Sleep across the Psychosis Continuum and its relationship to paranoid thinking.

Aliyah Rehman Bsc, MSc

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School Of Psychology
University of Glasgow
62 Hillhead Street
Glasgow
G12 8AD

Abstract:

Background: The present thesis sought to explore the relationship between sleep and paranoia, and investigate what factors mediate this relationship. The research was conducted at different levels, and in different groups including healthy members of the general population, people with a diagnosis of psychosis and clinicians. Method: in chapter 3, a cross-sectional study was conducted online to examine the relationships between sleep and paranoia in a non-clinical sample. Following this, chapter 4 outlines a systematic review that aimed to further understand how sleep has been investigated in clinical samples of people with psychosis. Next, chapter 5 examined the relationship between sleep disturbance and paranoia in a clinical sample using novel experience sampling methodologies. Finally, chapter 6 explored clinician perceptions of sleep problems in people with psychosis. Results: chapter 3 found evidence for a mediation model whereby sleep predicted paranoia, and this relationship was mediated by negative emotions, alexithymia and perceptual anomalies. Chapter 4 revealed that there is a range of methodologies used to assess and measure sleep and identified areas of bias. Chapter 5 found no relationship between sleep and paranoia in a clinical sample of people with psychosis. Finally, chapter 6 found that clinicians are fully aware of the range and types of sleep problems in people with psychosis but lack the training and skills to treat sleep problems. Discussion: Overall, the relationship between sleep and paranoia is inconsistent. Sleep disturbances are common and should be treated in people with psychosis. More work is required to develop effective intervention strategies to address the range and type of sleep disturbances found in people with psychosis.

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Abbreviations

AASM	American Academy of Sleep Medicine
CAPS	Cardiff Anomalous Perceptions Scale
CBT	Cognitive Behavioral Therapy
CBTi	Cognitive Behavioral Therapy for Insomnia
CMHT	Community Mental Health Team
DASS	Depression, Anxiety and Stress Scale
DSM	Diagnostic and Statistical Manual for Mental Disorders
EEG	Electroencephalography
ESRC	Economic and Social Research Council
ESM	Experience Sampling Methodology
ESS	Epworth Sleepiness Scale
GPTS	Green Paranoid Thoughts Scale
HADS	Hospital Anxiety and Depression Scale
ICD	International Classification of Diseases
ICSD	International Classification of Sleep Disorders
ISI	Insomnia Severity Index
MLM	Multi-Level Modelling
NA	Negative Affect
NAP	Non-Affective Psychosis
NREM	Non-Rapid Eye Movement Sleep
OASIS	Oxford Access for Students Improving Sleep
MEQ	Morning- Eveningness Questionnaire
PA	Positive Affect
PANAS	Positive and Negative Affect Schedule
PLE's	Psychotic Like Experiences
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PSG	Polysomnography
PSQI	Pittsburgh Sleep Quality Index
REM	Rapid Eye Movement
SCI	Sleep Condition Indicator
SCN	Suprachiasmatic Nucleus
SE	Sleep Efficiency
SOL	Sleep Onset Latency
SWS	Slow Wave Sleep
TAS	Toronto Alexithymia Scale
TIB	Time in Bed
TST	Total Sleep Time
VLPO	Ventro-Lateral Pre Optic Nucleus
WASO	Wake After Sleep Onset

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1 An introduction to Psychosis and the Psychosis Continuum

This opening chapter aims to 1) define and provide an historical overview of psychosis 2) define alternative models of psychosis including the continuum and single symptom approach and 3) give an introduction to paranoia.

1.1 What is psychosis?

Psychosis is defined as a loss of contact with reality and loss of ego boundaries (Arciniegas, 2015). Psychosis is normally defined on the presence of positive symptoms (e.g. hallucinations and delusions). In addition to positive symptoms, those with psychosis may also experience negative symptoms such as anhedonia and alogia (Kay, Fiszbein, & Opler, 1987). Schizophrenia is the most well-known example of a condition where someone experiences psychosis and the two terms are often used interchangeably. However, it is important to note that psychosis is not limited to schizophrenia, and can be found in other conditions and medical disorders (Arciniegas, 2015). In the first section I will outline and describe the phenomenology of positive and negative symptoms.

1.2 Positive symptoms

Positive symptoms are unusual thoughts and perceptions, associated with loss of contact with reality. Positive symptoms can be seen as exaggerations of normal sensations, feelings and behaviours. (Kay et al., 1987).

1.2.1 Hallucinations

Hallucinations are defined as sensory perceptions that occur in the absence of external stimuli (Arciniegas, 2015). Hallucinations can occur in all 5 senses, and can be tactile, auditory, visual, to do with taste or smell. For example, experiencing smells that others cannot detect would be an example of an olfactory hallucination (Kopala, Good, & Honer, 1994). It has been estimated that around 70% of people diagnosed with schizophrenia experience

hallucinations (Sartorius et al., 1986). Typically, the most prevalent hallucinations are auditory in nature, followed by visual with the others being reported much less frequently (Bauer et al., 2011). A more recent study highlighted that multi-modal hallucinations are more common than uni-modal hallucinations. In other words, people with psychosis are more likely to experience more than one type of hallucination simultaneously than just experience one (A. Lim, Hoek, Deen, & Blom, 2016).

1.2.2 Delusions

Delusions are beliefs that are held with conviction, even if there is evidence that contradicts the belief (Bentall, Corcoran, Howard, Blackwood, & Kinderman, 2001). Delusions vary greatly in content and fall on a continuum from mis-interpretations of experiences, to bizarre, distressing delusions that are often associated with emotional distress (Arciniegas, 2015; Freeman, Garety, & Kuipers, 2001). One of the most common delusional beliefs is persecutory or paranoid in nature. Other types of delusions include delusions of grandeur (false impression of one's importance), delusions of reference (where neutral or unrelated events start having personal significance) and somatic delusions (where the person feels their body/appearance is grossly abnormal). In terms of prevalence, a study reported that in a sample of 1,136 patients with a psychiatric diagnosis, persecutory delusions were most common, and that those with schizophrenia reported the most intense delusions (Appelbaum, Robbins, & Roth, 1999). Another study reported that more than 70% of people with a diagnosis for first episode psychosis experience delusions of persecution (Coid et al., 2013).

1.3 Negative Symptoms

Negative symptoms are those that are associated with reductions or deficits in normal behaviour(Andreasen, 1982). Negative symptoms can occur in various domains of functioning including speech or social behaviours (Aleman et al., 2017). Examples of negative symptoms include flat affect (lack of emotional expression), alogia (poverty of speech), anhedonia (inability to experience pleasure), social withdrawal and avolition (decrease in motivation). In terms of

prevalence, negative symptoms are common. One study in a sample of outpatients with schizophrenia spectrum disorders reported 60% experienced at least one negative symptom (Bobes, Arango, Garcia-Garcia, & Rejas, 2010). This study also reported that the most common negative symptom was social withdrawal. Negative symptoms have been linked to a range of areas of functioning including cognitive impairment, intellectual impairments, poor outcome, response to neuroleptic treatment and lowered quality of life (Andreasen, 1982; M. F. Green, Kern, Braff, & Mintz, 2000; Myin-Germeys & van Os, 2007).

1.4 Schizophrenia, psychosis: a historical overview

A historical overview of the evolution of psychosis and the term schizophrenia is presented next.

1.4.1 History

French Physician Philippe Pinel, is credited as one of the founding fathers of Psychiatry. One of his case studies presented in 1809 is regarded as one of the earliest descriptions of schizophrenia (Kyziridis, 2005). A student of Pinel, Jean Etienne Esquirol is credited with defining hallucinations, and distinguishing them from illusions. He also defined a condition called “monomania” which is similar to concepts of paranoia schizophrenia (Choong, Hunter, & Woodruff, 2007; Kyziridis, 2005). Bénédict Augustin Morel, a French psychiatrist can be credited with the identification of the term schizophrenia. In his 1860 textbook “Traite des Maladies Mentales” (Treatise on Mental Illness) he was to first describe the concept of “Dementia Praecox” (which later came to be known as schizophrenia). He used this term to refer to states of cognitive decline in young people (Berrios, Luque, & Villagrán, 2003).

1.4.2 Emil Kraepelin

The term “Dementia Praecox” was advanced by German psychiatrist Emil Kraepelin (1856-1926). Kraepelin’s pioneering work was based on his observations and clinical notes of patients in hospitals he worked in. He defined

"Dementia Praecox" as a disorder with poor prognosis, early onset and a number of symptoms associated with it (Mueser & Jeste, 2011). His well-known work also includes the taxonomy he created for classifying and categorizing mental disorders. He viewed mental illnesses as biological diseases and asserted that specific clusters of symptoms were characteristic of specific conditions (Greene, 2007). He also believed that there was a clear divide between normal and abnormal (Bentall, 2006). Through the years and in his revisions of his Textbook of Psychiatry he also argued for a distinction between manic depression and 'dementia praecox' (now known as schizophrenia). 'Dementia praecox' was seen as a progressive neurodegenerative disease with poor recovery, defined on the basis of symptoms of psychosis, whereas manic depression was defined on the presence of neurosis (depression, anxiety), seen as episodic and a disease with better prognosis (Ebert & Bär, 2010). This division between affective and non-affective psychosis is still present today and encapsulated within diagnostic systems (Bentall, 2006).

1.4.3 Eugen Bleuler

Eugen Bleuler was a Swiss psychiatrist, who revised some of the ideas Emil Kraepelin put forward. Unlike Kraepelin, Bleuler did not believe that the prognosis of 'dementia praecox' was as bleak as proposed and is credited for a change in the terminology and understanding of the term 'dementia praecox'. (Mueser & Jeste, 2011). In 1911 he coined the term "Schizophrenia", which come from the Greek root "schizo" (split) and "phrene" (mind). He used this term to refer to fragmented thinking, not a split personality as it is sometimes known (Kyziridis, 2005; Mueser & Jeste, 2011). He defined schizophrenia in terms of the 4'A's that he believed were fundamental symptoms characteristic of psychosis: Affect (inability to display appropriate emotions), Autism (social withdrawal), Ambivalence (depersonalisation) and Associations (loosening of thoughts/thought disorder). Furthermore, loosening of associations was also proposed to be a primary (core deficit) that underlies schizophrenia (Moskowitz & Heim, 2011).

1.4.4 Kurt Schneider

Schneider was a German Psychiatrist who attempted to further advance and refine schizophrenia by defining symptoms he saw as integral to its diagnosis. These are now known as First Rank Symptoms. These include audible thoughts; arguing or commenting voices; feeling controlled or influenced by an external force; thought withdrawal; diffusion of thought; and delusions (Mueser & Jeste, 2011). Second rank symptoms included other forms of hallucinations, depressive or euphoric mood changes, emotional blunting, perplexity, and sudden delusional ideas (Lake, 2012).

1.5 Diagnostic criteria: DSM and ICD- evolution and changes

There are two main classification manuals used to diagnose mental disorders, the Diagnostic and Statistical Manual of Mental Disorders (DSM; American Psychiatric Association, 2013) and the International Classification of Mental and Behavioral Disorders (ICD; World Health Organization, 1992). The DSM is in its 5th version which was released in 2013, while the ICD is currently in its 10th version. The ICD 11 is under development, and a draft version was released in June 2018 to allow translation to other languages. By 2022, ICD 11 will fully replace ICD10 (World Health Organization, 1992). The taxonomy and classification system developed by Emil Kraepelin formed the basis for these manuals. The criteria and diagnosis for schizophrenia and related conditions have all been influenced heavily by the work of aforementioned psychiatrists.

1.5.1 ICD V DSM

Table 1 and 2 presents the diagnostic criteria for diagnosis of schizophrenia based on DSM and ICD classification systems. In the DSM-V, schizophrenia comes under the category “Schizophrenia Spectrum and Other Psychotic Disorders” which also includes delusional disorder, schizophreniform disorder and schizoaffective disorder (APA, 2013). In the ICD 10 schizophrenia comes under the class of “Schizophrenia, schizotypal and delusional disorders.” Looking at tables 1 and 2, there are some similarities between the two classifications. For

example, both propose that the time frame for symptoms to be present is one month. Likewise, in both manuals, the diagnosis of schizophrenia cannot be attributable to substance mis-use. There are some key differences between the two manuals. Firstly, the ICD places more emphasis on Schneiderian first rank symptoms such as delusions of control, whereas the DSM does not. The DSM places more emphasis on the impact of psychosis on social /occupational dysfunction. This is not included in the ICD. Finally, the ICD includes sub-types of schizophrenia including paranoid and catatonic types. The DSM-V has no sub-types of schizophrenia.

Table 1: DSM criteria for schizophrenia

DSM-V (APA, 2013): Diagnostic criteria for Schizophrenia
A: Characteristic symptoms: Two or more for the following, each present for at least one month. At least one of these should be 1-3. -delusions -hallucinations -disorganized speech -negative symptoms
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).
C: Duration: Continuous signs of the disturbance persist for at least 6 months. This 6-month period must include at least 1 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).
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.
E. Substance/general mood condition exclusion 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.
F. Relationship to Global Developmental Delay or Autism Spectrum Disorder: If there is a history of autism spectrum disorder, or other communication childhood disorder, the additional diagnosis of schizophrenia is made only if prominent delusions or hallucinations are also present for at least 1 month (or less if successfully treated).

Table 2: ICD criteria for schizophrenia

ICD- 10- 1993: Diagnostic Criteria for Schizophrenia
Either at least one of the syndromes, symptoms, and sign listed below under (1), or at least two of the symptoms and signs listed under (2), Should be present for most of the time during an episode of psychotic illness lasting for at least one month (Or at some time during most of the days): 1) <u>At least one of the following must be present:</u> a) Thought echo, thought insertion or withdrawal, or thought broadcasting. b) Delusions of control, influence or passivity, clearly referred to body or limb Movements or specific thoughts, actions or sensations; delusional perception. c) Hallucinatory voices giving a running commentary on the patient's behavior, or discussing the patient among themselves, or other types of hallucinatory voices coming from some part of the body. d) Persistent delusions of other kinds that are culturally inappropriate and completely impossible (ex: Being able to control the weather).
2) <u>Or at least two of the following:</u> a) Persistent hallucinations in any modality, when occurring every day for at least one month, when accompanied by delusions without clear affective content, or by persistent over-valued ideas. b) Neologisms, breaks or interpolations in the train of thought, resulting in incoherence or irrelevant speech. c) Catatonic behavior, such as marked apathy, paucity of speech, and blunting or incongruity of emotional responses.
3) <u>Most Commonly Used Exclusion Criteria:</u> 1) If the patient also meets criteria for manic episode or depressive episode, the criteria listed under I (1) and I (2) above must have been met before the disturbance of mood developed. 2) The disorder is not attributable to organic brain disease, or to alcohol or drug-related intoxication, dependence, or withdrawal.

1.6 Epidemiology of Psychosis

The frequency of a psychosis can be presented in terms of incidence or prevalence rates. The incidence is the rate of new cases of a condition within a period of time e.g. per year. It may be measured as a frequency count, a rate, or a proportion (Saha, Chant, Welham, & McGrath, 2005). On the other hand, prevalence is the proportion of people who have a condition at a particular time. Prevalence can be reported in a number of different ways. Period prevalence is the proportion of people who have the condition during a particular period e.g. annual, point prevalence is the proportion of people who manifest the disorder at a particular point e.g. day. Lifetime prevalence is the proportion of people who have had the diagnosis at some point in their lives (Saha et al., 2005).

1.6.1 Prevalence

A systematic review based on 188 studies reported a point prevalence of 4.6/1000, period prevalence of 3.3/1000 and lifetime prevalence of 4.0/1000 for schizophrenia (Saha et al., 2005). These rates were similar to an older study that reported an overall prevalence rate of 4.6/ 1000 (Torrey, 1987). One study screened members of the general population (*N*=8,028) for bipolar and psychotic disorders (including schizophrenia). The lifetime prevalence for non-affective psychotic disorders was 1.94%, whereas for schizophrenia alone it was 0.87% (Perälä et al., 2007). Another study that provided a concise overview of prevalence (as well as incidence rates) reported that about 7 people per 1000 will be affected by schizophrenia during their lifetime (McGrath, Saha, Chant, & Welham, 2008).

1.6.2 Incidence

A study conducted in the UK reported that the incidence of both affective and non-affective psychosis was 32 per 100,000 (Kirkbride et al., 2012). A highly cited review reported a median incidence rate for schizophrenia being 15.2 per 100,000 (McGrath et al., 2008). Several environmental and biological factors have been linked to increased incidence of psychosis. Stress – vulnerability models propose that psychotic symptoms emerge when the threshold of stress,

exceeds the persons vulnerability levels (Myin-Germeys, Krabbendam, Delespaul, & Van Os, 2003). Moreover, it has also been proposed that increased emotional reactivity (increased negative affect) to stressors is the core mechanism that predisposes a person to psychosis (Myin-Germeys et al., 2003). This heightened affective response to stress can make individuals sensitive to biological and environmental risk factors (Read, van Os, Morrison, & Ross, 2005; van Os, Kenis, & Rutten, 2010). A number of these environmental and biological factors will be discussed next.

1.6.2.1 Cannabis use

The use of cannabis has long been associated with psychosis (Moore et al., 2007). In a longitudinal population study of 1923 individuals from the general population (ages 14-24), it was found that incident cannabis use predicted the risk of later psychotic symptoms (Kuepper et al., 2011). Furthermore, this was independent of a number of confounding variables such as age, childhood trauma and gender. A comprehensive and systematic review on this topic concluded that there was enough evidence to inform young people that cannabis use may increase their risk of psychosis later in life (Moore et al., 2007). Although the exact mechanisms by which cannabis use may increase risk for psychosis is not yet known, some research suggests that polymorphisms in the COMT gene are associated with greater risk of psychosis if cannabis is used (Caspi et al., 2005).

1.6.2.2 Trauma

Traumatic experiences such as child sexual and physical abuse have been causally linked to psychosis especially symptoms such as hallucinations (Read et al., 2005). This finding has been replicated in a more recent review, which also included a greater range of traumas as well as childhood adversities such as bullying (Varese et al., 2012). Potential pathways that may link trauma to psychosis include negative emotions, dysfunctional beliefs about the self, as well as biological factors such as increased reactivity to stress (Schäfer & Fisher, 2011).

1.6.2.3 Ethnicity

Elevated rates of psychosis have been consistently reported in people of ethnic minorities, especially those from African- Caribbean or African origin (Wessely, Castle, Der, & Murray, 1991). It has also been shown that the incidence of schizophrenia in non-white ethnic minorities is higher when the minority group form a smaller percentage of the local population (Boydell et al., 2001). This finding has been found in both first and second generation migrants, as well as those in minority groups who haven't migrated (Bresnahan et al., 2007; Cantor-Graae & Selten, 2005). Potential mechanisms and explanations for these findings are partly due to the social adversity and marginalisation that may be experienced by these ethnic groups (Morgan, Charalambides, Hutchinson, & Murray, 2010; van Os et al., 2010).

1.6.2.4 Urbanicity

A large number of studies have now shown that rates of psychosis are higher in urban areas (Kirkbride, Jones, Ullrich, & Coid, 2014). For example, in a longitudinal study of 4.4 million people in Sweden it was found that people living in the most densely populated area had a 68-77% greater risk of developing psychosis than those in less densely populated areas (Sundquist, Frank, & Sundquist, 2004). It has also been shown that moving from an urban to a rural environment brings about a decrease in risk for psychosis (Pedersen & Mortensen, 2001). It has been suggested that this effect may be moderated by social factors such as marital status or single parent families (van Os et al., 2010).

1.6.2.5 Early biological factors

A wide range of early prenatal factors including birth complications, maternal stress, viral and bacterial infections have been linked to incidence of psychosis (Buka et al., 2001; Hultman, Sparén, Takei, Murray, & Cnattingius, 1999). The evidence for these factors is not as strong as previously mentioned ones (van Os et al., 2010).

1.7 Rethinking psychosis

Psychosis has traditionally been viewed as a categorical diagnosis- an individual is given a diagnosis for a psychotic disorder based on the presence or absence of criteria as set out in a diagnostic manual (Bentall, 2006). This is rooted in the early classification systems developed by Emil Kraepelin. Diagnostic manuals provide useful tools and guidelines for both clinical and research use, and it can be the route by which an individual seeks treatment for the distress they are experiencing. Furthermore, to some people, a diagnosis may serve as useful explanation for distressing, confusing or emotional experiences. However, this approach does not come without its criticisms and intense debate regarding classification is ongoing.

The fundamental concepts of the categorical approach to defining mental illness include that there is a clear boundary between sick and normal, that there are discrete mental disorders and that these disorders have a biological basis and can be viewed in the same way as physical disorders (Bentall, Jackson, & Pilgrim, 1988). However, emerging evidence suggests that each of these assumptions can be challenged and cast doubts on the categorical classification systems.

1.7.1 Affective v non-affective psychosis

There has always been a divide between affective and non-affective psychoses, embedded within classification systems. This divide assumes that affective disorders (e.g. bipolar) and psychotic disorders (e.g. schizophrenia) are qualitatively distinct, and separate disorders (Freeman & Garety, 2003). One argument against a clear distinction between affective and non- affective psychosis is the co-morbidity across the two classes. For example, having one disorder e.g. schizophrenia, should mean there is an elevated risk for schizophrenia in the person's family as it is a biological disease with a genetic basis. However, relatives of people who have schizophrenia also have elevated risk for other disorders such as bipolar, and the same argument holds for bipolar disorder (Farmer, McGuffin, & Gottesman, 1987; Greene, 2007). This has led some to suggest that rather than distinct, or discrete, unrelated disorders,

perhaps affective and non-affective psychosis exist on a continuum (Crow, 1990). This distinction is also blurred by the presence of disorders characterized by both affective and psychotic symptoms, such as schizo-affective disorder and by the observations that diagnoses can change over time, and cut across the divide (e.g. depression developing into a psychotic disorder)(Angst, 2002). Furthermore, the role of emotion in psychosis has been undermined. Indeed, individuals with psychosis do experience affective symptoms such as depression and anxiety, and that these emotional experiences can be linked to their symptoms (Freeman, Garety, Kuipers, Fowler, & Bebbington, 2002). This has been long recognized and was central to Bleuler's concepts of schizophrenia. In his book he argued the case that emotion is important and that the affective experiences of people with schizophrenia are transformed into symptoms such as delusions and hallucinations (Moskowitz & Heim, 2011). It has been shown that the presence of affective symptoms such as anxiety can precede the development of psychotic symptoms (Tien & Eaton, 1992) and affective disturbances are early symptoms reported by people who go onto develop psychosis (Freeman & Garety, 2003). It is interesting to also note that Kraepelin himself, towards the end of his career questioned the divide between neurosis and psychosis (Greene, 2007).

1.7.2 Symptom structure of psychosis

One of the other debates centres on the symptom structure of psychosis. Traditionally, psychosis was split on the basis of positive and negative symptoms (Andreasen, Flaum, Swayze, Tyrrell, & Arndt, 1990). The diagnosis of schizophrenia is based on scores on the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987). However, over the years there have been numerous studies finding evidence that a two factor structure is not sufficient (van der Gaag et al., 2006). In fact, studies have found 3, 4, 5, 6 and even 7 factor models (Emsley, Rabinowitz, & Torreman, 2003; van der Gaag et al., 2006), suggesting that psychosis may be defined on a broader range of symptoms. The most common factor structure is a 5 factor one that includes affective symptoms (anxiety/depression), excitability/hostility and disorganisation/cognitive (Lehoux, Gobeil, Lefèbvre, Maziade, & Roy, 2009).

1.8 Alternative Approaches

While the discrete, categorical approach to classifying mental disorders may be the predominant system, it is not the only one. Alternative approaches to classifying psychosis are presented next.

1.8.1 Continuum approach to psychosis

The continuum model of psychosis suggests that rather than viewing symptoms as present/absent, they can be viewed on a continuum. One of the classic studies supporting this view was conducted by Strauss in 1969 who interviewed a large number of inpatients on their symptom levels. Rather than symptoms being simply rated as absent or present (and distressing), an additional option was provided, where symptoms could be rated as present but not severe or distressing. When given this added flexibility, it was found that many symptoms did not fall into clear present or absent categories, and a gradient existed. Many patients experienced mild forms of delusions and hallucinations suggestive of a continuum (Strauss, 1969). This concept has been extended to the general population, where it has been shown that symptoms associated with psychosis such as delusions, are endorsed by healthy members of the population (van Os, Hanssen, Bijl, & Ravelli, 2000). This model suggests that symptoms associated with psychotic illness lies at the extreme end of a continuum, whilst milder experiences can be found in people who do not have a diagnosis (van Os, Linscott, Myin-Germeys, Delespaul, & Krabbendam, 2009). There is considerable evidence for the utility of this model.

1.8.1.1 Evidence for a psychosis continuum in the general population

A body of evidence for the psychosis continuum comes from epidemiological studies. In these studies, individuals from the general population are questioned on their experience of Psychotic like experiences (PLE's) through self-reported questionnaires, or clinician rated measures. For example, as part of the National Comorbidity Survey, over 5,000 members of the general population were screened for psychotic symptoms. Results found that 28.4% of individuals endorsed a PLE but only 1% were rated as having a diagnosis of schizophrenia, highlighting that endorsing such symptoms does not mean presence of disorder

(Kendler, Gallagher, Abelson, & Kessler, 1996). Another study reported that in a sample of 875 students, a significant proportion reported PLE's. For example, 28% reported hearing voices, whilst 26% reported feeling that their thoughts were being taken away or not their own (Yung et al., 2009). In a comprehensive meta-analysis a median prevalence of PLE's was reported to be 5% (van Os et al., 2009). Prevalence rates can differ based on the instrument used to measure PLE's, the definitions and types of samples used. It has also been shown that the majority of PLE's are transitory and cause no distress to the individual, but that the persistence of these experiences can predict the development of psychosis (Poulton et al., 2000; van Os et al., 2009). Another form of evidence that supports the continuum approach is that PLE's measured in such populations share the same risk factors as in those with psychosis. For example, a higher prevalence of PLE's are reported in males, ethnic minorities and in people who experience stressful life events (L. C. Johns et al., 2004; van Os et al., 2009). Also, exposure of cannabis and other psychoactive drugs predict a higher prevalence of PLE's (van Os et al., 2009). For these reasons, researchers have argued that individuals who report PLE's are a valuable population to study, as it is likely to further knowledge about the causes and mechanisms underlying psychosis (Linscott & van Os, 2013).

1.8.2 Single symptom approach

Another alternative approach to studying psychosis is the single symptom approach, which is related to the continuum approach. The single symptom approach proposes that rather than study clusters of symptoms e.g. positive symptoms, single experiences should be studied. This is termed the single symptom or complaint orientated approach (Bentall, 2006). Evidence for this approach comes from factor analysis studies conducted on positive symptoms. These studies find positive symptoms are best represented by a number of underlying dimensions including paranoia and hallucinations (Armando et al., 2010; Wigman et al., 2011). The single symptom approach emphasizes studying single symptoms as they are complex in nature. For example, the factors that underlie hallucinations may be different from grandiose ideas and what causes and maintains paranoia is likely to be different to the factors that cause and maintain a visual hallucination (Bentall, 2006), although they may share some

common mechanisms (Bentall, 2006). It has been argued that symptom specific models can further advance theory and treatment development (Freeman et al., 2002). The next section is now going to narrow focus onto the most widely studied PLE: paranoia.

1.9 Paranoia

Paranoia is defined as the unfounded fear that others intend to cause the person psychological, physical or social harm (Freeman & Garety, 2000). Paranoid delusions are one of the most common delusional beliefs in people with psychosis (Freeman, 2007) and paranoia has been widely studied in the general population. Over the past few decades great gains have been made in understanding the nature, structure, prevalence of paranoia, and cognitive models have been developed (Freeman, 2007).

1.9.1 Frequency and structure of paranoia

Paranoid thoughts are very common in healthy members of the population. One study reported that 47% of a sample 324 college students reported an episode of paranoid thinking that involved a clear belief that someone intended to cause harm to them (Ellett, Lopes, & Chadwick, 2003). In a large scale epidemiological study in over 8,000 people, the paranoia item “Have there been times when you felt that people were deliberately acting to harm you or your interests?” was endorsed by 9% (L. C. Johns et al., 2004). In 1202 healthy individuals who completed an online survey about paranoid thoughts it was found that one third of individuals endorsed paranoid thoughts (Freeman et al., 2005). This study went one step further than just assessing prevalence- it also looked at the structure of paranoid thoughts. Paranoia was found to be arranged on a hierarchy with more common paranoid items being endorsed more frequently (e.g. concerns about social rejection) and rarer more severe paranoid thoughts (e.g. there is a conspiracy against me) being endorsed less frequently. These infrequent and more bizarre suspicions are characteristic of people who experience psychosis and seem to occur in line with more common and plausible experiences. In other words, more serious paranoid thoughts are built upon more frequent suspicions and emotional concerns (Freeman et al., 2005).

1.9.2 Occurrence and persistence of paranoia

A number of psychological processes have been linked to the development and persistence of paranoid thoughts in the general population, as well as in clinical samples. Emotion factors appear to play an important role, with depression, anxiety and worry predicting both the development and maintenance of paranoid thoughts (Freeman, 2007; Freeman et al., 2012). Anxiety in particular, shows a strong and consistent association with paranoia. This is not surprising as paranoia concerns anticipation of threat- a state that would cause anxiety (Freeman, 2007). Perceptual anomalies are also linked to paranoia. The presence of puzzling, odd internal experiences often precede development of paranoid thoughts. Examples of odd experiences may be subtle hearing changes, such as noises being louder than usual (Freeman, 2007). This route to paranoid thoughts has received little attention however, partly because it is difficult to measure and lack of a clear definition (Freeman, 2007). Cognitive factors have also been linked to paranoia. Within this domain, the most well studied factor has been the jumping to conclusions reasoning bias. Initially, this was investigated in people with psychosis who experience delusions (rather than paranoia specifically). Typically, in this task, individuals have to decide from which two jars beads have been drawn from. Both jars will contain beads of two colours, but in different proportions. For example, one jar will have 85 red beads and 15 green beads, and the other jar will have 85 green beads and 15 red beads. A bead is drawn one at a time and individuals can request a certain number before they decide which jar the beads are from. People with delusions request to see fewer beads and hence “jump to conclusions”(Garety & Freeman, 1999). These findings have been extended to paranoid delusions (Moritz, Van Quaquebeke, & Lincoln, 2012; Startup, Freeman, & Garety, 2008). In recent years, sleep disturbances have also been linked to paranoia, particularly insomnia (Freeman et al., 2012) and it has been hypothesized that this relationship is mediated by negative emotion (Freeman et al., 2010).

1.9.3 Psychological models of paranoia

There are two main models of paranoia. The model developed by Bentall et al., (1994), argues that paranoid beliefs are a defence against negative emotional

experiences. For example, they argue that individuals, who are paranoid, have latent negative beliefs about themselves, which are activated by negative experiences. By trying to avoid this negative activation, people with paranoia develop external- personal attributions to prevent negative beliefs about the self from emerging. For example, a negative experience may be attributed to being planned by another person who is malicious and out to get them (Bentall, Kinderman, & Kaney, 1994). A key prediction from this model is that self-esteem levels should be normal in people with psychosis, as paranoia serves as a defensive function against low self-esteem. However, research has found inconsistent results regarding self-esteem and a trend towards *lower* self-esteem (Freeman, 2007). In contrast, the model put forth by Freeman and colleagues (2002) gives a direct role of emotion in paranoia. In this model, paranoid thoughts are conceptualised as threat beliefs, which arise as explanations for anomalous, unusual or puzzling experiences that the person experiences. The search for meaning, is influenced by both cognitive and emotional factors, and within the model, there are cognitive and emotional pathways to paranoid thoughts. In the emotional pathway, it is proposed that individuals who experience more negative affect, such as anxiety or depression will be more likely to develop paranoid interpretations of anomalous experiences (Freeman et al., 2002). The paranoid thoughts therefore are negatively charged and are a direct reflection of the person's affective state. The cognitive pathway to paranoia occurs via reasoning biases such as jumping to conclusions which may limit the amount of information used to develop explanations. Furthermore, it is also proposed that cognitive and affective pathways to paranoia interact (Freeman et al., 2002). The strong relationship between affective states such as anxiety and paranoia provide support for direct relationships between emotion and paranoia, consistent with the Freeman model (Freeman, 2007).

1.10 Summary of chapter

This chapter defined and gave a historical context into psychosis. It also covered controversies around classification of psychosis and described alternative models of psychosis including the continuum and single symptom approach. These alternative models were applied to paranoia, which is the main symptom I focus on in my thesis.

2 An introduction to Sleep

Sleep and wakefulness are behavioural and neurobiological states experienced by all human beings and mammals. Typically, humans sleep in one consolidated bout for around 7 hours every night. Humans spend a third of their lives asleep, and it is now well established that a good night's sleep is essential for adequate health and wellbeing (Lockley & Foster, 2012).

2.1 What happens during sleep?

Sleep is not a simple passive process, it is a complex neurobiological state and a number of intricate changes occur when we sleep and between the transitions of sleep and wake. Our sleep at night is split into two main stages: non-rapid eye movement sleep (NREM) and rapid eye movement sleep (REM). These two stages alternate to form a NREM-REM cycle roughly every 90 minutes, 4-5 times a night (McCarley, 2007). The proportion of NREM and REM sleep in each cycle changes, with higher levels of NREM during the first few cycles and an increasing amount of REM in the later cycles (Fuller, Gooley, & Saper, 2006). The sleep stages are characterised by distinct electroencephalography (EEG) patterns.

2.1.1 Scoring of sleep

The stages of sleep have normally been classified and scored on the manual developed by Rechtschaffen and Kales (Rechtschaffen & Kales 1968). This manual classed sleep into specific stages: wake, stage 1, stage 2, stage 3, stage 4, REM sleep and movement time. Furthermore, stages 1, 2, 3, and 4 form NREM sleep, while stage 4 is classed as REM sleep. Moreover, stages 3 and 4 together are called slow wave sleep, which is the stage associated with deep sleep (Moser et al., 2009). In 2004, the American Academy of Sleep Medicine (AASM) revised the sleep stage scoring and this manual was published in 2007. Under the new guidelines, sleep stages can be scored as N1, N2, N3 (with N3 reflecting SWS, which were classically stages 3 and 4 under R and K scoring) or stage R for REM sleep (Moser et al., 2009).

2.1.2 NREM sleep

Stage N1 is characterised by theta waves, and this stage is similar to being in a state of relaxed wakefulness. Stage N2 sleep is characterised by short bursts of spindle activity called sleep spindles and high amplitude and low frequency events known as k complexes. During this stage our conscious awareness of the external environment fades but we can be awoken easily. Stage N3 is referred to as deep sleep or slow wave sleep (SWS) and is characterised by delta waves. The more sleep deprived an individual is, the more time they spend in SWS (Fuller et al., 2006). Therefore, NREM sleep can be seen as the stage of sleep associated with a slowing of an individual's body, as the breathing, heart rate and blood pressure falls and the sleeper becomes unaware of the external environment. NREM sleep takes up 75% of our sleep. Dreams from NREM sleep tend to be brief, fragmented and lacking emotion (McCarley, 2007).

2.1.3 REM sleep

Stage R sleep is defined by the presence of desynchronised, low voltage, mixed frequency beta brain waves. It is also characterized by bursts of rapid eye movements and paralysis of the body (McCarley, 2007). REM sleep is commonly referred to as paradoxical sleep because the brain is highly active, but the body is paralysed. REM sleep comprises 25% of our total sleep time (McCarley, 2007). The first REM period of the night is short, but these periods become longer as the night goes on. REM sleep is the stage of sleep associated with vivid, bizarre and emotionally salient dreams.

2.2 How is sleep/wake cycle governed? The two process model of sleep/wake regulation

The two process model of sleep/wake regulation was proposed in 1982, and it provides a useful framework by which to understand how the depth and timing of our sleep/wake cycle is controlled (Borbély, 1982). The model suggests that our sleep/wake cycle is governed by two mechanisms acting either in synchrony or in opposition to each other along the 24-hr cycle: the homeostatic process and the circadian process.

2.2.1 The sleep homeostat

The homeostatic process is also called process S or our level of sleep pressure. Our homeostatic drive is like an hourglass, the longer we are awake, the greater the homeostatic drive (or sleep pressure) and the greater the likelihood of falling asleep. This process coincides with a decreases in cognitive performance, alertness and an increase in sleepiness. Likewise, the longer we have been asleep, the lower the pressure to sleep and the likelihood of waking increases (Borbely, Achermann, Trachsel, & Tobler, 1989). One of the substrates linked to homeostatic control is adenosine. Increased adenosine is associated with an increased need to sleep, suggesting that adenosine, may be involved in the homeostatic control of sleep (Schwartz & Roth, 2008). The alerting effects of caffeine work by antagonizing adenosine receptors (Schwartz & Roth, 2008).

2.2.2 The circadian process

On the other hand, the circadian process, (also known as the circadian pacemaker or 'master clock') governs the timing and temporal organization of our sleep/wake cycle. The master clock is aptly located just above the optic chiasm, in a tiny region of the anterior hypothalamus called the suprachiasmatic nucleus (SCN). The location of our circadian clock allows it to keep track of the time of day based on light information via the retino-hypothalamic tract, which is then used to govern the timing of numerous physiological processes such as body temperature and the hormone melatonin, which promotes sleep. Humans are a diurnal species, and the circadian process promotes wakefulness by generating an arousal signal that increases in strength throughout the day and declines during the night (Dijk & Lockley, 2002). For example, when darkness falls our clock starts to prepare the body for sleep by increasing levels of melatonin and lowering body temperature which promotes sleep. As morning approaches, the light suppresses melatonin, body temperature rises, cortisol levels increase and waking occurs (Saper, Cano, & Scammell, 2005).

2.2.3 How the model works

The two process model states that at any given time, the degree of sleepiness and alertness is determined by the interacting influences of the two processes.

For example, in the evening it is the low circadian pressure to sleep that stops us from falling asleep when the homeostatic sleep drive is high. In this case, the two processes work against each other, which in turn ensure a consolidated bout of sleep or wakefulness. When the two processes work in synchrony, for example roughly 15 hours after wakefulness we fall asleep as both the circadian and homeostatic sleep drive for sleep is high (Borbely et al., 1989). More recently, the model has been reviewed and updated. One of these developments includes the emphasis on the continuous interaction between process S and C, rather than these two processes only interacting at sleep and wake. Another revision includes viewing the circadian clock as a maintainer of temporal integrity rather than the generator of circadian rhythms. Finally, the description highlights the role of energy metabolism, such that metabolic processes are modulated by the light/dark cycle (Borbely, Daan, Wirz-Justice, & Deboer, 2016). The neuroanatomical basis for the sleep wake cycle is located in the hypothalamus, with neurons in the ventro-lateral pre optic nucleus (VLPO) being active during sleep (homeostatic sleep pressure). In contrast the lateral hypothalamus contains populations of wake promoting 'orexinergic neurons' containing glutamate that project to arousal centres in the brain such as the brainstem promoting wakefulness (circadian) (Saper et al., 2005). The two process model is depicted in figure 1 which depicts how process S and process C interact and govern our sleep/wake cycle.

Figure 1: Two process model of sleep

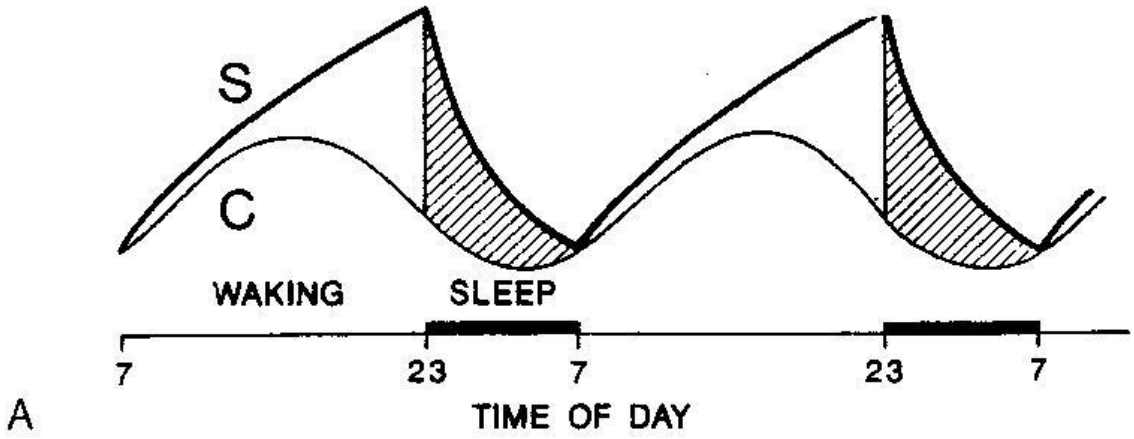


Figure 1 is taken from (Borbely and Achermann 1999).

2.2.4 Definitions

The previous sections aimed to provide a short overview on sleep/wake processes, and highlight the complexity of our sleep/wake rhythm and how it is governed. Sleep disturbance is a broad term that can be used to describe the range of sleep/wake difficulties that a person may experience. Sleep disturbance may come in the form of symptoms such as lack of sleep, trouble getting to sleep or issues with the timing of sleep and wake. Sometimes symptoms, if severe or persistent enough can lead to the development of a sleep disorder. According to the International Classification of sleep disorders (ICSD, 2014), sleep disorders can be categorised into 6 types. The categories include insomnia (e.g. difficulties falling asleep), parasomnias (e.g. nightmares, sleepwalking), circadian sleep/wake disorders (e.g. delayed sleep phase syndrome), disorders of hypersomnolence (e.g. narcolepsy), sleep related breathing disorders (e.g. sleep apnoea) and sleep related movement disorders (e.g. restless legs).

2.2.5 Sleep disorders

One of the most common sleep disorders is insomnia disorder which is characterised by the presence of difficulties initiating or maintaining sleep, or

reports of non-refreshing sleep that impact on daytime functioning (APA, 2013). Importantly, within the DSM -5 insomnia is viewed as a disorder in its own right that needs to be treated independently, regardless of any other co-morbid condition. Another common class of sleep disorders are those related to circadian rhythm disturbance. These disorders are characterised by a mismatch between a personals internal sleep/wake cycle and the external environment. For example, in delayed sleep wake syndrome (DSPS), individuals go to sleep and wake much later than they would like and this then begins to interfere with daily routines and commitments. Insomnia can be common symptom of DSPS as individuals may try to go to sleep early in order to get up for commitments such as word, but this goes against their internal cycle, causing difficulties getting to sleep (APA, 2013). Insomnia symptoms can be a common feature of other sleep disorders and it is important to adequately assess the nature of the sleep disturbance so as to provide the correct mode of treatment.

2.2.6 Impact of sleep disturbance: survey evidence

Sleep disturbance in general is associated with poor health and mental wellbeing. Indeed, a good night's sleep is becoming rare due to the 24-hour society we now live in. Advances in technology mean people are constantly on some form of screen including phones, IPAD's, laptops and TV's, all of which have negative effects on sleep. Furthermore, businesses open later, more people work through the night, and these all present new challenges and pressures to our sleep/wake rhythm (Lockley & Foster, 2012). Surveys conducted in the British public reveal some interesting insights into the sleep of Britons. The Understanding Society is a UK based longitudinal study funded by the Economic and Social Research Council (ESRC) which is following 40,000 individuals over time until March, 2018 collecting a wide range of data annually on economic and social circumstances as well as health information (http://www.esrc.ac.uk/research/our-research/understanding-society-the-uk-household-longitudinal-study/). Subsets of individuals have completed questions on sleep which is summarized in the Better of Sleep Better report (2011). Analysis of data from 14,000 UK households revealed that one in 10 people report taking sleeping medication on three or more nights a week and that women are more likely to report sleep difficulties. It was also found that across

gender and age, poor sleep was associated with poorer health (https://www.understandingsociety.ac.uk/research/publications/findings/early) . The Great British Sleep Survey which started in 2012, is another similar survey, which is solely focused on the sleep of over 20,000 Britons. Things that are keeping Britons up at night include physical features of the environment such as light, as well as cognitive factors such as thoughts about the future (Great British Sleep Survey, 2012). The survey also revealed that poor sleepers in comparison to good sleepers experience more fatigue, low mood, feel more alone and struggle to be productive.

2.2.7 Impact of sleep disturbance: experimental evidence

In line with subjective surveys, research has shown that sleep disruption at different levels has been associated with a range of adverse outcomes including cognitive impairment and emotion dysfunction.

2.2.7.1 Sleep disturbances and cognition

It has been shown that curtailment of sleep is associated with a range of cognitive impairments. In a meta-analysis it was concluded that sleep loss impairs accuracy and speed on a range of cognitive domains including attention, reasoning, short term memory and processing speed (J. Lim & Dinges, 2010) . Furthermore, sleep is actively involved in memory processing with evidence that the different sleep stages are linked to the processing of different types of memories. For example, NREM sleep has been linked to declarative memory, whilst REM sleep appears to have an important role in the consolidation of emotional memories, especially those that are negatively charged (Wagner, Kashyap, Diekelmann, & Born, 2007). These findings have real world implications as lapses in attention and memory can be responsible for fatal accidents, as well as errors made my physicians (Horne & Reyner, 1995; Lockley et al., 2004). Some of the effects of poor sleep can be remediated by normal sleep, highlighting the importance of a good night's sleep (Waters & Bucks, 2011).

2.2.7.2 Sleep disturbances and emotion

There is an intimate relationship between sleep and emotion. Consecutive nights of poor sleep is associated with feeling down and more easily irritated (Vandekerckhove & Cluydts, 2010). Under conditions of sleep loss, there is an increased reaction to negative stimuli (Franzen & Buysse, 2008). In a study on medical students it was shown that sleep loss amplified the negative emotional effects of a disruptive events, and decreased the positive effects of goal enhancing events (Zohar, Tzischinsky, Epstein, & Lavie, 2005). These findings also extend to the domain of emotion perception, with sleep disruption being linked to impaired ability to accurately rate emotions of others (Huck, McBride, Kendall, Grugle, & Killgore, 2008). Circadian disruption of sleep such as when timing of our sleep becomes disrupted is also linked to emotion. Intuitive examples of this include shift work and jetlag, which most of us experience as some point in our lives. But circadian disruption can also become apparent at a more day to day level, when our social and work/school commitments result in periods of sleep deprivation and light exposure at the wrong times (e.g. light at night). This can affect us all and is termed “social jetlag” (Roenneberg, Wirz-Justice, & Merrow, 2003). Social jetlag and misalignment of sleep timing is linked to increased depression, mood fluctuations, anxiety and anger (Levandovski et al., 2011; Pritchett et al., 2012).

2.3 Sleep and mental health

So far, we have seen that the sleep-wake cycle is a complex behavioural state regulated in numerous aspects of the brain, and that sleep disruption is associated with negative outcomes. The next section will focus on sleep in relation to mental health.

2.3.1 Sleep disruption in mental health disorders

Sleep disturbance is common in a wide range of mental health conditions. The classic meta-analysis by Benca et al., (1992) combined the results of 177 studies, including 7151 patients. Across all mental health conditions there was reduced sleep time and poor sleep efficiency compared to controls. Sleep disruption is becoming recognised as an important and potential mechanism that may be

linked to the symptoms associated with mental health disorders (Harvey, Murray, Chandler, & Soehner, 2011). The strongest support so far for sleep disruption is in affective disorders, but sleep disruption cuts across a broad range of mental health conditions including psychosis (Baglioni et al., 2016; Benca, Obermeyer, Thisted, & Gillin, 1992).

2.3.2 How is sleep linked to mental health disorders: the role of emotion?

The mechanism that may link together sleep and its presence in mental health disorders is emotion, as both sleep and emotion share some common neurobiology. It has been shown that sleep loss leads to decreased medial-prefrontal cortical activity and increased amygdala activation, suggesting that under conditions of poor sleep, our ability to regulate emotion is reduced (Yoo, Gujar, Hu, Jolesz, & Walker, 2007). The sleep wake cycle is governed in an intricate manner. During sleep neurons in the VLPO fire twice as fast, and they inhibit the wake promoting arousal systems through inhibitory neurotransmitters such as GABA and galanin (Saper et al., 2005). During wake, the ascending arousal system promotes wakefulness starting in the upper brainstem. The arousal system has multiple pathways and cell pathways that fire during wake and inhibit the sleep promoting VLPO including noradrenergic, serotoninergic, dopaminergic neurons (Saper et al., 2005). Emotion is also regulated by some of the same systems. For example, the amygdala is located in the forebrain and is involved in emotion processing and has connections with areas governing sleep and wakefulness. Through its connections, the amygdala not only has a role in emotion processing but also is involved in regulating brainstem neural mechanisms effecting sleep and wakefulness (Vandekerckhove & Cluydts, 2010).

2.4 Sleep in psychosis

The previous sections outlined that sleep disruption has negative consequences on functioning including an increase in mood disturbance, and that sleep disruption is commonly reported in psychiatric disorders. Emotion may be one mechanism linking sleep and psychiatric disorders. Going back over 100 years, sleep was acknowledged to be disturbed in people with psychosis. Severe sleep deprivation has been associated with inducing hallucinations and delusional

thoughts (Luby, Frohman, Grisell, Lenzo, & Gottlieb, 1960; West, Janszen, Lester, Lester, & Cornelisoon, 1962). However, it is only over the last few decades that sleep has been systematically investigated and thoroughly explored. It has been shown that disturbances of sleep are very common and found through all stages of the disorder and has been linked to psychotic symptoms including paranoia (Cohrs, 2008; Reeve, Sheaves, & Freeman, 2015).

2.5 Integration of chapters and aims of the thesis

Psychosis is commonly defined on the presence of positive symptoms such as paranoia, and within psychosis, schizophrenia is the most well studied disorder. It has been shown that symptoms of psychosis such as paranoia exist on a continuum in the normal population, and that the study of individual experiences can inform us about more severe forms of the disorder. In this thesis I focus on paranoia, and its relationship to an important correlate: sleep disturbance. Furthermore, negative emotionality is linked to both sleep and paranoia, and will be explored as a potential mechanism that could link sleep and paranoia together. The relationship between sleep, paranoia and negative emotion will be studied in both non-clinical and clinical samples (chapters 3 and 5). Chapter 4 will present a systematic review of literature investigating sleep in psychosis, with a specific focus on methodology. Finally, chapter 6 explores clinician perceptions of sleep in people with psychosis. This final chapter aims to identify gaps in treating sleep in psychosis and addresses how these can be overcome.

3 Sleep quality and paranoia: The role of alexithymia, negative emotions and perceptual anomalies

3.1 Introduction

Paranoia is defined as the unfounded fear that others intend to cause you harm, is a common and distressing experience reported by many individuals with psychosis (Freeman & Garety, 2000). Paranoid thinking is not confined to psychosis, and is reported by up to 30% the general population (Freeman, 2007; Freeman et al., 2005). Studying symptoms like paranoia at a sub-clinical level can further inform our knowledge about symptoms at a clinical level in line with psychosis continuum models and identify candidate variables for future clinical research (van Os et al., 2009).

Recent research has identified a robust link between sleep disturbances and paranoia. At the non-clinical level, sleep deprivation in healthy individuals lead to an increase in paranoid thoughts (Kahn-Greene, Killgore, Kamimori, Balkin, & Killgore, 2007). Another study administered the Oxford Sleep Survey which includes questions on sleep and PLE's to over 1000 students. Results found links between a number of sleep disorder symptoms such as insomnia, nightmare frequency and nightmare distress and PLE'S including paranoia (Sheaves et al., 2016). In a large –scale general population study conducted of 8,580 people, there were strong relationships between insomnia and paranoia. Insomnia was associated with an approximately two to threefold increase in paranoid thinking (Freeman et al., 2010). Prospectively, insomnia was also a significant predictor of new incidence of paranoid thoughts, suggestive of insomnia having a causal role (Freeman et al., 2012).

Furthermore, treating sleep disturbance with Cognitive Behavioural Therapy for Insomnia (CBTi) leads to improvements in sleep, paranoia, perceptual anomalies and emotional variables, in both clinical and non-clinical samples (Freeman et al., 2017; Freeman, Sheaves, et al., 2015; Myers, Startup, & Freeman, 2011).

With the link between sleep and paranoia being established, the next step turns to identifying how sleep and paranoia are related (Reeve et al., 2015). This question can be addressed by mediation analysis. Mediation is a regression based statistical approach that allows us to identify factors that significantly explain the variance between our independent (sleep) and dependant variable (paranoia) (Hayes, 2017). These factors are termed mediators and can be useful in helping us identify targets for treatments, as well as helping refine models of paranoid thinking.

Negative emotions such as anxiety and depression are linked to both sleep and paranoia (Baglioni, Spiegelhalder, Lombardo, & Riemann, 2010; Freeman et al., 2012) and have been identified as mediators. Indeed, research has shown that negative emotions account largely for the relationship between sleep and paranoia (Freeman, Pugh, Vorontsova, & Southgate, 2009; Mulligan, Haddock, Emsley, Neil, & Kyle, 2016). Along with negative emotions, another emotion related mediator that has been studied recently is emotion regulation. One study found that the effect of insomnia on paranoid ideation was mediated by a frequent use of ineffective strategies such as expressive suppression and an infrequent use of effective strategies such as reappraisal. This suggests there may be a number of emotional processes linking sleep to paranoia (Grezellschak, Lincoln, & Westermann, 2015)

Along with emotional processes, non-emotional factors such as perceptual anomalies may also mediate the link between sleep and paranoia (Freeman et al., 2010). Sleep deprivation has been known to induce perceptual anomalies such as hallucinations (West et al., 1962). More recently, a study showed that insomnia was associated with perceptual anomalies (hallucinations), even after controlling for negative emotions (Sheaves et al., 2016). Furthermore, perceptual distortions are considered central to paranoia (Freeman et al., 2002). No direct test of this exists although cannabis use which can induce anomalous experiences partially mediates the relationship between insomnia and paranoia (Freeman et al., 2010).

We sought to replicate and build on some of these findings. The main aim of our paper is to investigate the role of alexithymia as a potential mediator.

Alexithymia is an aspect of emotion that is concerned with an individual's ability to recognise, and verbalise their emotions (Bagby, Parker, & Taylor, 1994). Individuals with high alexithymia experience difficulties in identifying their emotions, describing their feelings, and exhibit an externally orientated style of thinking which can be accompanied with arousal (Bagby et al., 1994). Alexithymia is a relevant candidate as it linked to both sleep and paranoia. One study reported that that those with low levels of emotional awareness (high alexithymia) reported higher suspiciousness (Boden & Berenbaum, 2007). Higher levels of alexithymia in people with psychosis have also been reported in comparison to controls (Kimhy et al., 2014; van 't Wout, Aleman, Bermond, & Kahn, 2007). Furthermore, alexithymia is linked to a range of sleep disturbances including insomnia, daytime sleepiness and nightmares (Bauermann, Parker, & Taylor, 2008). Under conditions of sleep deprivation there is a decrease in emotional intelligence- a trait similar to alexithymia (Killgore et al., 2008). More specifically, this study reported a decrease in the intrapersonal functioning component of emotional intelligence which is concerned with knowing and understanding our feelings (Killgore et al., 2008).

Therefore, we predicted that alexithymia mediates the relationship between sleep quality and paranoia, in addition to negative emotional states such as anxiety and depression.

A secondary aim of our study was to test whether perceptual anomalies mediates the relationship between sleep and paranoia. To do so, we included a comprehensive measure of perceptual anomalies- the Cardiff Anomalous Perceptions Scale (Bell, Halligan, & Ellis, 2006).

In study 1 we hypothesised that 1) sleep quality, negative emotions, alexithymia and perceptual anomalies predict paranoid thoughts and 2) that the relationship between sleep quality and paranoia will be mediated by negative emotions, alexithymia and perceptual anomalies. Study 2 was conducted to try and replicate the mediation model we developed in study 1.

3.2 Study 1: Methods

3.2.1 Participants and procedures

In order to recruit a large sample, and provide a safe, environment for volunteers to disclose paranoid thoughts, an anonymous online survey was set up using Qualtrics (http://www.qualtrics.com/login/). The sample was recruited using the University of Glasgow's School of Psychology's online subject pool. Participants were excluded from the study if they reported a diagnosed psychiatric/physical condition, traumatic brain injury, recreational drug use and were aged under 16. The online survey was available online from 2012 to 2013. The study was approved by the University of Glasgow, School of Psychology Ethics committee.

3.2.2 Measures

3.2.2.1 Positive and Negative Affect Schedule (PANAS) (Watson, Clark, & Tellegen, 1988):

The PANAS has two ten -item subscales of positive (PA) and negative (NA) affect. The questionnaire has been psychometrically evaluated in non-clinical groups (Watson et al., 1988). The range of scores for each sub-scale ranges from 10-50, with higher scores meaning higher negative or positive affect. The PANAS can be used to assess affect on various time scales by altering the instructions. For the present study 'current moment' assessment was used. Internal consistency (α = .84).

3.2.2.2 Hospital Anxiety and Depression scale (HADS) (Zigmond & Snaith, 1983):

The HADS is a self-report rating scale designed to measure both anxiety and depression over the past week. It consists of two subscales, each containing seven items on a 4-point Likert scale (ranging from 0-3). It is scored by summing the ratings for the 7 items of each subscale to yield separate scores for anxiety and depression. The questionnaire has been psychometrically evaluated in non-clinical groups(Crawford, Henry, Crombie, & Taylor, 2001). Internal consistency (α = .82).

3.2.2.3 Toronto Alexithymia Scale (TAS-20) (Bagby et al., 1994).

Has a 3-factor structure. Factor 1 assesses difficulty in identifying feelings. Factor 2 assesses difficulty in describing feelings. Factor 3 assesses externally oriented thinking. Scores range from 20-100 with higher scores reflect higher alexithymia. There is no timescale for alexithymia as it is measured as a trait factor. The questionnaire has been psychometrically evaluated in non-clinical groups (Bagby et al., 1994).

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

The PSQI provides a reliable, valid, and standardized measure of sleep quality. Scores range from 0-21 with higher scores representing poorer sleep. A PSQI global score > 5 indicates that a subject is having severe difficulty in at least two areas, or moderate difficulty in more than three areas of sleep quality in the past month.The questionnaire has been psychometrically evaluated in non-clinical groups (Mollayeva et al., 2016)

3.2.2.5 Green Paranoid Thoughts Scale Part B (GPTS) (C. E. Green et al., 2008).

The G-PTS is a 16-item measure of paranoia, assessing ideas of persecution over the past month. Scores range from 16-80 with higher scores indicating greater levels of paranoid thinking. The questionnaire includes subscales for conviction, preoccupation, and distress. The questionnaire has been psychometrically evaluated in clinical and non-clinical populations. Internal consistency ($\alpha = .92$).

3.2.2.6 Cardiff Anomalous Perceptions Scale (CAPS) (Bell et al., 2006).

The CAPS is a 32-item questionnaire, developed in both non-clinical and psychosis groups, and assesses perceptual anomalies such as changes in levels of sensory intensity, distortion of the external world, sensory flooding and hallucinations. Scores range from 0-32, higher scores mean higher endorsement of perceptual anomalies. For the present study the time scale was changed to the ‘past month’ in order to provide a more current assessment of perceptual anomalies. Internal consistency ($\alpha = .88$). The questionnaire has been psychometrically evaluated in non-clinical groups (Bell et al., 2006).

3.3 Data Analysis and preperation

The GPTS showed high levels of skewness, which was expected as paranoia is thought to lie on a quasi- continuum, whereby 'many endorse few paranoid thoughts and few endorse many paranoid thoughts' (Freeman et al., 2005; Verdoux & van Os, 2002). To address this we dichotomised the variable. Subjects with paranoia scores at the 75th percentile or above were classed as the 'high paranoid' group and those below the 75th percentile as the 'low-paranoid' group (Stopa & Clark, 2001).

Next, linear regression models were run to test which variables significantly predicted paranoid group membership. Our dependent variable was paranoid group (0 = low paranoia, 1 = high paranoia). Forced entry and backward stepwise models were run to ensure reliability of results.

Mediation analysis was conducted using the SPSS macro PROCESS (model 4) which uses a bootstrapping approach to mediation (Hayes, 2012). Bootstrapping involves creating a repeated series of representations of the population by resampling from the current sample to replicate the original sampling procedure. For the current study, we chose to set the number of bootstrapping samples to 10,000. In turn, these 10,000 bootstrapping samples were used to generate a 95% confidence interval for the mediation effect. The mediation effect is statistically significant if the confidence interval does not contain the value of zero (Hayes, 2012). For ease of interpretation, standardised values are presented unless otherwise stated.

3.4 Results

3.4.1 Descriptive statistics and correlations

Table 3 presents all the descriptive information for the sample. A total of 401 individuals (*n*= 93 males, 308 females) completed the survey with a mean age of 24 (*SD*= 8.1, range 16-70). The correlations between all the variables are shown in table 4. Age was correlated with several our predictors including sleep quality, alexithymia and perceptual anomalies, therefore we included it as a co-variate in further analysis. A series of Mann- Whitney U tests revealed gender

was not related to any of our variables except anxiety and depression. Anxiety scores were significantly higher in females (*Mdn* = 8) than males (*Mdn* = 7), U = 11985.5, p = 0.01 and depression scores were significantly higher in males (*Mdn* = 5) than females (*Mdn* = 4), *U* = 12340.5, *p* = 0.04. As these differences are small, we chose not to include gender as a co-variate in further analysis.

3.4.2 Logistic regression

We first tested hypothesis 1 that sleep quality, negative emotions, alexithymia and perceptual anomalies predict paranoia. Descriptive statistics of the low and high paranoid group are presented in table 5. Mann Whitney u tests were used to test the validity of our grouping. Validity of our grouping was confirmed as the high paranoid group reported higher levels of negative affect, anxiety, depression, alexithymia, perceptual anomalies and paranoia. There were no differences in positive affect or gender.

Next, we ran logistic regressions with the predictors entered being age, negative affect, sleep quality, anxiety, depression, perceptual anomalies and alexithymia. Results of both logistic regressions are shown in table 6. A test of the full model against a constant only model (no predictors) was statistically significant, indicating that the predictors reliably distinguished between the paranoid and non-paranoid groups (c^2 = 69.078, p <.0.001). The Wald test was used to determine what predictors are significant. Significant predictors of paranoid group membership included negative affect, sleep quality, alexithymia and perceptual anomalies. Age, anxiety and depression did not significantly predict paranoid group membership. The log odds (Exp B) column in table 4 is an indicator of the log odds of being in the paranoid group due to a one point increase in the predictor variable. For example, a one unit increase in negative affect increases the odds of being in the paranoid group by 1.05, 95%CI [1.00-1.09]. Nagelkerke's $R^2$of .231 indicated that 23% of the variance was explained by the significant predictors. Similar results were obtained in the stepwise logistic regression which also found that negative affect, sleep quality, alexithymia and perceptual anomalies predicted paranoid group membership and this model explained 22% of the variance (Nagelkerke's $R^2$of .222). In sum, two

separate regression models showed that negative affect, alexithymia, perceptual anomalies and sleep quality predicted membership of the paranoid group.

Table 3: Sample demographics for study 1 (N=401)

	Mean	SD	Median	Range
Age	24.08	8.15	22.00	16-70
PSQI	6.56	3.27	6.00	0-21
PA	24.73	8.15	24.00	11-50
NA	15.87	6.44	14.00	10-40
HADS-A	8.15	3.91	8.00	0-20
HADS-D	4.59	3.28	4.00	0-19
TAS-20	48.08	11.55	48.00	23-79
GPTS	20.03	8.43	17.00	16-70
CAPS	3.73	4.73	2.00	0-28

Abbreviations: PSQI- Pittsburgh Sleep Quality Index, PA and NA- Positive and Negative Affect, HADS-A and D Hospital Anxiety and Depression Scale respectively, TAS-20 – 20-item Toronto Alexithymia Scale, GPTS- paranoia subscale of the Green Paranoid Thoughts Scale, CAPS- Cardiff Anomalous Perceptions Scale.

Table 4: Spearman rho correlations for study 1.

	Measure	1	2	3	4	5	6	7	8
1.	**Age**								
2.	**PA**	0.13*							
3.	**NA**	-0.12*	-0.02						
4.	**HADS- A**	0.00	-0.11*	0.47*					
5.	**HADS-D**	0.01	-0.29*	0.42*	0.46*				
6.	**PSQI**	-0.13*	-0.23*	0.24*	0.36*	0.35*			
7.	**TAS**	-0.18*	-0.28*	0.27*	0.43*	0.41*	0.33*		
8.	**GPTS**	-0.13*	0.09	0.28*	0.24*	0.20*	0.19*	0.30*	
9.	**CAPS**	-0.18*	-0.05	0.21*	0.29*	0.25*	0.23*	-0.29	0.39*

Abbreviations: PSQI- Pittsburgh Sleep Quality Index, PA and NA- Positive and Negative Affect, HADS-A and D Hospital Anxiety and Depression Scale respectively, TAS-20 – 20-item Toronto Alexithymia Scale, GPTS- paranoia subscale of the Green Paranoid Thoughts Scale, CAPS- Cardiff Anomalous Perceptions Scale. *p <0.05

Table 5: Descriptive information of the high and low paranoid groups for study 1.

	Low Paranoia (*n*=295) Mean (SD)	High Paranoia (*n*=106) Mean(SD)	Test Statistic (DF)	P Value
Gender (men: women)	69:226	24:82	x2 (1)=0.02	0.49
Age	24.59(8.66)	22.67(6.37)	*U*= 13569	0.04
PSQI	6.11(3.04)	7.81(3.57)	*U*=11073	<.001
PA	24.84(8.08)	24.42(8.39)	*U*=15039	0.56
NA	14.86(5.72)	18.67(7.46)	*U*=10768	<. 001
HADS-A	7.65(3.81)	9.55(3.87)	*U*=11334	<. 001
HADS-D	4.30(3.16)	5.38(3.50)	*U*=12642	<. 001
TAS-20	46.23(11.56)	53.25(9.85)	*U*=10092	<. 001
GPTS	16.60(0.95)	29.60(11.95)	*U*=000	<. 001
CAPS	2.77(3.53)	6.40(6.37)	*U*=9121	<. 001

Abbreviations: PSQI- Pittsburgh Sleep Quality Index, PA and NA- Positive and Negative Affect, HADS-A and D Hospital Anxiety and Depression Scale respectively, TAS-20 – 20-item Toronto Alexithymia Scale, GPTS- paranoia subscale of the Green Paranoid Thoughts Scale, CAPS- Cardiff Anomalous Perceptions Scale.

Table 6: Logistic regression of variables that predict membership of being in the paranoid group in study 1

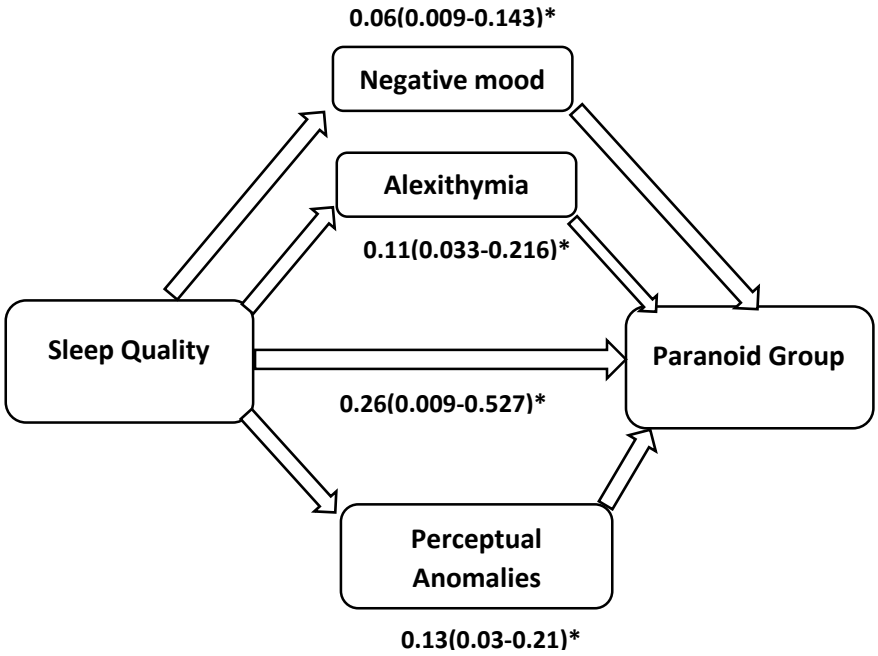
Model	B(SE)	Wald	Sig	Exp(B)	95% CI	
					Lower	Upper
Forced Entry model						
Constant	-3.85(0.82)	21.81	0.00	n/a		
Age	-0.22(0.01)	1.34	0.24	0.97	0.94	1.01
NA	0.04(0.02)	4.91	0.02	1.05	1.00	1.09
HADS-A	0.01(0.04)	0.10	0.74	1.01	0.93	1.09
HADS-D	-0.05(0.04)	0.72	0.27	0.95	0.86	1.04
PSQI	0.08(0.04)	4.39	0.03	1.09	1.00	1.18
TAS-20	0.03(0.01)	6.24	0.01	1.03	1.00	1.05
CAPS	0.10(0.02)	14.00	0.00	1.11	1.05	1.17
Stepwise model (Backward)						
Constant	-4.31(0.64)	44.90	0.00	n/a		
NA	0.04(0.01)	5.30	0.02	1.04	1.00	1.08
PSQI	0.07(0.04)	3.86	0.04	1.08	1.00	1.17
TAS-20	0.03(0.01)	6.96	0.00	1.03	1 .00	1.05
CAPS	0.10(0.02)	14.36	0.00	1.11	1.05	1.17

Abbreviations: PSQI- Pittsburgh Sleep Quality Index, PA and NA- Positive and Negative Affect, HADS-A and D Hospital Anxiety and Depression Scale respectively, TAS-20 – 20-item Toronto Alexithymia Scale, GPTS- paranoia subscale of the Green Paranoid Thoughts Scale, CAPS- Cardiff Anomalous Perceptions Scale.

3.4.3 Main analysis: mediation

We next tested hypothesis 2 that the relationship between sleep quality and paranoid thinking is mediated by negative emotion, by alexithymia and by levels of perceptual anomalies. As, anxiety and depression were not significant predictors of paranoia in the logistic regressions, we did not include these variables in mediation analysis. Paranoid group (high and low) was entered as the dependent variable, sleep quality as the predictor variable, age as a co-variate and alexithymia, negative mood and perceptual anomalies were entered as mediators. This model was significant as revealed by the bootstrapped confidence intervals all being above 0. The indirect (mediation) pathway from PSQI to paranoia via negative affect was significant *b*= 0.06 95%CI [0.009-0.143], the indirect (mediation) pathway from sleep quality to paranoia via alexithymia was significant *b*= 0.11 95%CI [0.033-0.216], the indirect (mediation) pathway from sleep quality to paranoia via perceptual anomalies was significant, *b*= 0.13 95%CI [0.03-0.21]. Finally, the direct pathway from sleep quality to paranoia was significant, *b*= 0.26 95%CI [0.009-0.527]. Together the results support our hypothesis and suggest that the relationship between sleep quality and paranoia is partially mediated by levels of negative affect, alexithymia and perceptual anomalies. This mediation model is depicted in figure 2.

Figure 2 Mediation model



3.5 Study 2: Introduction

In study 2 we aimed to replicate the mediation model in a second, independently collected data set. We hypothesised that the relationship between sleep quality and paranoia would be partially mediated by levels of negative affect, perceptual anomalies and alexithymia.

3.6 Participants, procedure and measures

The recruitment procedures, questionnaires and data analytical techniques used were identical to study 1. A separate Qualtrics survey was available online 2013-2015. Cronbach alphas were available for the following questionnaires: TAS-20 (α 0.85), GPTS (α 0.95), PANAS (α 0.84), CAPS (α 0.86), HADS D (α 0.74) and HADS A (α 0.80).

3.7 Results

3.7.1 Descriptive statistics and correlations

Table 7 presents all the descriptive information for the sample. A total of 402 (*n*=114 males, 288 females) individuals completed the survey with a mean age of 24 (*SD* = 10.8, range 16-77). Overall, the sample from study 2 was similar to the sample in study 1. This was confirmed by a series of Mann Whitney U tests, which revealed no significant differences between the samples in study 1 and 2 on anxiety, depression, positive affect, negative affect, sleep quality, alexithymia or perceptual anomalies (p>0.05). However, sample 2 (*Mdn*=18) reported slightly higher levels of paranoia compared to sample 1 (*Mdn*=17), U=62283, p=<0.001 and sample 2 were slightly younger (*Mdn*=20) than sample 1 (*Mdn*=22), U=70386, p=0.002. The correlations between all the variables are shown in table 8. Age was correlated with several our predictors including sleep quality, alexithymia and perceptual anomalies; therefore, we included it as a co-variate in further analysis. A series of Mann-Whitney U tests revealed that gender was not associated with any of the variables in this study, all p > 0.05.

Table 7: Sample demographics for study 2 (N=402)

	Mean	SD	Median	Range
Age	24.75	10.64	20.00	17-77
PSQI	6.24	3.01	6.00	0-16
PA	25.43	7.80	25.00	10-49
NA	15.09	5.87	13.00	10-42
HADS-A	7.96	3.83	8.00	0-20
HADS-D	4.19	3.04	4.00	0-17
TAS-20	48.20	11.70	48.00	22-81
GPTS	23.29	11.70	18.00	16-80
CAPS	3.56	4.50	2.00	0-24

Abbreviations: PSQI- Pittsburgh Sleep Quality Index, PA and NA- Positive and Negative Affect, HADS-A and D Hospital Anxiety and Depression Scale respectively, TAS-20 – 20-item Toronto Alexithymia Scale, GPTS- paranoia subscale of the Green Paranoid Thoughts Scale, CAPS- Cardiff Anomalous Perceptions Scale.

Table 8: Spearman rho correlations for study 2.

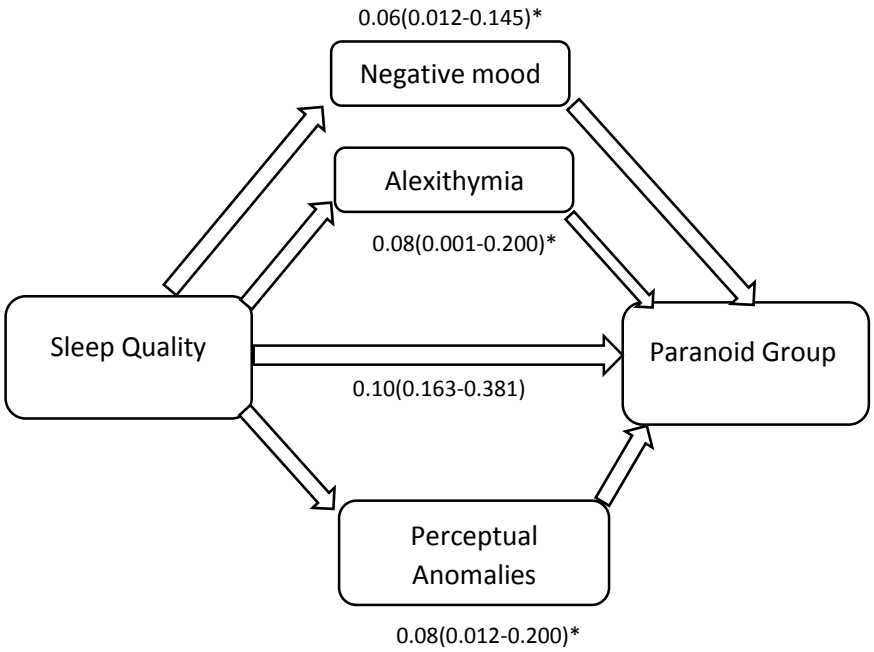
Measure	1	2	3	4	5	6	7	8
1. Age								
2. PA	0.17*							
3. NA	-0.13*	-0.09						
4. HADS- A	-0.10*	-0.17*	0.48*					
5. HADS-D	0.00	-0.33*	0.29*	0.47*				
6. PSQI	-0.07	-0.16*	0.24*	0.38*	0.33*			
7. TAS	-0.17*	-0.22*	0.25*	0.45*	0.51*	0.29*		
8. GPTS	-0.17*	0.04	0.31*	0.39*	0.26*	0.17*	0.41*	
9. CAPS	-0.19*	-0.02	0.18*	0.29*	0.27*	0.13*	-0.26*	0.45*

Abbreviations: PSQI- Pittsburgh Sleep Quality Index, PA and NA- Positive and Negative Affect, HADS-A and D Hospital Anxiety and Depression Scale respectively, TAS-20 – 20-item Toronto Alexithymia Scale, GPTS- paranoia subscale of the Green Paranoid Thoughts Scale, CAPS- Cardiff Anomalous Perceptions Scale.*p <0.05

3.7.2 Mediation analysis replication

Paranoid group was entered as the dependent variable, sleep quality as the predictor variable, age as a co-variate and alexithymia, negative mood and perceptual anomalies were entered as mediators. This model was significant as revealed by the bootstrapped confidence intervals all being above 0. The indirect (mediation) pathway to paranoia via negative affect was significant *b*= 0.06 95%CI [0.012-0.1450], the indirect (mediation) pathway from sleep quality to paranoia via alexithymia was significant *b*=0.0895%CI [0.012-0.200], the indirect (mediation) pathway from sleep quality to paranoia via perceptual anomalies was significant, *b*= 0.08 95%CI [0.012-0.200]. However, the direct pathway from sleep quality to paranoia was non- significant, *b*=0.10 95%CI [-0.1630-0.3813]. In sum, the relationship between sleep quality and paranoia was fully mediated by levels of negative affect, alexithymia and perceptual anomalies. This contrasts with study 1 which found partial mediation. This mediation model is depicted in figure 3.

Figure 3 Mediation model



3.7.3 Post hoc analysis

As the mediation models were different in study 1 and 2, we sought to explore the data in study 2 further by running post-hoc regression analyses to see whether we could replicate the regression results found in study 1. The predictors entered were age, negative affect, anxiety, depression, perceptual anomalies, sleep quality and alexithymia. A test of the full model against a constant only model (no predictors) was statistically significant, indicating that the predictors reliably distinguished between the paranoid and non-paranoid groups ($x^2 = 94.331$, $p < 0.0.001$). The Wald test was used to determine what predictors are significant. Significant predictors of paranoid group membership included anxiety, alexithymia and perceptual anomalies. Sleep quality, age, negative affect and depression did not significantly predict paranoid group membership. The log odds (Exp B) is an indicator of the log odds of being in the paranoid group due to a one point increase in the predictor variable. For example, a one unit increase in anxiety increases the odds of being in the paranoid group by 1.09, 95%CI [1.00, 1.19]. Nagelkerke's R^2 of 0.314 indicated that 31% of the variance was explained by the significant predictors. Similar results were obtained in the stepwise logistic regression which also found that anxiety, alexithymia and perceptual anomalies predicted paranoid group membership and this model explained 30% of the variance (Nagelkerke's R^2 of 0.30). In sum, two separate regression models showed that anxiety, alexithymia and perceptual anomalies predicted membership of the paranoid group. Similar to the mediation results, we found sleep quality did not predict paranoia. However, we also found that anxiety predicted paranoia rather than negative affect, as in study 1.

3.8 Discussion

Previous research has found that sleep is related to paranoia and that this relationship is mostly mediated by negative emotions (Freeman et al., 2010; Freeman et al., 2009). Non-emotional factors such as perceptual anomalies have also been proposed as potential mediators (Freeman et al., 2010). We sought to add to this previous work by testing whether alexithymia is related to paranoia and whether it mediates the relationship between sleep quality and paranoia. We also sought to test the role of perceptual anomalies as a mediating factor.

3.8.1 Sleep quality and paranoia

Our hypothesised mediation model proposed that the relationship between sleep quality and paranoia is mediated by alexithymia, negative emotions and perceptual anomalies. While this mediation model was found in both studies, we found discrepant results such that there was partial mediation in study 1 and full mediation in study 2. The discrepancy can be ruled out due to sample differences between study 1 and 2 as they did not significantly differ in levels of sleep quality. Furthermore, both the low and high paranoid groups in study 1 and 2 were similar and differed on the same variables. However, our answer may lie in the post-hoc regression analyses conducted in study 2 which found that sleep quality did not significantly predict paranoid group membership. This is surprising as several studies have reported links between a range of sleep disturbances and paranoia (Kahn-Greene et al., 2007; Sheaves et al., 2016).

The discrepancy could be due to our chosen measure of sleep. Sleep quality is a broad term and the PSQI measures a wide range of sleep disturbances rather than focus on a specific disturbance (Buysse et al., 1989). Research suggests that the relationship between sleep and paranoia is strongest for insomnia. Insomnia has been found to predict paranoia in cross-sectional studies (Grezellschak et al., 2015) but also predict the development of paranoid thoughts in a longitudinal study (Freeman et al., 2012). We propose that while sleep quality scores did not differ between study 1 and 2, the nature of the sleep disturbance may have. The participants in sample 1 may have experienced more insomnia in comparison to sample 2. This may have resulted in significant results in study 1

but not in study 2. Future research would benefit from focusing on specific sleep disturbances.

3.8.2 Alexithymia and paranoia

A novel finding in our study is the link between alexithymia and paranoia. Across both studies regression analyses showed that alexithymia predicted paranoia, independently of negative emotions, perceptual anomalies and sleep. Furthermore, we found some preliminary evidence that alexithymia may mediate the relationship between sleep quality and paranoia. This suggests that along with negative emotions, alexithymia is an additional emotional facet to consider when studying paranoia. Our emotions provide us with information on how we are feeling at a given moment. These emotions then help guide and direct us to make sense of the world, to make judgements about others behaviours, intentions and emotions (Boden & Berenbaum, 2007; Clore & Huntsinger, 2007). In alexithymia, this ability is diminished and this may make such individuals prone to faulty judgements and beliefs about others (including paranoid beliefs). This fits with a study reporting that low levels of emotional awareness (high alexithymia) was linked to higher levels of suspiciousness (Boden & Berenbaum, 2007). Another line of evidence for our claim comes from research looking at alexithymia and social dysfunction. One study found that individuals with difficulties identifying and describing feelings had significantly lower levels of social contacts, fewer acquaintances, and were more often unmarried (Kauhanen, Kaplan, Julkunen, Wilson, & Salonen, 1993). Higher levels of alexithymia have been reported in people with psychosis (van 't Wout et al., 2007) and alexithymia has been linked to poorer social functioning in such individuals (Kimhy et al., 2014).

The relationship between alexithymia and paranoia may have clinical implications. Individuals with psychosis who also experience alexithymia may be at risk of experiencing greater paranoia but struggle to convey their concerns to others. They may also experience lower levels of trust towards their clinicians. As such, their responses to treatment may be poorer (Gumley, 2011). Assessing alexithymia may be useful in clinical practise to identify individuals who may require support to understand and regulate emotions. This could be achieved in

clinical practice by including an assessment of alexithymia by using questionnaires such as the Toronto Alexithymia Scale. When individuals with alexithymia are identified, a focus on their emotional experiences could be incorporated into their CBT approach to sleep.

3.8.3 Negative emotions and paranoia

Across both studies we found that negative emotions predicted paranoia and mediated the relationship between sleep quality and paranoia. Negative emotions have been linked to paranoia in both cross-sectional and longitudinal studies (Freeman et al., 2010; Freeman et al., 2012). In particular, anxiety has a strong association with paranoia as they share many features such as the anticipation of threat and a worry reasoning style. The presence of perceptual anomalies differentiates anxiety from paranoia (Freeman, 2007).

However, we found discrepant results in regards to what negative emotion was significant, with study 1 finding that negative affect predicted paranoia whilst in study 2 it was anxiety. Depression did not predict paranoia in either study. One of the reasons for this may be because the samples in our studies had low levels of depression overall.

The HADS provides scoring criteria, with scores of 0–7 being normal, 8–10, being borderline and more than 11 being clinically significant levels (Zigmond & Snaith, 1983). In both samples, the mean depression scores in the low and high paranoid groups fell in the normal range. This may be why depression was not a significant predictor in our regression analyses. In contrast, our measure of negative affect was measured with the PANAS, which was developed to measure a range of affective states (Watson et al., 1988). The negative affect component covers a range of states such as jittery, guilt and ashamed and is a measure of overall distress rather than a specific type of negative emotion (Watson et al., 1988). These differences between measures may have contributed to the discrepant results. It is also worth noting that the timeframe of the questionnaires differed and may be another reason behind the different results. The HADS timeframe is the past two weeks, whereas the PANAS was measured at

the “current” level. The current timeframe captures momentary states which would experience more fluctuation than fortnightly levels.

3.8.4 Perceptual anomalies and paranoia

A consistent finding across both studies was that perceptual anomalies predicted paranoia and mediated the relationship between sleep quality and paranoia. It has been long proposed that delusions serve as explanations for odd or strange internal experiences (Maher, 1974). Furthermore, perceptual anomalies are incorporated within a cognitive model of paranoid delusions, where paranoid beliefs arise from an attempt to explain anomalous and odd internal experiences (Freeman et al., 2002). Indeed, research has shown that perceptual anomalies increase the risk for the development of delusional ideas (Krabbendam et al., 2004) and anomalies of experience caused by illegal drug use have also been linked to delusional ideation (D’Souza et al., 2005). Our mediation model suggests that individuals experiencing sleep problems may also experience an increase in perceptual anomalies which then leads to the development of paranoid thoughts.

3.8.5 Summary of findings

Taking all the mediation and regression results together, we can conclude that alexithymia, perceptual anomalies and negative emotions predict paranoid thoughts. The role of sleep quality is not clear, and our mediation model requires replication. In regards to effect size, our results were significant but small. For example, our regression models explained between 22–31% of the variance and many of the mediation effects could be considered small as they lie between 0.10 and 0.20 (Cohen, 1992). Although small, we feel they are clinically significant. A recent trial has found that improving sleep disturbance with CBTi in a student sample was associated with medium to large, sustained improvements in paranoia (Freeman et al., 2017). Furthermore, another study has found that the relationship between sleep loss (as found in insomnia) is associated with moderate to large effect size increases in paranoia and negative emotions. This study also found that negative affect accounted for 90% of the increase in paranoia after sleep loss (Reeve, Emsley, Sheaves, & Freeman, 2017). This highlights the usefulness of studying sleep and paranoia in non-

clinical samples, and that effects can be detected in non-clinical samples. This is complemented by work in clinical samples where CBTi is associated with large effect size reductions in sleep disturbance (Freeman, Waite, et al., 2015) and in paranoia, perceptual anomalies and mood variables (Myers et al., 2011). One potential reason for our small effect sizes in comparison to these papers is that they focused on insomnia, whereas we looked at sleep quality. It may also be the case that the effects we found in our mediation analysis would be larger and more exaggerated in a clinical sample who experience more severe sleep and mood disturbance.

3.8.6 Limitations

Several limitations of our study should also be noted when considering the results. Our study was cross-sectional and it is highly likely that the mediation model pathways proposed are interacting and bi-directional over time. Furthermore, the timeframe of our questionnaires also differed. The PANAS was measured at the moment level, whilst sleep quality and paranoia at the monthly level. Therefore, hypothesised causal links between variables should be interpreted with caution. To tease out causal effects experimental and randomised control trials are called for. Another way to look at causal effects could be to conduct experience sampling studies (Myin-Germeys et al., 2009). This approach allows temporal mapping of relationships and questions of directionality can be addressed. A recent study using this methodology found that the relationship between a range of sleep parameters and paranoia was mediated by negative affect (Mulligan et al., 2016).

The sample population was predominantly university students that may not be representative of the general population. However, students are one population that may experience higher levels of psychotic like experiences such as paranoia (Lincoln & Keller, 2008) suggesting that this is a useful population to study psychotic experiences in. The gender ratio of the sample was skewed with the majority of the sample being females. This is a finding that has been noted in other online survey studies of paranoia (Freeman et al., 2005). However, as there is some research to suggest that males may experience more alexithymia (Levant, Hall, Williams, & Hasan, 2009) future studies should aim for more

gender-balanced studies. All our variables were skewed which could have reduced power and the ability to detect certain relationships (Wilcox & Keselman, 2003). However, we dealt with the skewed data in a number of ways including bootstrapping making our results more reliable and robust. Another limitation is that all our measures were self-report and required the individual to accurately report their responses. The questionnaire assessment of paranoia has the additional limitation that it may capture paranoid thoughts that are justified suspicions to real threats. Nonetheless, laboratory based virtual reality experiments where unfounded paranoia can be tested have reached the same conclusions as questionnaire studies of paranoid thinking in non-clinical populations (Freeman et al., 2003).

We used the same recruitment method in sample 1 and 2 and have no way to know whether some participants completed the survey in both study 1 and 2. However, given that there is no incentive to complete the survey and that the survey is long and extensive, we feel it is unlikely that someone would complete the survey twice.

Finally, a concern may be whether the findings in non-clinical samples are generalizable to a clinical sample. However, it is now widely accepted that psychotic symptoms lie on a continuum with normal experience, that non-clinical and clinical symptoms share the same risk factors and the presence of non-clinical experiences increase the risk of clinical disorder (L. C. Johns et al., 2004; van Os et al., 2009).

3.8.7 Conclusions

In conclusion, we found inconclusive evidence for a link between sleep quality and paranoia. The current research also emphasises that alexithymia and paranoia are related. Alexithymia can easily be assessed and should be considered in studies of paranoid thinking and emotion.

4 A systematic review of sleep in people with non-affective psychosis: a methodological review

4.1 Introduction

Sleep is essential for adequate mental health and well-being, and occupies a third of the human lifespan (Baglioni et al., 2016). Sleep disturbances have long been associated with psychosis. (Reeve et al., 2015). Depending on the severity of the illness, sleep disturbances are found in as many as 80% of patients (Cohrs, 2008). One of the key findings is that regardless of illness stage, medication status or severity of illness, a range of sleep/wake disturbances are reported (Chouinard, Poulin, Stip, & Godbout, 2004; Mulligan et al., 2016; Reeve et al., 2015). Importantly, sleep is recognised by individuals themselves as an important treatment target and an important part of recovery (Auslander & Jeste, 2002; Waite, Evans, et al., 2016).

4.1.1 Sleep disruption

Sleep disruption is a broad term, and can encompass aspects of sleep on many different levels. Within the context of our review we view sleep disruption as a term that includes abnormalities in subjective or objective sleep, in the form of symptoms or disorders.

4.1.2 Sleep disorders

Sleep/wake difficulties can be roughly classified into 6 types according to the International Classification of Sleep Disorders (American Academy of Sleep Medicine;AASM, 2005). The 6 categories include insomnia (e.g. difficulties falling asleep, maintaining sleep), parasomnias (e.g. nightmares, sleepwalking), circadian sleep/wake disorders (e.g. delayed sleep phase syndrome), disorders of hypersomnolence (e.g. narcolepsy), sleep related breathing disorders (e.g. sleep apnoea) and sleep related movement disorders (e.g. restless legs). There is evidence for elevated levels for a number of these sleep disorders in people diagnosed with non-affective psychosis (NAP). The most well studied sleep disorder is insomnia which has a prevalence of around 6-10% in the general

population (American Psychiatric Association; APA, 2013). In people with NAP the rates are more than double with estimates ranging from 27-52% of (Freeman et al., 2009; Palmese et al., 2011; Xiang et al., 2009b). Sleep apnoea is another sleep disorder with elevated rates estimated to range from 20-57% compared to psychiatric and healthy controls (Myles et al., 2018; Takahashi et al., 1998; Winkelman, 2001). There is also some evidence that nightmare disorder is reported in as many as 55% of patients (Sheaves, Onwumere, Keen, Stahl, & Kuipers, 2015). Clear prevalence estimates are not available for circadian rhythm disorders or hypersomnia. However, there is evidence that symptoms associated with these disorders are present in people with schizophrenia (Hawley, 2006; Hawley et al., 2010; Wulff, Dijk, Middleton, Foster, & Joyce, 2012).

4.1.3 Sleep disturbances

Apart from sleep disorders, a range of other sleep difficulties have been reported in people with NAP. Disturbances of sleep continuity have been reported such as decreased total sleep time (TST), decreased sleep efficiency (SE), increased sleep onset latency (SOL) and increased wakefulness during the night (WASO)(Chouinard et al., 2004). Regarding sleep architecture, reductions in REM sleep latency, REM density and slow wave sleep have been reported by some authors (Poulin, Daoust, Forest, Stip, & Godbout, 2003; Yang & Winkelman, 2006), but not all (Chouinard et al., 2004; Lauer, Schreiber, Pollmacher, Holsboer, & Krieg, 1997). Some of the circadian disturbances reported in individuals include fragmented sleep/wake rhythms, irregular and delayed sleep patterns, increased daytime napping, delayed and blunted rhythms of melatonin (Bromundt et al., 2011; Monteleone, Maj, Fusco, Kemali, & Reiter, 1992; Monti et al., 2013; Wulff et al., 2012). Furthermore, there is also evidence that people with NAP reported subjectively poorer sleep quality, and dissatisfaction with sleep (Faulkner & Bee, 2017).

4.1.4 The measurement of sleep

Numerous methodologies exist to assess and quantify sleep disturbance. These methods can be broadly split into two categories: subjective (questionnaires and sleep diaries) and objective (polysomnography, actigraphy). Each method has its own advantages and disadvantages which are summarised in table 9.

4.1.4.1 Objective assessment

The gold standard assessment of sleep is polysomnography (PSG). PSG is most often conducted in a sleep lab, but ambulatory monitoring can be done (McCall, Erwin, Edinger, Krystal, & Marsh, 1992). PSG normally involves the simultaneous monitoring of electronic brain activity (EEG), muscle tone (EMG) and eye movements (EOG). Breathing flow and oxygen can also be recorded (oximetry)(Sadeh, 2011). A wide range of sleep parameters can be assessed and measured with PSG including sleep architecture, sleep stages, brain activity, eye movements and arousals. With the detailed information from PSG, sleep disorders can be accurately diagnosed (Sadeh, 2011). Recent advances in PSG include spectral analysis which looks at sleep microstructure (Poulin, Stip, & Godbout, 2008), and cyclic alternating pattern which looks at sleep instability (Ozone, Kuroda, Aoki, Manabe, & Itoh, 2013). When interpreting and assessing sleep PSG data, its limitations must be considered. Limitations include

Table 9: Overview of sleep methodologies

Method	What information it provides	Advantages	Disadvantages
Polysomnography Records biological changes occurring during sleep	Information on night-time sleep Information on sleep stages Objective assessment of sleep disorders	Objective Assessment of sleep disorders Assessment of sleep stages	Lower ecological validity(Requires person sleeping in an unnatural environment) Expensive Time consuming to code and analyse
Actigraphy Based on movement	Assessment of 24 hour sleep/wake patterns Can provide information on daytime sleep (naps) as well as overall activity levels	Objective Can assess sleep patterns for days and weeks Non invasive Give specific information on sleep patterns	Has tendency to score quiet rest as sleep Lower validity in clinical populations
Questionnaires/Diaries Subjective perceptions of sleep quality	Summaries of sleep quality Sleep diaries provide detailed information about sleep/wake patterns	Subjective perceptions of sleep Cheap and easy to administer	Can be difficult to provide global estimates of sleep e.g. sleep time over the past month. Memory biases Can lack validity

sleeping in a unique environment such as in the sleep lab which is not representative of natural sleep environments. Furthermore, it is costly, and requires overnight (often multiple nights) in a sleep lab and requires a trained sleep technician to score the data. It is also unable to capture daytime sleep episodes or to capture the day to day and night to night variability of sleep (Sadeh, 2011).

On the other hand, actigraphy is a method more suited to capture sleep and circadian rhythms. Actigraphy is a watch like device worn on the non-dominant wrist, which uses an accelerometer to record movement (Ancoli-Israel et al., 2003). These movement counts can be used to indirectly measure sleep/wake patterns. Actigraphy has the advantage of assessing both day and night time sleep across several days or weeks, and being worn in the participant's natural environment. Often the participant can also press a button called an event marker which is pressed when the participant goes to bed and wakes up, to accurately record sleep/wake times. Data from the actiwatch are downloaded and scored with the manufacturer's software and algorithms to score sleep and wake. Some actiwatches also incorporate light information to complement movement data. One of the limitations of actigraphy, and especially relevant to clinical samples is that it can be difficult to distinguish quiet rest from sleep, which may produce biased sleep estimates (Paquet, Kawinska, & Carrier, 2007). Often, sleep logs are also completed along with actigraphy to allow the researcher to score the data more accurately (Sadeh, 2011). Furthermore, actigraphy cannot be used to diagnose or screen for sleep disorders and it cannot provide information on sleep architecture (Sadeh, 2011).

4.1.4.2 Subjective assessment

Questionnaires are commonly used as they allow a quick assessment of sleep. A range of sleep questionnaires exist, each focused on specific aspects of sleep. The Pittsburgh Sleep Quality Index (PSQI) is the most widely used self-report method, and it provides a measure of sleep quality over the past

month (Buysse et al., 1989). Other questionnaires include those to assess daytime sleepiness such as the Epworth Sleepiness Scale (M. W. Johns, 1991). Specific sleep disorders such as insomnia can be assessed with the Insomnia Severity Index (ISI) (Morin, Belleville, Bélanger, & Ivers, 2011) and assessment of chronotype by the Morning-Eveningness Questionnaire (MEQ) (Horne & Ostberg, 1976). Questionnaires have the advantage of being quick and easy to administer, as well as being cheap. However, questionnaires are retrospective and do not allow variability of sleep to be reliably measured. More in depth subjective sleep assessments include the sleep diary which allows evaluation of sleep over numerous days (Carney et al., 2012). As sleep diaries are prospective, they reduce memory biases (Carney et al., 2012). Furthermore, sleep diaries can allow the assessment of additional variables that provide rich, detailed information about sleep, such as napping, nightmare frequency and distress. However, they require a level of commitment from participants, who must remember to complete the sleep diary daily.

4.1.5 The current review

A number of reviews currently exist, that have examined the association of sleep disturbances and impact on functioning, including symptomology (Barton, Kyle, Varese, Jones, & Haddock, 2018; Davies, Haddock, Yung, Mulligan, & Kyle, 2017; Reeve et al., 2015). However, a methodological review is missing. In this review we intend to provide a clear overview and evaluation of the methods used to assess and measure sleep in non-affective psychosis (NAP). The key questions that we ask in this review are what methods have been used to assess sleep in people with NAP and what are some of the areas of bias within these methods? Furthermore, we also seek to evaluate what aspects of sleep are disrupted in NAP, but in the context of the various methods and their limitations. More specifically we focus on 4 main sleep outcomes: sleep onset latency, total sleep time, sleep efficiency and wake after sleep onset (sleep continuity measures). We focus on these measures as they can be calculated by all sleep methodologies; actigraphy, subjective questionnaires and polysomnography allowing comparisons to be

made across methods. Secondary outcomes that we consider include those specific to each sleep methodology. Tables (10 and 11) provide definitions of the common sleep outcomes used. Within this review we focus on NAP which includes conditions such as schizophrenia. It is hoped that a comprehensive review and evaluation of the methods used to assess sleep will complement findings in other reviews, and guide future research and research agendas.

Table 10 Sleep continuity outcomes

Sleep variable	Definition
Sleep Onset Latency (SOL).	Time taken to fall asleep
Total Sleep Time (TST).	Total time spent asleep
Sleep Efficiency (SE).	Percentage of time in bed spent asleep
Wake After Sleep Onset (WASO).	The duration of wake during the night

Table 11 Sleep architecture outcomes

Sleep variable	Definition
Stage 1	Duration of stage 1 sleep presented in minutes or as a percentage of overall sleep.
Stage 2	Duration of stage 2 sleep presented in minutes or as a percentage of overall sleep.
Stage 3	Duration of stage 3 sleep presented in minutes or as a percentage of overall sleep.
Stage 4	Duration of stage 4 sleep presented in minutes or as a percentage of overall sleep.
Slow Wave Sleep	Amount of non-REM sleep stages 3 and 4 (also known as delta sleep)
REM sleep	Duration of REM sleep presented in minutes or as a percentage of overall sleep.
REM latency	The interval between sleep onset and the onset of the first REM sleep period.
REM density	The frequency of rapid eye movements during REM sleep.

4.2 Methods

The protocol and data extraction was conducted according to the 2009 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

4.2.1 Search and selection of studies

A search was carried out on Medline, Psychinfo and Web Of Science. Search terms included: Schizophrenia/Psychosis/psychotic disorder AND sleep or sleep disorders or circadian rhythms or actigraphy or polysomnography or sleep EEG. Appendix 2 contains the search terms in more detail. To enhance search sensitivity we conducted journal searches and examined the references of published articles for any additional references. We also contacted authors about any studies they are currently conducting or writing up that could be eligible for the systematic review.

Eligibility assessment for each study was conducted by AR, who screened each paper by examining the title and abstracts. After the initial screening of titles and abstracts, full texts were examined based on the exclusion criteria/inclusion criteria by AR. Where there was uncertainty, advice was sought from the co-authors (AG, SB) and a joint decision was made. After selection of studies based on inclusion/exclusion criteria, AR completed a risk of bias assessment of each study (see sections below). Bias assessment was also conducted by another person to check reliability of scoring and validate further the bias assessment tool. Disagreements were resolved with mutual agreement.

4.2.2 Inclusion and exclusion criteria

Inclusion criteria: (1) at least one of our primary sleep outcomes (sleep onset latency, wake after sleep onset, total sleep time and sleep efficiency), (2) study must report the sleep outcome values for the whole sample (3) participants who experience non-affective psychosis (4) studies published between 1953 (which is when REM sleep was discovered and polysomnography studies in sleep started) and 2017, and (5) studies written in English. Exclusion criteria: 1) non-clinical/analogue studies, (2) qualitative data, (3) single case studies, (4) at risk for psychosis studies, (5) studies in children, (6) conference abstracts, (7) book chapters, (8) review papers and (9) dissertations.

If there were multiple papers published by the same research group using the same sample, we selected the most relevant paper for the review. Typically, this meant we selected the paper that included the most information about sleep. If it was unclear whether publications from a research group used the same sample, we emailed the authors to clarify independence of the samples. If the authors did not respond, we selected the one paper that was most suitable for the review, for example the paper with the most sleep information.

4.2.3 Bias assessment

In line with the guidelines in the PRISMA statement and in the Cochrane handbook for systematic reviews we assessed included studies on their risk of bias (Liberati et al., 2009). For the purpose of our review we chose to use a modified version of the QUADAS-2 tool(Whiting et al., 2006). The QUADAS-2 includes a risk of bias judgement (high, low, or unclear) on 4 key domains: patient selection, index tests, reference standard and flow and timing. We refined the tool to fit with our systematic review, including a methodological component to rate each of the sleep methods used. A description of the development and piloting of the Risk of Bias tool is described in Appendix 1. Table 12, gives a brief overview of the components each study was rated on.

Table 12 Brief overview of risk of bias components rated in studies

Component 1: Patient Selection
Component 2: Baseline characteristics
Component 3: Actigraphy (Length of recording + distinguishing quiet rest from sleep)
Component 4: Polysomnography studies: (First night effect/participant instructions)

Component 5: Subjective sleep : (Use of validated measures)
Component 6: Power
Component 7: Missing data
Component 8: Completion rates
Component 9: Data analysis

4.2.4 Data extraction

Information that was extracted from each study included: 1) characteristics of the participants, (sample size, age, gender, method of diagnosis, and medication status), 2) the study design, 3) country research was conducted, 4) the methods used to assess sleep and 5) the tools used to diagnose psychosis. In studies that examine the influence of medications on sleep outcomes, we extracted the baseline sleep information, as our primary focus is on sleep, not changes in sleep with medications.

4.3 Results

A total of 2333 papers were identified through our search including databases and other sources. After removing duplicates 2215 papers were screened on the basis of their titles and abstracts. Of these, 1949 were excluded leaving 266 papers to be evaluated based on the full article. Of these 266 papers, 209 were excluded, leaving 57 studies included in our review. See figure 4 for a flow diagram of the search process.

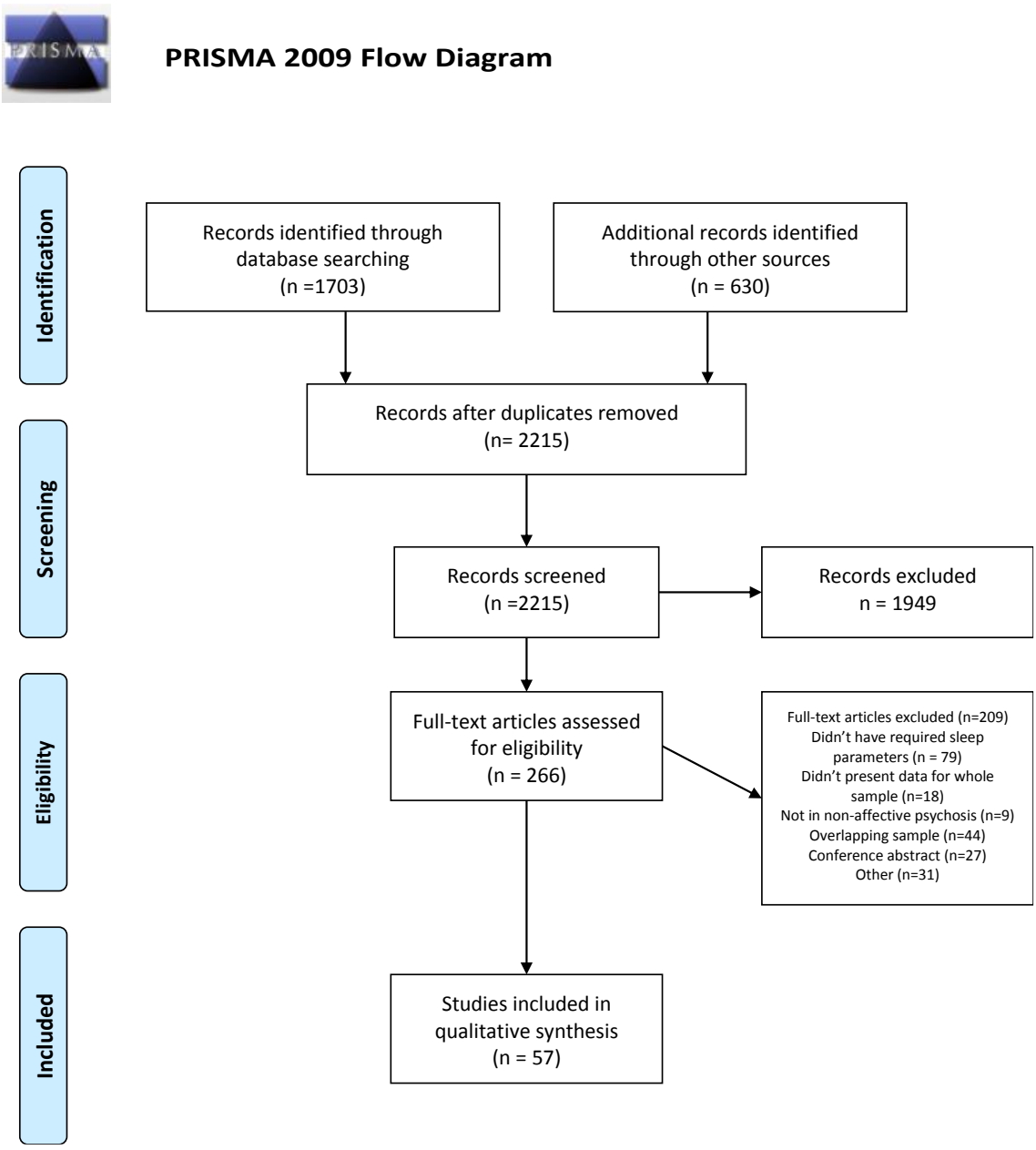
4.3.1 Sleep methodologies

From the 57 papers included in the review 8 papers used actigraphy as their primary measure of sleep, 6 papers used subjective assessment as their primary measure of sleep and 39 papers used polysomnography as the primary measure of sleep assessment. Four papers presented sleep data for more than one method: Bian et al (2016) used polysomnography and subjective assessment, Rotenberg et al., (2000) used polysomnography and subjective assessment, Wamsley et al., (2012) used polysomnography and actigraphy as sleep assessment measures and Mulligan et al., (2017) used actigraphy and sleep diary measures. For the purpose of this review the studies will be split into their method of assessment- subjective, actigraphy or polysomnography.

4.3.1.1 Subjective assessment

Description of studies

Figure 4 Flowchart of selection of studies



In terms of design, all were cross-sectional, except for one randomised control trial (Bosch et al., 2016). All patient groups were medicated, 4 studies were conducted in inpatients, 4 in outpatients, and 1 did not clarify patient status. Five studies included a control group, while 4 studies only had a patient group. The average sample size in subjective studies was 150. The median age of the sample across the studies was 42.0. In terms of gender, there were more males in the sample with an average ratio of 87:68 (average % males = 55). Three studies used a validated measure to assess sleep, the PSQI (Bosch et al., 2016; Yamashita et al., 2004) or the Carney sleep diary (Mulligan et al., 2016). All other papers used their own questions/interview, which are outlined in table 13.

4.3.1.2 Sleep continuity

There was a surprising lack of data on our sleep continuity measures. Of the 9 papers included in the subjective assessment, 1 study found an increased SOL compared to controls (Poulin et al., 2010), and one study found no difference compared to both healthy and psychiatric controls (Bosch et al., 2016) while the other 7 studies did not report SOL. In terms of TST, one study reported increased TST compared to controls (Poulin et al., 2010) one study found no difference between psychiatric and healthy controls (Bosch et al., 2016), whilst the other studies did not report TST. WASO was not reported as an outcome in any of the studies except one, finding no difference between patients, psychiatric controls and healthy controls (Bosch et al., 2016). In regards to SE, only one study reported it, finding no difference between patients and healthy controls (Poulin et al., 2010). These findings are summarised in table 14.

4.3.1.3 Other sleep outcomes

See table 13 for descriptions and additional outcomes of each study.

Table 13: Overview of subjective studies included

Study	Country	Design	Sample	Age Mean (SD)	Gender Male: female	Medication status	Primary Sleep measure	Additional sleep measures	Psychosis measure	Summary
Bian, 2016*	China	Cross-sectional	*N*=148 Schizophrenia inpatients	42(14.7)	77:71	All medicated during study	Self-edited questionnaire: 1 What time did you go to bed last night? 2 How long did it take you to fall asleep last night? 3 What time did you wake up this morning? 4 How long do you think that you slept last night?	No additional sleep measures	DSM-IV-SCID	Patients experienced sleep state mis-perception. They overestimated TST and SE but underestimated SOL.
Bosch, 2016	Holland	Randomised control trial	*N*=40 Schizophrenia outpatients *N*= 40 Depressed outpatients *N*=20 Healthy controls	42.2(10.11) 48.3(8.88) 33.0(11.27)	18:22 7:33 9:11	All medicated during study	Outcome sleep logs- 6 questions about sleep: 1. "Total sleep time", 2. "How many minutes awake during the night?" 3. "How many minutes awake before falling asleep?" 4. "How relaxing was your sleep?" 5. "Did you feel exhausted?", and 6. "How was your average	No additional sleep measures	Positive and negative affect schedule (PANSS).	Looked at sleep before and after acupuncture treatment. Acupuncture did not effect sleep or symptoms in schizophrenia group.

							performance level today?"			
Hou, 2016	China	Cross-sectional	*N*=623 Schizophrenia outpatients	47.7(10,3)	341:282	All medicated during study	3 questions on insomnia- over the past month Do you have difficulties in falling sleep?" for difficulty initiating sleep (DIS); "Do you have the difficulties in maintaining sleep and wake up often?" for difficulty maintaining sleep (DMS); and "Do you wake up in the midnight or early morning and have difficulties in falling sleep again?"	No additional sleep measures	ICD-10	TST reported by patients was 8.2 hours.18.1% were classed as short sleepers, 38.4% as medium length sleepers and 43.5% as long sleepers.
Muller, 2016	Germany	Cross-sectional	*N*=50 Schizophrenia patients *N*=60 Substance use disorders *N*=196 Anxiety and depression All inpatients	34.7 (11.3) 41.6(10.8) 58.1(16.2)	24:26 46:17 69:127	Medicated	Subjective question on sleep duration and quality. Sleep duration at night(i.e. weighted mean of workdays and weekends, mean hours)and sleep quality("non-restorative sleep"; 3	No additional sleep measures		20% of all patients had a sleep length lower than recommended in guidelines.

							pointscale:0 never,1 occasionally/some- times, 2 almost always)			
Mulligan, 2017*	UK	Cross-sectional	*N*=22 people with diagnosis of non-affective psychosis	37.4(10.4)	13:9	Medicated	Carney Sleep Diary-measured SE, TST and Sleep Quality	Insomnia severity index Brief screen for sleep disorders	ICD-1- and DSM-V	An experience sampling study. Findings were that next day symptoms and functioning were predicted by both subjective and objective sleep.
Okruszek, 2014	Poland	Cross-sectional	*N*=244 inpatients with non-affective psychosis *N*= 82 Non-psychotic disorders	28.2(7.0) 30.3(8.9)	144:100 40:42	All medicated during the study	Self-constructed questions for sleep quality, sleep duration, SOL, bedtime and awakenings during the night	Epworth sleepiness scale Stanford sleepiness scale	ICD-10	Schizophrenia patients slept longer than those with non-psychotic disorders. No diffs between groups on sleepiness
Poulin, 2010	Canada	Cross-sectional	*N*=150 Schizophrenia or schizo-affective outpatients *N*=80 Healthy controls	40.2 (9.2) 39.8 (9.9)	103:47 36:44	All medicated	Sleep Habits Questionnaire: Bedtime Rise time Alarm-clock use Naps SOL Nocturnal awakenings Refreshed in morning? Satisfied with sleep?	No additional sleep measures	DSM-IV	In comparison to controls, the patients had a longer SOL, TIB, TST and went to bed earlier, and woke later. No diffs on sleep quality sleep efficiency or sleep satisfaction or feeling

							All q's asked for weekday and weekends			refreshed in the morning.
Rotenberg, 2000 *	Israel	Cross-sectional	*N*= 20 Schizophrenia patients *N*= 10 Healthy controls	45.8 43.3	13:7 6:4	All medicated	Questions in morning on TST, SOL, number of awakenings, sleep depth and state after sleep.	No additional sleep measures	DSM-IV	Patients had longer SOL than HC, but no diffs on TST, or SE.
Yamashita,2004	Japan	Cross-sectional	*N*= 92 inpatients with schizophrenia	59.9(10.5)	48:44	All medicated	PSQI	No additional sleep measures	DSM-IV	Patients switched from first generation to second generation antipsychotic. Changes in sleep included better sleep quality, longer TST, lower SOL and higher SE.

*= study uses more than one sleep method.

Table 14: Sleep continuity in subjective studies

	SOL	TST	WASO	SE
Bian, (2016)	-	-	-	-
Bosch, (2016)	n/s	n/s	n/s	-
Hou, (2016)	-	-	-	-
Muller, (2016)	-	-	-	-
Mulligan, (2017)	-	-	-	-
Okruszek, (2014)	-	-	-	-
Poulin, (2010)	Longer in people with schizophrenia v controls.	Longer in people with schizophrenia v controls.	-	N/S
Rotenberg,(2000)	-	-	-	-
Yamashita, *2004)	-	-	-	-

Table 15: Bias assessment of subjective studies

Component	1: Patient selection	2: Baseline Characteristics	5: Subjective sleep assessment	6: Power	7: Missing Data	8: Completion Rates	9: Data Analysis
Bian, 2016	●	●	●	●	●	●	●
Bosch, 2016	●	●	●	●	●	●	●
Hou, 2016	●	●	●	●	●	●	●
Muller, 2016	●	●	●	●	●	●	●
Mulligan,2017	●	●	●	●	●	●	●
Okruszek, 2014	●	●	●	●	●	●	●
Poulin, 2010	●	●	●	●	●	●	●
Rotenberg, 2000	●	●	●	●	●	●	●
Yamashita, 2004	●	●	●	●	●	●	●

4.3.1.4 Bias assessment

See table 15 for table that conveys the risk of bias for each of the studies. Red dots represent high risk of bias, green represent low risk of bias and amber represents unsure about risk of bias. Across the subjective studies the two components with most studies at risk of bias was subjective sleep assessment and baseline characteristics. Across the subjective studies there were two areas identified as risk of bias. In the subjective sleep component (6/9 studies, 67%) were rated at risk or bias or unsure because they did not include validated measures of sleep. In the component of baseline characteristics (6/9 studies, 67%) were rated as risk of bias or unclear due to not having a control group or there being differences between controls and patients (e.g. age) that are not controlled for in the analysis.

4.3.2 Actigraphy assessment

4.3.2.1 Description of studies

In terms of design, all were cross-sectional. All patient groups were medicated. Eight studies were conducted in outpatients, 1 in inpatients and 1 used a mixture. The average sample size across the studies was 39. The median age of the sample across the studies was 42. In terms of gender, there were more males in the sample with an average ratio of 25:13 (average % males = 70). Actigraphs by various manufacturers were used to assess sleep and circadian rhythms. In three studies, the actiwatches also included light sensors (Afonso, Figueira, & Paiva, 2014; Martin, Jeste, & Ancoli-Israel, 2005; Wulff et al., 2012). See table 16 for overview of all the studies.

4.3.2.2 Sleep continuity

Of the 10 papers included in the actigraphy assessment, 4 reported a longer SOL in comparison to healthy controls, 1 reported a shorter SOL compared to controls, whilst 5 did not report on SOL. In terms of TST, 6 studies reported a longer TST, compared to healthy controls, whilst 4 studies did not report TST. WASO was only reported by two studies, one finding increased WASO

compared to healthy controls, and one finding no differences. In regards to SE, findings were mixed, one study reported lower SE compared to controls, and one study reporting higher SE. Three studies did not find significant differences between patients and healthy controls on SE, and 5 studies did not report SE. See table 17 for an overview of sleep continuity outcomes in actigraphy studies.

4.3.2.3 Other sleep outcomes

See table 16 for descriptions and additional outcomes of each study.

4.3.2.4 Bias assessment

See table 18 for table that conveys the risk of bias for each of the studies. Red dots represent high risk of bias, green represent low risk of bias and amber represents unsure about risk of bias. Across the actigraphy studies there were two areas identified as risk of bias. In the patient selection component (4/10 studies, 40%) were rated at risk or bias because they did not include enough information about patients e.g. inclusion/exclusion criteria not stated. In the component of actigraphy (4/10 studies, 40%) were rated as risk of bias due to not having multiple days or recording, or not including measures or criteria to distinguish between quiet rest and sleep.

4.3.3 Polysomnography assessment

4.3.3.1 Description of studies

Overall, there were 42 studies included in our PSG section. The median age of the sample across the studies was 30.2. The average sample size across the studies was 19. In terms of gender, there were more males in the sample with an average ratio of 13:6 (average % males = 70).The vast majority (*n*=35) were cross-sectional designs, often comparing the patient group to a control group on sleep variables. There were 7 treatment studies, of which 6 looked at the effects of anti-psychotics on sleep. Three studies looked at clozapine (Hinze-Selch, Mullington, Orth, Lauer, & Pollmacher, 1997; Lee, Woo, & Meltzer,

2001; Tsekou et al., 2015), 1 study looked at olanzapine (Salin-Pascual, Herrera-Estrella, Galicia-Polo, & Laurrabaquio, 1999), 1 study looked at chlorpromazine (Kaplan, Dawson, Vaughan, Green, & Wyatt, 1974) and 1 study looked at haloperidol vs thiothixene (Maixner et al., 1998). One study looked at the effects of bromocriptine, a dopamine agonist on sleep parameters (Brambilla et al., 1983). The medication status amongst the patients differed greatly, a number of studies were

Table 16: Summary of actigraphy studies included in the review

Study	Country	Design	Sample	Age Mean (SD)	Gender Male: female	Medication status	Sleep measure	Additional sleep measures	Psychosis measure	Summary
Afonso, 2014	Portugal	Cross-sectional	*N*= 34 outpatients with schizophrenia *N*= 34 Healthy controls	33.82 (8.30) 34.74 (8.60)	22:12 19:15	All medicated during study	Actigraphy (SOMNOWATCH)- 7 days Light sensory Activity in 1sec intervals	Pittsburgh sleep quality index (PSQI) Daily sleep logs	DSM-IV	Patients reported earlier bedtime, later wake time, longer SOL, longer TST, Lower SE & more awakenings Six patients' circadian rhythm disorders.
Bromunt, 2012	Switzerland	Cross-sectional	*N*= 14 Schizophrenia in & outpatients *N*= 23 Healthy controls	39.9(9.6) 64(5.4)	13:1 Not reported	All medicated during the study	Actigraphy (Cambridge neurotech) 21 days	PSQI Melatonin Daily sleep logs	PANSS, Brief Psychiatric Rating Scale, Clinical Global Impression	Patients displayed a range of sleep patterns from normal to fragmented. There was no relationship between positive symptoms and cognitive performance or sleep/wake measures.
Fang, 2016	Taiwan	Cross-sectional	*N*=199 Schizophrenia inpatients *N*=60 Healthy controls	44.0 (9.9) 41.1 (9.6)	122:77 34:26	Stable medication dose	Actigraphy(wActiSleep) 7 days Cole Kriple- Algorithm	No additional sleep measures	DSM-IV	A number of sleep parameters were associated with inflammatory markers
Reshef,2013	Israel	Cross-sectional	*N*= 20 schizophrenia outpatients	43.15(9.42)	10:10	All treated with medication	Actigraphy(MiniMotionlogger) 7 days 1 min intervals	PSQI Mini Sleep Questionnaire	ICD-10	Study compared subjective and objective sleep

							Automated scoring	Technion sleep questionnaire		after acupuncture treatment. After treatment there was an improvement on many subjective sleep parameters
Hofstetter, 2005	USA	Cross-sectional	*N*= 29 Schizophrenia outpatients	48(7)	27:2	All medicated	Actigraphy- Model #24.000, Ambulatory Monitoring Inc 21 days	PSQI	DSM-IV-TR	Only 7 patients agreed to wear actigraphy. Patients had short TST than controls.
			N= 200 Healthy controls from database	Not reported	Not reported					
Martin, 2005	USA	Cross-sectional	*N*= 28 Schizophrenia outpatients	58.3(9.8)	14:14	Medicated	Actigraphy(Actillume wrist) 72 hours Light sensor Cole-Kripke scoring algorithm 1 min intervals	Daily sleep diary	DSM-III- R or DSM-IV	Patients spent longer in bed, had more disrupted night-time sleep, slept more during the day, and had less robust circadian rhythms of activity and light exposure.
			N= 28 Healthy controls	57.3 (9.2)	14:14					
Mulligan, 2017	UK	Cross-sectional	*N*=22 patients with non-affective psychosis	37.4(10.4)	13:9	Medicated	Actigraphy (CamNtech) for 7 days 30 second epochs	Insomnia severity index. Brief screen for sleep disorders	ICD-1- and DSM-V	Findings were that next day symptoms and functioning were predicted by both subjective and objective sleep.
Wamlsey, 2012*	USA	Cross-sectional	*N*= 21 Schizophrenia outpatients	34(9)	17:4	Medicated	7 days actigraphy 15 second intervals Standard scoring algorithms	Daily sleep logs	DSM-IV	Sleep spindles were correlated with poorer memory performance in patient group.

			N= 17 Healthy controls	36(7)	14:3					
Waters, 2011	Australia	Cross-sectional	*N*= 6 Schizophrenia outpatients *N*=7 Healthy controls	44.33 (4.96) 42.71 (7.52)	5:1 4:3	Medicated	actigraphy ActiWatch 2 28 days	PSQI Daily sleep logs	ICD-10, DSM-V	Patients slept more and had longer SOL. In patients severity of symptoms also correlated with TST
Wulff, 2012	UK	Cross-sectional	*N*= 20 Schizophrenia outpatients *N*= 21 Healthy controls	38.8 (8.6) 37.5 (9.6)	15:5 13:8	Medicated	Actigraphy(Cambridge neurotech) 6 weeks 2 min intervals Light sensor	Melatonin PSQI Daily sleep logs	DSM-IV	Patients reported longer SOL, more TST, more variation, and later wake time V NC. Two subgroups could be found, one group with earlier bed and wake time and hypersomnia and a second with delayed sleep pattern.

Table 17: Sleep continuity outcomes for actigraphy

	SOL	TST	WASO	SE
Afonso, (2013)	Longer in SCZ	Longer in SCZ	-	Lower in SCZ
Bromunt,(2012)	-	-	-	-
Fang, (2016)	Longer in SCZ	Longer in SCZ	n/s	Higher in SCZ
Reshe, (2013)	-	-	-	-
Hofstetter, (2005)	Shorter in SCZ	-	-	-
Martin, (2005)	-	Longer in SCZ	Higher in SCZ	-
Mulligan, (2017)*	-	-	-	-
Wamsley, (2012)	-	Longer in SCZ	-	N/S

Waters, (2011)	Longer in SCZ	Longer in SCZ	-	n/s
Wulff, (2012)	Longer in SCZ	Longer in SCZ	-	n/s

Table 18: Bias assessment for actigraphy studies

Component	1: Patient selection	2: Baseline Characteristics	3: Actigraphy	6: Power	7: Missing Data	8: Completion Rates	9: Data Analysis
Afonso, 2013	●	●	●	●	●	●	●
Bromunt, 2012	●	●	●	●	●	●	●
Fang, 2013	●	●	●	●	●	●	●
Reshef, 2013	●	●	●	●	●	●	●
Hofstetter, 2005	●	●	●	●	●	●	●
Martin, 2005	●	●	●	●	●	●	●
Mulligan,* 2017	●	●	●	●	●	●	●
Wamsley, 2012	●	●	●	●	●	●	●
Waters, 2011	●	●	●	●	●	●	●
Wulff, 2012	●	●	●	●	●	●	●

conducted in medication naïve patients, in those unmedicated for a set period of time, or those were medicated during the study. The majority of the studies were conducted in inpatients (*n*=29), 5 were conducted in outpatients, 1 was conducted in a mixed in and outpatient sample and in 7 studies in/out patient status was unclear. See table 19 for an overview of PSG studies.

4.3.3.2 Bias assessment

See table 21 for table that conveys the risk of bias for each of the studies. Red dots represent high risk of bias, green represent low risk of bias and amber represents unsure about risk of bias. Across the polysomnography studies there were two areas identified as risk of bias. In the polysomnography component (37/42 studies, 89%) were rated at risk or bias or unsure because they did not include an adaptation night or minimise the use of caffeine and napping on recording days. In the component of power (36/42 studies, 85%) were rated as risk of bias or unclear due to small samples and it being unclear whether non-significant results are related to small samples.

4.3.3.3 How was sleep assessed?

PSG was conducted either in the patients ward or at sleep centres. There was a great deal of variation in the number of nights of recording conducted, ranging from 1-11. Thirty studies scored the sleep data using Rechtschaffen and Kales criteria, whilst 6 studies used the more recent American Academy of Sleep Medicine scoring criteria (2015). In 5 studies the scoring criteria wasn't clear and 1 study used criteria by (Dement & Kleitman, 1957).

4.3.3.4 What aspects of sleep are disrupted?

There were a great number of sleep variables reported within PSG studies. To try and narrow down and summarise the range of sleep variables, we split the variables into different categories. Furthermore, we report of the differences between patients and healthy controls, rather than with other psychiatric

groups. For a comprehensive analysis of sleep in psychosis compared to other conditions see Baglioni et al., 2016.

4.3.3.4.1 Sleep continuity

There were 28 studies with a control group, or with comparison data available between groups. Each of our variables was reported at different levels. For SOL, there were 23 studies that had data available. Of these 23, 13 reported a higher SOL, and 10 reported non-significant results. No studies reported a shorter SOL. For TST 22 studies had data available. Of these 22, 6 reported reduced TST, 2 reported increased TST and 14 reported non-significant findings. For WASO, there 9 studies of which 7 reported increased WASO and 2 reported non-significant results. Finally, for SE, 21 studies had data. Of these 21 studies, 11 reported a reduced SE and 10 reported non-significant findings. See table 20 for an overview of sleep continuity findings in PSG studies.

4.3.3.4.2 Stage 1 and 2 sleep.

Stage 1 and 2 sleep was presented in minutes or as percentage as overall sleep. There were no consistent findings. For stage 1 sleep, there were data available from 21 studies. Of these 21 studies, 5 reported an increase in S1, and 16 reported non-significant results. For Stage 2 sleep, there were data available from 22 studies. Of these 22 studies 6 reported a decrease in S2, and 2 reported an increase in S2, while 14 studies reported non-significant findings.

4.3.3.4.3 Slow wave sleep (Stage 3 and 4).

For stage 3 sleep, there were data available from 11 studies, of which 1 reported reduced S3 and 10 reported non-significant results. For stage 4 sleep, there were data available from 10 studies of which 3 studies reported reduced S4 and 7 reported non-significant results. For SWS (stage 3 and 4 combined) data were available from 21 studies, of which 6 reported reduced SWS and 15 reported non-significant results.

4.3.3.4.4 REM variables (REM sleep, REM latency, REM density)

The vast majority of the studies reported no differences in any of the REM parameters. For REM sleep, there were 27 studies, of which only 1 reported reduced REM sleep and 26 reported non-significant results. For REM-L, there were 18 studies of which 2 reported a reduced REM-L and 16 reported non-significant results. Finally, for REM-density there were data available from 9 studies, of which 1 reported increased REM-density, and 8 reported non-significant results.

4.3.3.4.5 Sleep microstructure:

The previously reported variables are those that can be classed under sleep macrostructure, and done with classical scoring methods that focus on the temporal organisation of sleep. In recent years there has been an increase in techniques aimed to assess sleep at a deeper level, and study the dynamics of sleep in greater detail. Some of these methods include spectral analysis, cyclic alternating pattern, micro-arousal analysis as well as the study of spontaneous events such as sleep spindles and K complexes. The following section will summarise sleep micro-structure in schizophrenia that were found in our included papers.

Eight studies included in our review focused on spindle analysis. The main finding was that people with schizophrenia report lower spindle amplitude, lower spindle duration and a reduced number of spindles (Ferrarelli et al., 2010; Goder et al., 2015; Manoach et al., 2014; Sasidharan et al., 2017; Schilling et al., 2017; Wamsley et al., 2012). Of note, two studies reported no differences on spindle density (Poulin et al., 2003; Van Cauter et al., 1991). Furthermore, one study by Schilling et al., (2017) reports a deficit only in fast sleep spindle density.

Ferralli 2010 looked at slow wave analysis, and variables that measure cortical synchronization during slow waves. There were no differences between control and patient groups on slow wave analysis patterns. Another study

looked at delta wave counts, finding that the group with schizophrenia reported lower delta wave sum counts and counts per minutes compared to controls (Ganguli, Reynolds, & Kupfer, 1987). Keshavan et al., (1998) conducted period amplitude analysis and power spectral analysis. The period amplitude analysis revealed that patients had reduced average delta wave count in the first NREM period in the 1-2 HZ range. Spectral analysis showed that patients had reduced spectral power in the delta and theta ranges and most prominent in the 1-2 Hz delta range compared to the 0.5-1 Hz range (Keshavan et al., 1998). Oh (2017) conducted spectral analysis and found that during N2 sleep 0.5-1Hz was lower in the schizophrenia group with higher theta and beta values. During N3 sleep alpha activity was higher in patients. Sasidharan (2017) conducted power spectral analysis and neuroloop gain analysis showing overall sleep instability in the schizophrenia group. For example, they had more awakenings in the first and third sleep cycles and unstable stage transitions. Sekimoto (2011) conducted delta half wave analysis and found that patients with schizophrenia showed lower total delta wave counts during all-night sleep than did control subjects in all regions. Finally, a study looked at high frequency activity and found that the schizophrenia patients showed higher gamma power (Tekell et al., 2005).

Table 19: overview of PSG studies included in the review

Study	Country	Design	Sample	Age Mean (SD)	Gender Male: female	Medication status	Sleep measure	Psychosis measure	Summary
Appelberg, 1997	Finland	Cross-sectional	*N*= 20 inpatients with non-affective psychosis	30.4	Not reported	Drug free for one week before recordings	2 nights PSG	DSM-111	Interleukin levels correlated negatively with a range of sleep parameters.
Bian, 2016	China	Cross-sectional	*N*=148 Schizophrenia inpatients	42(14.7)	77:71	All medicated during study	1 night PSG	DSM-IV-SCID	Patients experienced sleep state mis-perception. They overestimated TST and SE but underestimated SOL
Brambilla, 1983	Italy	Single blind treatment study-bromocriptine Treatment	*N*= 6 Schizophrenia inpatients	Not reported	3:7	Withdrawn meds 3 weeks before study	PSG- 3 nights before treatment, an every two nights during treatment	Research Diagnostic criteria (RDC) BPRS	No significant effects of the agonist on sleep
Chaparro-Vargras, 2016	Germany	Cross-sectional study	*N*=10 Schizophrenia (inpatients) 10 healthy controls 10 insomnia	31.7(10,2) 31.5(11.3) 31.3(10.1)	5:5 5:5 4:5	Medicated	2 nights PSG	DSM-IV-R	Similar sleep continuity across groups.
Feinberg,1965-	USA	Cross-sectional	*N*=18 Schizophrenia inpatients *N*=10- non-hospitalised controls	Not reported	Not reported	Not reported	4-5 nights PSG	Not reported	Schizophrenia group took longer to fall asleep than the control group.
Ferrarelli 2010	USA	Cross-sectional	*N*=49 patients with schizophrenia *N*=44 healthy controls *N*=20 non-scz patients	38.2 (10.6) 36.7 (7.8) 34.75 (8.6)	33:16 29:15 5:15	Medicated	PSG- 1 night	DSM-IV	Schizophrenia patients had increased SOL in relation to HC. No other sleep differences were significant. Schizophrenia patients also had whole night deficits in other sleep parameters such as

									spindle power and amplitude.
Ganguli 1987	USA	Cross-sectional	*N*=8 Schizophrenia (Inpatients) *N*=8 Delusional Depression *N*=16 Non - delusional depression *N*=16 Healthy controls	21.5(4.0) 41.4(12.1) 25.8(2.5) 22.8(2.9)	6:2 3:5 5:11 6:10	Unmedicated	2 nights PSG	RDC, BPRS	Schizophrenia group had decreased sleep continuity compared to delusional depression group. Schizophrenia group also had diminished delta counts and decreased total delta wave count
Genzel, 2015	Germany	Cross-sectional	*N*=16 Schizophrenia *N*=16 Healthy controls *N*=16 Depression	39.1(8.7) 41.8(10.1) 46.8(8.6)	8:8 8:8 10:6	Medicated	2 nights PSG	DSM-IV, ICD-10	No diffs on sleep continuity
Gillin, 1974	USA	Cross-sectional	*N*=8 Schizophrenia (Inpatients) *N*=8 Non- Psychotic controls (inpatients)	25 26	3:5 3:5	Unmedicated for 3 weeks prior study except 1	9-11 nights PSG	Ward psychiatrists	REM deprivation study. Actively ill schizophrenics are less likely than control psychiatric patients to exhibit a normal REM rebound. No diffs on TST.
Goder, 2004	Germany	Cross-sectional	*N*=17 Schizophrenia (inpatients) *N*=17 Healthy controls	31(Median) 31 (Median)	10:7 10:7	Medicated	2 nights PSG	ICD-10	Patients spent more TIB, Longer SOL, poorer SE, More awakening, more S1, Less SWS and longer latency to SWS and poorer sleep quality on PSQI. Reductions in SWS & SE correlated with poorer spatial recall. Same sleep findings remained in sub sample of patients who were med naïve.

Goder, 2015	Germany	Cross-sectional	*N*=16 Schizophrenia *N*=18 Healthy controls	29.4(6.4) 28.3(6.1)	7:9 9:7	Medicated	2 nights PSG	ICD-10	Patients spent more TIB and slept longer compared to NC. Sleep spindle density also reduced.
Hinze-selch,1997	Germany	Longitudinal-clozapine treatment study	*N*=13 Schizophrenia (inpatients)	34.6(9.8)	6:7	Med free for at least 6 months	PSG before and after clozapine. Adaptation night included.	DSM-III-R, BPRS.	Clozapine lead to an overall improvement of sleep including TST and SE.
Hudson, 1993	USA	Cross-sectional study	*N*=8 Schizophrenia *N*=19 Mania *N*=19 Depression *N*=19 Healthy controls (All inpatients)	27.9 (6.8) 26.5 (5.5) 24.4(4.4) 24.5(3.2)	Not reported	Unmedicated 2 weeks prior to study and no neuroleptic 4 weeks before study	2-4 nights PSG	DSM-III-R. BPRS	Patient groups all reported similar levels of sleep disturbance. There were no diffs across groups on SOL, stage 2, 3, and REM.
Kaplan, 1974 (placebo condition)	USA	Longitudinal - chlorpromazine	*N*=13 Schizophrenia (inpatients)	28.8	All male	Drug free, and then given chlorpromazine	7 nights PSG	3 different psychiatrists	Chlorpromazine improved sleep parameters including SOL, TST,NREM time and REM activity and density
Kempeaners, 1988	Belgium	Cross-sectional	*N*=9 Schizophrenia inpatients *N*=9 Depression inpatients *N*=9 Healthy controls	25.6(2.6) 23.9(5.6) 25.1(3.0)	All male	Med free for 1 month before study	3 nights PSG	RDC, SADS	Schizophrenia group had longer SOL, and more stage 1 sleep than controls. They also had less stage 3 sleep than depression group.
Keshavan, 1998	USA	Cross-sectional	*N*=30 Schizophrenia inpatients *N*=30 Healthy controls	30.9(8.5) 30.9(8.2)	17:13 17:13	19 Med- naïve 11- med free period (average 97 weeks)	2-3 nights [SG	DSM-III-R	Patients had reduced delta sleep. Also had longer SOL, shorter TST, lower SE and higher WASO than controls.
Lauer, 1997	Germany	Cross-sectional	*N*=22 Schizophrenia inpatients	32.7(8.6)	14:8	Drug naive	2 Nights PSG	DSM-III-R, BPRS	Patients had lower TST, lower SE, and longer SOL, WASO,

			N=20 Healthy controls	30.7(6.7)	13:7				more awakenings and less S2 sleep than controls.
Lee, 2001	Korea	Clozapine treatment study	*N*=5 Schizophrenia inpatients *N*=5 Healthy controls	33(5.1) 32.4(7.4)	All male	Drug free for at least 7 days (ranged 16-31)	PSG before and during clozapine treatment. 2nights	DSM-III-R	Patients had decreased SE, TST, S2 sleep and increased duration of awakening compared to controls. During treatment, there was an improvement of sleep after 3-4 days and this effect was stable weeks after.
Lusignan, 2010	Canada	Dream collection study- cross-sectional	*N*=14 Schizophrenia (Outpatients) *N*=15 Healthy controls	25.5(3.2) 22.3(4.2)	13:1 12:3	Medicated	3 nights PSG	DSM-IV-TR	No diffs in sleep parameters between the two groups. NREM sleep mentation similar between groups
Maixner, 1998	USA	Treatment study: haloperidol or thiothixene	*N*=14 Schizophrenia (inpatients)	27.7	12:2	2 weeks med free before study	Pre and post medication PSG 2 nights	DSM-III-R	Sleep improved with neuroleptic treatment including SOL, TST and SE. Stage 3 sleep also improved.

Manoach, 2014	USA	Cross-sectional	*N*=15 Schizophrenia *N*=11 Clinical controls *N*=25 Healthy controls *N*=19 First degree relatives	28(8) 27(7) 27(7) 14(4)	11:4 6:5 16:9 9:10	Anti-psychotic naïve	2 nights PSG	DSM-IV	Sleep spindle deficits were also reported in early course, antipsychotic naïve patients with schizophrenia. Schizophrenia patients also reported poor sleep.
Oh, 2017	Korea	Cross-sectional	*N*=9 Schizophrenia *N*=10 Healthy controls	30(13.6) 30.3(8.4)	6:3 7:3	8 Medicated, 1 antipsychotic naïve	PSG- unclear- seems to be one night	ICD-10	Patients had longer SOL and TIB compared to NC. EEG spectral activity abnormalities were also present.
Ozone, 2013	Japan	Cross-sectional	*N*=7 Schizophrenia	34.6(14.5)	4:3	Medicated	1 night PSG	ICD-10	Schizophrenia had poor sleep with score of 9 on PSQI, and all slept more than 7 hours with a high sleep efficiency.
Poulin, 2003	Canada	Cross-sectional	*N*=11 Schizophreniform (inpatients) *N*=11 Healthy controls	29.6(15.8) 25.3(11.3)	6:5 8:3	Neuroleptic naive	2 nights PSG	DSM-IV	Patients had higher SOL, decreased stage 4 duration, reduced rapid eye movement (REM) sleep latency, and normal sleep spindles and REMs densities

Ramakrishnan, 2012	Germany	Cross-sectional	*N*=20 Schizophrenia (outpatients)	41.25 (8.7)	8:12	Medicated	PSG- 1 night?	DSM-IV	Sleep parameters related to enhanced performance on cognitive tasks
Reich,1975	USA	Cross-sectional	*N*=29 Schizophrenia (inpatients)	24.0 (1.8)	12:17	At least two weeks med free	4 nights PSG	Diagnostic interview	This study compared the effects of illness stages and between schizophrenia and schizophrenia-affective. Acute had less SWS, and less time spent asleep. Acute schizophrenia had shorter rem l than schizophrenia affective. Latent schizophrenia had <SOL and > rem latency than schizophrenia affective.
Riemann, 1995	Germany	Cross-sectional	*N*=10 Schizophrenia (inpatients) *N*=10 Depression (inpatients) *N*=10 Healthy controls	15.8(1.8) 16.5(1.7) 16.6 (1.9)	4:6 2:8 7:3	At least one week drug free, 2 were drug naïve	3 nights PSG	DSM-III-R	Sleep continuity was impaired in schizophrenia.
Roschke, 1995	Germany	Cross-sectional	*N*=13 Schizophrenia (inpatients) *N*=13 HC age and gender matched	28(5)	11:2	Med free for 3 months	2 nights PSG	DSM-III-R	The only sleep parameter that differed between the two groups was REM –Latency. The patient group had a short REM-Latency.

Rotenberg, 2000	Israel	Cross-sectional	*N*=20 Schizophrenia *N*=10 Healthy controls	45.8 43.5	13:7 6:$	Medicated	3 nights PSG	DSM-IV	Patient group reported longer SOL and more awakenings. On sleep architecture they had longer duration of first rem period and higher eye movement density.
Salin Pascual, 1999	Mexico	Treatment study-Olanzapine	*N*=20 Schizophrenia (inpatients)	33.6(10.7)	9:11	Drug free 2 weeks before study. Given Olanzapine	5 nights PSG: Acclimatize night Screening night Baseline night Olanzapine nights	DSM-IV	Olanzapine improved a range of sleep parameters including less wake time, less stage 1 sleep, more stage 2 sleep, more slow wave sleep, longer TST and increased REM density.
Sarkar, 2010	India	Cross-sectional	*N*=20 Schizophrenia (Inpatients) *N*=14 first degree relatives *N*=20 Healthy controls	26.60 (5.29) 31.71 (11.80) 29.25 (10.14)	All male	Drug naive	1 night PSG	ICD-10	Patients had a lower TST and lower stage 2 duration than both control groups. Patients also reported lower stag 3 latency, stage 4 duration and stage 1 and 4 TST.
Sasidharan, 2017	India	Cross-sectional	*N*=45 Schizophrenia (outpatients) *N*=39 Healthy controls	27.78 (6.75) 27.26 (4.59)	32:13 28:11	Drug free for at least 3 months or drug naïve	1 night PSG	DSM-IV	Patients had differences in sleep macro and microarchitecture including increased stage transitions

Schilling, 2017	Germany	Cross-sectional	*N*=17 Schizophrenia (inpatients) *N*=13 First degree relatives *N*=17 Healthy controls	29.94 (10.60) 33.31 (14.05) 26.53 (8.78)	10:7 6:7 11:6	Medicated	2 nights PSG	DSM-IV-TR	Fast spindle density was reduced in patients and relatives and this was associated with decreased memory performance.
Sekimoto, 2011	Japan	Cross-sectional	*N*=17 Schizophrenia (outpatients) *N*=18 Healthy controls	30.4 (7.2) 28.5 (7.3)	All male	Mixed: 3 neuroleptic naïve 2 no meds for 4 weeks 12 on stable med	2 nights PSG	DSM-IV	No significant differences in sleep continuity. Patients reported more stage 2 and less stage 4 + 4 and also had lower total delta wave counts.
Tekell,2005	USA	Cross-sectional	*N*=17 Schizophrenia (in and outpatients) *N*=15 Depression (outpatients) *N*=17 Healthy controls	35.5 (9.7) 36.7 (8.6) 30.3 (4.0)	14:3 12:3 14:3	Med free for 4 weeks	2 Nights PSG	DSM-III-R	No diffs in sleep continuity. Patients had less S2 sleep v healthy controls, and lower SE compared to both groups.
Tsekou, 2014	Greece	Treatment study-clozapine.	*N*=7 Schizophrenia (drug resistant, inpatients)	30.7(5.2)	All male	Medicated with risperidone This was then combined with dosage of clozapine.	4 nights PSG- 2 nights before clozapine and 2 nights after clozapine.	PANSS	No significant changes in sleep parameters with treatment- however study very underpowered.
Van Cauter, 199	Belgium	Cross-sectional	*N*=9 Schizophrenia (inpatients) *N*=9 Healthy controls	28.3(6.3) 29.7(5.4)	All male	Medication free for at least 9 weeks before study	4 Nights PSG	RDC, BPRS	Patient group had a longer SOL and lower SE. Differences in sleep architecture were also found including less stage 1 and 2 and REM sleep in the patient group
Van kammen, 1994	USA	Cross-sectional	*N*=28 Schizophrenia (Inpatients)	33.9(6.4)	All male	Med free for 12 days before the study	3 nights PSG	DSM-III-R	Diazepam-binding inhibitor-like immunoreactivity (DBI-LI) correlated with REM latency, stage 1 and 4 sleep.

Wamsley, 2012*	USA	Cross-sectional	*N*=21 Schizophrenia (Outpatients) *N*=17 healthy controls	34 (9) 36 (7)	17:4 14:3	Medicated	2 Nights PSG	DSM-IV	No diffs on sleep architecture between groups. Spindle abnormalities were found in patient group. .
Wyatt, 1970	Not reported	Cross-sectional	*N*=8 Schizophrenia (inpatients) *N*=6 Healthy controls	21.8	2:6 4:2	Not on meds at time of admission	3- 10 nights PSG		Patient group had longer SOL and less NREM sleep and less REM activity
Yang, 2006	Korea & USA	Cross-sectional	*N*=15 Schizophrenia (inpatients) *N*=15 Healthy controls	40.6(3.7) 40.2(4.1)	All men	Free from meds 2 weeks prior to study but were allowed medication for sleep onset insomnia.	2 nights PSG- not all patients complied.	DSM-IV	Patient group had more TIB, WASO, longer SOL AND lower SE. There were also differences on sleep architecture.
Zarcone, 1997	USA	Cross-sectional	*N*=20 Schizophrenia or schizo-affective inpatients	33.9 (6.7)	All male	Free from meds 2 weeks prior to study	3 nights PSG	RDC, BPRS	SOL was correlated with thinking disturbance on the brief psychiatric rating scale.

Table 20: Sleep continuity in PSG studies

Study	SOL	TST	WASO	SE
Feinberg,1965-	Longer in scz	-	-	-
Ferrarelli, 2010	Longer in SCZ	n/s		
Ganguli, 1987	n/s	-	Higher in SCZ	-
Genzel,2015	-	n/s	-	-
Gillin, 1974	-	-	-	-
Goder, 2004	Longer SOL	Shorter TST	-	Lower in SCZ
Goder, 2015	n/s	Longer TST	-	N/S
Hudson, 1993	n/s	Shorter TST	-	Lower in SCZ
Kempeaners, 1988	Longer in SCZ	N/S	-	n/s
Keshavan, 1998	Longer in SCZ	Shorter TST in SCZ	Higher in SCZ	Lower in SCZ
Lauer, 1997	Longer in SCZ	Shorter in SCZ	Higher in SCZ	Lower in SCZ
Lee, 2001	N/S	Shorter in SCZ	Higher in SCZ	Lower in SCZ
Lusignan, 2010	-	N/S	-	N/S
Manoach, 2014	-	N/S	Higher in SCZ	Lower in SCZ
Oh, 2017	Longer in SCZ	N/S	N/S	N/S
Poulin, 2003	Longer in SCZ	N/S	-	N/S
Riemann, 1995	n/s	-	-	Lower in scz
Roschke, 1995	n/s	n/s	-	n/s
Rotenberg, 2000	Longer in SCZ	N/s	-	n/s
Sarkar, 2010	N/S	Shorter in SCZ	-	N/S
Sasidharan,2017	Longer in SCZ	Longer in SCZ	Longer in SCZ	Lower in SCZ
Schilling, 2017	N/S	-	-	N/S
Sekimoto, 2011	N/S	N/S	-	N/S
Tekell, 2005	n/s	n/s	-	Lower in SCZ
Van Cauter, 1991	Longer in SCZ	N/S	-	Lower in scz
Wamsley, 2012	-	n/s	n/s	-
Wyatt, 1970	Longer in SCZ	-	-	-
Yang, 2006	Longer in SCZ	N/S	Longer in SCZ	Lower in SCZ

Please note- for this table, only studies that compared sleep parameters to a control group are included, otherwise the table would be too big

Table 21 the bias assessment for PSG studies

Component	1: Patient selection	2: Baseline Characteristics	3: PSG	6: Power	7: Missing Data	8: Completion Rates	9: Data Analysis
Study							
Appelberg, 1997	🔴	🔴	🟠	🟠	🔴	🟢	🟢
Bian, 2016	🟢	🔴	🔴	🟢	🟢	🟢	🟢
Brambilla, 1983	🔴	🔴	🔴	🔴	🔴	🔴	🔴
Chaparro-Vargras, 2016	🟢	🟢	🔴	🔴	🟢	🟢	🟢
Feinberg,1965-	🔴	🟠	🔴	🔴	🟢	🟢	🟢
Ferrarelli, 2010	🟢	🟠	🔴	🟢	🟢	🟢	🟠
Ganguli, 1987	🟠	🟢	🔴	🔴	🔴	🟢	🟢
Genzel ,2015	🟢	🟢	🔴	🔴	🟢	🟢	🟢
Gillin, 1974	🔴	🟠	🟠	🔴	🟢	🟢	🟢
Goder, 2004	🟢	🟢	🟢	🔴	🔴	🟢	🟢
Goder, 2015	🟠	🟢	🔴	🔴	🟢	🟢	🟢
Hinze- selch, 1997	🟠	🔴	🟢	🔴	🟢	🟢	🟢
Hudson, 1993	🔴	🟠	🔴	🔴	🔴	🟢	🟢
Kaplan, 1974 (placebo condition)	🔴	🔴	🔴	🔴	🔴	🟢	🟢
Kempeaners, 1988	🔴	🟢	🟠	🔴	🔴	🟢	🟢
Keshavan, 1998	🔴	🟢	🟠	🟢	🟢	🟢	🟢
Lauer, 1997	🟠	🟢	🟢	🔴	🟢	🟢	🟢
Lee, 2001	🔴	🟢	🔴	🔴	🟢	🟢	🟢
Lusignan, 2010	🟢	🔴	🔴	🔴	🟢	🟢	🔴
Maixner, 1997	🔴	🔴	🔴	🔴	🟢	🟢	🟢
Manoach, 2014	🟢	🔴	🟠	🔴	🟢	🟢	🟢
Oh, 2017	🔴	🟢	🔴	🔴	🔴	🟢	🟢
Ozone, 2013	🟢	🔴	🔴	🔴	🟢	🟢	🟢
Poulin, 2003	🔴	🔴	🔴	🔴	🟢	🟢	🟢
Ramakrishnan, 2012	🟢	🔴	🟠	🔴	🟢	🟢	🟢
Reich, 1975	🔴	🔴	🔴	🔴	🟢	🟢	🟢
Riemann, 1995	🔴	🟢	🔴	🔴	🟢	🟢	🔴
Roschke, 1995	🔴	🟢	🔴	🔴	🟠	🟢	🟢

Rotenberg, 2000	🔴	🟠	🔴	🟠	🟢	🟢	🟠
Salin Pascual, 1999	🟢	🔴	🟠	🟠	🔴	🟢	🟢
Sarkar, 2010	🔴`	🟢`	🔴	🟠	🟠	🟢	🟢
Sasidharan,2017	🟢	🟢	🔴	🟢	🟢	🟢	🟢
Schilling, 2017	🟢	🟢	🔴	🔴	🔴	🟢	🟢
Sekimoto, 2011	🔴	🟠	🔴	🔴	🟢	🟢	🟢
Tekell, 2005	🟠	🟢	🔴	🔴	🟢	🟢	🟢
Tsekou, 2014	🔴	🔴	🔴	🔴	🔴	🟢	🟢
Van Cauter, 199	🔴	🟢	🟠	🔴	🟢	🟢	🟢
Van kammen, 1994	🔴	🔴	🟢	🟢	🔴	🟢	🟢
Wamsley, 2012*	🟢	🟢	🔴	🟢	🟢	🟢	🟠
Wyatt, 1970	🔴	🟠	🔴	🔴	🟢	🟢	🟠
Yang, 2006	🔴	🟢	🟢	🔴	🟢	🟢	🟢
Zarcone, 1997	🔴	🔴	🔴	🟠	🔴	🟢	🟢

4.4 Discussion:

Sleep disturbances are well documented in schizophrenia and a range of methods have been used to measure sleep in this population(Cohrs, 2008). The aim of our review was to critically evaluate the methods that have been used to measure sleep in NAP. We did this by conducting bias assessments of all of the included studies. We also sought to report what aspects of sleep are disrupted and consider these in the context of our bias assessments.

Numerous reviews and studies have reported that sleep continuity is commonly disrupted in people with NAP, including increased SOL and a decreased TST (Chouinard et al., 2004; Cohrs, 2008). In our review we recorded 4 measures of sleep continuity- SOL, SE, WASO and TST. Our findings provide mixed support for disruption of sleep continuity. Firstly, there were numerous studies that did not report these measures, or did not have a control group to compare the measures to. Secondly, for each of our 4 outcomes, there were non-significant findings also reported. Thirdly, across methodologies, sleep continuity measures differed. For example, actigraphy had a trend towards increased TST, whilst PSG reported lowered TST in comparison to healthy controls, while no conclusions could be made from subjective studies. However, in line with previous research, the direction of the measures were more consistent. For example, for the studies that found significant differences in SOL, this was always in the direction increased SOL except for one study (Hofstetter, Lysaker, & Mayeda, 2005). Likewise, for WASO and SE, this was almost always in the direction of more severe disturbance in the NAP sample. Therefore, we can conclude that there is evidence for disruption of sleep continuity, but that this is not a consistent finding across all studies.

Our review rated each study on risk of bias, and the components rated provide some insight into potential reasons for inconsistent results.

Across all three of our methodologies, there were some common areas of bias that emerged. In the domains of patient selection, studies were rated as risk of bias if they did not include important demographic information on patients such

as age, gender as well as inclusion/exclusion criteria or if they included unrepresentative samples. Likewise, numerous studies lacked control groups, or included unmatched groups. In future, studies should include clear information on the sample that includes inclusion/exclusion criteria, how samples were selected and important demographics such as age and gender. In terms of power, this was an area of bias across all three methodologies. Small samples make it difficult to exclude type 2 error, and can contribute to inconsistent results between studies. Power was especially an issue in PSG studies which were often conducted in small samples but the range in our studies was large- from 5 to 148 patients (Bian et al., 2016; Lee et al., 2001). The majority of studies were conducted in sample sizes of 20 participants or less. PSG is a costly and time consuming technique and this limits sample sizes. However, this makes it difficult to exclude type 2 error and can contribute to inconsistent results between studies. A potential area for future research may be conducting polysomnography at home in people with psychosis. This may be a more viable and ecologically valid way to measure sleep architecture.

Our review also identified some method –specific areas of bias, and will be discussed in relation to each methodology next.

4.4.1 Polysomnography

Out of the 3 methods assessed in our review, PSG was the most commonly used method to assess sleep and the majority of the studies were conducted in inpatient samples. In our review, 42 studies used PSG. We found some evidence for disruption of sleep architecture, in the direction of lowered S1 sleep and reduced SWS, indicating more light sleep and less deep sleep. There were no consistent effects for REM sleep variables. These findings correspond with a recent review of PSG sleep studies who concluded that both sleep architecture and continuity were disturbed (Chan, Chung, Yung, & Yeung, 2017) as well as with a review that compared sleep across different mental disorders (Baglioni et al., 2016).

Sleep microstructure has also been assessed with PSG, and in particular sleep spindles have been investigated. Sleep spindles are a hallmark of S2 sleep and are generated in the thalamus (Manoach, Pan, Purcell, & Stickgold, 2016). Various aspects of spindles have been assessed and studies find a reduction in spindles, lowered amplitude and lowered spindle duration (Ferrarelli et al., 2010; Goder et al., 2015; Manoach et al., 2014; Sasidharan et al., 2017; Schilling et al., 2017; Wamsley et al., 2012). Other aspects of sleep also disrupted include delta waves and more sleep instability(Ganguli et al., 1987; Keshavan et al., 1998; Sasidharan et al., 2017). These investigations are promising and have potential to highlight more fine grained sleep changes, which may help further our understanding of the relationship between sleep and its impact in psychosis. For example, spindle density has been linked to memory performance (Schilling et al., 2017).

However, one of the most striking findings from the bias assessment was that 69% of the studies were rated at risk of bias based on their PSG methodology. Using our bias tool, studies were rated at risk of bias if they did not include an adaptation night to rule out the first night effect (Agnew, Webb, & Williams, 1966) or if it was unclear if they restricted napping and caffeine on day of recording. Not including an adaptation night in PSG studies is problematic as it does not allow the participant to adapt to the unique environment of the sleep lab, and the sleep on the first night is unlikely to reflect their typical sleep(Agnew et al., 1966; Toussaint et al., 1995). Furthermore, night sleep can be affected by napping in the day (Borbély, 1982), as well caffeine use which is an adenosine antagonist (Fisone, Borgkvist, & Usiello, 2004) and has alerting effects and may influence sleep parameters. Based on this criteria, 69% of the PSG studies included in our review were rated at risk of bias. When interpreting findings from PSG studies, it is important to consider them in light these methodological limitations.

4.4.2 Actigraphy

Actigraphy studies revealed that people with NAP report more sleep during the day, and are more likely to experience delayed and fragmented rhythms

indicative of circadian disruption. In terms of actigraphy methodology, studies were rated at risk of bias if they did not include at least a week or recording, or if there was no attempt to distinguish period of quiet rest from sleep, through use of sleep logs or diaries. Based on this criteria, 40% of the studies were rated at risk of bias. Looking at these studies in more detail, 3 were rated at risk of bias because they did not distinguish quiet rest from sleep and 1 because they only recorded 3 days. These criteria were selected as sleep is a variable experience, and in order to capture accurate estimate, multiple nights of recording are recommended (Aili, Astrom-Paulsson, Stoetzer, Svartengren, & Hillert, 2017; Ancoli-Israel et al., 2015; Briscoe et al., 2014). The use of detailed sleep logs and diaries that include information on times patients are resting, or have taken the actiwatch off is recommended to prevent over scoring of sleep time (Lichstein et al., 2006).

4.4.3 Subjective assessment

As with PSG and actigraphy, our coding revealed some areas of potential bias. Studies using subjective assessment were rated as risk of bias if they did not include validated measures of sleep. According to this criteria, 66% of studies were rated either at risk of bias, or unclear due to lack of information. The majority of studies used their own developed questions or did not clearly specify the questions used in the studies. A great number of validated questionnaires exist that should be used in future research. When using sleep diaries, we recommend the use of the validated Carney Sleep Diary (Carney et al., 2012). Without using validated questionnaires, the reliability and validity of questions becomes problematic.

4.4.4 Limitations of the current review

Meta-analysis could not be conducted due to inconsistent reporting of sleep parameters. We did not report on correlates of sleep disturbance in people with psychosis. But this has been covered extensively in previous reviews (Davies et al., 2017; Reeve et al., 2015). Furthermore, we did not capture every potential

area of bias within the methodologies, although our tool provides a good starting point. For example, within polysomnography blind scoring was not assessed.

4.4.5 Strengths of the current review

We have conducted a comprehensive review of sleep methods used in NAP. Our review also went one step further in that we provided a comprehensive assessment of bias, and identified unique aspects that can be addressed in future research.

4.4.6 Overall summary

Sleep has been measured by a variety of methods and has helped revealed the sleep disturbances that are commonly reported in people with NAP. However, our review identified a number of important methodological weaknesses in study designs that call into question the strength of some of these findings. Our review also bought to the surface that many studies report non-significant results in relation to sleep disturbances. Addressing these methodological weaknesses will help tease out more clearly what aspects of sleep are disrupted in people with NAP, which in turn can help inform and better tailor sleep interventions.

4.4.7 Recommendations for future studies

- All studies should carefully and clearly report important demographic information about their patient samples, with inclusion and exclusion criteria.

- Sample size should be justified e.g. through power calculations.

- Missing data should be clearly stated and any strategies used to deal with missing data.

- Completion rates should be reported/information on drop-outs provided such as reasons for exiting the study.

- Studies using PSG should include an adaptation night to allow participants to accustom to the sleep lab, as well as eliminate napping and caffeine influences on recording days.

- Studies using actigraphy should record at least 7 days to provide more reliable estimates, and include the addition of sleep logs/diaries when scoring actigraphy data.

- Studies using subjective sleep measures should use the appropriate validated questionnaires for the aspect of sleep they are interested in. If using sleep diaries, we recommend using the Gold Standard Carney Sleep Diary (Carney et al., 2012).

5 The role of sleep in predicting paranoia in non-affective psychosis: an experience sampling study

5.1 Introduction

As many as 30-80% of people with a diagnosis of NAP conditions such as schizophrenia report sleep disturbances (Cohrs, 2008). Sleep disruption appears to be a persistent issue that is found in medicated, and non-medicated samples, as well as during acute and stable phases, (Poulin et al., 2003; Ruhrmann, Schultze-Lutter, Salokangas, & et al., 2010). Importantly, sleep disturbances are linked to a range of outcomes including severity of symptoms, mood, and quality of life (Cohrs, 2008; Mulligan et al., 2016) and patients report sleep is an important treatment target (Waite, Evans, et al., 2016). Together, this emphasises the importance of understanding the nature and correlates of sleep problems in people diagnosed with psychosis.

5.1.1 What aspects of sleep are disrupted?

Measured both subjectively and objectively, a range of sleep and circadian disturbances have been reported in people diagnosed with schizophrenia. For example, one study in a sample of 30 participants reported that over half the sample experienced moderate to severe levels of insomnia (Freeman et al., 2009). Other studies have also reported elevated levels of insomnia, although the prevalence estimate varies (Palmese et al., 2011; Xiang et al., 2009a).Nightmares are also prevalent. One study in a sample of 40 participants experiencing psychotic symptoms, reported that 55% reported weekly distressing nightmares (Sheaves et al., 2015). As well as nightmares and insomnia, circadian disruption in the form of sleep/wake pattern irregularity and alterations in circadian rhythms of melatonin are also found (Bromundt et al., 2011; Wulff et al., 2012). There is also some evidence for hypersomnia which is conceptualised as excessive daytime sleepiness. Estimates of excessive daytime sleepiness range from 32- 58% (Sharma, Dikshit, Shah, Karia, & De Sousa, 2016; Wichniak et al., 2009). This evidence suggests that a range of sleep disturbances are common in people diagnosed with schizophrenia.

5.1.2 The relationship between sleep disturbances and paranoia

Sleep disturbance has been linked to increased severity of symptoms (Cohrs, 2008; Mulligan et al., 2016). In particular, strong relationships between sleep and paranoia have being found in both clinical and non-clinical samples (Freeman et al., 2012; Myers et al., 2011). In a longitudinal study, insomnia predicted the onset of paranoid thoughts in the general population (Freeman et al., 2012). In a clinical sample, improving sleep using cognitive behavioural therapy for insomnia (CBTi) was associated with reductions in both paranoia and insomnia (Myers et al., 2011). Investigating mechanisms linking sleep to paranoia is the next step, with evidence being found for negative emotional states (Freeman et al., 2010; Scott, Rowse, & Webb, 2017) and levels of emotional awareness (Rehman, Gumley, & Biello, 2018). This research suggests that levels of negative emotions may be a key mediator in the relationship between sleep and paranoia. Our aims are to understand and further explore these relationships, taking into account limitations of prior work.

5.1.3 Limitations of previous research

In studies examining paranoia and sleep, paranoia is often measured in terms of frequency. This research excludes other important dimensional aspects of paranoid beliefs. For example, paranoia has dimensions of distress, pre-occupation and conviction associated with it (Freeman & Garety, 2000; Freeman et al., 2005) and these aspects of paranoia could also be considered in relation to sleep. Another limitation of prior work is that it is cross-sectional in nature limiting inferences regarding causality (Mulligan et al., 2016). There is therefore a need to understand these relationships as they unfold in daily life. It has been shown that both sleep and psychotic symptoms show variability and are dynamic states. For example, paranoia fluctuates with changes in mood and self-esteem (Thewissen, Bentall, Lecomte, van Os, & Myin-Germeys, 2008). Sleep has also been found to show daily variation (Buysse et al., 2007). Another study found that next day mood was linked to prior night's sleep in patients with depression suggesting a temporal relationship between sleep and mood (de Wild-Hartmann et al., 2013).

5.1.4 Experience sampling method (ESM)

To capture relationships at a daily level ESM requires participants to answer questions about mood, context and symptoms, several times a day for consecutive days, usually at random moments signalled on a smartphone (Myin-Germeys et al., 2009). ESM yields high levels of ecological validity, in comparison to retrospective techniques, as it allows experiences to be captured as they unfold in daily life. ESM has been used in a wide variety of psychiatric conditions including psychosis, borderline personality disorder, depression and eating disorders, with high levels of adherence and acceptability reported (Myin-Germeys et al., 2009). To date, there has only been one study using ESM to investigate relationships between sleep, symptoms and mood in people with NAP. This study found that both subjective and objective sleep predicted next day psychotic symptoms including paranoia and delusions of control (Mulligan et al., 2016). The study also found that the relationship between sleep and next day paranoia was mediated by negative affect, supporting studies conducted using retrospective measures. Our study differs from the Mulligan study in that they focused on a range of symptoms including delusions of grandeur, control and hallucinations. Furthermore, they also selected a sample of patients with experiencing insomnia symptoms, whereas in this study patients did not have to have a specific sleep complaint.

5.1.5 Current study and aims

We sought to investigate whether sleep predicts variation in frequency, distress, pre-occupation and conviction dimensions associated with paranoia. Furthermore, we sought to examine the temporal relationship between sleep and paranoia. We did this by investigating whether levels of state paranoia were predicted by levels of preceding state sleep, and whether this relationship was mediated by levels of negative affect.

5.1.6 Hypotheses

- Subjective sleep measured by a sleep diary will predict levels of paranoia, as well as distress, pre-occupation and conviction measured at the daily level.

- Levels of sleep at one moment, will predict paranoia at the next moment, and this will be mediated by levels of negative affect (time-lagged analysis).

5.2 Method

5.2.1 Participants

The study was reviewed and approved by the Greater Glasgow and Clyde National Health Service (NHS) Research Ethics Committee (REC) ref: 14/WS/0124 and by local research and development offices. To be eligible for the study participants had a diagnosis of non-affective psychosis (schizophrenia, schizoaffective disorder, delusional disorder, schizophreniform disorder, psychotic disorder not otherwise specified) in accordance with International Classification of Diseases-10 (ICD-10; World Health Organization, 1992). Participants were aged between 18-65, had been on a stable medication regime for the past month and were able to give full informed and written consent. Exclusion criteria included alcohol or drug dependence, head injury, neurological illness, night shift work or having travelled across time zones in the past month. There were two routes for recruitment for participants- they could be referred to the study by their clinical team or they could self-refer through adverts that were put up in local centres about the study.

5.2.2 Baseline questionnaire measures:

A range of sleep questionnaires were select in the study to capture a range of sleep and circadian disturbances. All questionnaires were administered face to face with patients and this allowed any confusion about wording or questions to be dealt with directly. All measures were administered by the first author (AR).

5.2.2.1 Wilson-Screening for Sleep Disorders

This algorithm serves as a screening tool for sleep disorders including narcolepsy, sleep apnoea, parasomnias, restless legs and circadian rhythm sleep disorders. No one in our study met the criteria for any of the sleep disorders. The screening tool is published in (Wilson et al., 2010).

5.2.2.2 Pittsburgh Sleep Quality Index (Buysse et al., 1989)

The PSQI provides a reliable, valid, and standardized measure of sleep quality. Scores range from 0-21 with higher scores representing poorer sleep. A PSQI global score >5 indicates that a participant is having severe difficulty in at least two areas, or moderate difficulty in more than three areas of sleep quality in the past month. Internal consistency of the PSQI is high α = .83 (Buysse et al., 1989).

5.2.2.3 Epworth Sleepiness Scale (M. W. Johns, 1991)

The ESS provides an assessment of daytime sleepiness. Respondents are asked to rate, on a 4-point scale (0-3), their usual chances of dozing off or falling asleep while engaged in eight different activities. Most people engage in those activities at least occasionally, although not necessarily every day. The ESS score (the sum of 8 item scores, 0-3) can range from 0 to 24. The higher the ESS score, the higher that person's 'daytime sleepiness'. The questionnaire takes no more than 2 or 3 minutes to answer. Internal consistency in the study was α =0.75.

5.2.2.4 Sleep Condition Indicator (Espie et al., 2014).

The SCI is a screening measure for insomnia based on the DSM-V criteria for insomnia disorder. We used the short form which has 2 items. Internal consistency in the study was α=0.80.

5.2.2.5 Nightmare Frequency:

This was assessed by asking participants how often they experienced nightmares, with options ranging from never to more than once a day.

5.2.2.6 Nightmare Distress Questionnaire (Belicki, 1992)

Includes 13 items rated on a five-point scale to assess the degree of self-reported distress attributed to nightmares. Internal consistency in the study was α=0.80.

5.2.2.7 Morning Eveningness Questionnaire: (Horne & Ostberg, 1976)

The Horne-Ostberg Morningness Eveningness Scale is used to distinguish between chronotypes (whether one is a morning or an evening person). Scores range from 16 to 86, corresponding to extreme eveningness (lower numbers) to extreme morningness (higher numbers). Questions focus on individual preferences for sleep and wake times. Internal consistency in the study was α=0.70.

5.2.2.8 Toronto Alexithymia Scale (Bagby et al., 1994)

The TAS -20 includes 20 items and measures 3 factors of alexithymia. Factor 1 assesses difficulty in identifying feelings. Factor 2 assesses difficulty in describing feelings. Factor 3 assesses externally oriented thinking. Scores range from 20-100 with higher scores reflect higher alexithymia. Internal consistency in the study was α =0.85.

5.2.2.9 Depression, Anxiety and Stress Scale (Lovibond & Lovibond, 1995)

The DASS-21 is a self-report measure in which participants rate the frequency and severity of experiencing negative emotions over the previous week. Frequency/severity ratings are made on a series of 4-point scales (0=did not apply to me at all, 3=applied to me very much, or most of the time). Internal consistency in the study was α=0.96.

5.2.2.10 Green Paranoid Thoughts Scale Part B (C. E. Green et al., 2008)

The G-PTS is a 16-item measure of paranoia, assessing ideas of persecution over the past month. Scores range from 16-80 with higher scores indicating greater levels of paranoid thinking. The questionnaire includes subscales for conviction, preoccupation, and distress. The questionnaire has been psychometrically

evaluated in clinical and non-clinical populations. Internal consistency in the study was α=0.97.

5.2.3 Daily measures and ESM

5.2.4 Consensus Sleep Diary.

The Consensus Sleep Diary (CSD; (Carney et al., 2012) was completed by participants each morning to measure subjective sleep parameters. The CSD has been credited as a gold-standard sleep diary (Carney et al., 2012). Participants filled out the sleep diary for 2 weeks. From the sleep diary, we extracted sleep a range of measures including sleep onset latency (SOL), total sleep time (TST), wake after sleep onset (WASO), sleep efficiency (SE), and time in bed (TIB) as predictors of paranoia.

5.2.4.1 ESM sampling

All participants completed the ESM procedure on smartphones (Galaxy Fame by Samsung) that they kept during the course of the study. Between the hours of 10am and 10pm, participants were prompted 8 times a day to complete questions on mood, sleep, symptoms as well as their current context (See appendix for a full list of items). Participants received a beep notification in semi-random order within 90 min intervals, with a random beep occurring during that interval.

Once beeped, the questionnaire was available for up to 15 minutes as research shows answers within 15 minutes are valid (Delespaul, deVries, & van Os, 2002). The questions took on average 2-3 minutes to complete. The ESM questions were administered on an app called PsyMate which can be downloaded from App stores. The phones only contained this App on it and patients were not able to use the phone to receive calls or send texts.

5.2.4.2 ESM procedure

All participants attended a pre-experimental meeting, where they were shown how to use the phone, access the questionnaire when prompted with a beep and

go over 2 practise questionnaires together. They then took the phone with them for 8 days and had access to the main researcher AR if they had any technical issues or problems with the phone. Following completion of the ESM period, participants were given a de-brief, and completed a comprehension questionnaire to ensure they understood the questions, the phone and that they followed the instructions correctly. Through the course of the study, two participants reported feeling paranoid about the phone and whether they were being recorded secretly. The researcher AR met with these patients to re-assure them. Following this, the participants went onto complete the study. All the phones were returned, and the procedure seemed acceptable to patients.

5.2.4.3 ESM items:

5.2.4.3.1 Paranoia

Paranoia items were taken from a previous study that used these items to study variations in paranoia (Thewissen et al., 2008). The paranoia scale items included “I feel suspicious” and “I feel others may hurt me.” These two items formed the paranoia scale (α=0.72 over the subject mean scores). Following completion of paranoia items, patients were then asked to report their levels of distress, pre-occupation and conviction associated with the paranoid thoughts. Patients were asked: How much are the thoughts about others hurting causing you distress? How much are the thoughts about others hurting you pre-occupying your mind? How convincing are the thoughts about others hurting you? These items measured distress, pre-occupation and conviction. All the paranoia items were rated on a 6 point likert scale (1=not at all to 6=very).

5.2.4.3.2 Other experiences

While paranoia is the main symptom we are interested in, we also included measures of delusions of grandeur and reference, taken from a prior study (Ben-Zeev, Morris, Swendsen, & Granholm, 2012) and taken from the comprehensive assessment of at risk mental states (CAARMS) (Yung et al., 2005). Items for visual and auditory hallucinations were taken from (Delespaul et al., 2002) and the CAARMS. These items were included so patients did not guess the aims of the

study, and to reduce demand characteristics. The reliability of these items were also lower, and not included in our analyses.

5.2.4.3.3 Emotion items

To examine mood, 3 items were included to measure positive mood and 7 items were included to assess negative mood. Items were selected from other papers measuring mood using ESM. The items were rated on a 6 point likert scale (1=not at all to 6=very). The negative affect scale items included “I feel insecure, stressed, lonely, guilty, irritated, down and anxious”. These seven items formed the negative affect scale (α=0.83 over the subject mean scores). Positive mood wasn’t related to study hypotheses but was included alongside negative affect. The positive affect scale items included “I feel cheerful, relaxed and content”. These three items formed the positive affect scale (α=0.78 over the subject mean scores).

5.2.4.3.4 Sleep items

At every notification beep, participants completed questions on current levels of sleep. The items were rated on a 6 point likert scale (1=not at all to 6=very). Sleep items were taken from the Daytime Insomnia Symptom Scale (Buysse et al., 2007) which has been previously validated in an insomnia population. The 3 sleep scale items included “I feel sleepy, fatigued and exhausted”. These three items formed the sleep scale (α=0.84 over the subject mean scores).

5.2.4.3.5 Additional items

Finally, a series of questions about context were asked. Whilst contextual items are not related to the current studies hypotheses, it has been suggested that additional information not related to the study be included to prevent subjects from predicting the aims of the study, which may lead to demand characteristics and introduce bias into the study. See appendix 3 for a full list of items.

5.2.5 ESM data analysis

Multilevel modelling (MLM) techniques are an alternative of the more often used unilevel linear regression analyses and are ideally suited for the analysis of ESM data, in which repeated ESM observations (beep level) are nested within persons (subject level) (Myin-Germeys et al., 2003). As observations from the same subject are more similar than observations from different subjects, the residuals are not independent. Multilevel regression techniques take this into account. In the current data set we ran a two level model whereby observations at level 1, were nested within participants at level 2. Random effects were specified maximally, in accordance to (Barr, Levy, Scheepers, & Tily, 2013). All analyses were conducted in R using the lme4 and lmerTest packages (Bates, Mächler, Bolker, & Walker, 2014; Kuznetsova, Brockhoff, & Christensen, 2017; RCoreTeam, 2013). Level 1 and 2 variables were inspected for normality by inspection of histograms, which revealed skewness across most of the variables. Therefore, we ran the analysis with skewed predictors both log transformed, and untransformed data. The results remained consistent across both analyses. There is also debate on how to centre variables within MLM. Therefore, we ran our analysis centred (level 1 at group mean and level 2 at grand mean) as well as uncentred. Our results remained unchanged; therefore for ease of interpretation z scored and centred models are presented. See (https://osf.io/4e86c/) for data analysis code that includes both uncentred and centred models.

5.3 Results

Thirty-four potential participants expressed interest in taking part in the study, of which 23 met inclusion criteria. Eight were excluded because they did not meet diagnostic criteria, 1 was excluded because they moved out of area during the study and 2 declined to participate after receiving study information. In regards to recruitment, 16 were recruited via clinical teams, 3 self-referred and 4 were recruited from charities or other organisations.

5.3.1 Characteristics of the sample

The mean age of patients was 46 (*SD*= 9.5) and there were 15 males and 8 females. On average, patients had 11 years of education (range 2-20). In terms of employment, all but 2 were unemployed. All participants were in receipt of antipsychotic medication, with most on more than one type. For full list of medication and doses see appendix 4. We do not have patient info on duration of illness or info about previous hospitalisations. In our sample of 23 patients, 5 were classed as good sleepers (PSQI score <5), 17 as poor sleepers (PSQI score >5) and for one person there was no PSQI score. See table 22 for descriptive statistics of the sample.

Table 22: Characteristics of the sample

	Mean(SD)	Median	Range	Possible range for questionnaire
Sleep quality	9.2(4.19)	10	1-18	0-21
Sleepiness	6.19(4.61)	6	0-17	0-24
Insomnia	2.9(2.44)	2	0-8	0-8
Chronotype	52.6(7.49)	54	37-65	16-86
Nightmare distress	25.8(13.60)	24	13-52	13- 65
Mood (dass total score)	29.5(17.6)	26.5	4-60	0-63
Alexithymia	59.0(8.8)	59	40-77	20-100
Paranoia	40.2(22.0)	33	16-80	16-80

5.3.2 Retention and adherence

In accordance with previous ESM schizophrenia studies (Delespaul et al., 2002; Myin-Germeys et al., 2003), participants had to complete at least 33% of the experience sampling activations in order for their data to be considered valid and included in the data analysis. Based on this, 20 participants were included in

the ESM data analysis. Two participants did not respond to enough beeps and 1 participant could not complete the ESM as they had shaky hands, meaning that 87% of the sample successfully completed the ESM procedure.

5.3.3 Justification of using MLM

The intraclass correlation co-efficient (ICC) explains the proportion of variation that is explained between subjects (level 2) and within subjects (level 1). The ICC value was 0.71 for paranoia, 0.66 for distress associated with paranoia, 0.67 for pre-occupation associated with paranoia and 0.71 for conviction associated with paranoia. These values suggest that there is variance at both levels of analysis and MLM is suited for this data set.

5.3.4 Main analysis:

Hypothesis 1: Subjective sleep measured by a sleep diary will predict levels of paranoia, as well as distress, pre-occupation and conviction measured at the daily level. Sleep diary measures were averaged over the 2-week period as there were missing data and individuals did not always write the date within their sleep diary. Therefore, sleep diary measures were treated as a level 2 variable and used to predict paranoia measured at the daily level (level 1). Descriptive values for the variables are presented in table 23. A random intercepts model was run with SOL, TST, WASO, TIB and SE as predictors and paranoia as the dependent variable. None of our sleep diary variables predicted paranoia. See table 24 for results for this model.

Table 23: Values for sleep diary measures (n=20)

Predictor	Mean	SD	Range
SOL	47.0	27.5	4-104
TST	444.3	216.5	40-1105
SE	73.2	16.5	43-97
WASO	36.1	35.0	0-140
TIB	551.7	146.5	85- 752

Table 24: The fixed effects for the model predicting whether sleep diary variables predict paranoid thinking

	Estimate(SE)	Tvalue(df)	*p value*
Intercept	1.98 (0.29)	6.78(13)	.280
SOL	-0.27 (0.31)	-0.88(13)	.394
TST	-0.10 (0.49)	-0.20(13)	.840
SE	-0.03 (0.42)	-0.07(13)	.945
WASO	0.25 (0.42)	0.59(13)	.560
TIB	0.25 (0.54)	0.46(13)	.649

Do sleep diary variables predict distress associated with paranoia?

None of our sleep diary variables predicted distress associated with paranoia. See table 25 for the results from this model.

Table 25: The fixed effects for the model predicting whether sleep diary variables predict distress associated with paranoid thinking

	Estimate (SE)	Tvalue(df)	p value
Intercept	1.92 (0.28)	6.65(13)	.555
SOL	-0.13 (0.30)	-0.44(13)	.665
TST	0.07 (0.48)	0.15(13)	.878
SE	0.02 (0.42)	0.05(13)	.960
WASO	0.34 (0.41)	0.83(13)	.419
TIB	0.08 (0.53)	0.15(13)	.880

Do sleep diary variables predict preoccupation associated with paranoia?

None of our sleep diary variables predicted pre-occupation associated with paranoia. See table 26 for results of this model.

Table 26: The fixed effects for the model predicting whether sleep diary variables predict pre-occupation associated with paranoid thinking

	Estimate (SE)	Tvalue(dof)	*p value*
Intercept	1.92 (0.28)	6.65(13)	.555
SOL	-0.13 (0.30)	-0.44(13)	.665
TST	0.07 (0.48)	0.15(13)	.878
SE	0.02 (0.42)	0.05(13)	.960
WASO	0.34 (0.41)	0.83(13)	.419
TIB	0.08 (0.53)	0.15(13)	.880

Do sleep diary variables predict conviction associated with paranoia?

None of our sleep diary variables predicted conviction associated with paranoia. See table 27 for results of this model.

Table 27: The fixed effects for the model predicting whether sleep diary variables predict conviction associated with paranoid thinking

	Estimate (SE)	T value(dof)	P Value
Intercept	1.92 (0.29)	6.56(13)	.799
SOL	-0.16 (0.31)	-0.52(13)	.610
TST	0.06 (0.49)	0.13(13)	.896
SE	0.05 (0.43)	0.13(13)	.899
WASO	0.35 (0.42)	0.83(13)	.422
TIB	0.07 (0.54)	0.13(13)	.896

5.3.5 Time lagged analysis

Hypothesis 2: Levels of sleep at one moment, will predict paranoia at the next moment, and this will be mediated by levels of negative affect (time- lagged analysis).

To take advantage of the ESM design, we also tested whether paranoia measured at one timepoint (*t*) was predicted by sleep measured at the preceding timepoint (*t* – 1). Paranoia observations at the start of the day were excluded from analysis (as these observations had no preceding daily time point). This model excluded one participant who showed no variation in their sleep and paranoia scores (all their responses were scored as 1). This model included sleep at *t* and *t*-1 as a Level-1 predictors, thereby controlling for sleep at *t*. Sleep at *t-1* did not predict paranoia at *t*, *B* = -0.01 (*SE* = 0.02), *p* = 0.687. Full time lagged results are presented in table 28.

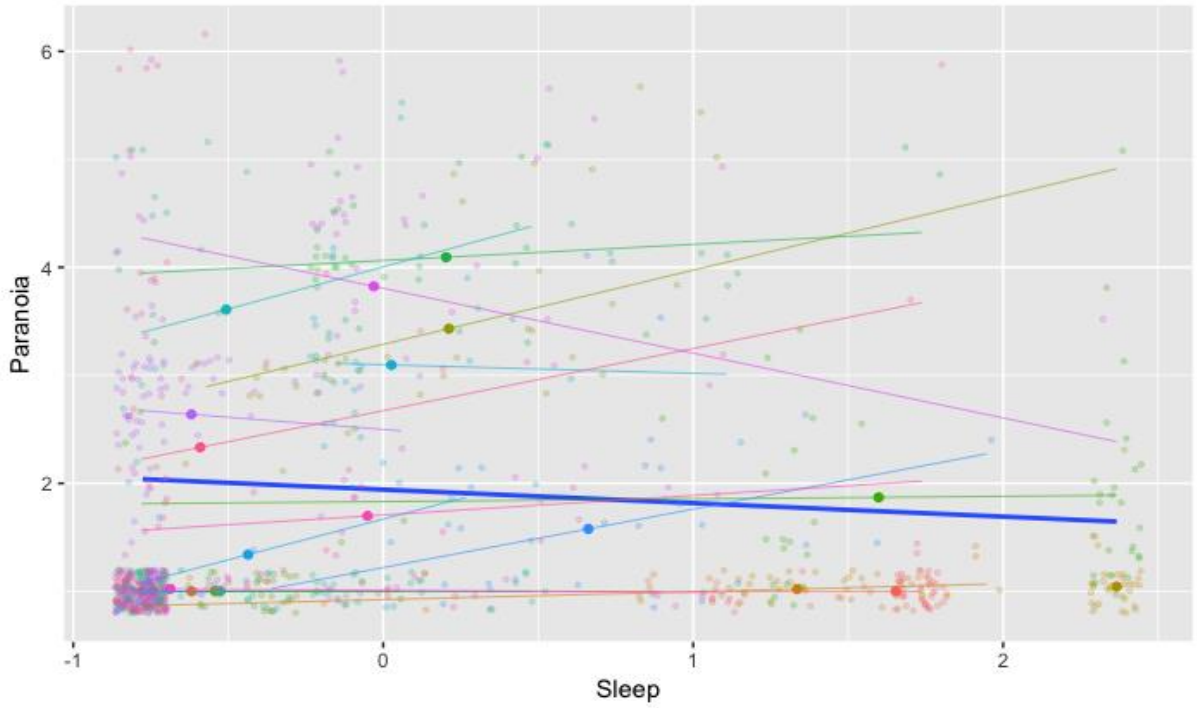
Table 28: Time lagged analysis of whether sleep predicts paranoia at the daily level

Predictor	Estimate (SE)	T value (DoF)	P Value
Sleep at current time	0.05(0.04)	1.40(50)	0.15
Sleep at T- 1	-0.01 (0.02)	-0.40(79)	0.68

5.3.6 Summary of results

Our results did not support our hypotheses, sleep diary variables were not related to paranoia, or distress, pre-occupation and conviction associated with paranoia. Furthermore, there was no temporal or time lagged relationship between sleep and paranoia. However, inspection of individual plots of paranoia and sleep suggested that there may be there may be some patients, where there is a positive relationship between sleep and paranoia, some for whom it is negative, while others in our sample showed little or no variation. See figure 5.

Figure 5 Individual relationships of paranoia and sleep measured at the daily level



In this figure, each line represents an individual person, and the relationship between sleep and paranoia measured at the daily level (level 1). From the graph, it seems there are a sample of patients who have a positive relationship between sleep and paranoia and some who have a negative. Furthermore, there also appears to be a cluster of patients (bottom left of image) who showed very little variance during the ESM procedure. The solid blue line shows the overall regression line for all patients.

5.3.7 Post-hoc analyses

5.3.7.1 Sensitivity analysis:

As a check, we ran our analysis without patients who showed little or no variance. We defined lack of variance as having less than a one-point difference between the patient's maximum and minimum score across all observations. This excluded 10 patients from the sample, leaving 10 in the analysis. Excluding these individuals did not change the pattern of results between sleep diary variables and paranoia, distress, pre-occupation or conviction.

5.3.7.2 Moderation analysis:

Our next approach was to examine whether the within person association between sleep and paranoia (level 1) varied as a function of level 2 questionnaires (moderation analysis). For example, this would allow us to examine whether the relationship between sleep and paranoia varies as a function of PSQI score (level 2 variable), such that those with poorer sleep quality (higher PSQI) having a positive relationship between sleep and paranoia. This analysis may help us tease out whether there are some patients who do exhibit a relationship between sleep and paranoia. We conducted this analysis by including an interaction term between sleep (level 1) with sleep questionnaires measured at level 2. If the interaction term is significant, it suggests moderation exists, and results will be explored further. We ran a separate model for each of our questionnaires: PSQI, ESS, SCI, nightmare distress and MEQ. There was no significant moderation for PSQI, ESS, MEQ, nightmare distress or SCI. However, it was interesting to note a near significant interaction effect for ESS, B = -0.07 (SE = 0.03), p =0.06. This analysis is available here https://osf.io/4e86c/.

5.3.7.3 Comprehension of method:

Upon completion of the study, patients were asked 8 questions regarding the ESM procedure, which showed that they found the procedure acceptable, understood the instructions given to them, and could, read and understood the questions asked. It is unlikely that our results are a result of not following or

understanding the ESM procedure. A list of all the items is included in appendix 5.

5.4 Discussion

The aims of our study were to test whether subjective sleep measured by a sleep diary predicts frequency, distress, pre-occupation and conviction dimensions of paranoia. We also sought to test whether there was a temporal relationship between sleep and paranoia that was mediated by negative affect. We tested these relationships using ESM in a sample of people with non-affective psychosis. In our study, the key finding was that there was no clear relationship between sleep and paranoia.

Against our hypotheses and the previous literature we did not find any relationship between sleep disturbance and paranoia (Freeman et al., 2010; Freeman et al., 2012; Rehman et al., 2018; Scott et al., 2017). We conducted two types of analysis. In the first we tested whether sleep diary measures predicted dimensions of paranoia such as frequency, distress, conviction and pre-occupation. None of our results were significant. However, we could not conduct more fine grained analysis such as looking at whether subjective sleep the previous night predicts next day paranoia due to missing data in our diary. This was an unfortunate limitation of our study. We had to aggregate our sleep diary measures and this may have limited variance and our ability to detect relationships. In the second analysis, we tested whether there was a temporal association between sleep and paranoia, measured at the daily level. Again, we found no significant temporal relationship; levels of sleep at one time point, did not predict paranoia at the next time point. Therefore, we could not go on to test our mediation model of negative affect. One explanation for our results may be to do with our measure of sleep. Our items of sleep measured at the daily level included sleepiness, fatigue and exhaustion. These items may tap into a different aspect of sleep that is not related to paranoia. For example, fatigue is generally associated with depleted energy and weakness (Pigeon, Sateia, & Ferguson, 2003) whereas paranoia is associated with heightened arousal and alertness (Freeman et al., 2002). We may have measured aspects of sleep

associated with low arousal and deactivation that would not be related to paranoia. This could be a potential explanation for the lack of significance. However, when conducting moderation analysis, there was a near significant interaction for the ESS. In other words, the relationship between sleep and paranoia measured at the daily level may be moderated by levels of sleepiness. The relationship between sleepiness and paranoia has not been explored and requires further investigation.

The findings suggest that the type of sleep disturbance related to paranoia is specific. Indeed, the majority of studies that have found a relationship between sleep disturbance and paranoia have been primarily measuring insomnia (Freeman et al., 2010; Freeman et al., 2012; Mulligan et al., 2016; Myers et al., 2011). Insomnia and paranoia share a number of emotional factors that may drive the relationship, such as negative emotionality (Freeman et al., 2010; Mulligan et al., 2016).

For example, it has been shown that when adding affective measures such as anxiety and depression, the relationship between insomnia and paranoia are reduced (Freeman et al., 2010). In our study, patients with and without sleep disturbance were eligible and our sample is likely to be more heterogeneous and non-specific. Even though sleep disturbances were common in our sample, a wide range of sleep disturbances were reported. It is unclear how prevalent or dominant insomnia difficulties were in our sample; our measure of insomnia was based on only two items.

However, it is important to note that there are some sleep disturbances that do not have such a clear link to symptoms. For example, a study found profound sleep and circadian disturbances in people with schizophrenia, which was independent to their symptoms at the time (Wulff et al., 2012). This finding has also been reported in other studies measuring circadian functioning (Bromundt et al., 2011; Martin et al., 2001). It may be also that there was a high level of circadian disturbance in our sample. Given that the majority of our sample was unemployed, they may have experienced lack of routine and this can cause body clocks to become out of sync with the environment (Boivin, 2000). As we did not

have any objective measure of sleep in our study, this is speculative. Including actigraphy would have helped to visualise whether they were circadian disturbances in our sample. Clearly, future research is required to closely examine whether aspects of sleep and circadian functioning are linked to paranoia. A recent review concluded that the relationship between various sleep disturbances and psychotic symptoms requires further work (Reeve et al., 2015).

Another important finding in our study was that there was a sub-sample of patients who reported very little or no variation in their sleep, mood or symptoms over the course of the ESM framework. Sensitivity analyses with and without these 10 patients made no difference to the results. However, it is worthwhile to speculate why these patients showed such little variation. It is unlikely to be due to not engaging or understanding the ESM procedure, as all patients completed a questionnaire which showed that they had no issues with the procedure. One potential explanation may be alexithymia. Alexithymia is a trait whereby individuals have difficulties in understanding what they are feeling, or being able to verbalise how they feel (Bagby et al., 1994). Research has also shown that alexithymia is common in individuals with schizophrenia and found elevated in comparison to the general population (Kubota et al., 2012; van 't Wout et al., 2007). It is possible that these individuals may struggle with the experience sampling procedure. Based on a cut off for alexithymia (TAS scores >61) 10 patients in our sample could be classed as alexithymic, of which 4 were from the low-variance group. This could potentially explain the low variance in some participants, but is not a full explanation. Another potential reason could be that the sampling procedure was not long enough to capture the full range of experiences for some of the patients and that we sampled some patients during a “good week”. To our knowledge, a sub-sample with lack of variation has not been reported before in ESM studies of people with NAP. Another potential explanation for lack of results in our study is the role of negative symptoms. Negative symptoms can be associated with lack of emotional expression, social withdrawal and inability to experience pleasure (Andreason, 1982). Individuals with elevated negative symptoms may have found it difficult to express their

feelings and experiences, and this could have contributed to some of the null findings reported. As we have no information to the levels of negative symptoms we cannot test this explanation. Finally, the potential effects of seasonality and circadian variability is worth noting. The recruitment process lasted between winter of 2014, and ended in spring of 2016, meaning that patients were recruited in all seasons. It has been shown that sleep shows a seasonal pattern, with sleep time being longer and sleep being delayed in the winter (Kohsaka, Fukuda, Honma, Honma, & Morita, 1992; Oyane, Ursin, Pallesen, Holsten, & Bjorvatn, 2008), These effects have been partially attributed to lack of daylight (Friborg, BJORVATN, Amponsah, & Pallesen, 2012). Furthermore, mood has been shown to have both seasonal and circadian patterns, with positive mood peaking at noon and in the evening (Hasler, Mehl, Bootzin, & Vazire, 2008) and depressive symptoms being higher during winter months (Tonetti, Barbato, Fabbri, Adan, & Natale, 2007). Given these findings, perhaps there may be different relationships between variables such as sleep and mood depending on the season. As we did not have equal numbers of people across different seasons, we cannot test this.

Finally, despite our lack of significant results, we note that sleep disturbances were present in our sample. There was evidence of disturbance of sleep continuity, with patients taking more than 30 minutes to fall asleep, and being awake during the night. The self- reported sleep disturbance values are similar to other samples of patients who were recruited on the basis of experiencing poor sleep (Freeman et al., 2005; Mulligan et al., 2016). Specific sleep disturbances were also common in our sample; only 5 of the patients in the sample could be classed as good sleepers. Furthermore, 6 of the patients reported excessive sleepiness (10 or more on ESS) and nightmares and insomnia were also reported. Previous research has found levels of insomnia; nightmares and circadian disruption to be elevated in people with a diagnosis of schizophrenia (Cohrs, 2008; Freeman et al., 2010; Freeman et al., 2012; Wulff et al., 2012) and our findings are in line with this.

5.4.1 Limitations

Several limitations of our study should be considered when interpreting the results. Our study was fully subjective, and we did not have any objective measures of sleep. Both objective and subjective sleep are disrupted in people with schizophrenia and including actigraphy measures would have given deeper insight into sleep patterns. Furthermore, a recent study reported that the interaction between subjective and objective sleep was a stronger predictor of psychotic symptoms than using one method alone (Cosgrave et al., 2018). Due to the diverse medication profile patients were on, we could not test whether medication was linked to some of the results. Most patients being on multiple medications with some patients being on more than one anti-psychotic and many were on medications for other health conditions including high blood pressure, back pain and migraines (see appendix 4). The complex medication profiles of patients is likely to have an effect on mood, sleep and general well-being which could have influenced some of our results. However, this is representative of a typical outpatient sample. Moreover, in our study inferences about causality cannot be made. Although time-lagged data takes us closer to making causal inferences, the relationship could also exist in the opposite direction (e.g. paranoia predicting sleep). We ran this analysis as a check, and paranoia at *t*-1 did not predict levels of sleepiness at the next time point

5.4.2 Conclusions

We did not replicate the relationship between sleep disturbance and paranoia in a sample of medicated outpatients with schizophrenia. However, sleep disturbance was present within our sample which supports the continued development of therapeutic interventions to improve sleep and circadian disturbances (Reeve et al., 2015).

6 Clinician perceptions of sleep problems, and their treatment, in patients with non-affective psychosis.

6.1 Introduction

Sleep problems may well be a prominent concern for individuals with non-affective psychosis diagnoses such as schizophrenia, with estimates of the prevalence of sleep disturbance ranging between 30 and 80% (Cohrs, 2008). A range of sleep disorder problems have been reported in this patient group including insomnia (Cohrs, 2008), circadian rhythm disruption (Wulff et al., 2012) hypersomnia (Okruszek et al., 2014) and nightmares (Sheaves et al., 2015). It is not clear yet what causes the sleep problems in people with psychosis, but a number of candidates have been proposed. A recent twin study found overlap in the genetic and environmental causes of both sleep disturbance and psychotic experiences such as paranoia (M. J. Taylor, Gregory, Freeman, & Ronald, 2015). Antipsychotic medications are known to interact with neurotransmitter systems that are involved in sleep/wake regulation and this may cause some sleep problems. For example, clozapine can increase sedation and aripiprazole has been linked to insomnia (Krystal, Goforth, & Roth, 2008). Another candidate is mood. Elevated levels of depression and anxiety which are common in people with psychosis, also increase the risk for sleep problems such as insomnia (Baglioni et al., 2010). Psychotic experiences such as paranoia and voices may contribute to sleep disturbance (Jeppesen et al., 2015; Waite, Myers, et al., 2016). Finally, the high co-morbidity of physical health problems in people diagnosed with schizophrenia may also contribute to poor sleep (Kalucy, Grunstein, Lambert, & Glozier, 2013). The view now stated in DSM-5 is that sleep problems should be assessed and treated irrespective of other psychiatric difficulties (AmericanPsychiatricAssociation, 2013). Clinical guidelines recommend hypnotics for acute insomnia and cognitive behavioural therapy (CBT) for persistent insomnia (Morin & Benca, 2012). There is emerging evidence that CBT, suitably adapted, can improve sleep in people with psychosis and may also lower levels of delusions and hallucinations (Myers et al., 2011). A pilot randomised clinical control trial with 50 patients with current delusions and

hallucinations in the context of non-affective psychosis found that an eight session CBT intervention led to very large improvements in sleep (Cohen's effect size 1.9, CI=0.9, 2.9) (Freeman, Waite, et al., 2015). Adaptations for CBT in people with psychosis used in this trial have been described (Waite, Evans, et al., 2016) including a greater focus on circadian rhythm disruptions and the interaction with psychotic experiences. Furthermore, a recent qualitative study from this trial noted how highly valued the treatment of sleep problems is for this patient group (Waite, Myers, et al., 2016). However, the level of recognition in services of the extent of sleep problems in patients with psychosis and subsequent assessment and treatment in standard care has not been assessed. The aim of the current study was to address this gap.

6.2 Methods

A 16 item online survey was delivered using Qualitrics survey software (Qualtrics, Provo, UT). As there was no suitable questionnaire available to assess clinician perceptions, the authors generated questions based on their own research and clinical experience. We wished to devise a questionnaire that would generate descriptive data that could inform future knowledge exchange aimed at facilitating discussion and debate about research and clinical priorities for clinicians and other stakeholders. A process of discussion and refinement lead to questions that spanned 3 areas of sleep: the prevalence/types of sleep problems (e.g. What are the most common complaints patients with psychosis report about their sleep?), the impact/causes (e.g. In your view, what causes the sleep problems in people who experience psychosis?) and the assessment/treatment (e.g. What methods do you use to treat sleep problems in patients with psychosis?). Furthermore, to gain more insight into what barriers currently exist in clinical practise, two open ended questions were included: 'In your view, are there any barriers to treating sleep problems in patients with psychosis?' 'Are there any other comments you wish to add about sleep in your patients with psychosis?' The full list of questions is included in appendix 6.

6.2.1 Participants

Emails containing the survey link were sent to clinical teams treating patients experiencing psychosis in 2 NHS localities: Glasgow Greater Glasgow & Clyde and Oxford Health NHS Foundation Trust. The survey was also advertised in staff newsletters and on posters in staff rooms. The study was reviewed and approved by the University of Glasgow ethics committee (reference: 200140033).

The instructions displayed to clinicians on the survey included:

"The questions in the survey ask about sleep in individuals with non-affective psychosis (e.g. schizophrenia, schizoaffective disorder and other non-affective psychotic disorders). Please answer the questions in relation to patients with non-affective psychosis."

6.2.2 Data analysis

Descriptive statistics are presented for clinician responses to the questions. Reported percentages do not always add up to 100% because clinicians could select more than one answer for a number of the questions. The two open ended questions were analysed qualitatively using the Framework Analysis approach (Ritchie & Spencer, 2002), since the data were collected in accordance with our priori aims and objectives. Framework Analysis is a flexible approach to generating themes and organising different types of qualitative data (Pope, Ziebland, & Mays, 2000; Ritchie & Spencer, 2002). Analysis of clinician comments was conducted by AR, following the 5 steps outlined in Ritchie & Spencer (2002). Analysis of clinician comments was conducted by AR, following the 5 steps outlined in Ritchie & Spencer (2002). These 5 steps were familiarisation with the data (reading and re-reading comments), developing themes (identifying key issues and concepts within the comments), indexing (linking the themes to the data), charting (re-arranging data according to theme it fits with) and interpretation of the whole dataset (linking the findings to the original research question). The credibility of the coding and thematic analysis was checked by AG.

6.3 Results

6.3.1 Clinician characteristics and type of service:

111 clinicians completed the online survey. A range of professions participated: psychiatric nurses *(n*=43, 39%), psychiatrists *(n*=38, 34%), psychologists (*n*=13, 12%), occupational therapists (*n*=7, 6%), social workers (*n*=6, 5%) and other (n=4, 4%). Almost half the clinicians were based in adult community mental health centres (CMHT's) (*n*=52, 47%). Other service types included early intervention services (*n*=22, 20%), inpatient wards (*n*=20, 18%), crisis service teams (*n*=1, 1%), primary care teams (*n*=1, 1%) and other (*n*=15, 13%).

6.3.2 Prevalence and types of sleep problems

Sleep problems were considered as very common in patients with psychosis, with all clinicians reporting sleep problems in their patients. Difficulties falling asleep (insomnia) and oversleeping (hypersomnia) were the most commonly reported sleep complaints, followed by issues with the timing of sleep (circadian rhythm disturbance). See table 29 for full description of the questions and responses.

Table 29: Clinician reports of sleep disorder prevalence rates and types of sleep disorders in patients with psychosis.

	0	1-20%	21-40%	41-60%	61-80%	81-100%	Unsure	
What percentage of patients that you see with psychosis, also have sleep problems? N (%)	0	*N*=8(7%)	*N*=28, (25%)	*N*=18, (16%)	*N*=32, (29%)	*N*=14, (13%)	*N*=11, (10%)	
	Insomnia	**Sleep Related Movement Disorder**	**Sleep Related Breathing Disorder**	**Hypersomnia**	**Circadian Rhythm Disruption**	**Narcolepsy**	**Parasomnias**	**Other**
What are the most common complaints patients with psychosis report about their sleep? (Select all that apply)	*N*=97, (87%)	*N*=28, (25%)	*N*=7, (6.3%)	*N*=79, (71%)	*N*=57, (51%)	*N*=2, (2%)	*N*=30, (27%)	*N*=2, (2%)

6.3.3 Impact/causes of sleep problems:

Sleep problems were viewed to have a negative impact in a wide range of domains with nearly all (*n*=104, 93%) clinicians reporting that sleep problems have a negative impact on daytime functioning. No clinician endorsed the item "there is no link between sleep and psychosis". The majority of clinicians (*n*= 104, 93%) endorsed the option that the relationship between sleep problems and psychosis is bidirectional (i.e. that both sleep and psychotic symptoms influence each other). A small number of clinicians endorsed a unidirectional relationship, i.e. the view that sleep problems make psychotic experiences worse (*n*=2, 2%), or that psychotic experiences make sleep problems worse (*n*=3, 3%) and (*n*=2, 2%) were unsure.

Various causes were reported to cause sleep problems in people with psychosis. Poor sleep hygiene was the most commonly reported cause of sleep problems and negative symptoms was the least commonly reported cause. A number of clinicians (n=18, 16%) stated other causal factors (e.g. lack of daytime activity, smoking and illicit drug use). See table 30 for full description of the questions and responses.

6.3.4 Assessment/treatment:

6.3.4.1 How often do you formally assess sleep problems in people with psychosis?

Over half of clinicians (*n*=60, 54%) were unsure about how often they were formally assessing sleep problems. Twenty- three (21%) reported assessing sleep problems in the majority of their patients, 13 (12%) reported assessing sleep in around half of their patients, 11 (10%) reported assessing sleep in a minority of their patients and 4 (3%) reported assessing sleep rarely or never.

Table 30 Clinician reports of the impact and causes of sleep problems in patients with psychosis.

	Mood	**Positive Symptoms**	**Negative Symptoms**	**Cognition**	**Physical Health**	**Social Functioning**	**Daytime Functioning**
In your view, do the sleeping problems that patients with psychosis experience have a negative impact in any of the following domains? (Select all that apply)	*N*=101 (91%)	*N*=78, (70%)	*N*=79, (71%)	*N*=93, (84%)	*N*=89, (80%)	*N*=96, (87%)	*N*=104, (94%)
	Sleep problems are one factor that can make psychotic symptoms (positive and/or negative) worse	**Psychotic Symptoms (positive and/or negative) are one factor that can make sleep worse**	**Both are true (the relationship between sleep and psychosis is bi-directional)**	**Unsure**	**Sleep and Psychosis are not related**		
What is your understanding of the relationship	*N*=2, (2%)	*N*=3, (3%)	*N*=104, (93%)	*N*=2, (2%)	*N*=0, (0%)		

between sleep and psychosis?							
	The sleep problems are a consequence of medication	**The sleep problems are a result of poor sleep hygiene (e.g. too much caffeine, napping)**	**The sleep problems are a consequence of affective symptoms (e.g. Low mood, anxiety)**	**The sleep problems are a consequence of positive psychotic symptoms**	**The sleep problems are a consequence of negative psychotic symptoms**	**Other**	
In your view, what causes the sleep problems in people who experience psychosis? (Select all that apply)	*N*=64, (58%)	*N*=87, (79%)	*N*=71 (64%)	*N*=79, (71%)	*N*=61, (55%)	*N*=18, (16%)	

6.3.4.2 What methods do you use to assess sleep problems in people with psychosis?

The majority of clinicians (*n*=92, 83%) reported assessing sleep by informally asking patients. This is followed by 18 (16%) using structured interviews, 4 (4%) using self-report tools and 2 (2%) using objective methods (e.g. actigraphy). Twelve clinicians (11%) used 'other' methods of assessment which included observations in wards, sleep diaries and verification from family/friends.

6.3.4.3 What methods do you use to treat sleep problems in patients with psychosis?

A range of treatment methods were used by clinicians with the most common being sleep hygiene (*n*=104, 94%), and CBT was least frequently endorsed (*n*=13, 12% delivering the intervention; *n*=19, 17% referring for CBT intervention). Medication was commonly used for treating sleep problems: hypnotics (*n*=64, 58%), antipsychotics (*n*=49, 44%), antidepressants (*n*=42, 38%) and anxiolytics (*n*=30, 27%).

6.3.4.4 What form of sleep treatment would you recommend for a patient with long-standing sleep difficulties and psychotic symptoms?

Fifty-seven (51%) clinicians recommended multiple sleep treatments including medication, sleep hygiene, online self-help and CBT. A number of clinicians recommended a single treatment: 45 (40%) recommended sleep hygiene, 27 (24%) recommended medication, 24 (22%) recommended CBT and 16 (14%) recommended online self-help.

6.3.5 Qualitative analysis

From the qualitative analysis, 3 themes emerged regarding barriers to treating sleep problems in people with psychosis. The first theme was termed "Patient Related Factors" which could be further split into two subthemes i) "Lifestyle of the Patient" and ii) "Illness Related Factors". "Lifestyle of the patient" included aspects of the patients life that can act as a barrier to treatment such as lack of routine, alcohol/drug dependence, lifestyle habits, social support, individual

differences and motivation levels. The second subtheme, “Illness Related Factors”, included severity of disorder, stage of illness, affective disturbance, capability of patient and medication and their side effects. The second theme was termed “Service Related Factors” which included lack of time, lack of awareness of sleep as a problem, resources, access to treatments, training needs, and acting as barriers. We also noted that a number of clinicians perceived there to be no barriers to treating sleep problems. The third and final theme was termed “Other Environmental Factors”, and this included barriers that are found on wards and in prisons. Example quotes from each theme are presented in table 31.

Table 31 Qualitative themes with example quotations

Theme one: Patient related Factors		Theme 2: Service Related Factors	Theme 2: Other environmental factors
Sub Theme 1 Lifestyle of patient	Sub theme 2 Illness related factors		
"Lifestyles can also contribute to poor sleep hygiene and patients may have a reluctance to engaging in work to improve daily structure"	"Patient too unwell to follow treatment and advice, too anxious to follow any plan"	"Time pressure"	"Chaotic and noisy wards"
"Sleep problems more likely where there is alcohol or substance misuse or dependence"	"Medication side effects- particularly sedation leading to poor sleep patterns"	"Lack of knowledge in staff"	"Inpatients have trouble sleeping because hospital wards are not conducive to good sleep"
"Motivation and willingness to do the work necessary"	"Patients may be reluctant to engage, suspicious, or fearful of the process"	"Lack of knowledge and resources to treat sleep problems"	"In prisons, there is a reluctance to prescribe sedative medication because of its 'street value' amongst prisoners - makes treating sleep problems in the prison (a very big problem) difficult."
	"In an acute state I think you have to take a medication route before even thinking about CBT for insomnia…"	"Clinicians may not assess complaints of sleep problems in sufficient detail"	"lack of therapeutic interventions on ward"
		"It appears to me to be a significant issue that often seems neglected or viewed as a symptom of mental distress"	

6.4 Discussion

This is the first study to ask clinicians about their perceptions of sleep in people with non-affective psychosis. There was a clear disconnect: the importance of sleep in psychosis was well-recognised but assessment and treatment were limited. Clinicians also reported a number of barriers to treatment implementation.

We found that clinicians were highly aware of the range of sleep problems that present in people with psychosis, particularly insomnia, hypersomnia and circadian rhythm disturbance. In the present study clinicians also identified a link between poor sleep and several domains of functioning including level of symptoms, mood and daytime activities. There is some support for these claims with poor sleep being associated with lower quality of life (Hofstetter et al., 2005) increased positive symptoms (Afonso, Brissos, Figueira, & Paiva, 2011) and impaired cognitive functioning in people with psychosis (Bromundt et al., 2011). Other work in support of clinician opinions comes from research finding links between sleep disturbance and impaired physical health and mood disturbance (Cappuccio, Cooper, D'Elia, Strazzullo, & Miller, 2011; de Wild-Hartmann et al., 2013; D. J. Taylor et al., 2007). These findings suggest that not only are sleep problems common and diverse, but that poor sleep may be negatively affecting many areas of functioning in people with psychosis. This emphasises the importance of treating sleep problems in this population.

Clinicians also reported multiple causes of the sleep problems. Causal factors identified included poor sleep hygiene, positive symptoms, affective symptoms, followed by medications and negative symptoms. Work on the causes of sleep problems in people with psychosis is currently underway. There is growing evidence to suggest that sleep problems may precede the onset of psychosis, with a recent review concluding that sleep disturbance is very common in individuals at risk for psychosis (Davies et al., 2017). For example, in one longitudinal follow up study in people at risk for developing psychosis, sleep disturbance predicted transition to psychosis (Ruhrmann et al., 2010). Another line of work has examined the relationship between sleep disturbance and

individual psychotic experiences (Reeve et al., 2015). For example, in a large – scale general population study conducted in 8,580 people, insomnia was associated with an approximately two to threefold increase in paranoid thinking (Freeman et al., 2010). A follow up study reported that insomnia was also a significant predictor of new incidences of paranoid thoughts, suggestive of insomnia having a causal role (Freeman et al., 2012). The Oxford Access for Students Improving Sleep (OASIS) trial is currently underway testing the potential causal relationship between insomnia, paranoia and hallucinations (Freeman, Sheaves, et al., 2015). Other additional causal factors identified by clinicians were also reported as barriers to treating sleep problems in people with psychosis such as lack of routine, low levels of daytime activity and drug/alcohol dependence. Another barrier recognised by some clinician's concerned medications and their side effects. Although anti-psychotics are the recommended treatment for psychosis and such medications tend to improve sleep continuity, (Cohrs, 2008; Monti & Monti, 2004) their side effects such as sedation may cause further sleep problems.

Clinicians mainly assessed sleep complaints in people with psychosis by informally asking them about their sleep. Few used objective (e.g. actigraphy) and subjective methods (questionnaires), although a number of clinicians (n=10, 15%) used structured interviews to assess sleep. Patients own informal accounts of sleep problems are a quick and easy way to gain an impression of sleep problems when clinical time is limited. However, an in-depth and accurate assessment of sleep problems is critical in identifying the most appropriate treatment pathway that can target the specific sleep problem. Clinicians identified time as a barrier to treating sleep problems. This barrier could be addressed by making available brief and validated questionnaires that can assess the severity of the sleep problem and allow monitoring of sleep over time such as the Sleep Condition Indicator and the Epworth Sleepiness Scale (Espie et al., 2014; M. W. Johns, 1991). The Sleep Condition Indicator has been developed specifically for clinicians to assess insomnia quickly and accurately. The short two-item version would be a particularly useful initial screening tool to assess insomnia severity in people with psychosis and sleep problems (Espie et al., 2014).

It was also found in the study that clinicians were treating sleep problems but mainly by use of sleep hygiene techniques, despite the very limited effectiveness of such approaches (Morgenthaler et al., 2006). There was also a reliance on medications such as hypnotics, which should only be used only for short periods of acute insomnia (Morin & Benca, 2012). Critically, we found that even though clinicians would recommend a range of treatments including CBT, the numbers of clinicians actually referring people with psychosis to such services is much lower. According to recent guidelines, CBT is the recommended treatment for persistent insomnia and use of medications for other psychiatric disorders are not currently recommended (APA, 2013; Morin & Benca 2012). Some of the barriers identified by clinicians may explain the discrepancy between recommendation of CBT and low referral rates such as lack of access to sleep treatments. This barrier could be addressed by making CBT more widely accessible. Other barriers reported by clinicians include those specific to patients such as low motivation to change habits. These are barriers that can be addressed by highlighting the importance of good sleep, and empowering people with psychosis to gain control of their own sleep using evidence based techniques (Waite, Myers, et al., 2016).

Finally, clinicians also noted that barriers to treating sleep problems exist in very specific environments such as inpatient wards and prisons. For example, assessing and treating sleep problems may be difficult in wards due to noise levels, night- time observations and limited resources to implement interventions. More work is required to address these barriers.

The findings of our study should be viewed in light of some limitations. Firstly, clinicians who are interested in sleep would be more aware of sleep problems and may have been more motivated to complete the survey, and this may well have biased our sample. The survey was also completed mainly by psychiatrists and psychiatric nurses and completed from clinicians in only two NHS trusts, one of which was the site for an intervention study for sleep in patients with psychosis. In spite of this, the results of the survey within the group are clear: sleep problems are considered very common in people with psychosis but services are currently limited in their responses to this issue.

6.4.1 Clinical implications and recommendations for future studies

Sleep problems are very common in people with psychosis and this makes developing treatment pathways an important clinical aim (Waite, Evans, et al., 2016). Greater awareness about the importance of sleep amongst both staff and people with psychosis is also required. Training programmes would enable staff to identify, assess and treat sleep problems. We call for more research on understanding the causes of sleep problems in non-affective psychosis and testing the implementation of evidence- based sleep interventions in patients with non-affective psychosis. More work is also required to identify the impact of different medications on sleep.

7 General Discussion

7.1 Summary of findings

Chapter 3 described two studies that investigated the relationship between sleep quality and paranoia in healthy non-clinical samples. It was hypothesised that this relationship would be mediated by negative emotions, alexithymia and perceptual anomalies. These relationships were investigated on an online survey, which allowed for large samples. In study 1 of chapter 3 we found perceptual anomalies, negative affect and alexithymia partially mediated the relationship between sleep and paranoia. This in line with other studies that have also found negative emotion to be a significant mediator (Freeman et al., 2010; Scott et al., 2017). Our study was also novel, in that it was the first study to test another facet of emotion- levels of emotional awareness measured by alexithymia. Furthermore, this study provided a direct test of whether perceptual anomalies predicted paranoia. Together, the first study in this chapter highlighted that emotional and non-emotional factors play a role in the sleep- paranoia relationship. Study 2 was conducted to confirm and replicate the findings of study 1 and to test robustness of these findings. The addition of study 2 however, painted a more complex picture. Firstly, instead of partial mediation there was full mediation. In other words, negative emotion, alexithymia and perceptual anomalies fully explained the relationship between sleep and paranoia. Secondly, the aspect of negative emotion differed. In study 1 it was negative affect, while in study 2 anxiety was the mediator. Reasons for discrepant results were explored by conducting linear regressions. It was revealed that in study 2, sleep quality was not a significant predictor of paranoid thoughts. Therefore, we could not fully replicate the results of study 1. Sample differences across studies were ruled out as a reason for discrepant results. Instead, it was hypothesised that the nature of sleep disturbance in the participants of sample 1 may differ from those in study 2 and this may explain the differences. For example, the relationship between sleep and paranoia is strongest for insomnia and there may have been more insomnia in participants of study 1. As we used a general measure of sleep quality, we could not directly test this.

In chapter 4, a synthesis and systematic review of sleep disturbance in people with psychosis was conducted. The review was unique in that it looked at sleep in psychosis from a methodological viewpoint. What methods have been used to investigate sleep in people with psychosis, and where are there methodological weaknesses in the studies? Main findings of this study included that a range of subjective and objective methods have been used and that a wide range of sleep disturbances have been reported. However, the review called into question some of the strength of these findings as there were areas of bias identified. Some of these biases were common across all methods such as power. Unique areas of bias were also identified, such as not including an adaptation night in PSG studies. There was also no one sleep parameter that was reliability disrupted in people with psychosis.

Next in chapter 5, we sought to extend the findings of chapter 3 by looking at sleep and paranoia in a clinical sample of people diagnosed with NAP and we considered some of the limitations outlined in chapter 4. In chapter 5, a wide range of validated sleep questionnaires were used to quantify the levels of sleep disturbances found and to look at what aspects of sleep are disrupted. Furthermore, we also used ESM and sleep diaries to try and investigate the relationship between sleep and paranoia in more detail. The findings from this study were surprising as across two different types of analyses, we did not find significant relationships between sleep and paranoia. We also couldn't test mediation models due to the lack of relationship between sleep and paranoia. On closer inspection, this may be partially due to the heterogeneous sample, and because of the measurement of sleep. However, sleep disturbances were common in the sample.

Finally, in chapter 6 we investigated clinician perceptions of sleep to try and understand what is happening in clinical practise. Across two NHS trusts- Glasgow and Oxford, it was found that clinicians reported high levels of sleep disturbances in people with NAP and that they felt sleep was related to areas of functioning including symptoms, and mood. A key finding was that even though sleep problems were common, clinicians did not have the time and resources to

adequately assess and treat sleep problems. Table 32 presents a summary of the results from this thesis.

7.2 Synthesis and discussion of findings

Taking the findings of the chapters together paints a complex picture. Across clinical and non-clinical samples, there was no consistent relationship between sleep and paranoia. The systematic review also highlighted methodological weaknesses in sleep studies in people with NAP. However, in clinical practise, sleep disturbances are very common and clinicians are trying to treat them. The findings of the clinician survey are in line with qualitative studies of sleep in people with psychosis. In two separate qualitative studies it has been reported that people report poor sleep, and that they believe sleep has an impact on daily functioning including mood and symptoms (Faulkner & Bee, 2017; Waite, Evans, et al., 2016). The findings of the thesis can be summarised into two main findings: there was no clear link between sleep and paranoia, but that sleep disturbances are common in people with psychosis. These two findings will be discussed next in more detail.

7.2.1 The relationship between sleep and paranoia.

Sleep is a complex state, and can be measured and assessed on different levels, and in different ways, and this can contribute to mixed results across studies. The approach in this thesis has been to focus on one symptom common in psychosis: paranoia. However, sleep has been measured using a range of different questionnaires. This raises the question – which aspects of sleep should be measured and focused on? Currently, insomnia has been the most well studied sleep disturbance in psychosis and in relation to paranoia. The group led by Daniel Freeman has found that insomnia predicts paranoid thinking in both clinical and non-clinical samples (Freeman et al., 2010; Freeman et al., 2012; Myers et al., 2011) in both cross-sectional and longitudinal designs. Another form of evidence comes from treating sleep and examining the impact improving sleep has on paranoia. In a pilot trial of CBTi it was found that there were large effect size reductions in sleep, mood and paranoia. However, in a RCT of CBTi, there were large improvements in sleep, but only a small correlation of

improvements in sleep with levels of paranoia (Freeman, Waite, et al., 2015). It has also been shown that improving sleep via digital CBTi in a non-clinical sample who experience insomnia, is associated with an improvement in paranoia (Freeman et al., 2017). Given these findings then, why was there not a relationship of sleep and paranoia in the studies in this thesis? The most likely reason for this is that we did not include a specific measure of insomnia. For example, in chapter 3 I used the PSQI which is a measure of general sleep quality. Sleep quality can be influenced by numerous factors, and it is likely that insomnia was not the only factor contributing to poor sleep. In chapter 5 the short version of the SCI was used to assess insomnia, which may not have been extensive enough to capture insomnia in my sample. Another reason is also that previously mentioned studies that have examined sleep and paranoia, have used highly selected samples who report insomnia and paranoia. For example, criteria to be included in clinical trial that investigated if CBTi improved sleep and symptoms was evidence of persistent paranoia for at least 3 months and evidence of clinical insomnia (Freeman, Waite, et al., 2015). Therefore, these studies are more powered and able to capture the relationship. In contrast, in both chapter 3 (non-clinical sample) and 5 (clinical sample), to be included participants did not need to report insomnia or paranoia, creating more heterogeneous samples. This also suggests that there are people who have a diagnosis of psychosis who experience poor sleep, but this is not related to presence of paranoia. In other words, sleep disturbance can occur on its own, without it being linked to specific symptoms.

7.2.2 Sleep disturbances are common in people with psychosis

An important finding reported in chapter 5 is that a range of sleep disturbances were common in the sample of people with psychosis, with most participants being scored as poor sleepers. Sleepiness and nightmares were also common. This is also observed in clinical practise as outlined in chapter 6. Therefore, while the research on insomnia and paranoia is building up, the impact of other sleep disturbances on areas of functioning such as symptoms is yet to be explored. For example, in the clinician survey in chapter 6, hypersomnia was the second mostly commonly reported sleep complaint identified. Prevalence rates

for hypersomnia in psychosis range from 32-58% (Sharma et al., 2016; Wichniak et al., 2009) however the impact of hypersomnia in relation to symptoms has not be assessed. Whilst clinicians identified movement related disorders and breathing also being common, prevalence rates are not available. Their impact remains unknown. Regarding circadian disturbance, a number of studies have documented circadian disturbances in people with psychosis (Bromundt et al., 2011; Wulff et al., 2012). In these studies, there was no relationship to symptoms, however they did not focus on specific symptoms such as paranoia. This highlights that there is a range of sleep disturbances that have not yet been systematically investigated in people with psychosis, and their impact has not been studied.

7.2.3 Limitations of the thesis

There are some limitations in this thesis that deserve comment. Firstly, the thesis has examined sleep throughout the chapters using subjective measures only. Although only validated measures have been used, the addition of objective measures would have helped complement the subjective data. It is to be noted that I did originally include actigraphy in chapter 5. However, the database this data was stored on became non-functional and the data was lost. In the case of chapter 3, it would not have made sense to use actigraphy due to the large sample sizes recruited. Another limitation is the lack of control sample in chapter 5. There are also limitations with the patient sample. There was no information on their symptom levels or previous hospitalisation information. This would have helped provide a fuller account and description of the patient sample. Furthermore, the medication profiles were diverse and most were on multiple medications. It is not clear how the combination of different medications may influence sleep. However, an unmedicated sample would not be representative of a psychosis outpatient sample. In terms of chapter 6, there may be a bias in the clinicians who completed the survey, as only those who were aware and dealing with sleep problems would be likely to complete it. This may have inflated the findings. Nonetheless, the findings still point to the fact that sleep problems are a common complaint in people with psychosis, and some clinicians are actively trying to treat sleep.

7.2.4 Directions for future research

This thesis has documented that the relationship between sleep and paranoia is more complicated than first appears. This relationship may be specific only to patients who report clinically relevant levels of insomnia and persistent paranoia. This thesis also identified that a range of sleep problems are common in people with psychosis, and are commonly being reported by patients in clinical practise. Many unanswered questions remain. More specifically there is a need to a) Further understand the relationship between insomnia symptoms and paranoia and to understand the mechanisms underlying the relationship, b) understand the nature and impact of sleep disturbances in people with psychosis and c) refine and further develop sleep interventions that address the range of sleep disturbances experienced in people with psychosis. Each of these points will be expanded on in the next section.

7.2.4.1 Further understand the relationship between insomnia and paranoia

It is clear now that a relationship between insomnia symptoms and paranoia exists, which is partially mediated by negative affect (Freeman et al., 2010). There is a need to refine this model further and test other theoretically relevant mediators. In chapter 1, perceptual anomalies and emotional awareness were also meditators. As we focused on sleep quality and not insomnia symptoms, it would be of interest to test whether these factors also mediate insomnia and paranoia. Furthermore, cognitive factors have not been investigated in the insomnia-paranoia relationship. It has been shown that the reasoning bias jumping to conclusions is associated with delusional thinking, and may be relevant for paranoia (Freeman, Pugh, & Garety, 2008; Moritz & Woodward, 2005). As poor sleep is also associated with lowered cognitive functioning (Alhola & Polo-Kantola, 2007) this could be a potential target of study. Furthermore, in chapter 5, we also measured dimensions of paranoia- distress, pre-occupation and conviction. Research examining how insomnia symptoms relate to these dimensions would also be important. For example, are insomnia symptoms related to distress associated with paranoia, as well as frequency? Distress is often associated with negative emotions, so this could be a potential route to explore. Insomnia symptoms are multi-faceted, and can be defined by

difficulties in initiating sleep, maintaining sleep or early morning awakening (APA, 2013). One study found that perceived problems in initiating sleep was related to paranoia, but not problems maintaining sleep (Scott et al., 2017). This study was conducted in a non-clinical sample and requires replication in a patient sample. By identifying more closely which dimensions of insomnia and paranoia are linked, and how they are mediated, provides useful targets that can be used to refine sleep interventions that are currently being used (Freeman, Waite, et al., 2015).For example, if sleep initiation problems are most relevant for paranoia, CBTi elements that address this can be used in treatment. This also gives more options to people with psychosis on what's aspects of insomnia they may want to improve on and promotes more autonomy in their treatment.

7.2.4.2 Understand the nature and impact of sleep disturbances in people with psychosis

Given the wide range of sleep disturbances reported in psychosis, there is a need to document and understand their impact on areas of functioning. This is a difficult feat and made more complicated by factors such as medication status and co-morbid health problems. Longitudinal studies that follow people at risk for psychosis can help document changes in sleep, and how this might relate to symptoms. Such a study would be able to tease out if there is a threshold of sleep disturbance that must be reached before an individual develops psychosis and how sleep- symptom relationship might change over time, without the confounds of medication

Table 32 Summary of thesis findings

Chapter 3	Chapter 4	Chapter 5	Chapter 6
No consistent link between sleep quality and paranoid thinking. Study was conducted in non-clinical sample. Effects were small.	A systematic review was conducted in 58 studies that have investigated sleep in people with psychosis. Key methodological areas of bias were outlined. The review calls into strength some of the sleep-psychosis findings.	A novel experience sampling study was conducted investigating sleep in people with psychosis. Subjective sleep was investigated. Sleep diary variables did not predict paranoia. There was no time-lagged temporal relationship between sleepiness and paranoia. A sub-group of participants showed no variation in their responses	An online survey in 111 clinicians was conducted to investigate their perceptions of sleep. All clinicians believed there is a relationship between psychosis and sleep. Framework analysis was conducted on open ended clinician responses to investigate barriers to assessment and treatment of sleep. Barriers related to patients (lifestyles), service facilities (lack of time) and environmental factors.

Great gains have been made in understanding the relationship between insomnia and paranoia, but other psychotic symptoms also deserve attention. For example, the relationships between sleep and grandiosity, hallucinatory experiences remain relatively unexplored (Reeve et al., 2015). In study 5 we included delusions of reference, grandiosity as well as hallucinations as additional measures. But these were not reliable (as indicated by low cronbach alphas) and were endorsed at low levels and therefore exploratory analysis could not be done. An ESM study of sleep and psychotic symptoms found relationships between sleep and next day auditory hallucinations and delusions of control (Mulligan et al., 2016). Furthermore, the focus on specific symptoms, also applies to specific sleep parameters. Using the ICSD can serve as a useful framework for classifying different sleep conditions. Within this, sleep is split into- insomnia, hypersomnia, circadian disturbance, parasomnias, sleep related movement and sleep related breathing. Each type of sleep disturbance has specific treatment strategies associated with it. For example, disorders of circadian timing are caused by mis-alignments of internal and external time, and treatment involves reducing the mis-alignment via behavioural techniques such as chronotherapy and light therapy (Wilson et al., 2010). There is evidence for increased prevalence of circadian rhythm disruptions in people with psychosis (Wulff et al., 2012), but circadian treatments have not been trialled yet.

There is also a need to document how sleep impacts other areas of functioning apart from symptoms as sleep disturbance persists even after symptoms are treated (Baandrup, Jennum, Lublin, & Glenthoj, 2013). In chapter 6, clinicians identified domains of functioning that they believe sleep to effect, including cognition, social functioning, and physical health. The impact of sleep upon these areas of functioning are well documented. Poor sleep has negative effects on a range of cognitive variables including memory and attention (J. Lim & Dinges, 2010), and sleep effects socio-emotional functioning including emotion perception (Beattie, Kyle, Espie, & Biello, 2015) and insomnia has been linked to physical health problems and inactivity (Sutton, Moldofsky, & Badley, 2001). However, these relationships have not been investigated yet in people with psychosis. One route that might be promising is the investigation of sleep in relation to negative symptoms. Negative symptoms are common and prevalent in

people with psychosis and are linked to cognitive disturbance (Bobes et al., 2010; Myin-Germeys & van Os, 2007). Some evidence exists of a relationship between sleep and negative symptoms (Kato et al., 1999; Tandon et al., 1992). However, these studies have been conducted using PSG methods and may be at risk of bias as outlined in chapter 4. Therefore, a systematic investigation of sleep and negative symptoms is required.

In chapter 4, the systematic review identified potential areas of bias that may occur including those specific to different sleep methodologies. These factors should be considered in the design of studies to produce more rigorous and reliable results. Furthermore, in addition to this, the field of sleep and psychosis would be further advanced by adhering to the principles of open science. In chapter 5, our ESM data and code were freely made available and is accessible here (https://osf.io/4e86c/). This is an important step in increasing clarity and promoting replication in psychology.

7.2.4.3 Refine and further develop sleep interventions that address the range of sleep disturbances experienced in people with psychosis.

Sleep has been identified as a potential causal factor in the development and maintenance of psychotic symptoms (Freeman et al., 2012) and a few studies have shown that improving sleep can improve symptoms. In people with insomnia, CBTi is the recommended treatment (Morin & Benca, 2012) and this has been adapted and tested in people with psychosis. In a pilot trial of 15 people with persistent insomnia and paranoid delusions, four sessions of CBTi were administered that covered sleep hygiene, psycho-education and stimulus control (Myers et al., 2011).This study found there were large improvements in sleep and paranoia. There were also improvements in mood and perceptual anomalies, which may be mechanisms that mediated the change. In a large scale RCT, effectiveness of CBTi was compared to standard care. Again, there were large improvements in sleep, although the effects on symptoms were inconclusive (Freeman, Waite, et al., 2015). However, one explanation for the small effects on symptoms is that large improvements in sleep, leads to a reduction in emotional distress. Given that emotional distress is strongly associated with paranoia, by targeting this mediating variable, there may not be

changes in paranoia detected. In a more recent study, the effectiveness of CBTi was tested in a sample of people who are at risk for psychosis, again finding large improvements in sleep. There were also improvements in mood and symptoms including paranoia (Bradley et al., 2018). These are promising results. However, in order to take this research further, we still need to understand what components of CBTi are effective, and treatments need to be refined to adapt to more specialised populations. For example, in chapter 6, clinicians identified sleep disturbances in psychiatric wards and in prisons. These unique environments pose some challenges. In wards, noise and light levels which would be covered in sleep hygiene modules cannot be easily modified. There has also been some research to suggest that short sleep on inpatient wards is associated with next day aggression in people with psychosis (Langsrud et al., 2018). In a pilot study, CBTi was administered to people on an inpatient ward who were experiencing an acute episode of psychosis or bipolar disorder. The CBTi was adapted to meet the needs of the ward environment. For example, enhanced light exposure was administered via light boxes and encouraging walks outside. The sleep treatment was associated with improvements in sleep, wellbeing and being discharged earlier (Sheaves et al., 2017). This provides some preliminary evidence that sleep can be treated on wards.

So far CBTi has been delivered in patient samples face to face (Freeman, Waite, et al., 2015; Myers et al., 2011). However, online treatment methods could be another option. In the OASIS trial, sleep treatment was administered online (Freeman, Sheaves, et al., 2015). Could this be another mode of treatment for people diagnosed with psychosis? Research suggests that people with psychosis are open to using the internet and smartphones for mental health treatment (Lal & Malla, 2015; Palmier-Claus et al., 2013).The “Early signs Monitoring to Prevent relapse in psychosis and prOmote Wellbeing, Engagement and Recovery” (EMPOWER) study is using technology- an app on a smartphone that allows individuals to self- monitor a variety of experiences such as self -esteem and symptoms. When individuals start to experience problems, they can be contacted directly and supported (https://empowerstudy.net/). Sleep lends itself to be treated online and this form of treatment has yet to be investigated in a clinical population. This would fit in with a stepped care approach where

online CBTi could be administered when people report sleep problems as this would be more cost-effective and less intensive than face to face (Espie, 2009).

7.2.5 Conclusions

In this thesis, in both a clinical and non-clinical sample, we did not find a consistent relationship between sleep and paranoia, which contradicted a body of research (Freeman et al., 2010). One main reason for this was likely to be because we did not include specific measures of insomnia. In this thesis we also found that sleep disturbances are varied in people with psychosis and a common complaint in clinical practise. Therefore, the need to understand the nature and impact of sleep in this population is critical. A set of suggestions for future research was outlined.

Appendix 1: Bias assessment tool piloting

We chose to include the 5 components (patient selection, confounding variables, power and missing data and statistical analysis) because these are most commonly reported in other checklists and assessment tools (Crowe & Sheppard, 2011; Sanderson, Tatt, & Higgins, 2007).

For the methodological component we developed a component that allows us to rate bias for each type of sleep methodology (actigraphy, subjective sleep assessment and polysomnography). In actigraphy for example, some have questioned its validity in clinical samples, as it has a tendency to score quiet rest as sleep (Paquet et al., 2007). Therefore, actigraphy may be less accurate in populations with sedentary lifestyles such as in schizophrenia. Studies that do not include any methods to distinguish quiet rest from sleep, are likely to have biased estimates of sleep, such as over-scoring total sleep time. Likewise, for accurate sleep parameter estimates, at least 7 days of recording are recommended (Aili et al., 2017). Studies with less than 7 days, could be at risk for bias.

In regards to polysomnography, bias may occur if an adaptation night is not included to allow individuals to accustom themselves to the strange sleeping environment of the sleep lab. This phenomenon is known as the first night effect, whereby individuals sleep worse on the first night in a new environment than they would at home (Agnew et al., 1966; Toussaint et al., 1995). Therefore, PSG studies without an adaptation night may be at risk for bias. The second area is the use of caffeine and presence of napping. Caffeine has alerting effects, and may influence sleep estimates (Van Dongen et al., 2001). Likewise, napping in the daytime may also effect sleep at night (Dinges, 1992). Therefore, PSG studies that do not limit the use of napping and caffeine on sleep recording days may be at risk for producing biased sleep estimates.

Finally, for subjective sleep studies, those that do not use validated questionnaires or who do not present psychometric data for their own developed questionnaires may be at risk for producing biased sleep estimates.

To assess reliability 3 people (AR, and two individuals not involved in the systematic review) completed the tool for 6 studies. Agreement was relatively high (>70% agreement) for all domains except missing data (50%) agreement, and most inconsistencies concerned rating studies at high risk of bias or unclear. Thus the tool was edited and modified with clearer instructions. Therefore, in the final assessment tool each study is scored for risk of bias on several components.

Domain	Description	Bias Assessment (low (0), high (1), unclear).
Patient Selection: Component 1 Criteria for high risk of bias (1): Patients are not representative OR if inclusion/exclusion criteria isn't stated OR criteria is inappropriate OR if important information on patients is missing e.g. medication info, or age. Criteria for low risk of bias (0): If there is appropriate inclusion/exclusion criteria stated, and enough information about patients is provided and if patients are representative. Rate studies as unclear if study doesn't meet criteria for low or high bias.	Describe methods of Patient Selection e.g. where recruited from, inpatients/outpatients Did the study have appropriate inclusion/exclusion criteria (Y/N/U) Was there enough information on patients selected? (Y/N/U) Were the patients representative (Y/N/U)	Could the selection of patients have introduced bias?

Baseline characteristics component 2 Criteria for high risk of bias (1): There is no control group OR if patient and control groups differ on important variables e.g. age, gender, and these factors are not controlled for in any statistical analysis. Criteria for low risk of bias (0): There is a control group, if the groups are well matched or if differences between groups are controlled for in analysis. Rate study as unclear if it doesn't meet criteria for low or high bias.	Describe patient and Control group Is there a control group? (Y/N) Are there differences between the two groups e.g. on demographic variables(Y/N/U/NA) Are differences controlled for in analysis?(Y/N/U/NA)	Could differences between the groups have introduced bias?
Sleep Methodology: Actigraphy component 3 Criteria for high risk of bias (1): If there is no explicit statement about distinguishing quiet restfulness from sleep e.g. through sleep logs OR if there are less than 7 days of actigraphy recording.	Describe actigraphy methodology e.g. number of days recorded, scoring criteria. Did the study record sleep at least 7 days?(Y/N/U)	Could actigraphy methodology have biased the study?

Criteria for low risk of bias (0) If there is an attempt to distinguish quiet restfulness from sleep e.g. through sleep logs AND if the recording period is 7 days or more. Rate study as unclear if it doesn't meet criteria for low or high bias	Was there an attempt to distinguish quiet rest from sleep?(Y/N/U)	
Sleep Methodology: Polysomnography component 4 Criteria for high risk of bias (1): If sleep is only recorded for one night, i.e. no reference to first night effect, or no adaptation night OR if there are no instructions to participants e.g. refraining from caffeine, that may produce biased sleep estimates Criteria for low risk of bias (0): If more than one night of recording is conducted, AND there are instructions on days of sleep recordings are stated e.g. participants were asked to refrain from caffeine. Rate study as unclear if it doesn't meet criteria for low or high bias	Describe PSG methodology e.g. number of nights, scoring, Did the study take into account the first night effect(Y/N/U) Was there pre- sleep lab recording instructions to participants e.g. avoid caffeine(Y/N/U)	Could polysomnography methodology have biased the study?

Sleep Methodology: Subjective Sleep Assessment component 5 Criteria for high risk of bias (1): If non-validated measures of sleep are used OR if there is no psychometric/reliability data for authors own questionnaire Criteria for low risk of bias (0): Study at low risk of bias if validated measures of sleep are used or if authors present psychometric data to validate their questions. Rate study as unclear if it doesn't meet criteria for high or low bias	Describe sleep measurement e.g. questionnaires used Did study use validated measures of sleep?(Y/N/U) If not, is psychometric data available for their questionnaire/diary?(Y/N/U/NA)	Could sleep measurement have biased the study?
Power: component 6 Criteria for high risk of bias (1): If the sample size is too small (e.g. <10) or if the study has no justification for the sample size (e.g. through power analysis) Criteria for low risk of bias (0): If sample size is large, if it is justified or power calculations are conducted.	Describe how sample size was chosen e.g. power calculations Did study conduct power analysis (Y/N/U) Did study justify their sample size (Y/N/U)	Could sample size or power have biased the study?

Rate study as unclear if it doesn't meet criteria for high or low bias		
Missing Data component 7 Criteria for high risk of bias (1): If there is data missing, if there is no explicit mention of missing data and results suggest there may be or if there are no strategies to deal with missing data or if no degrees of freedom are presented to calculate missing data Criteria for low risk of bias (0): If missing data is stated and the number is low, or strategies to deal with missing data are used or degrees of freedom or other data is presented that suggests no/little missing data. Rate study as unclear if it doesn't meet criteria for high or low bias.	Describe any missing data reported, how missing data was handled. Did study report missing data?(Y/N/U) Was missing data handled appropriately? (Y/N/U/NA)	Could missing data have biased the study?
Completion Rates component 8 Criteria for high risk of bias (1):	Describe completion rates or numbers used in analysis	Could completion rates have biased the study?

If dropout rate not reported or if there is a high dropout rate or if drop outs differ from completers on important variables Criteria for low risk of bias (0): If there are very few or no drop outs, If dropouts do not differ from completers or if completion rates are explicitly reported and reason for non-completion reported. Rate studies as unclear if it doesn't meet criteria for high or low bias	Did the study report completion rates? (Y/N/U) Did study report why individuals dropped out? (Y/N/U) Were completers and non-completers compared on main variables e.g. age (Y/N/U)	
Data Analysis: component 9 Criteria for high risk of bias (1): If inappropriate statistics are used or if important variables between groups e.g. age or gender are not controlled for in analysis. Criteria for low risk of bias (0): If appropriate statistics are used and any important co-variates and any group differences are controlled in analysis.	Describe data analysis methods e.g. tests used. Did the study use the appropriate statistics for the data(Y/N/U) Did the study control for baseline differences (if any) in statistical analysis?(Y/N/U/NA)	Could methods of data analysis have biased the study?

Rate studies as unclear if it doesn't meet criteria for high or low bias		
Other component 10	Describe any other areas in the study identified that bias may have occurred.	

Appendix 2: Search terms for systematic review

Ovid MEDLINE R and In-Process & Other Non-Indexed Citations.	1. Sleep 2. Schizophrenia 3. 1 and 2 4. Psychosis 5. 1 and 4 6. Psychotic disorder or psychotic disorders/ 7. 1 and 6 8. sleep disorders or Sleep Wake Disorders 9. 8 and 2 10. 8 and 4 11. 8 and 6 12. Circadian rhythms.mp. or Circadian Rhythm/ 13. 12 and 2 14. 12 and 4 15. 12 and 6 16. actigraphy.mp. or Circadian Rhythm/ or Actigraphy/ or Monitoring, Physiologic/ 17. 16 and 2 18. 16 and 4 19. 16 and 6 20. Polysomnography.mp. or Polysomnography/ 21. 20 and 2 22, 20 and 4 23. 20 and 6 24. Polysomnography/ or Sleep/ or Sleep, REM/ or sleep EEG.mp. or Sleep Stages/ 25. 24 and 2 26. 24 and 4 27. 24 and 6 Limit all to (Full text, English language, year = 1953 and Humans). Limit 1,2 and 4 to title. .mp. indicates a multi-purpose keyword search

We will adapt the search strategy, for use in other databases (Web of Science and PsycINFO) as appropriate.

Appendix 3: ESM items

Item type	Items	Scale
Sleep	I feel sleepy, fatigued, exhausted	1-6 point likert scale(not at all to very)
Paranoia	I feel suspicious, I feel that others may hurt me	1-6 point likert scale(not at all to very
Reference	I feel that someone is communicating with me through the TV or radio I feel that things happening around me have special meaning	1-6 point likert scale(not at all to very)
Grandeur	I feel I have special powers to do things that nobody else can I feel like I am especially important	1-6 point likert scale(not at all to very)
Delusional dimensions Each type of delusion was also rated on the distress, pre-occupation and conviction associated with it.	How much are the thoughts about (X) causing you distress? How much are the thoughts about (X) pre-occupying your mind? How convincing are the thoughts about (X)?	1-6 point likert scale(not at all to very)
Hallucinations (auditory and visual)	I hear things I hear things that others can't	Yes/no

	I see phenomena I see things that others don't seem to	
Emotions Negative mood Positive mood	I feel: Insecure, lonely, anxious, irritated, down, guilty, stressed I feel cheerful, relaxed, and content.	1-6 point likert scale(not at all to very)
Context	Who are you with at the present moment? What are you doing at this moment? Did this beep disturb you? Since the last beep have you taken any other substances? Since the last beep have you had any caffeine? Since the last beep have you had anything to eat? (yes/no)	(Categories: nobody/partner/family/friends/strangers) (Categories: nothing/working/leisure/other) (Yes/ no) (yes/no) (yes/no) (yes/no)

Appendix 5: Comprehension of ESM procedure

Question	Average score (1= strongly disagree, 7= strongly agree)
Could you read the text on the phone screen clearly?	6.5
Did you find it awkward to operate the phone?	1.6
Were the verbal instructions you received about using the phone clear?	6.6
Were the questions that you answered on the phone difficult or unclear?	1.7
Did you find it aggravating or stressful to use the phone?	2.1
Were the number of beeps acceptable?	6.6
Was the time taken to complete the questions acceptable to you?	6.6
Were there any technical or other problems that meant you had problems answering some of the questions?	2

Appendix 6: Clinician survey questions for chapter 6.

Question(s)	Answer options
What is your job title?	Choice from: Psychiatrist, Psychiatric Nurse, Psychologist, OT, Social Worker, Primary Care Team, or Other.
What type of service are you based in?	Choice from: Inpatient Ward, Adult Community Health Team, Early Intervention Services, Crisis Resolution Team, Primary Care Team or Other.
Where are you based?	Choice from: Oxford, Glasgow, Birmingham, Manchester, Edinburgh, Liverpool.
What percentage of patients that you see with psychosis, also have sleep problems?	Choice from: -0% -1-20% -21-40% -41-60% -61-80% -81-100%
What are the most common complaints patients with psychosis report about their sleep? (Select all that apply)	(More than one option can be selected) -Insomnia (difficulties getting to sleep or staying asleep) -Sleep related movement disorders (e.g. restless legs syndrome, periodic limb movements) -Sleep related breathing problems (e.g. sleep apnoea)- --- -Hypersomnia (sleeping for very long periods, feeling tired in the day) -Circadian Rhythm disruption (e.g. mistimed sleep: going to bed too early, or very late) -Narcolepsy -Parasomnias (e.g. nightmares or sleepwalking) -Other
In your view, do the sleeping problems that patients with psychosis experience have a negative impact in any of the following domains? (Select all that apply)	(More than one option can be selected) - Mood (e.g. anxiety) - Positive symptoms (e.g. paranoia) - Negative symptoms (e.g. anhedonia) - Cognitive functioning (e.g. attention)

	- Physical health (e.g. feeling unwell) - Social functioning (e.g. relationships) - Daytime activities (e.g. attending appointments)
In your view, what causes the sleep problems in people who experience psychosis? (Select all that apply)	(More than one option can be selected) - The sleep problems are a consequence of medication - The sleep problems are a result of poor sleep hygiene (e.g. too much caffeine, napping) - The sleep problems are a consequence of affective symptoms (e.g. Low mood, anxiety) - The sleep problems are a consequence of positive psychotic symptoms - The sleep problems are a consequence of negative psychotic symptoms - Other
What is your understanding of the relationship between sleep and psychosis?	-Sleep problems are one factor that can make psychotic symptoms (positive and/or negative) worse -Psychotic Symptoms (positive and/or negative) are one factor that can make sleep worse -Both of the above are true (it works both ways) -Unsure -Sleep and Psychosis are not related
How often do you formally assess sleep problems in people with psychosis?	-Rarely/Never -In a minority of cases -In around a half of cases -In the majority of cases (75%) -In nearly all or all patients with psychotic symptoms
What methods do you use to assess sleep problems in people with psychosis? (Select all that apply)	-Informally ask patient -Objectively assess sleep (e.g. EEG, Neck Circumference) -Psychometric self-report (e.g. Administer the Insomnia Severity Index Questionnaire) -Structured Interview Assessment -Other

How often are you treating sleep problems in people with psychosis?	-Rarely/Never -In a minority of cases -In around a half of cases -In the majority of cases (75%) -In nearly all or all patients with psychotic symptoms
What methods do you use to treat sleep problems in patients with psychosis? (Select all that apply)	Choices from: -Antipsychotics -Hypnotics -Anxiolytics -Antidepressants -Refer for Cognitive Behavioral Therapy for Insomnia -Deliver Cognitive Behavioral Therapy for Insomnia -Sleep Hygiene Tips -Offer Psychoeducation materials -There are no effective treatments for sleep problems in people with psychosis -Other
In your view, are there any barriers to treating sleep problems in patients with psychosis?	Open ended answer
What do you think could be the benefits of improving sleep in people who experience psychosis? (select all that apply)	-None -Improved psychotic symptoms -Improved affective symptoms -Increased energy -Increased engagement in activities -Improved physical health -Other
What form of sleep treatment would you recommend for a patient with long-standing sleep difficulties and psychotic symptoms? (Select all that apply)	-Medication -Sleep Hygiene Tips (from a leaflet or website) -Online self-help -Cognitive Behavioral Therapy for Insomnia -All of the above
Are there any other comments you wish to add about sleep in your patients with psychosis?	Open ended answer

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