls. Taken together, these highlight a substantial difference in subjective sleep quality and insomnia between groups.

The sleep-wake patterns were objectively monitored long-term for three weeks using wrist-worn actigraphs with an integrated light sensor (MotionWatch 8, CamNtech Ltd.) (see Section 3.3 for further details). Psychotic experiences were measured using the Prodromal Questionnaire 16 Item Version (PQ16) (see Section 1.2). Feelings of depression and anxiety were taken from the Depression, Anxiety and Stress Scale (DASS; Section 2.2.1.2; Henry & Crawford, 2005) and were found to correlate highly with self-reported sleep ratings; therefore these variables were excluded as predictors in the model due to risks of multicollinearity.

5.2.2 Modelling

Multivariate Poisson regression analyses were used to investigate which parameters of sleep best predicted the difference in psychotic experiences (PQ16) between groups. Possible predictor

variables for PQ16 were PSQI, ISI, WASO, TST, fragmentation, SOL, and variability in both sleep onset and duration. Due to concerns with collinearity, PSQI and ISI were not included in models together.

Model selection was based upon Akaike's Information Criterion (AIC), using forward selection and backwards elimination (see Section 2.2.4 for further details). All statistical analyses were performed in R (R Core Team, 2014).

5.3 Results

The sample comprised of 43 students: 21 in the insomnia group (mean age=23.9 years, SD=3.6, 13 women) and 22 controls (mean age=22.8 years, SD=3.2, 11 women). The mean PSQI of the insomnia group was 10.1 (SD=2.2) compared to 2.4 (SD=0.8) for the controls. The mean ISI was 14.4 (SD=3.3) for the insomnia group compared to 1.3 (SD=1.3) for the controls. For a review of the actigraphic differences between groups please refer to **Table 4.1**

As mentioned in Section 4.3.4, a Wilcoxon Rank-Sum test indicated that the median PQ16 score in the insomnia group (median=3) was significantly higher than the control group (median=1, 95% CI [1.00-4.00], W=70.5, $p<0.001$, **Figure 5.1**). Our best model of fit included an interaction between PSQI (the subjective measure) and TST (objective measure) (see **Table 5.1**; β=-0.13, SE=0.05, z=-2.58, $p<0.01$).

Predictor	β	SE	Z	p
Intercept	-2.98	3.16	-0.95	0.34
PSQI	1.07	0.34	3.13	<0.01
TST	0.35	0.46	0.76	0.45
PSQI:TST	-0.13	0.05	-2.58	<0.01

Table 5.1: Poisson regression model with PQ16 as the outcome measure (n=42). PSQI (Pittsburgh Sleep Quality Index), TST (Total Sleep Time, as measured by actigraphy) and their interaction feature as predictor variables. One participant was excluded due to incomplete questionnaire data.

A graphical representation of the interaction can be seen in the right-hand plot in **Figure 5.1**. The solid blue line represents the predicted rate of psychotic experiences with a self-perception of good sleep (PSQI score of 3), whereas the solid red line shows the equivalent with a self-perception of poor sleep (PSQI score of 9). This highlights that the impact of TST and subjective sleep quality on psychotic experiences is different for the insomnia group as opposed to the control group.

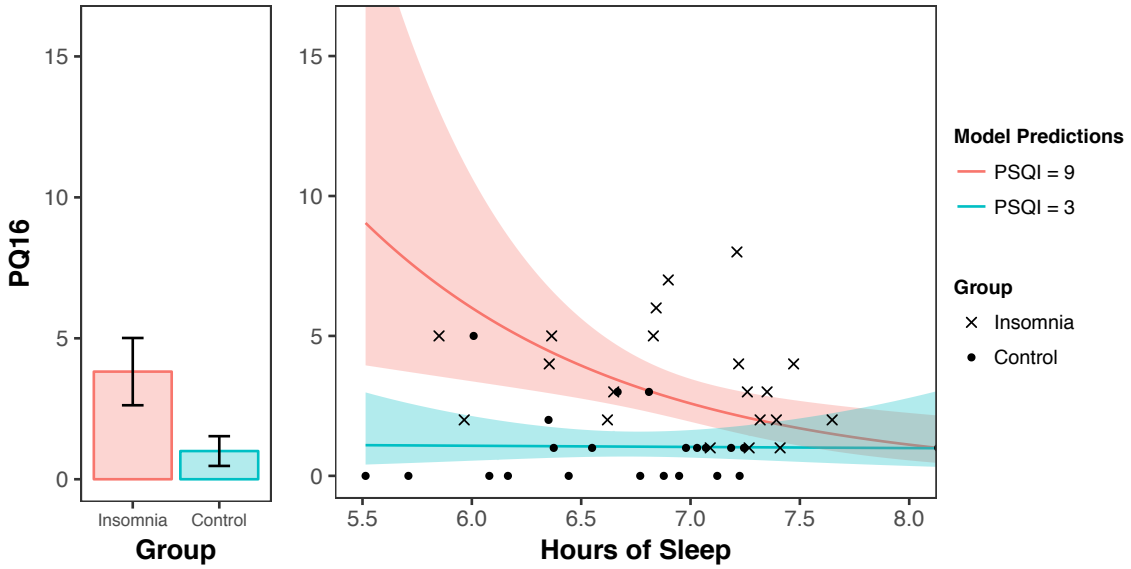

Figure 5.1: *Left:* Mean number of psychotic experiences endorsed on the PQ-16 by the insomnia and control groups. Error bars represent the standard error in each group. *Right:* The interaction between PSQI (subjectively perceived sleep quality) and hours of sleep (objective). Number of psychotic-like experiences endorsed on the PQ-16 (y-axis) against hours of sleep (x-axis, total sleep time as assessed by actigraphy). The predicted rates of psychotic experiences are shown for insomnia with perceived poor sleep (red) and controls with perceived good sleep (blue). Lower hours of sleep alone are not predictive for psychotic-like experiences, as indicated by the blue line, but are in combination with perceived poor sleep quality (red line). The shaded areas around each represent 95% confidence intervals.

Two items of the PQ16 refer to avolition (akin to depression) and social anxiety (Ising et al., 2012). As a means of verification to ensure these items were not overly influential on the model, we examined the breakdown of positive responses to PQ16 items across the cohort (**Figure 5.2**). This distribution highlights that while avolition and social anxiety are amongst the highest scoring items in the questionnaire, they are still lower than derealisation and thought broadcasting, and are on parity with absorption - all of which are considered core symptoms of psychosis.

To further ensure that these two items did not overly influence the modelled relationship, the modelling process was repeated with the items excluded from the PQ16 score of each participant (**Table 5.2**). This highlighted an additional main effect of standard deviation of sleep onset (β=0.58,

SE=0.21, z=2.71, p<0.01). This suggests that the variability in the onset of sleep is also important in the prediction of PEs, with greater variability predicting a greater PQ16 score.

Predictor	β	SE	Z	p
Intercept	-2.43	3.68	-0.66	0.51
PSQI	1.22	0.42	2.93	<0.01
TST	0.15	0.54	0.28	0.78
St. Dev. Sleep Onset	0.58	0.21	2.71	<0.01
PSQI*TST	-0.15	0.06	-2.48	0.01

Table 5.2: Poisson regression model with 'PQ14' as the outcome measure – i.e. with avolition and social anxiety items removed from the PQ16 score (n=42). The standard deviation of the sleep onset now features.

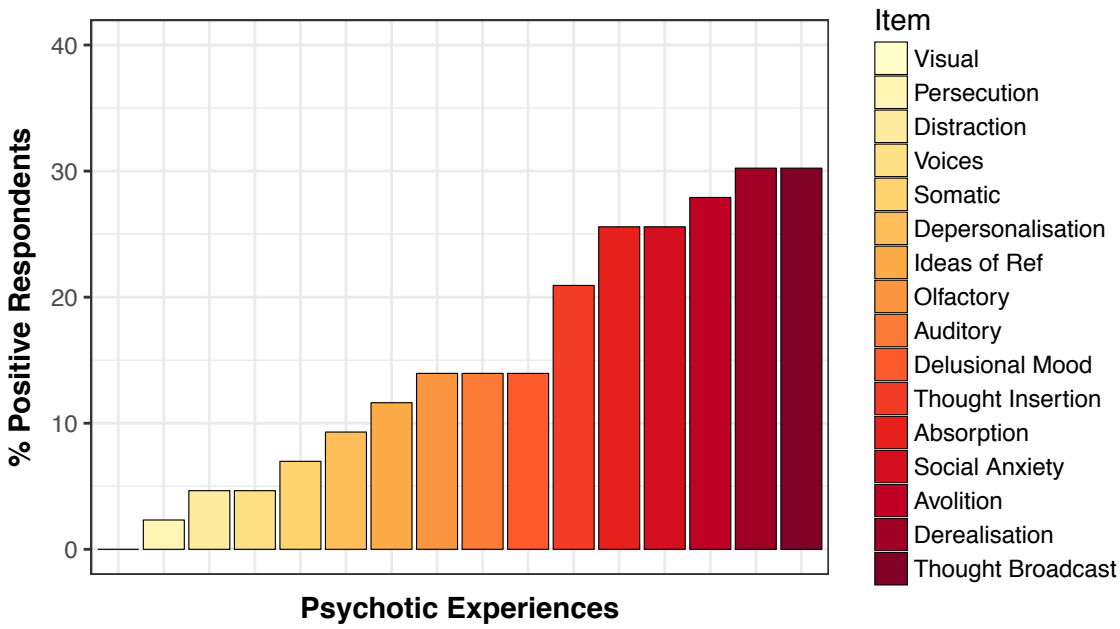

Figure 5.2: Distribution of items endorsed on the PQ16 (n=42). Social anxiety and avolition are amongst the most highly endorsed items on the PQ16, however, thought broadcasting and derealisation are more frequently endorsed in this cohort.

5.4 Discussion

When objective sleep measures of poor and good sleepers were examined, we found an interaction between objective and subjective sleep in the prediction of psychotic-like experiences. The model suggests a perception of good quality of sleep offers sufficient protection from psychotic-experiences,

even with sleep below seven hours per night. If sleep quality is perceived as poor but objectively of substantial length (above 7.5 hours), the risk of psychotic-like experiences is negligible: the same as with a perception of good sleep. However, with poor perceived sleep quality this risk progressively starts to increase with decreasing hours of sleep. Therefore, we find the combination of perceived poor sleep and an actual lack of sleep predicts the greatest risk in psychotic experiences.

Studies to date report associations between subjective measures of sleep and psychotic-like experiences in community samples and highlight that shared environmental influences and genetic lineage contribute to these associations (Taylor et al., 2015). However, this study is the first to consider how objective, actigraphy-derived, measures and data modeling can be implemented to increase our understanding of this relationship. Despite sounding intuitive, this concomitance of biological and psychological factors of sleep has not been reported in the context of psychotic symptomatology before. Furthermore, there is currently strong overreliance on subjective sleep measures, including the PSQI, in assessing risk in psychiatric populations (Buysse, Ancoli-lsrael, Edinger, Lichstein, & Morin, 2006; Fairholme & Manber, 2015). Sleep quality questionnaires may not only capture sleep quality but also distress and anxiety in individuals with psychiatric comorbidity, due to retrospective recall bias as has recently been shown by Hartmann and colleagues (2015). Given this psychological bias and the enormous variation in sleep-wake patterns in humans, these findings reinforce the necessity for both subjective and objective sleep measures in clinical trials and practice when investigating psychotic symptomatology. For patients with an insomnia complaint, quantitatively shorter sleep may indicate a more severe biological phenotype as proposed in Vgontzas et al., (2013), which may merit a separate targeted sleep treatment.

A number of caveats merit mention. First, self-report measures are open to bias due to the variability in response style, for example participants having a lower threshold for complaints or a more liberal response style. This is particularly relevant for PLEs (Rossi et al., 2016). Second, while actigraphy is an objective proxy measurement for sleep-wake parameters derived from long-term rest-activity patterns, overnight polysomnography is still considered the gold standard for determining an individual's total sleep time and overall sleep architecture (Krystal & Edinger, 2008). Actigraphy was selected for this model as it incorporated three weeks of data, which was deemed to be more representative of the participant's sleep habits and timing than overnight polysomnography. Third,

with smaller samples, there is an increased risk of Type II errors (Batterham & Hopkins, 2006). To combat this, model selection for this study was done based on AIC values to negate an overreliance on p-values.

These results provide a starting point for further research. Future studies should aim to test the predictive power of this model by replicating the finding across larger community samples and different groups at risk of psychosis, thereby aiming to understand if the model can be generalised - or indeed, how it differs along the affective-psychosis continuum, unbiased by pre-defined clinical categories.

Chapter 6:
A Longitudinal High-Resolution Examination of the Role of Sleep Disturbances in Paranoid and Dissociative Experiences

Following on from Chapter 5, which examined objective and subjective sleep parameters that may predict the occurrence of PLEs, this chapter aims to further discover the intricacies of the sleep-PLE relationship by using a higher resolution sampling method and longitudinal format.

6.1 Introduction

A recent study by Mulligan, Haddock, Emsley, Neil, & Kyle (2016) furthered the understanding of sleep's role in the formation of psychotic experiences by using the novel combination of both objective and subjective measures of nightly sleep periods with an experience sampling method (ESM) to investigate 'in vivo' psychotic symptoms gathered five times a day. From a sample of 22 patients with schizophrenia, 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 longitudinal study to predict psychotic symptom severity based on objective and subjective measures of nightly sleep.

There is increasing evidence to suggest that PEs are common not only in those who suffer from psychotic disorders, but also in the general population (with an estimated prevalence of 7%; Linscott & van Os, 2013; Section 1.2). This provides evidence for the notion of an "extended psychosis phenotype", i.e. the notion of a continuum of psychotic experiences that ranges from everyday experiences endorsed by the general population to chronic schizophrenia.

Based on the evident co-occurrence of SCRD and psychosis phenotypes in the general population (Section 1.11), and further to our results from Chapter 5, we hypothesised that healthy young adults with self-reported insomnia would endorse a greater number of psychotic-like experiences than those with self-reported good sleep longitudinally across a three-week period. We tested the relationship between psychosis and sleep in several ways, to understand (i) whether it is bi-directional, (ii) whether it operates in several directions because of additional domains, or (iii) whether specific aspects mediate interactions in a specific order.

6.1.1 Domains and Dimensions

Section 1.1 details the structure of psychosis, with four different domains: paranoia, grandiosity, hallucinations and thought disorder (Allardyce et al., 2007). At a subclinical level, one would not expect to see high numbers of hallucinations and delusions endorsed.

Results from the OWLS survey identified that heightened PSQI significantly increase the odds of 'cognitive disorganisation' (CD). Section 2.6.1.2 emphasised that the three items of the PQ16 which are branded as CD are also considered the core symptoms of dissociation, which are increasingly becoming of interest in psychosis research (Varese et al., 2011), and show strong ties to SCRD (Section 2.6.1.2). Given participants for this study were selected on their PSQI scores, we chose depersonalisation, derealisation and absorption (collectively branded as dissociation) and paranoia as our primary outcome measures of PEs.

Three further reasons informed the decision to select paranoia and dissociation for this study. First, they both lie on a continuum. As such, minor experiences are considered common in the healthy population (Ross, Joshi, & Currie, 1991). Given the groups in our cohort are ostensibly 'healthy', it was necessary to choose symptoms more prevalent in the general population. However, in both

paranoia and dissociation, levels of severity increase with an elevated risk for the development of psychotic disorders (Fischer & Elnitsky, 1990; McKay, Langdon, & Coltheart, 2005; Nelson et al., 2009). Second, disturbed sleep has been documented to underpin experiences of both paranoia and dissociation in both clinical and non-clinical populations which permits greater ability to interpret the findings as relevant to clinical populations (Freeman et al., 2010; Freeman, Pugh, Vorontsova, & Southgate, 2009; Kahn-Greene et al., 2014; van der Kloet et al., 2013; 2014; van der Kloet, Giesbrecht, Lynn, Merckelbach, & de Zutter, 2012a; van der Kloet, Merckelbach, Giesbrecht, & Lynn, 2012b). Furthermore, as the main focus of this study was to understand ways in which poor sleep could provoke PEs in healthy individuals, it was important to choose symptoms that have been identified as having a relationship with sleep.

Third, it has been hypothesised that dissociation and paranoia lie upon the same continuum, with dissociation as a pre-emptive state to paranoia in patients with diagnoses of psychosis. A study by Freeman and colleagues (2013) found that worry induction in psychotic patients led to the occurrence of "unreality of self", "unreality of surroundings", "perceptual alterations" and "temporal disintegration" but, importantly, did not lead to increased hallucinations (Freeman et al., 2013) . These are, however, core experiences of dissociation. A following study by Cernis et al., (2014) found that a greater endorsement of dissociative experiences was associated with higher paranoia and anxiety in psychotic patients. Furthermore, the association between paranoia and anxiety was no longer significant when controlling for dissociation. The authors concluded that the results are consistent with the view that anxiety may cause dissociation that in turn contributes to experiences of paranoia. To date, though this has been suggested in the literature, it has yet to be formally investigated which calls for the studying of the directionality of multidimensional items (Černis et al., 2014).

The purpose of this study was thus to monitor the two groups described in Section 3.3.1 (a good sleeping group and an insomnia group) for a period of three weeks and to investigate whether either objectively or subjectively poor sleep was related to the endorsement of psychotic symptoms the following day. To our knowledge, this is the first study to investigate whether insomnia renders individuals at a higher risk of psychotic experiences the following day. We added resilience to our set of daily measures as a secondary outcome measure as, to our knowledge, no study has investigated

how resilience may relate to sleep and psychotic symptoms, despite its increasing importance in mental health research and its strong relationships with functioning, wellbeing (Windle, 2010) and more recently sleep (Kohler, Chatburn, & Coussens, 2013).

In the Mulligan ESM study, the five time points were collapsed into one by taking the average across the day so that the one time point for sleep could be more easily compared to the day's experiences (Mulligan et al., 2016). As such, it was decided to extend this protocol to a period of three weeks to increase its power, whilst requiring participants to report their symptoms at just one time point per day (in the evening before bedtime reflecting upon the whole day).

This is not strictly an ESM protocol per se, but rather an online daily-diary with an extended longitudinal format of three weeks. Numerous studies to date have highlighted the mediating role of negative affect in the relationship between insomnia and PEs, so the participants were required to complete a brief daily online survey of anxiety, mood, dissociation and paranoia combined with daily completion of sleep-activity diary and the wearing of an actiwatch for the duration of the three-week period.

6.1.2 Hypotheses

In the present study we address whether insomnia sufferers are at a greater risk of PEs and whether sleep disturbance the night before predicts subsequent PEs the following day. Our hypotheses are that: (1) the insomnia group would score higher on schizotypal traits, daily dissociation and daily paranoia; (2) the insomnia group would endorse a greater number of paranoid and dissociative experiences across the three weeks; (3) following on from the results from Mulligan and colleagues (2016) and work from Chapter 5, both a combination of poor subjective sleep quality and objective sleep quality would equate to the greatest risk of PEs the following day (even when controlling for low mood and anxiety); (4) the relationship between sleep and PEs would be mediated by anxiety; and (5) in line with previous research by Freeman et al., (2013) and Cernis et al., (2014) the endorsement of paranoia would be predicted by the presence of dissociation (Černis et al., 2014; Freeman et al., 2013).

With our secondary outcome measure, we predict that: (6) both objective and subjective sleep the night before will significantly predict resiliency that day; and (7) lowered resilience will predict subsequent paranoia and dissociation.

6.2 Methodology

6.2.1 Participants and Recruitment

Please refer to Section 3.3.1.

6.2.2 Procedure and Design

Participants were asked to complete an online daily diary via LimeSurvey (Schmitz, 2012) of their mood, anxiety, paranoia and dissociation every evening before bedtime for a three-week period. Participants who had not completed their daily diary by 10pm each evening were sent an email reminder to do so by the principal investigator. Alongside the daily diary entries, participants were also asked to wear an actiwatch and complete a paper sleep diary. Finally, participants were also asked to complete their 'trait' dissociation, paranoia and resilience, depression, anxiety, schizotypal traits and psychotic-like experiences to allow for group comparisons and state-trait comparisons between measures.

6.2.3 Baseline (or Trait) Measures

Prodromal Questionnaire 16 Item Version (PQ16; Cronbach's α=0.77; Section 2.2.2.3; Ising et al., 2012).

Depression Anxiety and Stress Scale (21 Item Version, Cronbach's α=0.94; Section 2.2.2.3; Henry & Crawford, 2005).

Green Paranoid Thoughts Scale (GPTS; Cronbach's α=0.97; Green et al., 2008). The GPTS is a trait measure of paranoia. It contains 32 items that can be divided into two 16-item subscales. Part A includes items referring to ideas of social reference (e.g., 'I spent time thinking about friends gossiping about me'). Part B evaluates persecutory thinking (e.g., 'Certain individuals have had it in for me'). All items are rated on a 5-point scale, with higher scores indicating greater levels of paranoid

thinking. For both subscales, the minimum and maximum scores are 16 and 80 respectively. The questionnaire has been psychometrically evaluated in clinical and non-clinical populations. It has good internal consistency and test-retest reliability (Green et al., 2008).

Dissociative Experiences Scale II (DES; Cronbach's α=0.95). The DES-II (Bernstein, Putnam, Ross, & Torem, 1993; Carlson & Putnam, 1993) is a self-report scale of trait dissociation. It requires participants to indicate on 100 mm visual analogue scales (anchors: 0=never; 100=always) to what extent they experience 28 dissociative experiences in daily life. Van Ijzendoorn and Schuengel (1996) provide meta-analytic evidence for the sound psychometric properties of the DES (van Ijzendoorn & Schuengel, 1996).

Brief Resilience Scale (BRS; Cronbach's α=0.89; Smith et al., 2008). The BRS is used to assess resilience (as defined as the ability to bounce back from stress). There are three positively worded items (e.g., 'I tend to bounce back quickly after hard times') and three negatively worded items (e.g., 'It is hard for me to snap back when something bad happens'). The items were scored on a five-point scale from 1 (strongly disagree) to 5 (strongly agree). A review by Windle, Bennett, & Noyes, (2011) demonstrated the BRS to have good psychometric properties.

Schizotypal Personality Questionnaire- Brief Revised (SPQ-BR; Cronbach's α=0.93; Callaway, Cohen, Matthews, & Dinzeo, 2014). Schizotypal traits were assessed using the SPQ-BR. The SPQ-BR consists of 32 items organized into seven trait subscales: (1) Odd Beliefs or Magical Thinking, (2) Unusual Perceptual Experiences, (3) Excessive Social Anxiety, (4) Odd or Eccentric Behavior, (5) Odd Speech, (6) No Close Friends and Constricted Affect, and (7) Ideas of Reference and Suspiciousness. Participants responded to items using the 5-point Likert scale format ranging from 1 (strongly disagree) through 3 (neutral) to 5 (strongly agree). For each derivative score of the SPQ-BR, higher values reflect greater schizotypal trait severity. This measure has displayed good psychometric properties (Callaway et al., 2014).

6.2.4 Daily Sleep Measures

6.2.4.1 Sleep and Activity Diary

The sleep and activity diary is a self-report instrument that examines sleep patterns, adapted from the Consensus Sleep Diary (Carney et al., 2012), containing questions about sleep patterns (time of lights out and time of final awakening) and dream occurrence. Sleep quality was recorded by asking participants to circle a number between 1 and 10 in response to the question, 'How well did you sleep last night on a scale of 1 to 10 (1 being awful and 10 being excellent)?'. In order to gain insight into an individual's daily rhythms, participants were asked to report their activities throughout the day for each day in the study. Special attention was paid to noting down certain events, such as taking the watch off, turning the lights off/on, being awake in bed, taking medication, taking naps, doing very low activity tasks (e.g., reading, watching TV, or studying) or exceptionally high activity tasks (e.g., playing sports) and also if they were ill at any point. Participants were asked to complete the sleep items every morning and to keep their diaries with them throughout the day with a view to filling in their activities as and when they happen. Sleep diaries are a commonly used and valid means of collecting data regarding daily activities and sleep perceptions (Cheek, Shaver, & Lentz, 2004).

6.2.4.2 Actigraphy

Please refer to Section 3.3 for a detailed overview of the actigraphy protocol. For these analyses only TST, SOL and WASO were used to minimise the number of predictor variables in the analysis.

6.2.5 Daily Measure Questionnaires

Peritraumatic Dissociative Experiences Questionnaire (PDEQ; Marmar, Weiss, & Metzler, 1997) is designed to assess dissociative experiences that occurred following a traumatic event. Participants answer on a Likert scale (1=not at all true, 2=slightly true, 3=somewhat true, 4=very true, 5=extremely true) the degree to which they experienced depersonalization, derealisation, amnesia, out of body experiences, altered time perception and body image. The original version consists of 10 items, from which we used six non-trauma related dissociative experiences to cover each of the three core aspects of dissociative experiences (depersonalisation, derealisation and amnesia/absorption; Ross et al., 1991). These were: (1) "I had moments of losing track of what was going on. I 'blanked out' or 'spaced out' or in some way felt that I was not apart of what was going on"; (2) "I found that I was on 'automatic

pilot'. I ended up doing things that I later realised I hadn't actively decided to do"; (3) "My sense of time changed. Things seemed to be happening in slow motion"; (4) "There were moments when my sense of my own body seemed distorted or changed. I felt disconnected from my own body, or it was unusually large or small"; (5) "I felt confused; that is, there were moments when I had difficulty making sense of what was happening"; and (6) "I felt disorientated; that is, there were moments when I felt uncertain about where I was or what time it was".

Social State Paranoia Scale (SSPS; Freeman et al., 2007) has 10 items measuring recent paranoid thinking in a social situation, derived from a clear definition by Freeman and Garety (2000): the individual believes that harm is occurring, or is going to occur, to him or her and that the persecutor has the intention to cause harm. All measure items contained both elements of threat and intention (i.e., clear persecutory thinking was assessed; Freeman & Garety, 2000). Each item is scored on a 5-point scale (Do not agree – Totally agree). Higher scores indicate greater levels of persecutory thinking. In the scale, five items concerning neutral views of the people in the social situation and five items concerning positive views of the people in the social situation are dispersed. These positive and neutral items are used to form two subscales to establish the divergent validity of the State Social Paranoia Scale (SSPS), but are not considered of psychometric interest in their own right. It is helpful in understanding the estimates of divergent validity to remember that it is possible for participants to view certain experiences throughout the day negatively but others positively. It has shown good psychometric properties with both clinical and nonclinical participants (Freeman et al., 2007).

Brief Resilience Scale (BRS; Smith et al., 2008). The BRS is used to assess resilience, as defined as the ability to bounce back from stress. To evaluate how resilient people were feeling on a particular day, we edited the baseline (or trait) BRS to make it suitable for daily report. The scoring for this measure was identical to the original.

State Trait Anxiety Inventory – Short Form Version (STAI; Marteau & Bekker, 1992; Spielberger et al., 1970). The STAI is composed of 6 brief items ('I feel calm', 'I am tense', 'I feel upset', 'I am relaxed', 'I feel content', and 'I am worried'), to each of which there are four possible responses ('not at all', 'somewhat', 'moderately' and 'very much'). The responses are scored from 1 to 4, with reverse marking for items 1, 4 and 5. The scores across the six items are aggregated to provide the STAI

score. This measure has been psychometrically evaluated in clinical and non-clinical populations. It has acceptable reliability and produces scores similar to its full form (Marteau & Bekker, 1992).

6.2.6 Affect Grid (Mood)

Mood was evaluated using an affect grid, where a participant selects a box on a grid based on that which was originally designed by Russel, Weiss, & Mendelsohn (1989). Participants were given instructions to "use the following grid to rate how you are feeling at the moment. The further to the top of the grid indicates the more energy you have. The further to the right of the grid indicates the more pleasant or positive you feel." For these analyses, only the x-axis measuring how pleasant or positive the participant felt was used. The axis runs on a scale of 1 to 10, with 1 representing very unpleasant and low mood and 10 indicating very high or positive mood. As with the questionnaires, the affect grid was administered online via LimeSurvey (Schmitz, 2012).

6.2.7 Statistical Analyses

Statistical analyses were performed within the R statistical environment (R Core Team, 2012).

6.2.7.1 Psychometric Outcomes

All measures were examined for their distributional properties. With the exception of resilience and schizotypy, all measures presented with skewed distributions. As such Wilcoxon rank sum tests with continuity corrections were employed. For these skewed measures, the median (with standard deviations in brackets) and the test statistic 'W' were reported. For resilience and schizotypy, Welch's two sample t-test was employed, and means were reported (rather than medians).

p-values reported were corrected for multiple testing using the Benjamini & Hochberg correction method (Benjamini & Hochberg, 1995). This correction controls for false discovery rate, as opposed to the more commonly employed Bonferroni method, which controls for the family-wise error rate.

6.2.7.2 Modelling Analyses

To thoroughly assess the impact of both objective and subjective sleep from the night before on dissociation and paranoia the following day, we performed multivariate logistic Generalised Estimating Equation (GEE) modelling. GEE models are a multivariate regression method that

accounts for the correlation between repeated observations when analysing longitudinal data. We used GEE models because of the correlated values of the observations for participants made each day (O'Connor et al., 2009).

These models were used to estimate the probability of attainment of paranoia and dissocation given a set of predictor variables (i.e. TST, WASO, SOL, Anxiety, and Mood). The outcome measures (paranoia and dissociation) were binarised, i.e. the outcome was rendered to be 0 or 1, to account for their skewed distributions and the low number of endorsements over the three-week period. Modelling with paranoia and dissociation as continuous outcome variables leads to models that are more easily interpreted, but it also allows individuals who score highly on these outcomes to have an undue influence on the outcome. Hence, we binarised these variables using thresholds described below. Odds ratios were used to measure the effect size, are were derived by taking the exponential of the relevant GEE model coefficient.

Given the large number of possible combinations of the baseline measures for inclusion in a model, we performed model selection based upon the Quasi Information Criterion (QIC) to objectively assess the relative quality of a set of candidate models for further consideration (Pan, 2001). Automated model selection (via forward selection and backwards elimination procedures as described in Chapter 4) is not possible with GEE models. As such, candidate models were scientificallly-informed, starting with one or two predictors and then gradually increased in complexity. The QIC measures the relative quality of a collection of models and features a penalty for the model's complexity, thus discouraging overfitting. The QIC is an alternative to the more commonly used Akaike's Information Criterion (AIC), which is also used to measure the relative quality of a statistical model for a given dataset (Bozdogan, 1987). AIC cannot be applied to the GEE models described here, hence we used the QIC (Pan, 2001).

When the QIC of two models were very similar, the principal of parsimony was employed and we thus favoured the simpler model (Sober, 1981). When the model of best fit was selected, a group variable was added and the model was checked for 'biologically plausible' interactions based on our knowledge from the literature to see if these improved the model of fit. Again, the model possessing the lowest QIC went forward for further investigation.

GEE models are unable to account for missing values in the dataset; hence, we excluded all observations within a day for a participant when one of the measures was missing. This removed 28% of the responses (n=282), meaning the final number of observations for analysis was n=764.

6.3 Results

6.3.1 Participants

Please refer to Section 5.2.1.

6.3.2 Sleep and Psychiatric Measures – Group Comparisons

Differences between the good sleepers and insomnia group in the baseline psychiatric measures can be found in **Table 6.1**. Group comparisons showed the insomnia group scored significantly higher on depression, anxiety, stress, dissociation, schizotypy, psychotic-like experiences and resilience ($p<0.05$ when corrected for multiple comparisons) but not on either subscale of paranoia ($p=0.122$ for social reference; $p=0.156$ for persecution). A visual representation of these differences is displayed in **Figure 6.1**.

Measure	Good Sleepers	Insomnia Group	t/W	p
Depression (DASS-21)	1.50(2.43)	7.00(4.95)	79.0	<0.001
Anxiety (DASS-21)	1.00(1.32)	4.00(3.79)	84.5	<0.001
Stress (DASS-21)	1.00(2.63)	4.00(4.63)	117.0	<0.001
Dissociation (DES)	5.67(7.22)	10.36(13.23)	173.5	0.029
Paranoia (Social Reference; GPTS)	19.50(8.91)	24.00(12.11)	203.0	0.122
Paranoia (Persecution; GPTS)	16.00(3.28)	17.00(11.82)	215.0	0.156
PLEs (PQ16)	1.00(1.32)	3.00(2.86)	70.5	<0.001
Resilience (BRS)	3.78(0.63)	3.11(0.73)	3.26	<0.01
Schizotypy (SPQ-BR)	33.79(18.63)	49.91(18.15)	-3.01	<0.01

Table 6.1: Median/mean scores and standard deviations (in brackets), highlighting group differences in baseline psychiatric measures (n=47). All measures except resilience and schizotypy presented with skewed distributions. As such Wilcoxon rank sum test with continuity correction was employed. For these measures the median and the test statistic 'W' was reported. For resilience and schizotypy, the mean and Welch's two sample t-test were reported. p-values reported here were corrected for multiple testing using the Benjamini & Hochberg correction method.

Following from our first hypothesis, we investigated whether the insomnia group endorsed a greater number of paranoid experiences over the three weeks in the study. Despite showing no group differences in paranoia across on the GPTS (**Table 6.1**), a Wilcoxon rank-sum test showed that the insomnia group endorsed a greater number of paranoid experiences ($W=106250$, $p=0.045$) when compared to the good sleepers. The insomnia group were also found to endorse a greater number of dissociative experiences across the three weeks when compared to the good sleeping group ($W=85347$, $p<0.001$). A Wilcoxon rank sum test indicated that the insomnia group also scored significantly higher on daily anxiety ($W=90$, $p<0.001$), as well as significantly lower on daily mood ($W=400$, $p=0.001$) and resilience ($W=400$, $p<0.001$), when compared to the good sleeping group. Paranoia was no longer significant when accounting for multiple testing by adjusting p-values using the Benjamini and Hochberg method ($p>0.05$).

6.3.3 Exploration of Daily Measures

By computing serial pairwise correlations, we investigated the extent to which the daily measures were a good proxy for the trait measures. All trait measures highlighted moderate to strong correlations when compared to the state measures (please refer to **Table 6.2**).

Trait Measure	State Measure	r	p
Anxiety (DASS 21 item Version)	State Trait Anxiety Inventory (STAI)	0.39	<0.001
Dissociative Experiences Scale (DES)	Peri-traumatic Dissociative Events Questionnaire (6 items; PDEQ)	0.36	<0.001
Brief Resilience Scale (BRS)	BRS (edited)	0.33	<0.001
Depression (DASS 21 Item Version)	Mood (measured via an interactive mood grid)	-0.25	<0.001
Paranoia (GPTS)	Social State Paranoia Scale	0.26	<0.001

Table 6.2: Comparison of correlations between trait and state measures. p-values reported here were corrected for multiple testing using the Benjamini & Hochberg correction method.

Prior to exploring the third hypothesis, a priori associations were investigated between the daily measures as a check for multicollinearity and to examine trends in the data (**Table 6.3**). Daily paranoia (denoted by total paranoia count over the three weeks) had moderate correlations with anxiety, resilience, dissociation and mood, but was not significantly correlated with any of the sleep measures. Similarly, dissociation was significantly correlated with anxiety, resilience and mood.

Furthermore, dissociation was also significantly correlated with WASO. Paranoia was not correlated with any measures of sleep: neither subjective nor objective.

	TST	WASO	SOL	SS	ANX	RES	PAR	DISS
TST	-							
WASO	.14	-						
SOL	-.12	.07	-					
SS	.10	-.15	-.13	-				
ANX	.06	.08	.03	-.26	-			
RES	-.10	-.17	-.05	.18	-.66	-		
PAR	.00	.03	.03	.02	.27	-.21	-	
DISS	-.06	.12	.03	-.08	.32	-.35	.29	-
MOOD	-.03	-.07	-.01	.19	-.70	.57	-.28	-.24

Table 6.3: Correlations between the daily state measures used in the modelling analyses. TST=Total Sleep Time, WASO=Wake After Sleep Onset, SOL=Sleep Onset Latency, SS=Subjective Sleep, ANX=Anxiety, RES=Resilience, PAR=Paranoia, and DISS=Dissociation. The Bonferroni correction was applied (as a conservative correction to adjust for multiple comparisons), using a family-wise error rate (FWER) of α=0.05. Shaded cells indicate significant correlations, i.e. with $p < \alpha/m$ (where m=36 is the number of tests performed).

6.3.4 Predicting Paranoia

The paranoia threshold was set at 11 (minimum score=10). From five candidate models, the model ('Model 6') with mood, anxiety and dissociation as predictor variables resulted in the lowest QIC value, indicating the best model of fit (**Table 6.4**). The addition of neither group, nor of interaction terms, improved the fit of the model; therefore 'Model 6' was taken forward for further examination (**Table 6.5**). This model highlights mood (OR=0.81, 0.66-0.99, p=0.02), anxiety (OR=1.12, 1.01-1.23, p=0.03) and dissociation (OR=1.11, 1.02-1.20, p=0.02) to all be significant predictors of paranoia. This suggests a one-point decrease in mood would predict a 19% increase in chance that the individual would endorse a paranoid experience, assuming all other variables are kept constant. Similarly, a one-point increase in anxiety or dissociation increases the chances of a paranoid experience by 12% and 11% respectively that day, assuming all other variables are kept constant.

6.3.5 Predicting Dissociation

The modelling process was then repeated using dissociation as the primary outcome measure. Dissociation was binarised at a score of 8 or above (minimum score=7), as a score of 7 was deemed less likely to be clinically relevant. From five candidate models, dissociative symptoms were best predicted by 'Model 18' (**Table 6.4**). The addition of group as a predictor variable did not improve the fit of the model, but conversely, the addition of paranoia and an interaction term of WASO and Anxiety enhanced the model fit. 'Model 18' highlights a significant main effect of TST (OR=0.67, 0.51-0.89; $p<0.01$) and a significant interaction term for WASO and Anxiety ($p<0.05$). This suggests a one-hour decrease in TST would predict a 33% increase in chance that an individual would endorse a dissociative experience (at a score of 8 or above), assuming all other variables are kept constant. The nature of the interaction between WASO and Anxiety is displayed in **Figure 6.2**. This plot highlights the role of WASO to be most potent in the presence of high anxiety when predicting dissociative experiences.

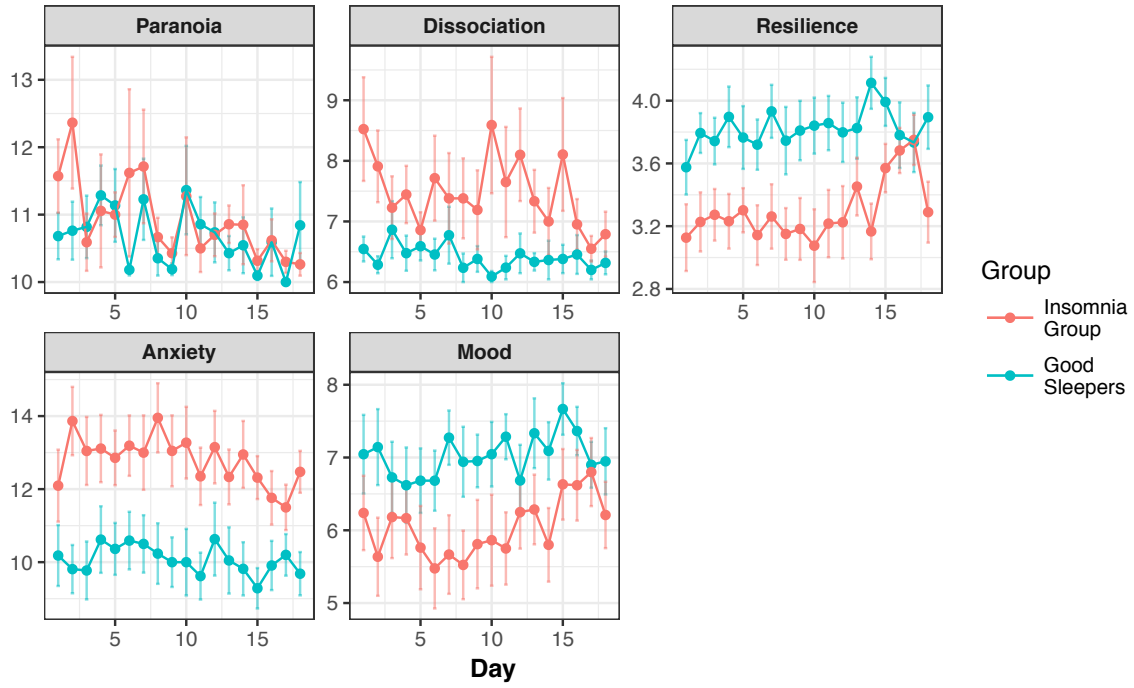

Figure 6.1: Line graphs highlighting the different daily ratings of paranoia, dissociation, resilience, anxiety and mood. The trajectories of these variables are tracked across the three-week period of the study. There appear to be discernable trends across the groups in all measures apart from paranoia.

Model	Predictor Variables for Paranoia	QIC
1	Subjective Sleep Quality	615
2	TST	614
3	**Mood & Anxiety**	**543**
4	Subjective Sleep, Mood, Anxiety, TST, WASO	546
5	Subjective Sleep, Mood, Anxiety, TST, WASO, SOL	548
Further Investigation		
6	**Mood, Anxiety and Dissociation**	**539**
7	Mood, Anxiety, Dissociation and Group	544
8	Mood, Anxiety, Dissociation, Mood*Anxiety	544
9	Mood, Anxiety, Dissociation, Anxiety*Dissociation	541
Model	**Predictor Variables for Dissociation**	**QIC**
10	Subjective Sleep Quality	505
11	TST	503
12	Mood & Anxiety	460
13	**Subjective Sleep, Mood, Anxiety, TST, WASO**	**437.7**
14	Subjective Sleep, Mood, Anxiety, TST, WASO, SOL	439.9
Further Investigation		
15	Subjective Sleep, Mood, Anxiety, TST, WASO, Group	438
16	Subjective Sleep, Mood, Anxiety, TST, WASO, Paranoia	435
17	Subjective Sleep, Mood, Anxiety, TST, WASO, Paranoia, Group	435
18	**Subjective Sleep, Mood, Anxiety, TST, WASO, Paranoia, WASO*Anxiety**	**433**
19	Subjective Sleep, Mood, Anxiety, TST, WASO, Group, Paranoia, WASO*Anxiety	434

Table 6.4: QIC estimates for Generalised Estimating Equation (GEE) models, with paranoia and dissociation as the outcome measures.

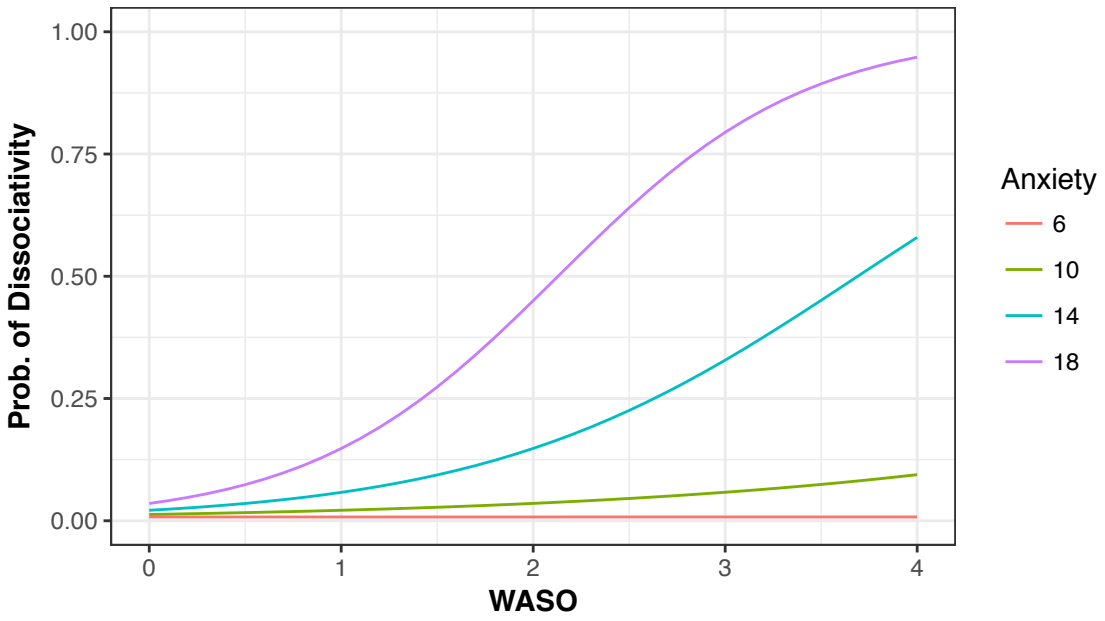

Figure 6.2: Interaction plot highlighting the relationship between WASO and anxiety. The probability of dissociative experiences is measured between impossibility (0) and certainty (1). With low anxiety (blue line), the probability of a dissociative experience is very low irrespective of WASO. However, when anxiety is very high (red line), the probability of a dissociative episode rapidly grows in the presence of high WASO.

6. Paranoia (n=167)	**Odds Ratio (95% CI)**	**β**	**SE**	**Wald**	**p**
Intercept	--	-2.56	1.18	4.68	0.03
Mood	0.81 (0.66, 0.99)	-0.21	0.10	5.95	0.02
Anxiety	1.12 (1.01,1.23)	0.11	0.05	4.91	0.03
Dissociation	1.11 (1.02,1.20)	0.10	0.04	5.15	0.02
18. Dissociation (n=115)					
Intercept	--	-3.23	2.21	2.14	0.14
Subjective Sleep	0.95 (0.78, 1.16)	-0.05	0.10	0.20	0.65
TST	0.67 (0.51, 0.89)	-0.40	0.14	8.29	0.004
Mood	1.13 (0.92, 1.37)	0.12	0.10	1.36	0.243
Anxiety	1.09 (0.88, 1.36)	0.09	0.11	0.58	0.444
WASO	0.46 (0.19, 1.93)	-0.78	0.72	1.18	0.277
Paranoia	1.09 (0.99, 1.21)	0.09	0.05	2.76	0.096
Anxiety*WASO	1.13 (1.02, 1.25)	0.12	0.05	5.10	0.024

Table 6.5: Models investigating the impact of sleep, mood and anxiety on paranoid and dissociative experiences on a daily basis. Subjective sleep quality is based on daily self-report from the sleep diary. TST=Total Sleep Time; WASO=Wake After Sleep Onset; and SOL=Sleep Onset Latency. WASO, TST and SOL are derived from the actigraphic data.

6.3.6 Predicting Total Sleep Time and WASO Duration

In order to test for reverse causality between paranoia and dissociation and sleep, we inverted the models, considering TST, WASO and following-day subjective sleep quality day as the outcome measures. For this set of models, it wasn't necessary to binarise the data, since each outcome variable was measured continuously and presented with a normal distribution. We considered 'full' models with all possible predictors (mood, anxiety, dissociation, paranoia, and objective/subjective sleep), and tested whether the addition of 'group' improved the model. **Table 6.6** shows a summary of the QIC estimates for these models, and **Table 6.7** shows the resulting final models.

Model Predictors	Outcome	QIC	QIC_g
Sub. Sleep, Mood, Anxiety, Dissociation, Paranoia	TST	1272.90	**1262.80**
Sub. Sleep, Mood, Anxiety, Dissociation, Paranoia	WASO	**344.9**	349.9
TST, WASO, Mood, Anxiety, Dissociation, Paranoia	Sub. Sleep	2806.6	**2584.0**

Table 6.6: QIC estimates for GEE models with TST, WASO and Subjective Sleep as outcome measures. QIC values are reported both with (QIC_g) and without (QIC) the covariate of group.

Our model for TST ('Model 19', see **Table 6.7**) indicated subjective sleep quality and paranoia to be significant predictors of TST obtained that night. A one-point increase in subjective sleep quality predicted a 6-minute increase in TST that night, and the endorsement of paranoia during the day predicted a 2.4-minute reduction in TST that night. Consequently, a paranoia score of 10 (which would require a participant to 'agree a little' on 10 of the 20 paranoia items or 'totally agree' on two paranoia items) would predict a 24-minute decrease in TST that night.

Our model for WASO ('Model 20', see **Table 6.7**) indicated that dissociation and subjective sleep were significant predictors of that night's WASO. A one-point decrease in subjective sleep quality would predict a 3-minute increase in WASO, and a one-point increase in dissociation equated to a 2.4-minute increase in WASO; consequently, a 10-point increase in dissociation would predict a 24-minute increase in WASO. With reference to our earlier model for dissociation, this indicates that the relationship between WASO and dissociation is bi-directional.

Predictor Variables	β	SE	Wald	p
Model 19: TST				
Intercept	6.42	0.61	109.68	<0.001
Subjective Sleep	0.10	0.04	7.89	0.005
Mood	-0.01	0.04	0.16	0.686
Anxiety	0.02	0.02	0.57	0.451
Dissociation	-0.01	0.02	0.60	0.437
Paranoia	-0.04	0.02	4.20	0.04
Group	0.33	0.19	2.73	0.10
Model 20: WASO				
Intercept	1.67	0.34	23.51	<0.001
Subjective Sleep	-0.05	0.02	5.52	0.02
Mood	-0.01	0.02	0.48	0.49
Anxiety	-0.00	0.01	0.06	0.81
Dissociation	0.04	0.01	7.44	0.0064
Paranoia	-0.01	0.01	0.17	0.68
Model 21: Subjective Sleep				
Intercept	6.85	1.08	40.09	<0.001
TST	0.23	0.09	6.33	0.0119
WASO	-0.35	0.19	3.58	0.0584
Mood	-0.05	0.05	1.22	0.2691
Anxiety	-0.13	0.04	9.34	0.022
Dissociation	0.10	0.54	3.53	0.0603
Paranoia	0.05	0.05	1.31	0.2529
Group	-1.19	0.28	17.94	<0.001

Table 6.7: Models testing for reverse causality using TST, WASO and subjective sleep quality as primary outcome measures (n=764). TST=Total Sleep Time and WASO=Wake After Sleep Onset. WASO and TST were derived from the actigraphic data.

Finally, subjective sleep quality was predicted by TST, anxiety and group ('Model 21', see **Table 6.7**), with a one–hour increase in TST score equating to a 0.23-point increase in subjective sleep quality. As subjective sleep quality is measured on a scale of 1 to 10, and a one-hour decrease in TST is a

considerable decrease in sleep, this is a not a substantial effect size. A one-point increase in anxiety would predict a 0.13-point reduction in subjective sleep quality. As anxiety varies up towards scores of 18 (see **Table 6.7**), anxiety is a much more potent predictor of subjective sleep quality compared to TST. Consequently, a 10-point increase in anxiety would result in a 1.3-point decrease in subjective sleep quality. Finally, having a general negative perception of your sleep (an elevated ISI and PSQI) predicts a 1.19-point decrease in subjective sleep quality, assuming all other variables are kept constant (**Table 6.7**).

6.3.7 Secondary Outcome Measure: Predictors for Resilience

The final step in the modelling process was to understand how sleep might relate to resilience as our secondary outcome measure. For this set of models, it was not necessary to binarise the data, given each participant reported a level of resilience each day and the data were approximately normally distributed; therefore, Gaussian models were applied. Given the significant correlation between WASO and resilience ($r=-0.17$, $p<0.01$), we added WASO as a potential predictor alongside mood and anxiety, leading to the best model of fit ('Model 25', **Table 6.8**).

Model	Predictor Variables	QIC
22	Subjective Sleep Quality	558.7
23	TST	571.0
24	Mood & Anxiety	353.0
25	**Mood, Anxiety, WASO**	**352.5**
26	Subjective Sleep, Mood, Anxiety, TST, WASO	365.4
27	Subjective Sleep, Mood, Anxiety, TST, WASO, SOL	362.0
Further Investigation		
28	Mood, Anxiety, WASO and Group	363.1
29	Mood, Anxiety, WASO, WASO*Anxiety	357.7
30	Mood, Anxiety, WASO, WASO*Mood	356.0

Table 6.8: QIC Estimates for Generalised Estimating Equation models employing resilience as the outcome measure.

This model of best fit, 'Model 25', indicates that mood, anxiety and WASO are all significant predictors of resiliency. A one-point increase in mood results in a 0.09-point increase in resilience that day, assuming all other variables are kept constant. Similarly, a one-point increase in anxiety would predict a 0.12-point decrease in resilience, and a one-hour increase in WASO the night before would predict a 0.17-point reduction in resilience the following day.

Given these findings, we return to our primary outcome measures (and our earlier models of best-fit), and test the addition of resilience as a predictor variable. **Table 6.9** indicates that the addition of resilience to our earlier 'Model 18' leads to resilience being the strongest predictor of dissociative experiences, with a one-point decrease in resilience predicting a participant to be almost three times (286%) more likely to endorse a dissociative experience (at a score of 8 or above), assuming all other variables are held constant (OR=0.35; 0.20-0.63; $p<0.001$). Furthermore, even when controlling for anxiety, mood and resilience, TST is still a significant predictor of dissociation, with a one-hour reduction in TST increasing the risk of a dissociative experience the following day by 64%, assuming all other variables are held constant (OR=0.61, 0.44-0.84, $p=0.002$). The interaction between WASO and anxiety is also still significant with the addition of resilience to the model.

Unlike dissociative experiences, we found that the addition of resilience to our model of best fit for predicting paranoia ('Model 6') was not worthwhile, with resilience not significantly predicting paranoia.

	Odds Ratio	β	SE	Wald	p
Model 25: Resilience					
Intercept		4.43	0.41	114.74	<0.001
Mood		0.09	0.03	13.01	<0.001
Anxiety		-0.12	0.02	28.16	<0.001
WASO		-0.17	0.08	4.32	0.037
Model 18: Dissociation (with the addition of resilience as a predictor)					
Intercept	--	1.71	2.56	1.09	0.505
Subjective Sleep	0.95(0.78, 1.16)	-0.05	0.10	0.24	0.624
TST	0.61(0.44, 0.84)	-0.49	0.16	9.90	0.002
Mood	1.25(0.98, 1.58)	0.22	0.12	3.10	0.078
Anxiety	0.98(0.79, 1.22)	-0.02	0.11	0.05	0.828
WASO	0.40(0.08, 1.90)	-0.92	0.78	1.42	0.234
Resilience	0.35(0.20, 0.63)	-1.04	0.29	12.60	<0.001
Anxiety*WASO	1.13(1.00, 1.27)	0.12	0.06	4.34	0.037
Model 6: Paranoia (with the addition of resilience as a predictor)					
Intercept	--	-3.07	1.53	4.06	0.044
Mood	0.80(0.67, 0.96)	-0.22	0.09	6.41	0.011
Anxiety	1.13(1.02, 1.25)	0.12	0.05	4.99	0.026
Dissociation	1.13(1.04, 1.22)	0.12	0.04	5.81	0.016
Resilience	1.12(0.83, 1.77)	0.11	0.19	0.32	0.569

Table 6.9: Summary of the model of best fit for resilience (n=722), alongside the earlier best models of fit for dissociative experiences and paranoia, now with resilience added. The dissociation model is based on a dissociative threshold of 8, and the paranoia model is based on a paranoia threshold of 11.

6.4 Discussion

In a group of 21 insomnia sufferers and 23 good sleepers recruited from Oxford, we found that insomnia sufferers endorse significantly higher levels of both paranoia and dissociation across the three week period when compared to the good sleeping group. However, when correcting for multiple comparisons, paranoia was no longer significant. The insomnia group also presented with significantly lower mood, lower resilience and higher anxiety across the three weeks. This coincided with their trait data, with the insomnia group scoring significantly higher on anxiety, lower on mood and resilience, higher on dissociation and schizotypy. Globally this adds further support to the relationship between sleep and emotional dysregulation discussed in Section 1.9.1.

With the exception of paranoia, these findings were in line with the predictions of our first and second hypotheses that the insomnia group would endorse greater dissociation across the three weeks, as well as endorse a higher number of psychotic-like experiences and schizotypal traits.

Our third hypothesis was that both a combination of poor subjective and objective sleep quality would lead to the greatest risk of PEs the following day, even when controlling for anxiety and depression. This was only partially supported by our findings. Modelling the data using both objective and subjective measures of sleep, we found that only mood, anxiety and dissociation significantly predicted the endorsement of paranoia that day. None of the sleep measures were found to predict paranoia. Conversely, TST, WASO and anxiety were all found to significantly predict dissociation, with a significant interaction between anxiety and WASO, whereby at low levels of anxiety, the effect of WASO was considerably reduced. This also partially supported the fourth hypothesis that the role of sleep disturbances in the formation of psychotic experiences would be mediated by anxiety, as it was found to be the case for dissociative experiences only.

As a secondary outcome measure, we predicted that both objective and subjective sleep would predict self-reported resilience the following day. This was only partially supported by our analyses. Heightened WASO the night before predicted a lower self-report of resilience the following day, but subjective measures of sleep did not predict subsequent resilience. We also hypothesised that lowered resilience would predict the endorsement of paranoia and dissociation that day. Again this was only

partially supported by our results. Decreased resilience increased the chances of only a dissociative experience. No direct relationship between resilience and paranoia was found.

Analyses identified the relationship between WASO and dissociation as being bi-directional, with WASO predicting dissociation the following day, and dissociative experiences that day predicting greater WASO the following night. Similarly, same-day anxiety and membership of the insomnia group were highlighted as the most prominent predictors of poorer subjective sleep quality that night. Finally, dissociation predicted paranoid experiences, but paranoia did not significantly predict dissociative experiences, which supports of the notion of dissociative experiences being considered as the mediating or precipitating symptom for psychotic experiences, as proposed by Varese and colleagues (Varese et al., 2011). Interestingly, models testing for reverse causality also highlight higher paranoia to predict lower total sleep time that night, indicating the direction of the relationship between sleep and paranoia to be uni-directional, with paranoid thoughts fuelling sleep disturbances that night, even when controlling for mood and anxiety. On the other hand, sleep itself is not predictive of paranoia the following day.

These results are also in support of those presented in Chapter 2, adding further weight to the role of dissociative symptomatology in the sleep-PLE relationship. Dissociative symptoms in the OWLS survey were the only category of psychotic symptoms to be predicted by PSQI (and were here predicted by TST and WASO). As was seen here, paranoia in the OWLS survey was primarily predicted by negative affective, but not any sleep based measures. This demonstrates that the findings and predictions made using a large community survey sample (based on self-report measures) are translatable to a smaller-sample, higher resolution, longitudinal study format which combines subjective and objective measures of sleep, adding weight to our findings here.

Taken together, these results can be combined to formulate a complex interconnected negative feedback loop that originates with objectively poor sleep and can take different paths beyond this point. As such, the relationship between objective and subjective sleep and psychotic-experiences could be described as having alternate pathways in their prediction of paranoia and dissociation (**Figure 6.3**, **Figure 6.4**, and **Figure 6.5**). This does suggest a more nuanced relationship between

sleep and PLEs than that of Chapter 5 as risk alters based on the presence of objective or subjective sleep disturbances.

The disparity in predictions made between objective and subjective sleep is quite striking. Both resilience and dissociation are uniquely predicted by objective sleep parameters (WASO and TST). Resilience itself is a strong predictor of dissociative experiences, and in turn, dissociation predicts paranoia. Conversely, subjective sleep has much stronger ties to negative affect (low mood and anxiety). This is reflected in the correlations between measures, with subjective sleep quality displaying stronger correlations with mood ($r=0.19$) and anxiety ($r=-0.26$) than with objective sleep parameters such as WASO ($r=-0.15$), SOL ($r=-0.13$) and TST ($r=0.10$, $p<0.05$). Furthermore, anxiety experienced during the day and belonging to the insomnia group were the two significant predictors of poorer subjective sleep quality experienced that night, further demonstrating the relationship between negative affect and subjective sleep quality.

A final observation to discuss is the disparity between state (daily) and trait questionnaires. Investigating group differences, we found that the insomnia group (i.e. those who self-report poor sleep quality) score higher on depression, anxiety, stress, resilience, dissociation and psychotic-like experiences. But when investigating relationships on a daily basis, we found the 'group' variable rarely improved the fit of the model. Thus on a daily basis, identifying as a poor sleeper did not predict symptoms, but reporting poor sleep that night and objectively experiencing poor sleep (higher WASO and lower TST) did significantly predict these experiences.

6.4.1 Sleep and Psychotic Experiences as Transdiagnostic Markers of Poor Mental Health

This study adds further support to the notion that insomnia is a transdiagnostic phenotype across a gamut of psychiatric disorders (Benca, Obermeyer, Thisted, & Gillin, 1992; Harvey et al., 2011). The sample used in this study would be considered "healthier" than those studied in sleep clinics, where confounds of other health problems, habits or behaviours (e.g. smoking, high BMI) make it difficult to narrow findings down to being a by-product of the sleep complaint. This study succinctly demonstrates that while the hypotheses are focused upon understanding how poor sleep may relate

to the occurrence of psychotic experiences, the insomnia group score highly on every psychiatric outcome measured (with the exception of paranoia) - not just psychotic experiences. This is unsurprising, as insomnia has been a risk factor for (preceding) the development of depression, anxiety and suicide (Baglioni et al., 2011).

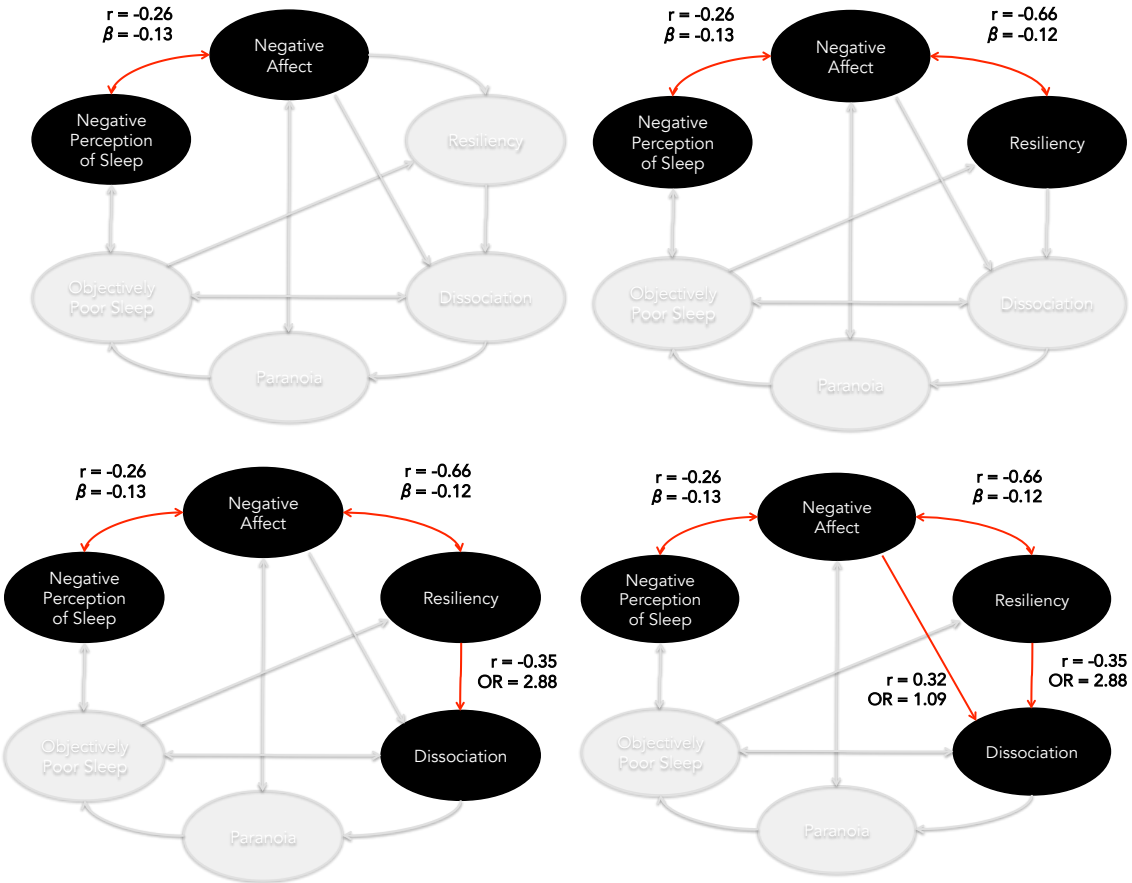

Figure 6.3: The relationship between subjective sleep and dissociative symptoms. Black arrows indicate the direction of the negative feedback loop, ultimately leading to dissociative experiences, while beginning with a negative perception of sleep. Red arrows inside the circle indicate 'shortcuts' within the system. We see that a negative perception of sleep predicts negative affect (top left), which in turn predicts resiliency (top right). Resiliency itself is a strong predictor of dissociative symptoms (bottom left). Negative affect, which is peripherally connected to dissociation via resilience, is also a direct predictor of dissociative symptoms, and can thus `shortcut' the loop (bottom right).

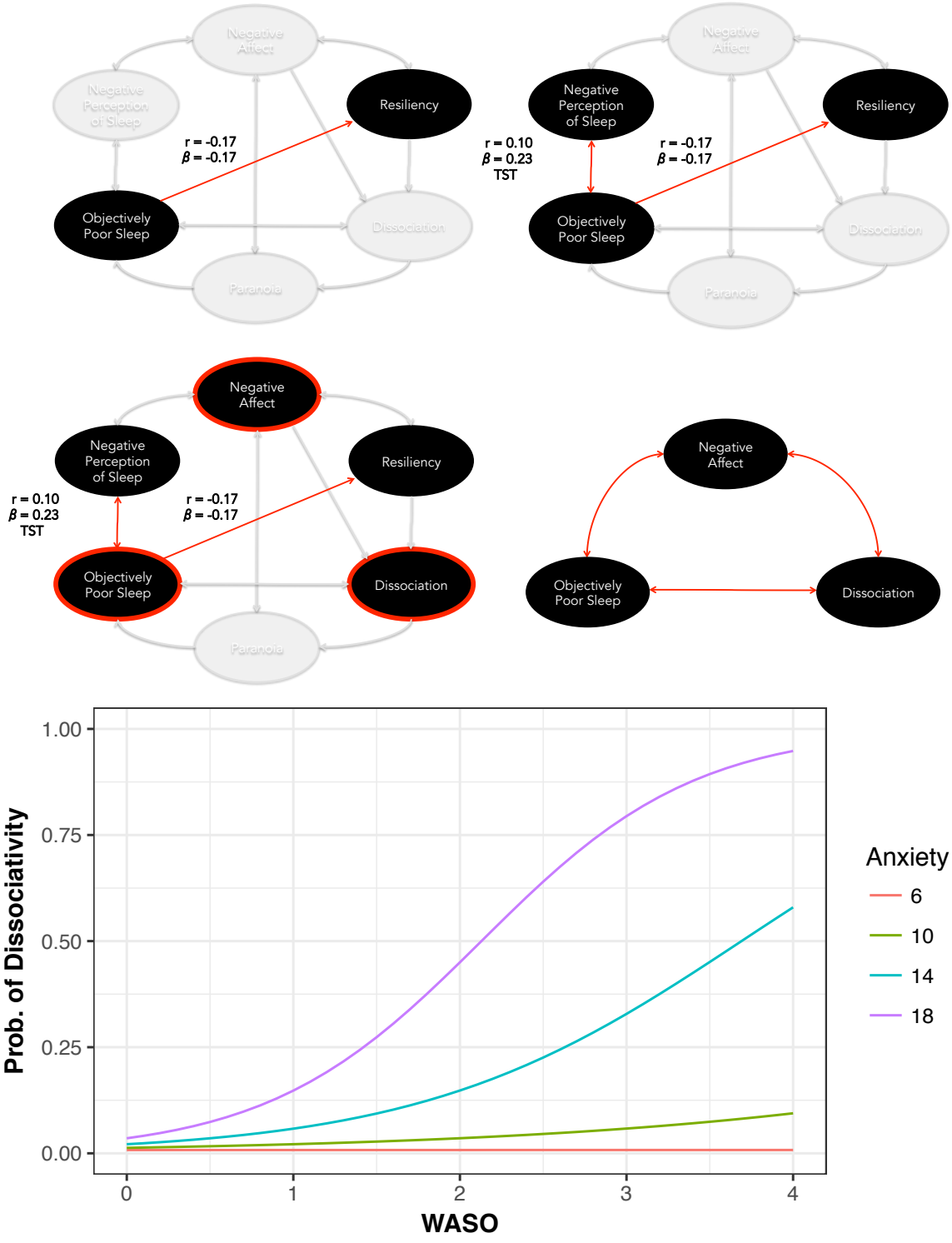

Figure 6.4: The relationship between objective sleep and dissociative experiences. While subjective measures of sleep possess stronger ties with negative affect and predict dissociative experiences through this pathway. Objectively poor sleep can 'shortcut' to predict resiliency (*top left*), which itself is a strong predictor of dissociative symptoms. Objectively poor sleep, as one would anticipate, also predicts a negative perception of sleep (*top right*). Finally, objectively poor sleep (WASO) can also shortcut the system straight to dissociative symptoms, but this relationship is mediated by anxiety (*centre left*) as demonstrated by the interaction graph above.

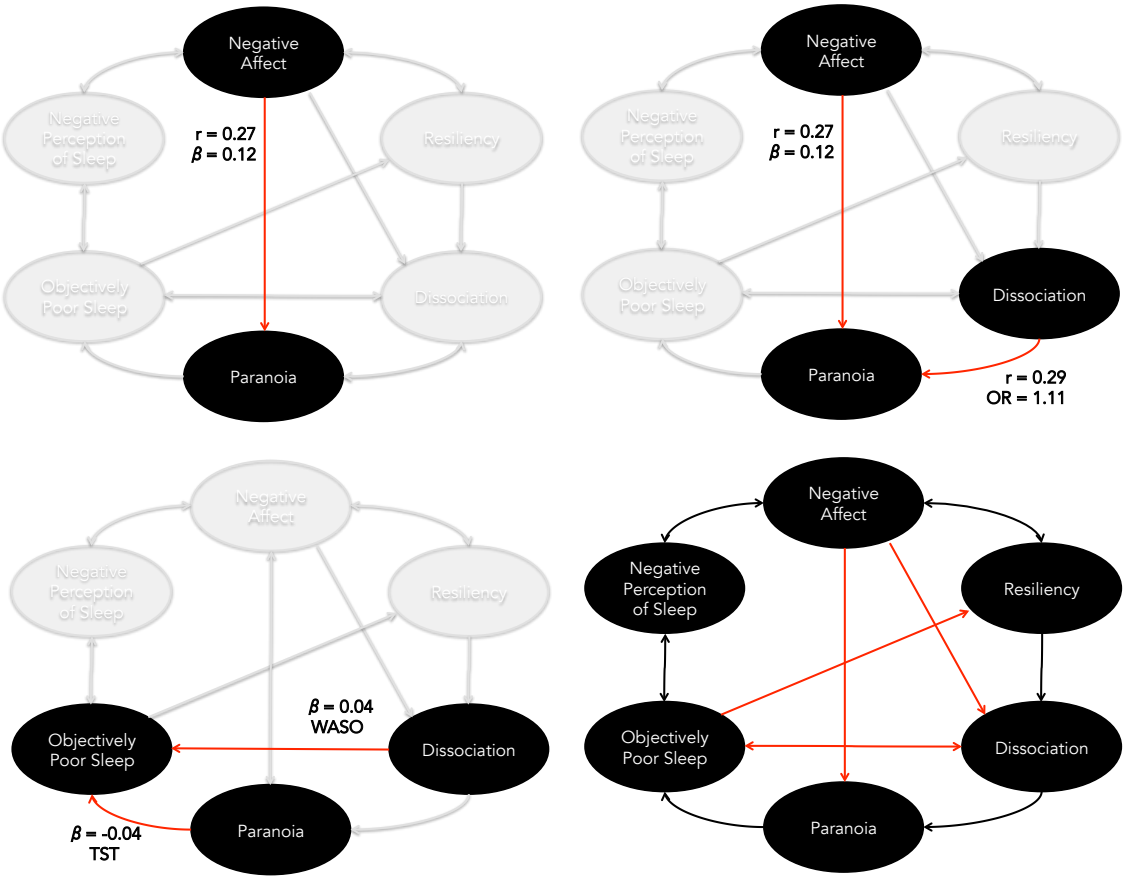

Figure 6.5: *Top left and top right:* The relationship between negative affect, dissociation and paranoia. Paranoia is predicted by negative affect, which is itself predicted by a subjective perception of sleep. Paranoia is also predicted by dissociation, which itself is predicted by WASO, negative affect and resilience (all of which have ties to sleep). Paranoia is therefore peripherally influenced by sleep, whereas dissociative symptoms appear to have more direct ties to objective fluctuations in sleep parameters.

Bottom left: The closure of the feedback loop is highlighted, with paranoid and dissociative experiences that day predicting objectively poorer sleep the following night (but not subjectively poorer sleep). This relationship was only found to be bi-directional for dissociative experiences but not paranoia. This refuels the occurrence of objectively and, indirectly, subjectively poor sleep.

Bottom right: The negative feedback loop of psychotic experiences, sleep and negative affect. Black arrows illustrate the direction of the negative feedback loop, ultimately leading to dissociative and paranoid experiences. Certain relationships are bi-directional as indicated by double-headed arrows, while others are uni-directional, as indicated by single headed arrows. Red arrows illustrate 'shortcuts' in the system predictions. Objective and subjective ("Negative Perception of Sleep") measures of sleep are inter-related as are 'Negative Perception of Sleep' / 'Negative Affect' and 'Negative Affect' / 'Resilience'. Objectively poor sleep directly predicts resilience and dissociative symptoms. A 'Negative Perception of Sleep' indirectly relates to dissociation and paranoia via stronger ties with 'Negative Affect', which directly predict the occurrence of paranoia and dissociative experiences. Dissociative experiences in turn predict paranoia. Furthermore, both dissociation and paranoia predict objectively poorer sleep the following night (but not subjectively poorer sleep). This relationship was only found to be bi-directional for dissociative experiences but not paranoia, creating a negative feedback loop refuelling the occurrence of objectively and, indirectly, subjectively poor sleep.

The relationship between sleep and psychosis cannot be reduced to poor sleep predicting psychotic symptoms; there is a highly complex hierarchical structure between these two variables. This highlights specificity in sleep's role for the formation of psychotic experiences: while the insomnia group endorsed significantly more paranoia and dissociation across the three-week period, sleep was only found to predict dissociation the following day, not paranoia. Furthermore, sleep's role became most apparent in presence of high anxiety. Paranoia was not predicted by sleep the night before but did predict sleep the following night. Relationships between anxiety, depression and insomnia are very well documented (please refer to Johnson et al., 2006) so it is likely that this is a potential pathway through which sleep could act on paranoia without holding a direct role itself. This is highlighted by the fact that poor sleepers trend on endorsing significantly more paranoid experiences throughout the three weeks of the study, along with significantly lower mood and higher anxiety.

Furthermore, paranoia was shown to correlate with resilience, which also has significant correlations with WASO. This would support the notion that sleep provides the buffer to reduce the risk of these experiences without sleep itself contributing to their formation, rather a lack of sleep can highlight inherent vulnerability. Evidence supporting this notion can be found by examining the extensive psychopathological differences between these two groups. The insomnia group, whilst only screened on their subjective sleep quality and insomnia symptomatology, show remarkable differences in their psychopathology, including significant differences in psychotic experiences, dissociation, stress, anxiety, depression and resilience. This would highlight sleep disturbances as an underlying transdiagnostic marker.

6.4.2 A Potential Role for Stress Reactivity?

It has been hypothesised that insomnia sufferers with normal sleep duration may experience adverse psychiatric outcomes (depression, for example) through psychological mechanisms; that is, via depressed mood, anxiety, intrusive thoughts and rumination. Conversely, insomnia with an objective short sleep duration may have stronger affiliations to biological mechanisms, such as hyperactivity of the HPA axis (Fernandez-Mendoza & Vgontzas, 2013). This is in part supported by our findings. We find that subjective sleep complaints have stronger ties with negative affect (high anxiety and low mood), whereas objectively poor sleep has stronger ties to dissociative experiences and resiliency (a psychometric predictor of stress reactivity and HPA axis functioning; Walker, Pfingst, Carnevali,

Sgoifo, & Nalivaiko, 2016). Furthermore, it has been suggested that stress sensitivity itself has a strong lineage in the patients who suffer from psychosis (Myin Germeys & van Os, 2007) and in those who have a genetic lineage of psychosis (Collip et al., 2011). Patients with schizophrenia have also been found to have severe objective disturbances in their sleep and circadian rhythms (Wulff et al., 2012). This is reflected in our results, as a one-point decrease in resilience almost triples the risk of a dissociative experience, even when controlling for anxiety and sleep. The role of the HPA axis in this model is further discussed in Chapter 7.

Finally, similarly to Chapter 5, our findings also corroborate the argument that insomnia with an objectively short sleep duration is the most biologically aggressive phenotype of insomnia disorder (Vgontzas et al., 2013). Objectively poor sleep leads to severe psychiatric symptomatology, but having both a negative perception and objectively poor sleep would result in the psychological (negative affect in this study) and biological (objectively poorer sleep and lowered resilience) pathways being activated. This would predict the greatest risk in experiencing both a dissociative and paranoid experience. This is further supported by the results of our analyses that reinforce the alternate paths. Outside of subjective sleep ratings, paranoia and dissociation are the strongest predictors of objectively disturbed sleep that night, whereas anxiety during the day was the only psychometric measure to predict a poorer perception of sleep that night.

6.4.3 Limitations

A number of caveats merit mention. Online daily diaries were filled out at home at varying times in the evening; as such, we have very little information about what participants were doing at the time of survey completion or what may have taken place during the day that might have impacted their answers. Participants were instructed to complete the survey at the same time each evening before they go to bed but there was heterogeneity as to when that occurred. Furthermore, the nature of the modelling described here is not well equipped for missing data, as such 28% of our data points had to be deleted from the analysis. Paranoia has been shown to be associated with sleep in previous research (Freeman et al., 2011; Kahn, Fridenson, Lerer, Bar-Haim, & Sadeh, 2014), but our results do not support the direct replication of this relationship on a daily basis (although predictors of paranoia are predicted by sleep parameters). However, this could have been due to the nature of the questionnaire, which may not assess a paranoia that is 'sleep-sensitive'.

Despite these caveats, this protocol holds the advantage of using a subsyndromal sample which is thereby free from confounds that clinical and patient cohorts carry (e.g. medication, physical health problems, changes due to changes in medication, BMI, side effects, impaired thinking, length of illness and cognitive bias due to awareness of illness; Wulff et al., 2012).

6.4.4 Conclusion

This study is unique in its approach to test whether the relationship between insomnia and psychosis can be seen bi-directionally using longitudinal high-resolution sampling. Sleep and circadian rhythm disruption in psychosis and schizophrenia has been established (and replicated) in the literature to date (Cohrs, 2008; Wulff et al., 2012). However, this is the first study to highlight evidence supporting the bi-directionality of this relationship, as well as the first study to incorporate resilience into a model to understand sleep's relationship with psychotic experiences. As such, we believe this to be both a novel and important contribution to the field. Future studies should aim to test the predictive power of this model by replicating the finding across larger community samples and different groups at-risk of psychosis, thereby aiming to understand if the model can be generalised - or indeed, how it differs along the affective-psychosis continuum, unbiased by pre-defined clinical categories.

Chapter 7:
An Investigation into HPA Axis Functioning and its Relationship to Resilience

The previous chapter investigated the ability of sleep to predict daily fluctuations in psychotic experiences. This chapter is designed to build upon the model generated and discussed in Chapter 6 with a view to incorporating the hypothalamus-pituitary-adrenal axis (HPA) functioning, a known modulator of the response to stress, into the model.

7.1 Introduction

As described in Section 1.9.2.2, the HPA axis is a major neuroendocrine system that permits adaptation to both bodily and environmental challenges through a complex hormonal cascade and regulatory negative feedback loop. The final product of this process is the release of the 'stress hormone' cortisol into the blood stream. The hormonal cascade originates in the paraventricular nucleus (PVN) of the hypothalamus, where corticotropin-releasing-hormone (CRH) is produced and released into the portal blood circulation. In parallel with CRH, vasopressin is also secreted into the portal blood. Together, CRH and vasopressin stimulate the production of adrenocorticotropic hormone (ACTH) at the anterior pituitary. By means of systemic blood flow, ACTH reaches the adrenal cortex. This incites the production and secretion of the glucocorticoid cortisol (Elder, Wetherell, Barclay, & Ellis, 2014; Fries et al., 2009). However, the secretion of cortisol is subject to a negative feedback loop, with its release signalling the inhibition of ACTH from the pituitary gland, which results in the inhibition of cortisol synthesis. This process is illustrated in **Figure 7.1**.

The SCN coordinates the HPA axis and links with the PVN of the hypothalamus, which results in the synchronisation of the time of day with neuroendocrine output (Buijs, Van Eden, Goncharuk, & Kalsbeek, 2003). This results in HPA axis activity following a distinct diurnal rhythm with repeated episodes of cortisol release that tend to be short in duration and high in amplitude (Fries et al., 2009). Cortisol production is at its highest during the second half of the night, and peaks in the early hours of the morning. After this peak, cortisol secretion engages in a continual decrease with its lowest point in the 24-hour cycle during the early hours of the night (Tsigos & Chrousos, 2002).

Overlaid on top of this distinct diurnal rhythm is a sharp increase in cortisol observed upon awakening. During this time, the level of cortisol can proliferate from anywhere between 38% to 75% above its levels upon awakening and takes approximately 30-45 minutes to reach this peak (Fries et al., 2009). This trend is labelled the Cortisol Awakening Response or CAR. Whilst the exact function of the CAR is still unclear, it is incrementally used as an index of HPA axis 'reactivity' which correlates with numerous psychosocial stress variables, health states and other stress responses (Clow, Thorn, Evans, & Hucklebridge, 2009; Schmidt-Reinwald et al., 1999). An individual's CAR may not only represent state-dependent anticipatory expectations of the upcoming day (Fries et al., 2009) but also a developmental sensitisation to stress during childhood (due to adverse experiences/dysphoric episodes) heightening an individual's reactivity to stress as an adult (Laurent, Gilliam, Wright, & Fisher, 2015).

Unlike other indicators of the HPA axis, cortisol (and the CAR) can be reliably measured in saliva with similar levels to those that are observed in plasma. Furthermore, it is present in approximately 73-77% of people and possesses moderate to high levels of intra-individual stability across two consecutive sampling days ($r=0.63$; Chida & Steptoe, 2009). This renders salivary CAR both an identifiable and reliable non-invasive proxy measurement of HPA axis activity and functioning, making it an increasingly more popular biomarker for research laboratories to employ (Wetherell et al., 2006).

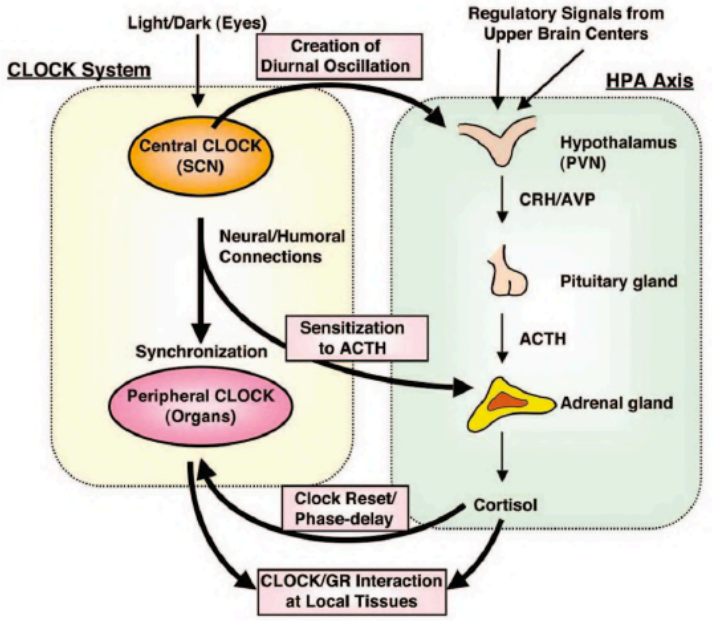

Figure 7.1: Cortisol synthesis and its relationship to the master clock. This figure is taken from Kassi & Chrousos (2013). The right hand side (green shading) highlights the process of cortisol synthesis. CRH is produced in the PVN. CRH and vasopressin (AVP; which is produced in parallel) are released into the portal blood circulation, which stimulates the production of ACTH at the anterior pituitary. Systemic blood flow allows ACTH to reach the adrenal gland, which initiates the production and secretion of cortisol. This process forms part of a negative feedback loop that subsequently inhibits ACTH from the pituitary gland, thus inhibiting cortisol synthesis.
The left hand side (yellow shading) demonstrates how the suprachiasmatic nucleus (SCN) orchestrates the daily diurnal rhythm of cortisol synthesis via efferent connections between the SCN to the CRH/AVP –containing neurons located in the PVN. The SCN also modulates sensitivity to ACTH via splanchnic nerve innervation to the adrenal medulla (by the action of epinephrine and other possible mediators). Peripheral clocks regulate the effects of glucocorticoids in local tissues through interaction between the CLOCK-related genes (Clock/Bmal1) and the glucocorticoid receptors (GR) forming part of the counter-regulatory feedback loop on the HPA axis. This is bi-directional, as synthesized glucocorticoids also act on the master clock to reset and phase-delay circadian rhythm through the expression of CLOCK-related genes (Kassi & Chrousos, 2013).

Despite the extensive amount of research into the CAR, knowledge of its role in sleep medicine 'is still in its infancy' (p.215, Elder et al., 2014). To date, it is not yet certain whether the CAR is related to either sleep duration or sleep disturbances. Self-reported short sleep duration has been associated with a steeper CAR in a large cohort of participants (n=2,751; Kumari et al., 2011). However, conflicting results have been reported with objective measures of sleep (please refer to Zhang et al., 2011). Furthermore, there are only three studies to date that examine the cortisol profile of insomnia patients; only one of these studies examines the CAR specifically (but only for 15 minutes after awakening; Backhaus et al., 2004). The earliest study is that by Vgontzas and colleagues (1997) who examined the 24-hour urinary cortisol in a small cohort of young insomnia sufferers (n=15). The results indicated that urinary free cortisol levels held a strong positive correlation with the amount of wake after sleep onset (WASO) experienced, suggesting both a disturbance in the HPA axis activity in

an insomnia cohort and that this disturbance was strongly related to the presence of disturbed sleep. This study had no control group, so it is not possible to reliably distinguish if the observed effects are indeed unique to an insomnia cohort or equally present in the healthy population (Vgontzas et al., 1998).

Following on from this, a study by Riemann et al. (2002) compared 10 drug-free patients suffering from insomnia with 10 age- and gender-matched healthy controls. All participants spent three consecutive nights in the laboratory, with polysomnography on the final night, and measurement of cortisol taken from 19:00h to 09:00h. No significant differences in the cortisol profile between insomnia patients and healthy controls were reported. More recently, Backhaus et al., (2004) examined the cortisol profile of insomnia patients compared to healthy controls for one week, with samples being taken upon awakening, 15 minutes post awakening and again before bedtime. They found the insomnia group (n=14) to have a blunted cortisol response upon awakening when compared to controls (n=15) but this was no longer evident at 15 minutes post awakening (Backhaus et al., 2004). These studies offer the advantage of having repeat samples, and two were conducted in a sleep laboratory, offering greater control over confound variables. However, they suffer from small sample sizes, and none of them routinely set out to examine the CAR specifically.

More generally, across numerous different conditions including cardiovascular, autoimmune, atopic, allergic and psychiatric disorders, a blunted CAR has been observed when comparing patients to healthy controls (Fries et al., 2009; Kudielka & Kirschbaum, 2003). Focusing specifically on psychopathology, this blunting has been observed in PTSD (Wessa, Rohleder, Kirschbaum, & Flor, 2006), depression (Stetler & Miller, 2005) and in those who are at 'ultra-high risk' for psychosis (Day et al., 2014). Due to its prevalence across various conditions, a 'blunted' CAR could be considered a transdiagnostic marker of poor mental health. Notably, however, conflicting results revealing an increased CAR have been reported for bipolar disorder (Deshauer et al., 2003) and in depressed patients (Bhagwagar, Hafizi, & Cowen, 2005). This may be as a result of the subtypes within these disorders, reflect differences in psychotropic medication, reflect underlying circadian phase misalignment (Kassi & Chrousos, 2013), or reflect how heterogeneous diagnostic categories are generally (Fries et al., 2009).

Thus, the goal of this study is to examine the CAR in our cohort of people, who either self-report as good sleepers, or have attenuated insomnia (refer to Section 3.3.1 for further details on the cohort). Previous literature on the CAR has highlighted that it is sensitive to variation in both age and gender (Almeida, Piazza, & Stawski, 2009). Controlling for this, our cohort is age and gender matched. Furthermore, CAR collection can be confounded in patient populations by comorbid medical problems, smoking status and variance in medication taken (Clow et al., 2009). To control for this, we compare our 'healthy' attenuated insomnia cohort to self-reported good sleepers, as described in Section 3.3.1.

Therefore, this study seeks to help clarify the presence of underlying differences in HPA axis activity (as measured via the CAR) in a young, 'healthy', age and gender control matched insomnia cohort, with a larger sample than previously examined: marking it the first study of its kind (Almeida et al., 2009). Furthermore, as was highlighted in the previous chapter, our attenuated insomnia group demonstrates higher scores across a number of different psychiatric symptoms including depression, anxiety, stress, dissociation and psychotic-like experiences. This study should therefore help clarify if a blunted CAR response is indeed an underlying difference in HPA activity that transcends different psychopathological diagnostic categories.

At least one recent study also suggests that the CAR might be related to the development of daily psychiatric symptoms. A case study by Stalder, Evans, Hucklebridge, & Clow (2010) examined the CAR for 50 consecutive days and showed that approximately 22% of the intra-individual variance in the CAR was explained by the prior day levels of mood (sadness/happiness) and anticipations/stress related to the current study day's activities. As a secondary outcome measure, we wish to further Stalder's work, examining the relationship between prior and prospective state measures and the CAR across a larger cohort of good sleepers and attenuated insomnia sufferers, with a view to helping understand how the HPA axis could be involved in the development of psychiatric symptomatology. This will help to inform whether HPA axis functioning could be an important component of the model of paranoia and dissociation discussed in Chapter 6.

Taken together, there are four hypotheses for this study:

(1) Based on the work by Backhaus et al., (2004), we predict that insomnia sufferers will have a significantly lower mean cortisol concentration for the first sample upon awakening when compared to the good sleepers.

(2) There will be significantly more variability in the CAR (as denoted by AUC_I and AUC_G – see Section 7.2) in the good sleeping group when compared to the insomnia group, denoting greater flexibility in the HPA axis.

(3) We have previously demonstrated that the insomnia group in this cohort display elevated scores of depression, anxiety, stress, dissociation and psychotic experiences. Given the array of literature on the blunting of the cortisol awakening response in different psychiatric populations, we predict there will be a significant blunting in the CAR response in the insomnia group when compared to the good sleeping group. Such blunting, if observed, would reflect the psychopathological differences between groups.

(4) Following on from the work of Stalder et al. (2010), we predict that prior anxiety and resilience will predict CAR and that CAR will be predictive of anxiety and resilience experienced that day, with a higher CAR denoting lower levels of anxiety and a higher resilience.

7.2 Methodology

7.2.1 Participants

The same cohort of subjects was used as from Chapter 3 onwards. Please refer back to Section 5.2.1 for descriptive statistics for each of the groups.

7.2.2 Procedure

The CAR collection was conducted in the participants' own homes to allow for a more naturalistic reflection of the CAR. The participants collected eight saliva samples on two self-selected days throughout the three-week study. Where possible, participants were asked to choose two consecutive days where they had no pressing commitments in the morning. Specifically, they were instructed to

choose mornings where they were permitted to stay in bed for the 60-minute collection period, with a view to gathering a CAR representative of that individual in a relaxed frame of mind. On collection mornings, participants were advised to collect immediately after awakening (T1) and then at 15-minute intervals for the three subsequent samples, resulting in four samples in total over a 45-minute period. Participants were advised to refrain from smoking and consuming alcohol the night before the collection morning. During the collection period, participants were also asked to refrain from eating, drinking liquids other than water (such as juice or caffeine) and brushing their teeth so as not to impact the cortisol concentration levels.

7.2.3 Cortisol Assays

For the assessment of cortisol estimates a radioimmunoassay was employed (adapted from Riad-Fahmy, Read, Gaskell, Dyas, & Hindawi, 1979; Seth & Brown, 1978; sensitivity: low=2.9 nmol/L ± 0.3 CV=11.9%; medium=16.3 nmol/L ± 0.9 CV=5.8%; high=45.8 nmol/L ± 2.6 CV=5.7%). The staff responsible for assaying the cortisol were blinded to the group allocations of each of the participants. The duplicate mean cortisol concentration was used in all analyses (Backhaus et al., 2004; Clow et al., 2009).

7.2.4 Measurement of the CAR

The CAR can be measured in several ways. For the purposes of this study, we examine the secretion of cortisol over the CAR period (one hour), which is expressed as in units of AUC or Area Under the Curve. This can be calculated in two ways, both of which are employed in this study. First, AUC can be examined with respect to zero, giving the 'Area Under the Curve Relative to Ground' or AUC_G. This gives a total measurement of the CAR output over the hour. Second, the 'Area Under the Curve with respect to Increase' or AUC_I can be examined by calculating the differences in increase between the first sample and all subsequent samples. Similar to AUC_G, AUC_I provides a measure of CAR output. The AUC_I is more reflective to the changes of the CAR across time but is very sensitive to the first measurement of cortisol. As such, both AUC_I and AUC_G will be reported upon in this study. For further information about the calculation the AUC_I and AUC_G, we refer the reader to the work of Fekedulegn and colleagues: all of the procedures employed here, including equations and calculation techniques, were based upon those they report (Fekedulegn et al., 2007).

7.2.5 Daily State Measures

Please refer to Section 6.3.3 for a detailed overview of each of the daily state measures used in this protocol.

7.2.6 Analysis

The different parameters of cortisol (AUC_I, AUC_G, variability in AUC_I, variability in AUC_G, and the level of cortisol present at the first time point) were examined for their distributional properties. Variability parameters were calculated using the differences in AUC_I and AUC_G between the two sampling days for each participant. Absolute values were taken, as negative values were not important in this context.

All of the cortisol measurements displayed non-normal distributions; therefore, non-parametric tests were employed to examine cortisol differences between the insomnia group and the good sleeping group. Group differences in AUC_I, AUC_G and variability parameters were determined by the non-parametric equivalent of the independent samples t-test: the Wilcoxon rank sum test (with continuity correction).

Statistical analyses were performed within the R statistical environment (R Core Team, 2012). For the linear mixed model analyses, the package 'lme4' was employed. A priori examinations of the distribution of the outcome measures took place before any analyses were conducted in order to ensure the correct analysis technique was selected. Where there were non-normal distributions, the models or hypothesis tests chosen were adjusted accordingly.

7.3 Results

Figure 7.2 highlights the CAR of the insomnia group when compared to the good sleepers. The change in the CAR response across time points seems to show a different trend across the two groups. At awakening, the insomnia group displays heightened mean cortisol concentration, which then appears to become level off to that of the good sleeping group. However, analyses of group differences in AUC_I showed that the difference in the trends of the two groups was not statistically

significant (W=1100; p=0.71). There were high levels of variability and overlap between groups, as demonstrated by the error bars in **Figure 7.2**. The difference in AUC_G between groups was also not statistically significant (W=970; p=0.70). The variability in AUC_I was higher in the insomnia group when compared to the good sleepers, but this again was not significant (W=220, p=0.72). Similar findings were obtained with the variability in AUC_G, with insomnia sufferers displaying more variable AUC_G compared to good sleepers, but again not significantly so (W=180, p=0.26). These results are summarised in **Table 7.1**.

Finally, previous literature on cortisol in insomnia shows that the first measurement of cortisol concentration upon awakening is significantly lower compared to healthy controls (Backhaus, et al., 2004). We examined to see if the data could support this finding. However, a Wilcoxon rank sum test highlighted no significant differences in the first measurement of cortisol between the insomnia group (mean ± standard deviation: 10.42±5.74 nmol min/L) and the good sleepers (9.67±4.77 nmol min/L; W=930, p=0.50).

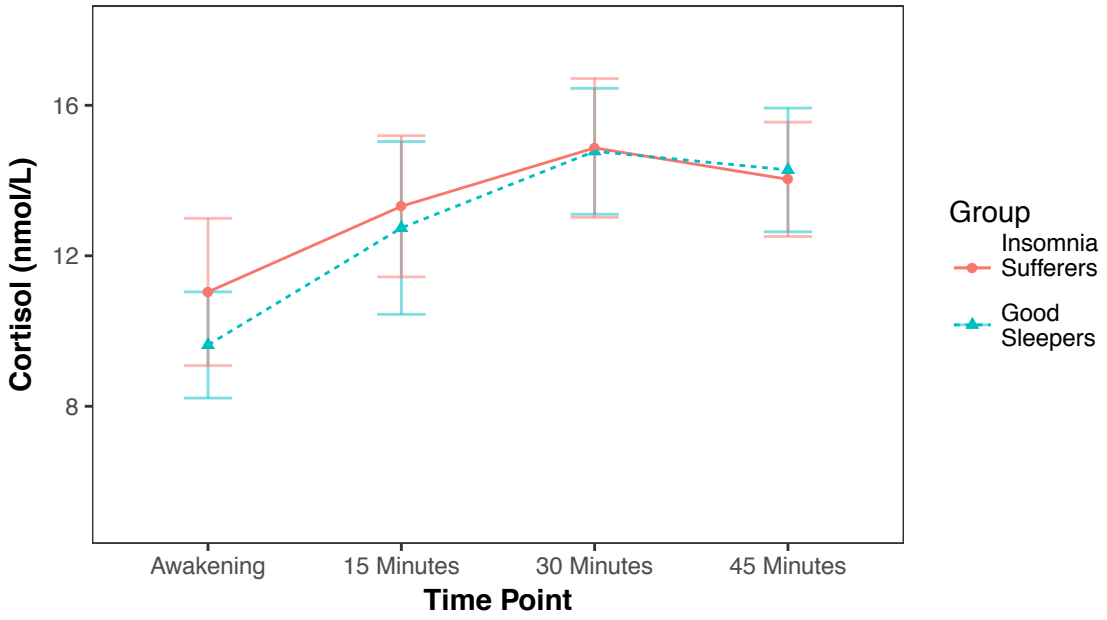

Figure 7.2: Cortisol awakening response for insomnia sufferers and good sleepers (n=45). The group mean cortisol concentrations, averaged at each time point across the two sampling days, are represented by the central dots. The vertical bars represent the standard error of these means. The insomnia group displays elevated cortisol at awakening, which appears to level off at time point two. The error bars highlight a high level of variability and overlap between groups. As such, this trend was not significant (W=1100, p=0.71).

	Insomnia Group (n=23)		Good Sleepers (n=22)		
	Median	Mean (SD)	Median	Mean (SD)	p
At Awakening	9.60	10.42 (5.74)	8.70	9.67 (4.77)	0.50
AUC_I	135.60	132.80 (151.80)	134.20	158.50 (156.89)	0.71
AUC_G	623.00	630.00 (279.20)	586.00	595.00 (265.00)	0.70
Variability in **AUC_I**	119.20	152.00 (110.88)	101.20	142.10 (112.37)	0.72
Variability in **AUC_G**	121.50	232.20 (228.10)	96.00	150.60 (157.83)	0.26

Table 7.1: Differences in cortisol measurements between insomnia sufferers and good sleepers (n=45). Two participants were excluded from the first three cortisol measurements, due to non-compliance (n=1) or an insufficient sample (n=1). Four participants were excluded from the cortisol variability measurements, due to non-compliance (n=1), an insufficient sample (n=1), or presenting differences in cortisol more than three standard deviations above the mean (n=2).

7.3.1 Impact of Objective and Subjective Sleep, Self-Reported Negative Affect, and Resilience on CAR

Results reported by Stalder et al., (2010) highlighted 22% of the intra-individual variance in the CAR was explained by the prior day levels of mood (sadness/happiness) and anticipations/stress related to the current day activities. As such, we wished to investigate if negative affect from the day before and sleep from the prior night impacted the CAR the following morning. A total of six participants were excluded from these analyses, due to non-compliance (n=1), malfunctioning acti-watches (n=2), insufficient cortisol sample (n=1) or missing data (n=2).

We used linear mixed models to predict mean AUC_G and AUC_I the following morning. Possible predictor variables for these models included group membership (insomnia or good sleeping group), TST and WASO (as measured actigraphically the previous night), subjective quality of the previous night's sleep (measured using the daily sleep diary), and self-reported anxiety and resilience the previous day.

Model selection was performed using a forward selection process, which is a standard procedure (see Section 2.2.4 for further details). Our baseline model featured a random factor for 'subject', to account for the repeat outcome measurements (two observations per participant – one for each of

the two collection mornings), and for the high amount of variability within each participant across collection days.

A summary of the iterative forward selection modelling process is presented in **Table 7.2**. Prior-day self-reported resilience was the only predictor variable to produce a drop in AIC value in the prediction of following-morning AUC_G (from 838.38 to 836.08) and AUC_I (from 796.24 to 794.54). This addition offered a significant improvement for AUC_G ($p=0.029$) and was just on the threshold for AUC_I ($p=0.054$). Exploration of the AUC_G model highlighted resilience the day before was found predict a lower AUC_G the following day ($\beta=-89.82$, $SE=40.33$), which would suggest that a 1-point increase in self-reported resilience predicts a 89.82 decrease in AUC_G the following morning.

Baseline Model	New Predictor	AIC_b	AIC_n	p
AUC_G				
Subject	Group	838.83	839.61	
	TST	838.83	840.78	
	WASO	838.83	840.52	
	Anxiety	838.83	840.79	
	Subjective Sleep	838.83	840.36	
	Resilience	838.83	**836.08**	**0.029**
AUC_I				
Subject	Group	796.24	797.48	
	TST	796.24	797.73	
	WASO	796.24	798.01	
	Anxiety	796.24	798.20	
	Subjective Sleep	796.24	798.03	
	Resilience	**796.24**	**794.54**	**0.054**

Table 7.2: Summary of forward selection modelling process for prediction of following morning AUC_G and AUC_I ($n=60$). Note that AIC_b is the model AIC for the baseline model, AIC_n is the AIC for the new (proposed) model, and Subject is the Participant ID (the random factor for these models).

7.3.2 Impact of CAR on the Prediction of Anxiety and Resilience

Next, we repeated the modelling process with anxiety and resilience as primary outcome measures. The CAR from that morning was now used as a predictor variable for these outcomes, although it wasn't possible to use both AUC_I and AUC_G as predictor variables due to concerns with multicollinearity. We proceeded with the AUC_I as it identifies the changes in the CAR over time with respect to the baseline measure. All significance testing was corrected for using the Benjamini Hochberg correction technique, which corrects for a false discovery rate as opposed to the family-wise error rate employed by the most commonly employed correction methods, such as the Bonferroni correction method (Benjamini & Hochberg, 1995).

A summary of the iterative forward selection modelling process is presented in **Table 7.3**. For our linear mixed models to predict anxiety, drops in AIC were observed with the addition of same-day mood ($p<0.001$), subjective quality of the preceding night's sleep ($p=0.026$), and group ($p=0.011$). Despite a one-point decrease in AIC, the addition of AUC_I was not found to significantly improve the model ($p=0.072$). For our linear mixed models predicting resilience as the primary outcome measure, drops in AIC were observed with the addition of same-day anxiety ($p<0.001$) and AUC_I ($p=0.028$). The addition of mood resulted in a two-point drop in AIC, but this was not found to significantly improve the model fit ($p=0.072$).

Summaries of the resulting linear mixed models for predicting anxiety and resilience can be found in **Table 7.4**. We can see that the best predictors of the endorsement of anxiety during the day were same-day mood ($\beta=-1.05$, $SE=0.117$), subjective sleep quality from the previous night ($\beta=-0.325$, $SE=0.167$) and group ($\beta=2.237$, $SE=0.752$). These estimates suggest a one-unit increase in mood would predict an average 1.05-unit decrease (of a possible maximum of 24) in anxiety, assuming all other factors are kept constant. Similarly, a one-unit decrease in the self-reported previous night's sleep quality would incur an average 0.325-point increase in anxiety the following day; thus, a five-point decrease in subjective sleep quality would predict a 1.625-point increase in anxiety, assuming all other variables are kept constant. The average group difference in anxiety is approximately 2.2, suggesting a member of the insomnia group would report anxiety on average 2.2 units above an otherwise perfectly equivalent member of the good sleeping group.

Baseline Model	New Predictor	AIC_b	AIC_n	p	p_{adj}
Anxiety					
Subject	Mood	320	278	<0.001	<0.001
Subject, Mood	TST	278	278		
Subject, Mood	Resilience	278	278		
Subject, Mood	Sub. Sleep	278	274	0.015	0.026
Subject, Mood, Sub. Sleep	WASO	274	276		
Subject, Mood, Sub. Sleep	Group	**274**	**268**	**0.0051**	**0.011**
Subject, Mood, Sub. Sleep, Group	AUC_I	268	267	0.063	0.072
Resilience					
Subject	Anxiety	136	122	<0.001	<0.001
Subject, Anxiety	WASO	122	123		
Subject, Anxiety	Sub. Sleep	122	123		
Subject, Anxiety	Mood	122	120	0.072	0.072
Subject, Anxiety	TST	122	122		
Subject, Anxiety	AUC_I	**122**	**118**	**0.020**	**0.028**
Subject, Anxiety, AUC_I	Group	118	120		

Table 7.3: Summary of forward selection modelling process for prediction of self-reported anxiety and resilience using group, same-day mood, resilience and CAR, and last-night sleep quality as predictor variables (n=60).

Outcome Variable	Predictors	β	SE	t
Anxiety	Intercept	18.934	1.74	10.90
	Mood	-1.048	0.117	-8.95
	Subjective Sleep	-0.325	0.167	-1.95
	Group	2.237	0.752	2.98
Resilience	Intercept	4.68	0.28	16.81
	Anxiety	-0.11	0.02	-4.40
	AUC_I	0.001	0.000377	0.66
	Group	0.151	0.227	0.66

Table 7.4: Linear mixed models for resilience and anxiety (n=60). In both models, subjects were specified as a random factor to control for their associated intraclass correlation (please see Oberauer & Kliegl, 2006).

Similarly, the best predictors of perceived resilience (based on our linear mixed effect model in **Table 7.4**) were same-day anxiety (β=-0.11, SE=0.02), AUC_I that morning (β=0.001, SE<0.001) and group (β=0.151, SE=0.227). These estimates suggest that a one-unit increase in anxiety would predict a 0.11-point decrease in resilience; that when compared to the insomnia group, belonging to the good sleeping group would predict an average 0.151 increase in perceived resilience; and finally, that a one-unit increase in AUC_I would predict a 0.001-point increase in resilience that day. However, as AUC_I varies within the hundreds (SD=151 for the insomnia group, and 156 for good sleepers), a one-unit variation is not particularly insightful. Rather, an increase in AUC_I by around one standard deviation would be predicted to lead to a 0.15-point increase in resilience that day. Given that the resilience outcome is an average score from a six- item questionnaire, the magnitudes of these effects are plausible.

7.4 Discussion

This chapter had four core hypotheses. First, based on the work by Backhaus et al., (2004), we predicted that insomnia sufferers would have a significantly lower mean cortisol concentration for the first sample upon awakening when compared to the good sleepers. We found no evidence to support this in our sample, as the difference between groups in mean cortisol for the first measurement was not found to be significant. This could be in part related to low power, but is more likely related to the large amount of inter and intra-group heterogeneity.

Second, we predicted there would be significantly more variability in the CAR in the good sleeping group when compared to the insomnia group. When taking the difference in AUC_I and AUC_G between the two sampling days for each participant and comparing groups, we found no evidence to suggest increased variability in the good sleeping group.

Third, based on results from the previous chapter investigating the differences in psychiatric profile between the good sleeping and the insomnia group, we predicted there would be a blunting in the CAR response in the insomnia group when compared to the good sleeping group, potentially highlighting the underlying psychopathological differences between the groups. We found no

evidence to suggest that the CAR profile or trajectory was different between groups, again most likely due to the large amount of heterogeneity between groups.

Finally, we investigated whether the CAR would be predictive of self-reported anxiety and resilience endorsed that day, with a higher AUC_I denoting lower anxiety and higher resilience that day. This was only partially supported by our results, with an increase in CAR in the morning significantly predicting an increase in resilience that day. No relationship with CAR and self-reported anxiety was found. We also investigated whether this relationship could be considered bi-directional, i.e. does self-reported anxiety or resilience the day before predict an increase in AUC_I or AUC_G the following day, with a view to furthering the results reported by Stalder et al. (2010). We did find evidence to support a bi-directional relationship between resilience and the CAR. Higher resilience the day before predicted a lower CAR at baseline (AUC_G) the following morning. However, a sharper curve (i.e. greater change in the CAR throughout the sampling period) predicted higher resilience that day. This is the first study to highlight a bi-directional temporal dynamic between cortisol and resilience on a daily basis. This also does coincide with the literature in that high levels of cortisol are seen in response to stress experimentally in people who are less resilient or who are put in stressful environments and circumstances (for a review, refer to Dickerson & Kemeny, 2004). However, a blunted cortisol response has been found to be associated with numerous psychopathologies (as mentioned in Section 7.1), which would imply lowered resilience.

We failed to replicate the results of Backhaus et al. (2004), who reported a significant difference in the first measurement of cortisol between an insomnia and control group. This is unlikely to be the result of a lack of power given the original sample reported upon in the Backhaus study consisted of just 14 insomnia patients and 15 healthy controls (as opposed to 21 insomniacs and 23 good sleepers in the current study). They did, however, repeat the cortisol collection for seven consecutive days for each group, which gives a much higher number of samples collected per person. Also, we used a subclinical or attenuated insomnia group, so it may be that these differences in HPA-axis functioning are not yet apparent at the threshold selected for this study. Taken together, the extensive heterogeneity denoted by large amounts of standard error within each group suggests that there are no distinguishable differences in cortisol profile between the two groups.

However, we did find that AUC_I was a significant predictor of self-reported resiliency that day, with a higher AUC_I (or increase with respect to baseline) predicting a higher endorsement of resilience. This relationship was found to be bi-directional as resilience both influences and is influenced by AUC_G and AUC_I respectively. Resilience, as measured in this context using the 'Brief Resilience Scale', is the ability to bounce back or adapt to daily adverse life events (Simeon et al., 2007). Recently, there has been an increasing interest in resilience research to attempt to identify biomarkers which may underpin its presence (Walker et al., 2016).

Three core studies were identified which examine the CAR as a biological determinant of resilience (for a review please refer to Walker et al., 2016). First, a study by Ruiz-Robledillo et al. (2014) examined the parents of children with a diagnosis of an Autism Spectrum Disorder (ASD) as exemplary of a cohort who engage in constant psychological strain. When the researchers split the cohort into high, medium and low levels of self-reported resilience (determined by the Brief Resilience Coping Scale; BRCS), they found that those who reported themselves as having low resilience demonstrated significantly higher levels of cortisol in the CAR when compared to children in the medium or high group (Ruiz-Robledillo, De Andrés-García, Pérez-Blasco, González-Bono, & Moya-Albiol, 2014). Second, a study by Inslicht et al., (2011) found in a large cohort of police officers (n=296) that an increase in the CAR at baseline measurement (during training academy before critical incident exposure) was predictive of greater peritraumatic dissociation and acute stress disorder symptoms across the first three years of police service (Inslicht et al., 2011). Conversely, a study by Heinrichs et al., (2005), when investigating professional fire fighters (n=43) immediately after basic training (at baseline) and then at 6, 9, 12 and 24 months, did not find diurnal salivary cortisol - a predictive pre-traumatic measurement of posttraumatic stress symptoms - at any of the subsequent follow ups. Please refer to **Table 7.5** for an overview of the results of these studies.

Thus, there is some, albeit inconsistent, evidence to suggest that cortisol may be a biomarker for resiliency, as measured by the vulnerability to psychopathology following stressful life events. A core difference worth noting in these studies to that of our own is that comparison with the CAR and the outcome is often separated by several months, despite research having highlighted how much the CAR varies on a daily basis (Almeida et al., 2009; Stalder et al., 2010). Furthermore, to convincingly demonstrate a relationship between cortisol and resilience, one would hope to produce evidence of a

dose-response relationship: something that none of the available research to date has achieved (Lightman, 2008). The results presented here, however, don't necessarily conflict with that of Ruiz-Robledillo et al. (2014) or that of Inslicht and colleagues (2011) as the models presented here would suggest that persistently lower resilience would produce increases in cortisol the following day. However, direct comparison between studies are troublesome due to the lengthy time periods between CAR measurement and the respective outcome measures.

Cohort	CAR	Resilience
ASD	↑	↓
Police	↑	↓
Fire-fighters	-	-
Good sleepers & Insomnia	↑**RES** = **AUC$_G$**↓	
	AUC$_I$↑ = ↑ **RES**	

Table 7.5: Summary of findings from studies investigating the relationship between cortisol and resilience. Our findings are presented in the bottom row.

These results are unique in the way in which they test the relationship between the CAR and the level of resilience reported that day. Due to data collection on multiple days, the current study also had the ability to identify the presence of a bi-directional relationship between cortisol and resilience on a daily basis. As such, these results also have interesting implications for the model described in Chapter 6. The addition of cortisol to the model highlights an alternate biological pathway through which resilience in the model can be enhanced or reduced and in turn how these enhancements or reductions in resilience could impact the HPA axis. While no sleep measures predicted the CAR directly, objectively poorer sleep (WASO) predicted a reduction in resilience, as did subjectively poorer sleep via negative affect. Lowered resilience itself was the single strongest predictor of a dissociative symptom that day, which in turn predicts paranoid symptomatology (**Figure 7.3**).

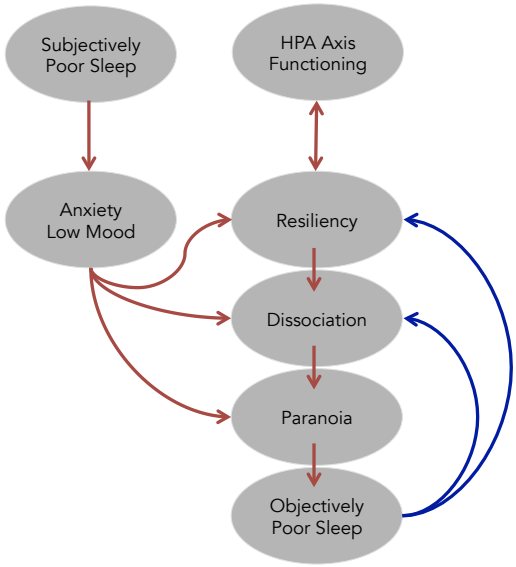

Figure 7.3: HPA axis functioning (measured by two days of CAR collection) and its relationship to daily measures of sleep and daily psychiatric symptomatology. HPA axis functioning, objectively poorer sleep and higher anxiety/lower mood predict subsequent resilience that day, which in turn predicts dissociative symptoms, which predict paranoia. The experience of paranoia then predicts poorer objective sleep the following night. Objectively poorer sleep then refuels the relationship with lowered resilience and greater dissociation. However, persistently lowered resilience also increases baseline cortisol levels the following day which is a potential mechanism by which hyperarousal of the HPA axis can lead to psychopathology (as mentioned above resilience then impacts and is impacted by psychotic symptoms and sleep respectively).

A number of caveats merit mention. First, whilst all participants were very clearly instructed about the protocol for the collection of cortisol at home, we have no insight as to how adherent the participants were to this protocol. Second, the CAR is consistently reported as a highly volatile biomarker which can be impacted by any number of confounding variables, including age, gender, menstrual cycle phase, light exposure, activity levels and exact time of collection, to name but a few (Fries et al., 2009). With little information about what the participant was doing at the time of collection, such confounding variables may have impacted the results. Furthermore, female participants were asked to complete the phase of their menstrual cycle on the collection sheet, however the responses were too few to be able to add this as a covariate to the model. Also, a number of participants reported taking oral contraceptives which either altered or inhibited their cycles, though the numbers were again too few to permit further examination.

These caveats notwithstanding, these results shed further light on the relationship between HPA axis functioning and the ability to deal with daily stressful life events. The effect size for AUC_I and resilience is small, which suggests there are many other contributing factors to predict self-reported

resilience (this study alone also highlights the role of anxiety and self-reported poor sleep). However, the relationship between resilience and AUC_G was more pronounced. As mentioned in Section 1.9.2.2, often the relationships with sleep and cortisol are small, yet it is considered that the repeated exposure to SCRD may over time cause more impactful dysregulation of HPA axis activity. The same would apply here, as this is a very short temporal examination into the HPA-resilience relationship, yet as above, repeatedly lower resilience may create more impactful long-term changes. While no significant differences between groups were found, this could be further clarified by repeating this study in more controlled environment (such as a laboratory) with longitudinal high resolution sampling (Lokhmatkina et al., 2013), which may help negate some of the extensive variability within each group, and could control for circadian phase (an example of a home study protocol which incorporates circadian factors is; de Weerth & van Geert, 2002). Future research should aim to replicate the relationship between cortisol and resilience that we have detailed here with larger samples and across difference psychopathologies to see if this can be replicated for an insomnia cohort and generalised to other diagnostic categories. Furthermore, experimental manipulations (inducing stress, for example) could shed further light on the temporal dynamic of the relationship between cortisol and resilience.

Chapter 8:
Concluding Remarks

This thesis was designed to understand whether a subjective complaint of poor sleep (in a healthy, young, gender-matched cohort) translated to an increased risk in PLEs, and in turn, what known overlapping mechanisms between SCRD and mental health were impacted in this cohort.

Chapter 2 aimed to empirically evaluate the predictions made by the psychosis-proneness persistence impairment model (van Os et al., 2009) and to understand whether SCRD may also be a risk factor impacting an individuals' position upon the continuum. It was found that while SCRD did increase the risk of PLEs, there was remarkable specificity in the type of SCRD (sleep quality, insomnia complaint, sleep timing) that impacted certain PLE categories (cognitive disorganisation, bizarre ideas and delusional mood respectively). This succinctly demonstrates the need for specificity when attempting to demarcate sleep's role in PLEs, as it is not anticipated that all forms of SCRD will unilaterally impact all types of PLEs - both of these are extraordinarily broad umbrella terms for an extensive range of experiences and phenotypes.

It was mentioned in Chapter 1 that there is a dearth of biologically driven research into sleep and PLEs. Chapter 3 proceeded to investigate the biological underpinning of a complaint of poor sleep, and examined objective measures (EEG) and markers of stress axis functioning via the sympathetic nervous system (heart rate and heart rate variability). The insomnia group were found to have objective differences in their PSG (with regards to sleep efficiency, WASO, time in bed and SOL). Analyses of arousals throughout the night highlighted the insomnia group to have greater arousal counts overall, but this difference was not significant when examining any one specific sleep stage. Following the results of Spiegelhalder et al., (2011), the dip in nocturnal HR was shown to be

attenuated in stages 2, 3 and 4 for the insomnia group, suggesting physiological hyperarousal during both wake and sleep could underpin an insomnia complaint. It was also highlighted through novel multiscale entropy analyses that the insomnia group featured decreased complexity in their nocturnal cardiac signal across stages 2, slow wave (3 & 4) and REM. It is thought that a decrement in complexity might be an indication of the degradation of cardiac control mechanisms that govern physiological arousal.

Chapter 4 aimed to further explore the physiological differences and differences in longitudinally measured sleep between groups. To provide a read-out of the master clock, examinations of the endogenous rhythm of melatonin were undertaken via urine sampling over a 48-hour period. Furthermore, actigraphy group differences were explored across the three weeks of measurement. Through these explorations, it was shown that the insomnia group had a longer sleep period, a slight delay in sleep offset and slightly elevated WASO. These findings highlighted the potential of fluctuations in sleep timing as opposed to differing architecture between groups. The slight delay in sleep offset and the elongated sleep period were married with a slight delay in the melatonin acrophase in the insomnia group, as well as a trend towards a difference in phase angle onset. Acrophase was correlated with sleep onset, offset and PSQI, and was also relatively correlated with PLEs (whilst not significant). Further, MLT acrophase demonstrated higher correlations with PLEs than both mania and depression, indicating some specificity in the relationship of sleep timing to PLEs.

Chapter 5 aimed to investigate the relationship between sleep and psychotic experiences with greater specificity using both objective and subjective sleep parameters. It was found that the best model of fit in the prediction of PLEs included an interaction between the subjective reporting of sleep quality (PSQI) and the objectively measured total sleep time from actigraphy. The combination of a poor perception of sleep and decreased total sleep time rendered an individual at the greatest risk of experiencing PLEs, highlighting the importance of objective sleep measurements when considering the nature of the relationship between sleep and PLEs. It is unclear whether the

Chapter 6 utilised an increased temporal resolution to further understand and expand upon the findings in Chapter 5. Beginning by examining the broader group differences in psychopathology, it

was shown that the insomnia group scored higher on all psychometrics (depression, anxiety, stress, dissociation, resilience and schizotypy) with the exception of paranoia. Daily measures of anxiety, mood, dissociation, resilience and paranoia were taken, and trends in these measures highlighted the insomnia group to persistently score more negatively on mood, anxiety, dissociation and resilience. The results of extensive modelling analyses highlighted dissociation to have direct ties with sleep (TST). It was also shown that anxiety interacts with sleep in the prediction of dissociation. Paranoia showed no direct relationship with sleep quality, but was peripherally related to sleep via anxiety and mood (both of which were impacted by sleep). The combination of these findings allowed for a complex negative feedback loop to be designed to describe the nature of the relationship between sleep, paranoia and dissociation, permitting much more nuanced interpretations of the relationship than that described in Chapter 5. Interestingly, the results presented here align with the results highlighted by the OWLS survey analysis in Chapter 2, where it was found that PSQI uniquely predicts risk for cognitive disorganisation. The three items of cognitive disorganisation overlap perfectly with the three categories of dissociation investigated daily with state measures in Chapter 6: depersonalisation, derealisation and absorption. Similarly, the OWLS survey analysis highlighted no direct ties between sleep and paranoia, but both analyses show relationships between paranoia, depression and anxiety.

Chapter 7 aimed to further examine the relationships described in Chapter 6 by investigating the cortisol awakening response between groups. While no group differences in cortisol measures existed, it was found that resilience was predictive of baseline cortisol levels that day and in turn that the steepness of the morning awakening response was predictive of resilience that day, permitting HPA axis activity to be built into the negative feedback loop described in the Chapter 6.

The core implications of this thesis can be described across three categories: (1) the importance of acknowledging the continuum of PLEs and psychopathology as a whole; (2) the importance of both understanding and implementing SCRD in a transdiagnostic approach to mental health; and (3) what our findings contribute to the understanding of the stress axis in Mental Health Disorders (and specifically PLEs). In this chapter, we discuss these core implications within the context of each of these three categories, and conclude by describing future directions of research to build upon this work.

8.1 Acknowledging the PLE Continuum

Chapter 2 highlighted that even at attenuated levels, considerably below the threshold of a clinical diagnosis, subgroups that endorse PLEs also display a substantial number of important health outcomes. These included increased prevalence of comorbid psychiatric diagnoses (namely depression and anxiety disorders - the second most costly category of brain disorder to the state; Fineberg et al., 2013) and of treatment outcomes, such as hospitalisation. In this circumstance, PLEs do not just become a risk for psychosis but an important metric for understanding an individual's wellbeing within existing psychiatric diagnoses. Using this line of thought, PLEs are important markers of severity in depression and anxiety associated with an increased need for care and greater risk of hospitalisation.

Conversely, Chapter 2 also presents the argument that investigating summary scores/metrics for PLEs may not prove fruitful in understanding their aetiology (particularly with respect to sleep). It opens the possibility that there may be many continua of the psychosis proneness continuum that need to be considered which highlight different pathways to psychosis via varied exposure to assorted risk factors. This notion is not novel in the literature but research formally testing some of these hypotheses is in its infancy (van Os, 2014).

8.2 Importance of a Transdiagnostic Approach when Considering SCRD in Mental Health

Throughout this thesis, it has been repeatedly underscored that the cohort phenotyped for their sleep here, whilst selected on sleep, score higher on every psychopathological outcome examined (barring paranoia). This gives substantial weight to the argument that it is exceptionally difficult to look at poor sleep or PLEs in isolation, but instead that they must be considered within a broader framework of co-existing mental health problems and that (as mentioned above) PLEs may be markers of poor health in and of themselves. The notion that sleep is a transdiagnostic feature of mental health is not novel (Harvey et al., 2011), but future research should aim to understand the specificities in SCRD and how they predict different symptomatic outcomes. The exploration of REM latency as a biomarker for depression is a good example of this (Lovato & Gradisar, 2014).

8.3 Understanding the Role of the Stress Axis in Mental Health Disorders and PLEs

This thesis highlights the insight provided by biologically driven research into the understanding of the common overlapping mechanisms between SCRD and mental health. Dysregulation in the stress axis, denoted by a low HRV, high nocturnal HR, decreased complexity in HR signal and a blunted CAR have been found across multiple mental health disorders - not just psychosis. Taken together, dysregulation of the stress axis, which is strongly under circadian control, is a strong contender in the sleep and mental health debate. Investigating whether these findings can be replicated in more clinical insomnia populations, across different patient groups, or finding whether the patterns of reduced complexity differ between groups, could all be of real promise to the field.

8.4 Future Directions of Research

First and foremost, future research should aim to replicate some of the findings discussed in this thesis. It would be beneficial to see if the specificity of SCRD and certain risk factors to different types of psychotic symptoms in Chapter 2 could be replicated with a larger multi-national sample with greater ethnic and educational diversity in the sample. As mentioned above, replicating the results of the MSE analyses in insomnia patients and also across different mental health disorders could give more insight into the complexity of arousal signals across mental health disorders.

The large number of participants that needed to be excluded from the analyses limited the melatonin analyses. Aiming to replicate the findings of a delayed acrophase in an attenuated insomnia sample (of similar age) with a larger sample size would be of real benefit to the field, as it opens the door to acknowledging whether certain insomnia complaints (or insomnia complaints made by certain age groups) may have greater ties to a misalignment between internal and externally regulated timing.

The interaction analyses of Chapter 5 would benefit from replication in both clinical and nonclinical samples, and across different types of psychiatric symptoms with a larger sample size, to see how generalisable the relationship is to other cohorts, whether the interaction is PLE-specific, and

depression/anxiety complaints are more related to the subjective perception of sleep (as Chapter 6 may suggest).

Chapter 6 provides a basis for understanding the occurrence of certain psychotic symptoms and how sleep may inform that relationship. Translating the model proposed here into clinical populations would be of real benefit to the field. Unconstrained by imprevalent endorsement of psychotic symptoms, it would be possible to opt for a higher resolution method than that used here (which only recorded one time point per day). Such options include using an experience-sampling method, which is often takes 3-5 time points per day, giving in-vivo measurement of psychotic symptoms.

Finally, Chapter 7 was largely limited by the extensive heterogeneity within groups. As such, it would be interesting to see if this could be resolved by more tightly controlled laboratory conditions, which would permit examining the CAR in the absence of confound variables.

Taken together, this thesis has examined some of the physiological pathways that may be related to a complaint of poor sleep, and some of the parameters of sleep that may have greater affinities to PLEs. In-depth phenotyping of sleep and circadian rhythms in human psychiatric research is still in its infancy, but this thesis provides a foundation of new studies and results to build upon in this field, and may pave the way for further novel insights into understanding the relationship between sleep and mental health.

Appendix A

A.1 Systematic Review of the Risk Factors for Psychosis

A systematic search was conducted to identify meta-analyses and systematic reviews reporting on associations between risk factors and psychosis.

A.1.1 Search Strategy

MEDLINE, PsycINFO, Embase, and Global Health databases were searched from inception to February 2014. Both title/abstract mapping (denoted by ti,ab.) and thesaurus mapping (articles selected based upon database-specific subject headings) were used. To identify articles looking into risk factors for psychosis, the following search terms were used: psychosis*.ti,ab. OR psychotic*.ti,ab. OR schizo*.ti,ab. AND risk*.ti,ab. OR suscept*.ti,ab. OR premorbid*.ti,ab. OR predispos*.ti,ab. OR vulnerab*.ti,ab. OR antecedent*.ti,ab. OR precursor*.ti,ab. (title/abstract mapping); exp risk factors/, or exp at risk populations/, or exp predisposition/, exp "susceptibility (disorders)"/, or exp premorbidity/ (thesaurus mapping). Finally, the risk factor search terms were limited to systematic reviews or meta-analyses ('risk factor search terms' AND 'psychosis search terms' AND 'systematic review*.ti,ab. OR meta analys*.ti,ab.'). Supplementary database searching was also used to identify additional articles on specific risk factors for psychosis.

A.1.2 Inclusion/Exclusion Criteria

We conducted the search with progressive increases in inclusion/exclusion criteria for each stage of screening. This included a title screen, abstract screen, and full article screen. Disagreements on including or excluding articles were resolved through group discussion.

Articles were searched for regardless of their publication status or language. To be eligible for inclusion, articles had to report that they were a systematic review or meta-analysis in the title, and report pooled data (e.g. OR, RR, effect size, or prevalence rates) for the factor of interest. Factors of interest were considered 'risk factors' and subsequently included in review if they met the a priori definition of being any attribute, characteristic, or exposure which increases the likelihood of developing the disorder, but not being associated with that disorder's symptomatology or associated as a comorbid condition. Thus, traits such as cognitive impairment were not included in our main analyses. Since this review is focused on environmental influences on psychosis, articles were excluded if they reported genetic risk factors for specific genes, risk factors at the level of neuronal function, brain activity or brain morphology, and animal based models.

When multiple articles were found for the same factor of interest but with varying definitions of psychosis, articles reporting data on the broadest definition for psychosis were favoured (e.g. an article on psychosis was favoured over an article on post-natal psychosis). When multiple articles were found for the same risk factor of interest, the most recent meta-analysis was given highest priority followed by the most recent systematic review.

A.2 Results

After a full article screen, 30 articles (27 meta-analyses and 3 systematic reviews) were included (see **Figure A.1** for a flowchart). From these papers, we identified 20 risk factors which were: presence of a family history of psychiatric disease, ethnicity, obstetric complications, parenting, child abuse (physical, emotional and sexual), migration status, cannabis use, traumatic life events, bullying, brain injury, Axis I diagnosis, gender, latitude and climate, paternal age, prenatal infections, season of birth, social withdrawal, urbanicity, childhood viral infections and 22q.1 deletion syndrome. An overview of these papers can be found in **Table A.1**.

A further two references investigating cannabis use are not included in the aforementioned table as one investigated the potential of an advance in the age of onset for psychosis (Large, Sharma, Compton, Slade, & Nielssen, 2011) and the other investigated the comorbidity of cannabis use disorders in schizophrenia (Koskinen, Löhönen, Koponen, Isohanni, & Miettunen, 2009). As these

studies did not set out to directly investigate the impact of smoking cannabis on the risks of developing a psychotic disorder, they were excluded (while cannabis use itself is considered a risk factor). A further paper on obstetric complications by Geddes et al., (1995) was also not listed as it is substantially older than that of Cannon et al., (2002). For definitions for each of the risk factors, please refer to **Table A.2**.

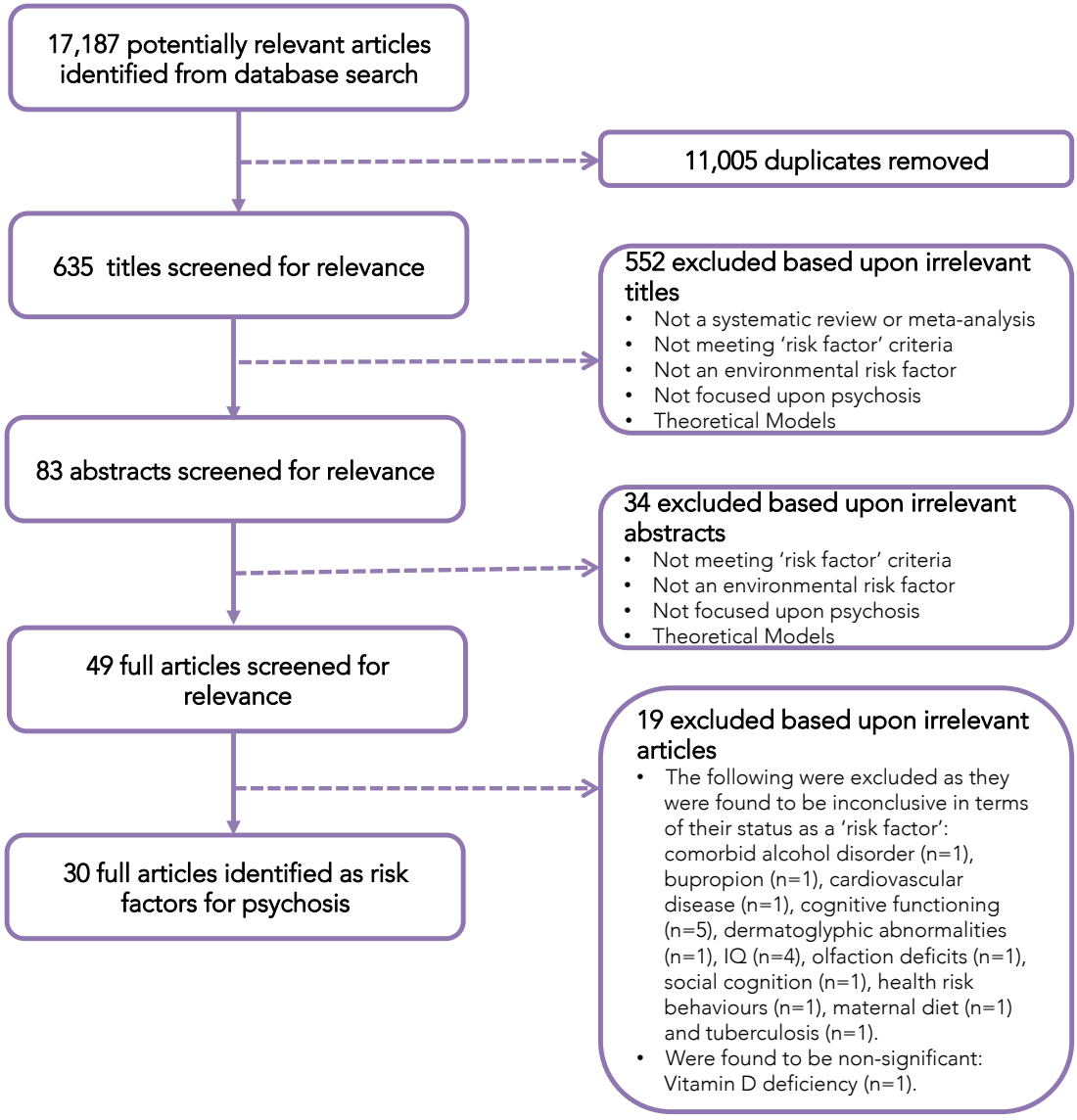

Figure A.1: Flow chart of systematic search strategy.

Risk Factor	Reference	Disorder	Type	K	N	Het.	Effect Size	CI
Family History	Rasic et al., 2013	BP, SZ, D	Meta	33	7021	S	2.7	2.2-3.4
	Van Snellenberg &Canada 2009	SZ, BP	Meta	66	47,777		8.38	NA
Ethnicity	Kirkbridge et al., 2012	SZ	Meta	5	1,423	S	2.4 - 5.9	3.4-9.2
Obstetric Complications	Cannon et al., 2002	SZ	Meta	8	1,923	NS	1.4 - 7.8	NA
Parenting	De Sousa et al., 2013	P	Meta	20	1,753	S	5.8	3.9 –8.5
Child Abuse	Matheson et al., 2013	SZ	Meta	25	1,681	S	3.6	2.1–6.2
	Varese et al.,2012	P	Meta	36	81,262	S	2.8	2.3–3.3
	Norman et al., 2012	D, SA, A, ED, SZ	Meta	388	1,186,074	S	1.4-2.3	1.2-5.7
	Chen et al., 2010	A, D, ED, SZ, BP	Meta	71	3,162,318	S	1.4-2.3	2.4 -3.9
Migration	Borque et al., 2011	SZ	Meta	21	67,551	S	2.1 - 2.3	N/A
	Cantor-Graae &Selten 2005	SZ	Meta	315	31,045	S	RR=2.7	2.3-3.2
Cannabis Use	Moore et al., 2007	P, A	Meta	33	61,485	NS	1.4-2.9	1.11-7.57
	Semple et al., 2011	P	Meta	11	113,802	NS	2.9	2.4-3.6
Traumatic Life Events	Beards et al., 2013	P	Meta	16	2,465	S	3.2	2.2–4.8
	Trevillion et al., 2012	D, A, ED, PD, BD, P	Meta	41	69,893	S	2.8 - 8.1	4.5–12.0
Bullying	Van Dam et al., 2012	P	Meta	14	2,883	N/A	2.3	1.5-3.4
Brain Injury	Molloy et al., 2011	SZ	Meta	9	169,925	S	1.65	1.2-2.3
Axis I Diagnosis	Achim et al., 2011	SZ	Meta	52	10,731	S	Varied	Varied
Gender	Aleman et al., 2003	SZ	Meta	38	N/A	S	1.42	1.3-1.6
Latitude and Climate	Cheng et al., 2008	SZ	Meta	9	3,365,722	S	1.51	1.3-1.8
Paternal Age	Miller et al., 2011	SZ	Meta	12	195.092	S	RR=1.66	1.5-1.9
Prenatal Infections	Khandaker et al., 2013	SZ	SR	21	1,217,472	S	N/A	N/A
Season of Birth	McGrath et al., 1999	SZ	Meta	12	20,017	S	1.04	0.9-1.1
	Davies et al., 2003	SZ	Meta	8	86,732,003	S	1.07	1.05-1.1
Social Withdrawal	Matheson et al., 2013	SZ	Meta	6	3,828	S	SMD=1.04	0.3-1.8
Urbanicity	Vassos et al., 2012	SZ	Meta	4	46,820	S	2.39	1.6-3.5
Childhood Viral Infection	Khandaker et al., 2012	SZ	SR	21	7	NS	RR=1.7	1.1-2.6
22q.1 Deletion Syndrome	Armando et al., 2013	SZ	SR	9	13,026	N/A	N/A	N/A
Epilepsy	Clancy et al.,2014	P	Meta	58	N/A	S	7.8	2.8-21.8

Table A.1: Overview of the risk factors identified based on a systematic review of the literature. Disorders are abbreviated as follows: SZ=Schizophrenia; BP=Bipolar Disorder; D=Depression; P=Psychosis; ED=Eating Disorders; A=Autism; PD=Personality Disorder; SA= Substance Abuse. The type of article is abbreviated to either Meta (meta-analysis) or SR (Systematic Review). Heterogeneity is abbreviated to either S (for significant) or NS (for not significant). Effect sizes are measured in odds ratios unless otherwise specified, as are confidence intervals. K refers to the number of studies included in the review, and N refers to the total number of participants included in the review.

Risk Factor	Explanation (according to the papers listed in Table A.1)
Family History	A first degree relative with a serious mental illness, the highest risk is for a parent with a diagnosis of schizophrenia.
Ethnicity	Identifying as a member from an ethnic minority grouping.
Obstetric Complications	A wide range of complications that can occur both during pregnancy and particularly delivery. Common complications include: low birth weight, prematurity, infections and illness during pregnancy.
Parenting Problems	A broad range of parenting behaviours have shown to have detrimental effects on development and mental health. The meta analysis detailed here refers to 'Parental Communication Deviance', which is a genre of communication that is vague, fragmented and contradictory between parents and children.
Child Abuse	The papers detailed here include definitions of childhood maltreatment, neglect and adversities, as well as physical, sexual and emotional abuse.
Cannabis Use	Smoking cannabis has been shown to advance the age of onset and is associated with a higher risk of developing psychosis (even when controlling for intoxication effects). It is not entirely clear what frequency/age or duration presents the greatest level of risk but a 50-200% increase in risk is observed in heavy/frequent users. A dose response effect was reported in every study examined by Moore et al., (2007).
Traumatic Life Events	A general definition of negative life events including personal grievance, being attacked, experience a divorce, domestic violence, etc. Risk increases with the number of traumas experienced and the age at which they occurred.
Bullying	Experience of bullying during primary school. Stronger associations are found with increased frequency, severity and duration of being bullied.
Brain Injury	Traumatic Brain injury is defined as cerebral trauma, head injury, craniocerebral injury, concussion or open head injury. This was not found to be a dose-response effect with the severity of head injury but the association was strengthened in those with a genetic predisposition to psychosis.
Axis I Diagnosis	Anxiety disorders are frequently comorbid with schizophrenia. However, it is unclear as to whether this is a risk factor to or a bi-product of schizophrenia itself.
Gender	Men are at a heightened risk of developing schizophrenia over women.
Latitude and Climate	Higher latitude and low ambient temperature present an increased risk for the development of schizophrenia.
Paternal Age	Older fathers (aged 50 and above) are at higher risk of having offspring with a diagnosis of schizophrenia. There is a small but significant risk (RR=1.08, 95% CI: 1.02-1.14) associated with younger fathers aged below 25 years also.
Prenatal Infections	Prenatal infections increasing the risk for schizophrenia encompass a broad range of phenomena including: herpes simplex virus type 2 (HSV-2), Toxoplasma gondii, exposure to influenza during early pregnancy and increased proinflammatory cytokines during pregnancy.
Season of Birth	Winter and spring births have a significant excess of schizophrenia diagnoses compared to summer/autumn births.
Social Withdrawal	The withdrawal from social interactions during childhood that are thought to inhibit or restrict the normal development of social cognition and functioning.
Urbanicity	Exposure to urban environments increases the risk of schizophrenia.
Childhood Viral Infections	A number of central nervous system viral infections during childhood increase the risk of schizophrenia including cytomegalovirus, mumps virus, CBV-5 meningitis, Tuberculosis and Chicken Pox.
22q.1 Deletion Syndrome	2q11.2 deletion syndrome (22qDS) is a genetic syndrome associated with a chromosome 22q11.2 deletion and variable phenotypic expression that commonly includes schizophrenia.
Migration	Includes varying risk from high-risk countries for both 1st and 2nd generation migrants.
Epilepsy	An epilepsy diagnosis increases the risk of psychosis seven-fold.

Table A.2: Definitions of the risk factors specified in **Table A.1**.

Appendix B

B.1 Risk Factors, Questionnaires and Sociodemographic Variables Employed in the OWLS survey

Item assessed	Assessment method
Psychosis symptomatology	Prodromal Questionnaire-16 (PQ16; Ising *et al.*, 2012).
Subjective sleep quality	Pittsburgh Sleep Quality Index (PSQI; Buysse *et al.*, 1989).
Insomnia	Short version of Sleep Condition Indicator (SCI-2; Espie *et al.*, 2014).
Social jetlag & mid-sleep time on free days	Munich Chronotype Questionnaire (MCTQ; Roenneberg *et al.*, 2003).
Axis I disorder symptomatology	Depression Anxiety Stress Scale-21 (DASS-21; Henry *et al.*, 2005)
Brain infection	'Have you ever suffered from encephalitis, meningitis or an infection of the brain before the age of 16 which required hospitalisation for more than one day?
Brain injury	'Have you ever suffered from a brain injury that required hospitalisation for more than one day?'
Cannabis use	A series of questions relating to current frequency of cannabis use, highest frequency of use and duration of most frequent use.
Childhood abuse	Questions on frequency of physical, sexual, psychological and emotional abuse before the age of 16 as used by Cuijpers *et al* (2011)
Childhood bullying	'When you were at school were you the victim of frequent bullying?'
Childhood social withdrawal	Four measures of social withdrawal as a child taken from items 42, 65, 88 & 111 from the Child Behavioural Checklist (CBCL; Achenbach et al., 1983) and edited to make appropriate for retrospective report
Diagnosis of a non-psychotic psychiatric disorder	Diagnoses and treatment used if applicable
Ethnicity	Ethnicity question taken from the national census
Family history of psychiatric disorders	Number of blood relatives diagnosed with a mental health disorder, their diagnosis, and treatment if applicable

Table B.1: Part I of list of risk factors and sociodemographic variables assessed by the OWLS survey, alongside the method of assessment (listing relevant questionnaires used, where relevant). List continued in **Table B.2**.

Item assessed	Assessment method
First or second generation migrant	Participants country of birth, participants country of permanent residence, parents country of birth
Gender	'What is your sex/gender?'
Help seeking behaviour	'Have you ever sought help for any of the above [psychosis-like] experiences?' (including counselling, GPs)
Lack of need for sleep	'During the past month, have you had much less sleep than usual, found you didn't really miss it and did this cause a problem?'. Adaptation of item 4 of the Mood Disorder Questionnaire (MDQ, Hirschfeld *et al.*, 2000).
Latitude	Participants clicked which region on a world map where they have lived the longest between the ages of 0-18 years
Obstetric complications	List of obstetric complications given. Participants were asked to ring their mother if willing.
Paternal age	'How old was your father when you were conceived?'
Season of birth	'What is your date of birth?'
Traumatic experiences	Life Threatening Experiences (LTE) scale with distress levels added (Brugha *et al.*, 1985)
Urbanicity	'Is where you have lived the longest between the ages of 0-18 years a densely populated crowded city?' Examples given.
22q11.2 deletion syndrome diagnosis	Diagnosis present: Y/N
Epilepsy	Do you suffer from epilepsy (Y/N)
Level of Education	What is the highest level of education you have ever completed? Are you currently working towards a higher level of education? Y/N If Y: What level of education are you currently working towards?

Table B.2: Part II of the list of risk factors and sociodemographic variables assessed by the OWLS survey, alongside the method of assessment (listing relevant questionnaires used, where relevant). List continued from **Table B.1**.

Appendix C

C.1 Defining Potential Predictor Variables for OWLS Survey Predictive Models

Item assessed	Method of Measurement
Outcome Measure	
PQ16 (psychotic experiences)	a. Count score (of 16 items) measured continuously b. A score above 5 c. A score above 5 with associated distress and help seeking behaviour
Sleep Predictor Variables	
PSQI (sleep quality)	Measured continuously (a score of 5 or above indicates poor quality sleep)
SCI-2 (insomnia)	Measured continuously (the lower the score the worse the sleep complaint)
MCTQ (Chronotype)	a. Chronotype category score (0=neutral; 1=morning type; 2=late type) b. MSFsc – measured in time continuously
MDQ (decreased need for sleep)	Measured categorically (0='No' to 4='Yes – Serious Problem')
Psychiatric Symptomatology Predictor Variables	
DASS 21 (Dep/Anx/Stress)	Measured categorically for depression, stress and anxiety (0='Never', 1='Sometimes', 2='Often', 3='Almost Always').
Risk Factor Predictor Variables	
Brain infection	Binary (Y/N)
Brain injury	Binary (Y/N)
Cannabis use -ever used	Binary (Y/N) - Have you ever taken cannabis?
Cannabis use - now	Measured categorically: in the past three months, how often have you used cannabis? (0='Never'; 4='Daily or Almost Daily'.
Childhood abuse	Categorical frequency of each physical, sexual, psychological and emotional abuse before the age of 16 (0='Never'; 5='Very Often').
Childhood bullying	Binary (Y/N)
CBCL (social withdrawal)	Sum of four questions with three categories (0='Never'; 1='Sometimes'; 2= 'Often').
Diagnosis of non-psychotic disorder	Binary – presence of any diagnosis (Y/N)
Ethnicity	Binary – A score of one is given when a respondent identifies as 'non-white'
Family history - First Degree (SZ/BP)	Binary (Y/N) - A First Degree Relative with schizophrenia/bipolar
Family history - First Degree (Other)	Binary (Y/N) - A First Degree Relative with other psychiatric diagnosis
First or second generation migrant	Binary – score given if respondent was a first/second generation migrant from a less developed or developing country to a first world country
Gender	Binary – if respondent endorses being 'male', a score of 1 is given.
Latitude	Binary – A score of 1 was given to participants who endorsed regions 1 or 2 indicating the most northern regions on a world map
Obstetric complications	Binary – If respondent endorses one or more obstetric complication a score of 1 is given.

Paternal age	Binary – If respondent endorses their father to be 50 or over at age of conception OR below 24 or below, a score of 1 is given.
Season of birth	Binary – if respondent has a birthday during the winter/spring months, a score of 1 is given.
Traumatic experiences	Measured continuously as count score for the number of traumas (out of a total 12) experienced.
Traumatic experiences - distress	Total of the distress associated with each trauma experienced (0= "Not Stressful", 1= "Slightly Stressful", 2= "Moderately Stressful", 3= "Very Stressful")
Urbanicity	Binary (Y/N)
22q11.2 deletion syndrome	Binary (Y/N)
Epilepsy	Binary (Y/N)
Covariates	
Level of education	This is categorised into 4 groups: low (pre A-level), medium (A-level, further college of education), high (bachelors), very high (MA/PhD).
Studying towards	Binary (Y/N)
Age	Measured continuously in years

Table C.1: Summary of variables measured by the OWLS survey, with descriptions of the data/type of measurement resulting from the survey.

Appendix D

	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13	Q14	Q15
Q1	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Q2	0.17	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Q3	0.07	0.15	-	-	-	-	-	-	-	-	-	-	-	-	-
Q4	0.15	0.20	0.22	-	-	-	-	-	-	-	-	-	-	-	-
Q5	0.22	0.24	0.19	0.24	-	-	-	-	-	-	-	-	-	-	-
Q6	0.13	0.12	0.15	0.19	0.21		-	-	-	-	-	-	-	-	-
Q7	0.29	0.16	0.09	0.18	0.20	0.12	-	-	-	-	-	-	-	-	-
Q8	0.14	0.15	0.23	0.23	0.26	0.23	0.14	-	-	-	-	-	-	-	-
Q9	0.22	0.18	0.17	0.18	0.30	0.18	0.23	0.22	-	-	-	-	-	-	-
Q10	0.12	0.18	0.15	0.15	0.23	0.13	0.16	0.19	0.27	-	-	-	-	-	-
Q11	0.26	0.18	0.12	0.17	0.29	0.15	0.21	0.16	0.38	0.25	-	-	-	-	-
Q12	0.15	0.17	0.23	0.28	0.29	0.17	0.19	0.27	0.31	0.24	0.24	-	-	-	-
Q13	0.16	0.13	0.23	0.26	0.26	0.24	0.15	0.40	0.25	0.21	0.17	0.30	-	-	-
Q14	0.26	0.20	0.13	0.20	0.28	0.18	0.30	0.22	0.27	0.22	0.30	0.24	0.23	-	-
Q15	0.13	0.21	0.19	0.18	0.21	0.17	0.16	0.30	0.27	0.30	0.21	0.28	0.27	0.23	-
Q16	0.15	0.16	0.18	0.16	0.19	0.11	0.13	0.18	0.25	0.19	0.21	0.21	0.15	0.20	0.25

Table D.1: Correlation matrix of OWLS survey responses to items within PQ16 questionnaire.

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