Sleep disturbances in schizophrenia spectrum and bipolar disorders

Dissertation for the degree of Philosophiae Doctor

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Sammendrag

I denne avhandlingen har vi undersøkt forekomsten av forskjellige søvnforstyrrelser hos mennesker med schizofreni-spektrum- og bipolare lidelser, samlet kalt alvorlig psykisk lidelse. Vi har sett på sammenhengen mellom søvnforstyrrelser og kliniske symptomer, funksjon og kognitive vansker, samt om sammenhengen mellom det å ha vært utsatt for traumer i barndommen og aktuelle kliniske symptomer og funksjon medieres av søvnforstyrrelser. Vi har hatt et overordnet transdiagnostisk fokus for å undersøke om forekomsten av de forskjellige søvnforstyrrelsene og assosiasjonen til kliniske utfallsvariabler gjør seg gjeldene på tvers av schizofreni-spektrum- og bipolare lidelser.

Vi fant at 78% av schizofrenigruppen, 69% av gruppen med bipolar lidelse og 39% av de friske kontrollene rapporterte symptomer på enten insomni, hypersomni eller forskjøvet søvnfaselidelse. Rund halvparten (47%) av den samlede pasientgruppen rapporterte symptomer på insomni, mens 28% rapporterte symptomer på hypersomni. En mindre undergruppe på 8% rapporterte symptomer på forsinket søvnfaselidelse. Forekomsten av søvnforstyrrelser var gjennomgående høyere hos deltagere med schizofreni sammenliknet med bipolar lidelse. Et viktig poeng her er at forskjellene mellom diagnosegruppene var små sammenliknet med forskjellene vi fant mellom den samlede pasientgruppen og kontrollgruppen. Den høye forekomsten av symptomer på insomni er i tråd med tidligere studier på schizofreni og bipolar lidelse. Det er gjort lite studier på hypersomni tidligere, og vår studie indikerer at dette er en hyppig forekommende søvnforstyrrelse i denne pasientgruppen som krever mer klinisk oppmerksomhet. Bruken av medisiner med sederende effekt forklarte delvis forekomsten av hypersomni. Et viktig aspekt her er at andelen kliniske deltagere som brukte medisiner med sederende effekt var høy, og peker på at reduksjon eller bytte av denne typen medisiner er viktig for å redusere forekomsten av hypersomni ved alvorlig psykisk lidelse. Særlig viktig er det å skreddersy den medikamentelle behandlingen for førsteganssyke pasienter med bipolar lidelse bedre, da vi fant at andelen som bruker medisiner med sederende effekt var spesielt høy i denne pasientgruppen.

Videre fant vi at deltagere som hadde søvnforstyrrelse hadde mer alvorlige kliniske symptomer, lavere funksjonsnivå og større kognitive vansker sammenliknet med deltagere uten søvnforstyrrelse. Disse funnene understreker viktigheten av å diagnostisere og behandle søvnforstyrrelser hos mennesker med alvorlig psykisk lidelse. Tidligere studier har små utvalg, har som regel ekskludert deltagere med alkohol- eller rusmisbruk, eller ikke kontrollert for medisiner med sederende effekt. Derfor utgjør det store utvalget vårt en åpenbar styrke. Det har også gjort at vi har kunnet kontrollere for disse potensielle konfunderende variablene, og vise at sammenhengen mellom det å ha en søvnforstyrrelse og mer alvorlige kliniske symptomer, lavere funksjonsnivå og mer kognitive vansker består.

Sammenhengen vi fant mellom søvnforstyrrelse og kognitive vansker ved alvorlig psykisk lidelse ble ikke funnet i den friskekontrollgruppen. Selv om noe av forklaringen på dette kan ligge i at kontrollgruppen var relativ liten og høyt fungerende sammenliknet med pasientgruppen, kan det også tyde på at de friske kontrollene drar på en reservekapasitet som gjør den kognitive fungeringen mer robust, mens den kognitive fungeringen ved alvorlig psykisk lidelse er mer sårbar.

Vi fant lite forskjeller mellom schizofreni og bipolar lidelse, hvilket tyder på at den høye forekomsten av søvnlidelser og assosiasjonene knyttet til kliniske utfallsmål gjelder på tvers av diagnosekategoriene. Disse funnene peker på at det kan være hensiktsmessig å implementere et bredere fokus på søvnforstyrrelser hos mennesker med alvorlig psykisk lidelse, snarere enn det diagnosespesifikke fokuset som preger feltet i dag.

I den siste artikkelen inkludert i denne avhandlingen fant vi at deltagere som hadde vært utsatt for barndomstraumer rapporterte høyere forekomst av symptomer på insomni sammenliknet med de som ikke hadde opplevd barndomstraumer. Omtrent en fjerdedel hadde både vært utsatt for barndomstraumer og rapporterte aktuelle symptomer på insomni. Når vi undersøkte forskjellige typer traumer fant vi at fysisk misbruk, emosjonelt misbruk og emosjonell neglekt var assosiert med aktuelle symptomer på insomni. Disse funnene var sannsynligvis drevet av schizofrenigruppen. Et av

hovedfunnene i denne avhandlingen er at insomni delvis medierer sammenhengen mellom barndomstraumer og mer alvorlige kliniske symptomer og funksjon. Dette funnet er viktig fordi det er godt etablert gjennom tidligere forskning at det å ha vært utsatt for barndomstraumer bidrar til et mer vedvarende og alvorlig sykdomsforløp ved schizofreni og bipolar lidelse, men drivkreftene i dette er mer uklare. Studien vår identifiserer symptomer på insomni som en signifikant bidragsyter i denne sammenhengen og peker med dette på viktigheten av mer fremtidig forskning på søvnforstyrrelser som potensielt behandlingsmål ved tidlig intervensjon.

Funnene i denne avhandlingen bør bidra til å øke bevisstheten rundt den høye forekomsten av søvnforstyrrelser ved alvorlig psykisk lidelse, samt gjøre klinikere mer oppmerksomme på sammenhengen mellom søvnforstyrrelser og mer alvorlige kliniske symptomer, dårligere fungering og kognitive vansker. Dette bør videre føre til at søvnforstyrrelser i mye større grad utredes og behandles med evidensbaserte behandlingsmetoder i klinisk praksis. Samtidig bør det stimulere til mer forskning på søvnforstyrrelser i risikogrupper og tidlig i sykdomsforløpet av alvorlig psykisk lidelse som ledd i å undersøke potensiale for søvnbehandling som tidlig intervensjon.

List of papers

Study I:

Sleep disturbances in schizophrenia spectrum and bipolar disorders – a transdiagnostic perspective.

Laskemoen, J.F., Simonsen, C., Buchmann, C., Barrett, E.A., Bjella, T., Lagerberg, T.V., Vedal, T.J., Andreassen, O.A., Melle, I., Aas, M.,

Comprehensive Psychiatry, 91, 6-12. doi:10.1016/j.comppsych.2019.02.006

Study II:

Do sleep disturbances contribute to cognitive impairments in schizophrenia spectrum and bipolar disorders?

Laskemoen, J.F., Buchmann, C., Barrett, E.A., Collier-Høegh, M., Haatveit, B., Vedal, T.J., Ueland, T., Melle, I., Aas, M., Simonsen, C.

European Archives of Psychiatry and Clinical Neuroscience, doi:10.1007/s00406-019-01075-0

Study III:

Sleep disturbance mediates the link between childhood trauma and clinical outcome in severe mental disorders

Laskemoen, J.F., Aas, M., Vaskinn, A., Berg, A.O., Lunding, S.H., Barrett, E.A., Melle, I., Simonsen, C.

Psychological Medicine, 1-10. doi:10.1017/S0033291720000914

Abbrevations

ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
BACS	Brief Assessment of Cognition in Schizophrenia
BMI	Body mass index
CBT	Cognitive Behavioral Therapy
CTQ	Childhood Trauma Questionnaire
CVLT	California Verbal Learning Test
D-KEFS	Delis Kaplan Executive Function System
DSM	Diagnostic Manual for Mental Disorders
GAF F	Global Assessment of Functioning Scale-Split version – function score
HVLT	Hopkins Verbal Learning Test
ICD	International Classification of Mental and Behavioral Disorders
ICDS	International Classification of Sleep Disorders
IDS-C	Inventory of Depressive Symptoms – Clinician rated scale
MANOVA	Multivariate analysis of variance
MCCB	MATRICS Consensus Cognitive Battery
NOS	Not otherwise specified
NORMENT	Norwegian Centre for Mental Disorders Research
NREM	Non-rapid eye movement
PANSS	Positive and Negative Syndrome Scale
PRIME-MD	Primary Care Evaluation of Mental Disorders
REM	Rapid eye movement
SCID	Structural Clinical Interview for DSM-IV Axis I Disorders
SPSS	Statistical Package for the Social Sciences
TOP	Thematically Organized Psychosis
TranS-C	Transdiagnostic Sleep and Circadian Intervention
WAIS	Wechsler Adult Intelligence Scale
WASI	Wechsler Abbreviated Scale of Intelligence
YMRS	Young Mania Rating Scale

1 Introduction

Sleep is vital to all living species and a main biological drive. We spend around ⅓ of our lives sleeping or having trouble doing so. Nevertheless, why we sleep remains an enigma. The focus on sleep in treatment of psychosis was, however, present when the concept of "dementia praecox" was introduced. Kraepelin wrote that "*Rest in bed, supervision, care for sleep and food, are here the most important requisites*" (p. 279) (Kraepelin, Robertson, & Barclay, 1919). Our knowledge about sleep has increased dramatically the past 20 years. It is now established that sleep has profound health-promoting benefits, and that poor sleep has equally debilitating effects on health. However, this knowledge is not utilized or implemented sufficiently in treatment of severe mental disorders (schizophrenia spectrum and bipolar disorders).

From clinical experience, I learned how common sleep problems are amongst patients with severe mental disorders. Reports of difficulties falling or staying asleep, not being able to get up in the morning, daytime sleepiness and napping, were frequent. Despite this, sleep disturbances were not systematically assessed, diagnosed or prioritized in treatment and patients were instead given medication when sleep became particularly difficult. It also reflected the traditional view that sleep disturbance is a symptom or consequence of psychiatric illness, resulting in sleep disturbance getting low priority as a treatment target in clinical practice. Information about sleep hygiene was often provided, but implementation of this advice in daily routines at the ward was not sufficient and of little benefit to the patients. This experience formed my interest in the significance of sleep disturbances, and the urge to raise awareness regarding the magnitude of sleep disturbances in severe mental disorders.

Increased knowledge the past two decades, however, supports the notion that sleep disturbances seem to be a causal factor in a wide range of psychiatric disorders (Pigeon, Bishop, & Krueger, 2017; Winokur, 2015). Conceptual changes have been made in the new versions of the diagnostic manuals that include sleep disorders (the Diagnostic Manual for Mental Disorders (DSM); International classification of Mental and Behavioral Disorders (ICD); International Classification of Sleep Disorders (ICSD), directing more

attention towards sleep disturbances in mental illness. Although the diagnostic evaluations of severe mental disorders made in the three studies included in this thesis (Laskemoen, Aas et al., 2020; Laskemoen, Buchmann, et al., 2019; Laskemoen, Simonsen, et al., 2019) are based on DSM-IV-TR (American Psychiatric Association, 2011), the newest version of DSM (DSM-5) now recommends that sleep disturbances should be assessed, diagnosed and treated irrespective of other psychiatric difficulties (American Psychiatric Association, 2013). This conceptual change was required since treating sleep disturbances are important *per se*, and because it emphasizes that sleep disturbances should be given higher priority in clinical practice. However, despite these recommendations, sufficient clinical attention to sleep disorders is still not provided. Several recent studies report that sleep disturbances are rarely assessed, diagnosed or treated properly in severe mental disorders (Barrett, Aminoff, Simonsen, & Romm, 2020; Kallestad et al., 2011; Rehman et al., 2017).

1.1 Schizophrenia spectrum and bipolar disorders

For simplicity, throughout this thesis schizophrenia spectrum disorders and bipolar disorders will be referred to as schizophrenia and bipolar disorder. When mentioning them together they will be referred to as severe mental disorders despite also being frequently referred to as psychotic disorders in the literature elsewhere.

1.1.1 Continuum model

The concepts of schizophrenia and bipolar disorder were introduced by the German psychiatrist Emil Kraepelin during late 19th century. Schizophrenia was then referred to as *dementia praecox*, described as an incurable psychotic disorder beginning after puberty, with a gradual progression leading to mental defect (Kraepelin & Defendorf, 1904). *Manic depressive insanity*, later labeled bipolar disorder on the other hand, "encompassed all the insanities whose primary symptoms were based in mood or affect" with a presumed better prognosis (Kraepelin & Defendorf, 1904). Since 1983 schizophrenia and bipolar disorder have been diagnostic categories defined in the DSM system by operational criteria based on the presence of symptoms, and not based on putative biological or psychological processes underlying each diagnostic category (Nieman & McGorry, 2015). According

to the DSM framework, schizophrenia and bipolar disorder (and all other psychiatric disorders) are separate entities with natural boundaries separating them (Dalal & Sivakumar, 2009). This categorical distinction between schizophrenia spectrum disorders and bipolar disorders has led to a common idea that they are fundamentally different. However, because of the clinical overlap and the presence of psychotic and affective symptoms in both disorders , schizophrenia and bipolar disorder have also been considered as part of the same dimension (Crow, 1990, 2008; Van Os et al., 1999) and consequently grouped together as *severe mental disorders*.

The continuum model is at the core of this dimensional understanding of the disorders, in which schizophrenia and bipolar disorder lie at opposite ends of a continuum with schizoaffective disorder in between (Craddock, O'Donovan, & Owen, 2009; Keshavan et al., 2011) and with schizophrenia considered more severe than bipolar disorder. There is however evidence for a substantial clinical, epidemiological and genetic overlap between the disorders, suggesting shared disease mechanisms (Lee et al., 2013; Lichtenstein et al., 2009; Maier, Zobel, & Wagner, 2006; Rowland & Marwaha, 2018; Sullivan et al., 2012). Particularly noteworthy are the overlapping psychotic- and affective symptoms; as more than half of those with a bipolar disorder experience psychotic symptoms (Grande, Berk, Birmaher, & Vieta, 2016; Keck et al., 2003) and affective symptoms are present in around half of those with schizophrenia (Owen, Sawa, & Mortensen, 2016; Romm et al., 2010; Xu, Li, Liu, & Zhong, 2018). Because of this, increased interest in the psychosis continuum model as a phenomenological symptom description have emerged (Sullivan et al., 2012). Particularly important for the current thesis are the overlapping features of sleep disturbance, cognitive impairment and the shared risk factor of childhood trauma between the two disorders.

There are several aspects to the debate regarding both the categorization of schizophrenia and bipolar disorder, and for the existence of separate psychiatric disorders in general. The arguments for replacing DSM by a valid nosology based on biomarkers, clinical staging, narrowly defined transdiagnostic symptom domains and coherent syndromes are common (Nieman & McGorry, 2015).

Firstly, DSM allows for multiple diagnoses per individual, reflecting the high frequency of comorbidity with the common occurrence of anxiety and depression as a typical example. Secondly, longitudinal studies suggest that symptoms are shared and sequenced across disorders and time (Kelleher et al., 2012; Lahey, Zald, Hakes, Krueger, & Rathouz, 2014; Merikangas et al., 2012; Nieman & McGorry, 2015) rather than parts of parallel pathways leading to different disorders as assumed by the DSM, although with limited scientific support. Thirdly, the presence of certain criteria regarding the duration of symptoms lead to specific thresholds for receiving a diagnosis (or not). This implies that with a duration criterion of e.g. one month a person with symptoms of posttraumatic stress disorder lasting for four weeks will be diagnosed with posttraumatic stress disorder, whilst a person with symptoms lasting three weeks will not. Consequently, the first person will be offered treatment whilst the other will not. Fourthly, there are more diagnostic criteria listed than the number needed to give a specific diagnosis, leading to highly heterogeneous symptom constellations within diagnostic categories.

Research into schizophrenia and bipolar disorder has, however, mainly been carried out separately for the two diagnostic categories, even if they recently also have been studied together as *severe mental disorders.* Consequently, in the present thesis, findings will be presented both separately for schizophrenia and bipolar disorder and jointly for severe mental disorders depending on the research studies referred to.

Schizophrenia spectrum disorders

In DSM-IV, the group of "Schizophrenia and other psychotic disorders" is divided into nine diagnostic subgroups (see appendix 1) with separate diagnostic criteria. Common to these subgroups is the presence of psychotic symptoms for a specific duration of time, independent of an affective episode. The term *schizophrenia spectrum disorders* include these nine subgroups with schizophrenia as the largest and the target for the majority of research, whilst schizoaffective disorder includes affective episodes and lies at the core of the continuum model. Therefore, focus will lie on the diagnosis of schizophrenia, yet also describing schizoaffective disorder.

Schizophrenia is a severe mental disorder with a lifetime prevalence of 1% (Owen et al., 2016). Age of onset is typically in late adolescence to early adulthood. The diagnosis is based on clinical observation with the most recent diagnostic criteria published in DSM-5 (American Psychiatric Association, 2013). However, the diagnostic evaluations of severe mental disorders included in this thesis are based on DSM-IV-TR. The criteria defining schizophrenia (Criteria A., appendix 1) in DSM-IV-TR consist of two main categories: 1) Positive symptoms including hallucinations and delusions (constituting a psychotic dimension) and disorganized speech and disorganized /catatonic behavior (constituting a disorganized dimension). 2) Negative symptoms including affective flattening, avolition and poverty of speech. At least two of these symptoms must be present for a significant portion of time during a 1-month period (or less if successfully treated) for the diagnosis of schizophrenia. Additional criteria include substantial occupational and social dysfunction for a significant proportion of time since the onset of the disorder, and continuous signs of the disturbances for at least 6 months. Moreover, schizoaffective and mood disorders must be excluded, as well as psychotic disturbances attributable to substance use/general medical condition or pervasive developmental disorder.

The distinction between schizophrenia and schizoaffective disorder concerns the presence of affective episodes. For schizoaffective disorder the main criterion is a minimum of one affective episode concurrent with symptoms meeting Criteria A. for schizophrenia during an illness period. During this same illness period, delusions and hallucinations must be present for a minimum of two weeks, in the absence of prominent affective symptoms. Taken together, one or more affective episodes must be present for a substantial part of illness duration in schizoaffective disorder. However, if an affective episode occurs in schizophrenia, it must be brief compared to illness duration.

Schizophrenia is a heterogeneous disorder with symptom constellation and severity that vary, the same is the case for number of episodes, treatment response and comorbidities. Recurrent

psychiatric problems are seen in approximately 50% of people with a diagnosis of schizophrenia, whilst 20% are reported to have chronic symptoms and disability (Owen et al., 2016). Affective symptoms are common, with more than 40% having depressive symptoms (Romm et al., 2010; Xu et al., 2018). Importantly, longitudinal studies also find that between 14-38% meet criteria for *clinical recovery* involving limited or no symptoms and adequate functioning for the last 1- 2 years (Hegelstad et al., 2012; Jaaskelainen et al., 2013; Lally et al., 2017). Moreover, *personal recovery* involving coping, participation and improved quality of life despite persisting symptoms, is also common (Jarden, Oades, & Slade, 2017).

The Norwegian National guidelines covering evidence based treatment of schizophrenia and other severe mental disorders (thus the bipolar disorders) recommend the use of antipsychotic medication combined with different psychosocial approaches such as Cognitive Behavioral Therapy (CBT) for psychosis, psychoeducational family interventions and music therapy, to mention but a few (Helsedirektoratet, 2013). Positive symptoms including delusions and hallucinations usually respond to antipsychotic medication. Negative symptoms and cognitive deficits are, however, less influenced by antipsychotic medication, and represent a treatment challenge. Many individuals also experience side effects of medication including lack of motivation, neurological side effects, serious weight gain, metabolic disturbances, sexual dysfunctions, restlessness, psychomotor problems and sedation (Nieman & McGorry, 2015). A large study (Lieberman et al., 2005) showed that 74% of patients stop taking their medication within 18 months because of side effect burden and other causes. Moreover, unemployment rates in schizophrenia are as high as 80-90% (Evensen et al., 2016; Lystad et al., 2016). Rates of morbidity and mortality are also high, with life-expectancy reduced by 10-20 years due to suicide and medical illnesses associated with poverty, social exclusion, poor medical care, and the effects of medications (Chesney, Goodwin, & Fazel, 2014; Colton & Manderscheid, 2006). Thus, despite positive outcome for a number of people, schizophrenia is a debilitating and costly disorder, both to individuals and to society.

Despite extensive research, the etiology of schizophrenia is not fully known. There is consensus that both environmental and genetic factors interact in a complex manner. Heritability rates are high (81%) (Sullivan, Kendler, & Neale, 2003), but genetic background alone is not sufficient for the disorder to develop. Several pre- and postnatal factors are suggested to be involved, including malnutrition and infection during pregnancy, birth complications, winter births, advanced paternal age and autoimmune illness (Khandaker et al., 2015; Murray & Fearon, 1999; van Os, Krabbendam, Myin-Germeys, & Delespaul, 2005). Environmental factors found to be particularly important are childhood trauma, cannabis use and migration (Selten & Cantor-Graae, 2005; van Os et al., 2005). Thus, schizophrenia is regarded a multifactorial neurodevelopmental disorder (Owen et al., 2016; Selemon & Zecevic, 2015). The wide range of genetic, epigenetic and environmental factors thought to play a role in disease development is both consistent with the extensive number of phenotypes, and to the dimensional term schizophrenia spectrum disorders.

Comprehensive neuropathology is associated with schizophrenia. Amongst these are both structural and functional brain abnormalities, especially in frontal areas of the brain (Ellison-Wright & Bullmore, 2009; Pu et al., 2017). Studies of structural and functional brain alterations point to abnormal integration of information, suggesting a dysconnectivity that may play an important role in the cognitive impairments frequently seen in schizophrenia (Brandt et al., 2015; Cocchi et al., 2014). Moreover, sleep disturbance is a common feature, and both sleep disturbance and cognitive impairments interfere with everyday functioning and quality of life, to the extent that they are suggested core features, despite not being part of the diagnostic criteria.

Bipolar disorders

In DSM-IV bipolar disorders are divided into four subgroups (appendix 2) with associated criteria. Common to these diagnostic subgroups is the presence of an affective episode (manic, hypomanic or mixed episode with the possibility of depressive episodes) for a specific duration of time, independent of psychosis. All the four diagnostic subgroups are included in the term *bipolar spectrum disorders,* which is used throughout this thesis. The distinction in DSM-IV criteria between

bipolar I, bipolar II and bipolar disorder not otherwise specified (NOS) are mainly related to severity of elevated mood. As the majority of cases in the bipolar samples in our study have a diagnosis of bipolar I disorder, this will be the focus of the present thesis.

The lifetime prevalence of bipolar I is approximately 1.0% (Merikangas et al., 2011), and the mean age of onset is in early adulthood usually around 23-24 years (Grande et al., 2016). The main criterion for bipolar I disorder is the minimum of one manic or mixed episode. Episodes of depression may also occur but are not a prerequisite. Furthermore, bipolar disorder is characterized by periods identified as depressive, mixed or manic. The phase between these periods is referred to as the inter-episode period or euthymia (Judd et al., 2003). A manic episode consists of elevated, expansive or irritable mood lasting for a minimum of 7 days. During this period a minimum of three other symptoms are also present (Appendix 2), causing impaired functioning. A hypomanic episode is milder. It also consists of elevated, expansive or irritable mood including a minimum of three other symptoms, but duration is set to at least 4 days, and the episode is not severe enough to cause marked impairment, necessitate hospitalization or include psychotic features. A depressive episode consists of a minimum of five depressive symptoms lasting for a minimum of two weeks, causing clinically significant social and/or occupational dysfunction (Appendix 2). A mixed episode consists of both manic and depressive symptoms lasting for a minimum of one week. To meet the diagnostic criteria of bipolar disorder I, II and NOS, affective episodes cannot be better accounted for by schizoaffective disorder, nor be superimposed on other psychotic disorders.

As in schizophrenia, bipolar disorders are considered heterogeneous, with great variability in type of mood episodes, frequency of relapses and dominant polarity. A history of psychotic symptoms is common and may be present in about 50% (Grande et al., 2016; Keck et al., 2003). Inter-episode periods may vary in length, and episodes in both length and severity (Anderson, Haddad, & Scott, 2012). The treatment recommendations from The Norwegian National Guidelines for bipolar disorders especially emphasizes psychoeducation and different types of psychological and

psychosocial therapy, including family therapy (Helsedirektoratet, 2012). Such treatment is combined with pharmacological treatment in which the main focus is stabilization of mood. Different psychotropic medication is used to treat manic and depressed episodes, and prophylactic treatment is used to prevent development of new episodes. Also recommended is facilitation of treatment integrated with work and school, called Individual Placement and Support. Bipolar disorder is one of the most disabling conditions worldwide (Disease, Injury, & Prevalence, 2018). Substance abuse, as well as morbidity and mortality rates are substantially increased, with particularly high suicide rates during depressive episodes (Grande et al., 2016). Although there is less research into recovery rates in bipolar disorder, the aforementioned longitudinal studies reporting that 14-38% meet criteria for *clinical recovery*, include participants with bipolar disorder (Hegelstad et al., 2012; Lally et al., 2017). Moreover, *personal recovery* is also reported in people with bipolar disorder (Veseth, Binder, Borg, & Davidson, 2012).

The etiology of bipolar disorder is also largely unknown. Bipolar disorder is considered multifactorial, with a complex interplay between environmental and genetic factors. This area is, however, less studied in bipolar disorder than in schizophrenia. Twin and family studies have demonstrated substantial evidence for a genetic contribution, with lifetime risk of first-degree relatives of 5-10% (Craddock & Jones, 1999). Large genome-wide association studies have identified multiple genetic loci associated with bipolar disorder, suggesting aggregated polygenic risk. However, the effect size of each single nucleotide polymorphism is small and together common variants are suggested to account for 25% of the heritability of bipolar disorders (Gordovez & McMahon, 2020). Further studies are needed to elucidate how genes of risk interact with environmental factors.

Some overlap in environmental risk factors is found between schizophrenia and bipolar disorder, including infections during pregnancy or early in life, birth complications, autoimmune illness, urban birth and upbringing, childhood trauma and cannabis use (Misiak et al., 2018). Severity of symptoms is seemingly related to exposure of childhood trauma and cannabis use in a dose–response manner

(Rowland & Marwaha, 2018). A recent review (Rowland & Marwaha, 2018), however, suggests the evidence for prenatal and perinatal risk factors for development of bipolar disorder are weak and inconsistent, compared to the evidence base for these risk factors for development of schizophrenia. Evidence for Toxoplasma gondii infection nevertheless seems more substantial (Del Grande, Galli, Schiavi, Dell'Osso, & Bruschi, 2017).

Importantly, bipolar disorder is associated with substantial impairment across several functional and health related domains, including cognitive impairments and sleep disturbances. Different types of sleep disturbances are even part of the episodic criteria for all types of mood episodes. The cognitive impairments and sleep disturbances however tend to persist also in inter-episode phases.

1.2 Sleep disturbance

Sleep serves many important functions and is integral to overall health. Sleep is considered vital for restoration of the brain and several body functions, and is critical for learning and memory consolidation (Krueger, Frank, Wisor, & Roy, 2016). Therefore, insufficient sleep manifests itself in multiple ways. Among the wide-ranging negative health outcomes associated with insufficient sleep are several types of mental illnesses, cardio vascular disease, diabetes, obesity, cancer and premature mortality (C. L. Jackson, Redline, & Emmons, 2015; Javaheri & Redline, 2017). In a 2018 report (Reneflot et al., 2018) the Norwegian Institute of Public Health pointed to an increasing prevalence of sleep problems and to their accompanying risk of health problems, sick leave and accidents. Despite this report and other reports emphasizing the important role of sleep, sleep problems receive surprisingly little focus by policy makers and other stakeholders.

When sleep problems reach a certain threshold regarding severity, frequency and length, they are regarded as a *sleep disorder* and assigned a *diagnosis*, rather than just seen as unspecific symptoms called *sleep disturbances*. Evaluation of *sleep disorders* is systematized in The International Classification of Sleep Disorders (ICDS), now in its third edition (ICDS-3)(American Academy of Sleep Medicine, 2014). This is the most widely used classification system for sleep disorders. Seven major categories of sleep disorders are included in the ICDS-3; insomnia, sleep-related breathing disorders,

central disorders of hypersomnolence, circadian rhythm sleep-wake disorders, parasomnias, sleep-related movement disorders and other sleep disorders. Corresponding diagnoses can be found within The International Classification of Mental and Behavioral Disorders (ICD-10). Also, the fifth edition of the Diagnostic and Statistical manual of Mental Disorders (DSM-5) classifies sleep disorders in a manner parallel to the ICSD-3 system.

All sleep disorders relevant to this thesis are characterized by a subjective experience of problems regarding quality, timing or amount of sleep. Although assessment of the *subjective experience* of sleep is crucial and lies at the core of the diagnostics, several sleep disorders require *objective assessment* using polysomnography. *Polysomnography* is used to investigate different stages of sleep, which may be divided into rapid eye movement (REM) and non-rapid eye movement (NREM) sleep. Based on the depth of sleep, NREM sleep may further be divided into stages 1, 2, 3 and 4. Stages 3 and 4 are often referred to as slow wave sleep or delta sleep based on their polysomnography patterns. Sleep is normally organized in cycles, starting with NREM stages 1 to 4 and finishing off with REM sleep. One cycle takes about 90 minutes, and these cycles continue through the night (Brown, Basheer, McKenna, Strecker, & McCarley, 2012). *Actigraphy i*s another objective measure of sleep. An actigraph is a watch-like device worn on the wrist obtaining information about movement and light exposure. This information is used to deduce sleep-wake cycles and circadian function. Polysomnography and actigraphy are the objective sleep measures most widely used in the sleep research cited throughout this thesis. However, a few studies apply *electroencephalography* to detect sleep spindles. Put simply, electroencephalography is used to measure the electrical activity of the brain. Sleep spindles are bursts of coherent brain activity most evident during stage 2 and are thought to mediate many sleep-related functions such as e.g. memory consolidation (Andrillon et al., 2011).

A wide range of *sleep disorders* and *disturbances* are often reported in psychiatric disorders, including alterations in sleep architecture (i.e., the amount and distribution of time spent in different

sleep stages), sleep apnea, insomnia, hypersomnia and delayed sleep phase, reduced need for sleep, nightmares and nocturnal panic (Harvey, 2008; Harvey, Murray, Chandler, & Soehner, 2011). Three of the most common and prominent *sleep disturbances* in psychiatric disorders include insomnia, hypersomnia and delayed sleep phase, and these constitute the focus of this thesis. Their diagnostic criteria (based on ICSD-3) and relevant epidemiologic factors are briefly outlined below. Obstructive sleep apnea and restless legs syndrome are two additional sleep disorders representing differential diagnoses to insomnia, hypersomnia and delayed sleep phase, used as exclusion criteria for participation in the studies comprised by the current thesis.

Insomnia

Insomnia is characterized by difficulty falling sleep, difficulty staying asleep and early morning awakenings without being able to return to sleep. Substantial symptoms during daytime, such as fatigue, sleepiness, inattention, mood disturbance/irritability, reduced motivation, and/or impaired performance must also be present to diagnose an insomnia *disorder.* Depending on its duration, insomnia is described either as short-term or chronic. In *short-term insomnia,* the symptoms are present for less than three months, and occur in response to an identifiable stressor that may be physical, psychological, psychosocial or interpersonal in nature. *Chronic insomnia* refers to insomnia symptoms occurring at least three times per week and persisting for at least three months (American Academy of Sleep Medicine, 2014). DSM-5 and ICD-10 use the duration criteria of 1 month for the diagnosis of insomnia and do not distinguish between short-term and chronic insomnia. *Other insomnia* is a diagnostic category in ICSD-3 comprising insomnia symptoms that do not meet criteria for the two other insomnia types. When diagnosing insomnia, the persons' own perceptions of their sleep problem is the main basis for a diagnosis. An insomnia diagnosis is thus a clinical diagnosis based on history and subjective report.

Insomnia is the most common sleep problem in the general population. Prevalence rates vary from 4%-48% (Ohayon, 2002; Roth et al., 2011). When manifestations of functional impairment are taken into account the rate is narrower; and between 5%-10% qualify for an insomnia diagnosis (Roth,

Roehrs, & Pies, 2007). Insomnia is more prevalently reported in older adults and in women (Ohayon, 2002). Moreover, studies suggest insomnia tend to be persistent with high relapse rates; 25% of individuals who remit report at least one relapse over a 3-year period (Morin et al., 2009). Also, individuals with insomnia symptoms that relapse are at risk of experience worsening of insomnia over time (Morin et al., 2009).

Hypersomnia

Central disorders of hypersomnolence is an umbrella term comprising disorders in which excessive daytime sleepiness, not due to any other sleep disorder, is the primary complaint. Excessive daytime sleepiness is defined as an urgent need to sleep or lapse into sleep during daytime. Sleepiness is defined as excessive when it causes subjective complaints or interferes with function. ICSD-3 differentiates between hypersomnias that are of central nervous system origin (narcolepsy type 1 and type 2), idiopathic hypersomnia, Kleine-Levin syndrome, or other hypersomnias that are related to or caused or by medical/psychiatric conditions or use of medication/substances (American Academy of Sleep Medicine, 2014). The focus of this thesis is "other hypersomnias" hereafter referred to as *hypersomnia*. Clinically hypersomnia comprises prolonged nocturnal sleep periods combined with excessive daytime sleepiness and unrefreshing naps that are not otherwise explained by medication or substance use, or a known medical condition (American Academy of Sleep Medicine, 2014). Excessive daytime sleepiness is distinct from mental and physical fatigue, which may present as difficulties initiating or maintaining activity. Although the terms fatigue and excessive daytime sleepiness are associated in people with a sleep disturbance (Valko, Bassetti, Bloch, Held, & Baumann, 2008), fatigue may worsen after activities whereas excessive daytime sleepiness may temporarily resolve. Moreover, a person experiencing excessive daytime sleepiness often falls asleep when sedentary, but a person experiencing fatigue my not be able to initiate sleep despite effort.

To *diagnose* hypersomnia, an evaluation of the excessive daytime sleepiness is crucial. Because no test is adequate to elucidate the cause of hypersomnia, history is important, including a detailed sleep history, to investigate if there are any signs of underlying sleep disorders causing insufficient

sleep. Use of medication and or substances should be listed to evaluate contributory agents. A physical examination should be carried out. The Epworth Sleepiness Scale is a standard measure of subjective sleepiness and may be useful in clinical practice. Polysomnography should be applied if obstructive sleep apnea, other periodic limb movement disorders, narcolepsy, other central hypersomnias, unexpected insomnia or seizures during sleep is suspected (American Academy of Sleep Medicine, 2014).

There is lack of systematic prevalence studies of hypersomnia, but a given estimate of the general population is 0.02–0.07% (Ohayon, 2007).

Delayed sleep phase

Delayed sleep phase is a disorder of the sleep-wake system. The regulation and consolidation of sleep is complex and depends on synchronization of two important factors; 1) the circadian process and 2) the sleep homeostatic process. The circadian process is regulated by our biological clock (located in the suprachiasmatic nucleus in the anterior hypothalamus) and aligns our sleep and wake episodes in relation to the dark and light phase, together with a wide range of other daily rhythms such as temperature, cortisol release and appetite. The homeostatic process regulates our need for sleep by building up a sleep pressure after prolonged wakefulness, which dissipates during sleep (Krueger et al., 2016; Wulff, Dijk, Middleton, Foster, & Joyce, 2012)

Delayed sleep phase is the most common circadian rhythm sleep-wake disorder, and is characterized by a phase delay in timing of the major sleep episode in relation to the light/dark cycle (Nesbitt, 2018). This sleep phase delay causes problems falling asleep at an appropriate time. Consequently, waking up at desired/conventional time also becomes difficult while sleep quality is often normal. Extrinsic factors such as traveling or shift work may contribute to circadian rhythm sleep-wake disorders, however intrinsic abnormalities of the circadian system itself is the focus of this thesis.

Although delayed sleep phase predominantly is a clinical diagnosis, based on history of abnormal sleep-wake patterns, self-reported measures such as sleep diary (recording bedtime and wake-up

time) is required to make a diagnosis of all intrinsic circadian rhythm sleep-wake disorders (American Academy of Sleep Medicine, 2014). Objective measures such as wrist actigraphy is considered a useful supplementary.

Delayed sleep phase often begins in adolescence (Nesbitt, 2018). The prevalence of delayed sleep phase is poorly described. A population-based study found a prevalence of 0.17% in the general population (Schrader, Bovim, & Sand, 1993).

Sleep terminology

An important note to make is that *sleep disorder diagnoses* and symptoms of *sleep disturbances* are often used interchangeably throughout the research literature, especially when it comes to insomnia and hypersomnia. More specifically, this means that insomnia may represent an *insomnia diagnosis* or *symptoms of insomnia*. This is for instance reflected in prevalence studies in which prevalence rates of insomnia vary according to level of measurement applied. Also, the terms hypersomnia, "hypersomnolence", "excessive somnolence," and "excessive daytime sleepiness" are used interchangeably. This mixed use of sleep disorder/symptoms terminology is also reflected in the various methodology used to assess sleep across the research literature, ranging from subjective measurement based on diagnostic assessments, validated and non-validated rating scales, single items from these rating scales together with objective measurements with laboratory-based polysomnography or wrist actigraphy.

While different *sleep disorders* are described as individual disorders, many symptoms of *sleep disturbances* occur together. For instance, hypersomnia and insomnia may co-occur in bipolar disorder (Kaplan, Gruber, Eidelman, Talbot, & Harvey, 2011; Kaplan & Harvey, 2009). Throughout this thesis the term *sleep disturbance* is used broadly, encompassing the manifestations of insomnia, hypersomnia and delayed sleep phase based on reported symptoms and not as diagnoses meeting specific diagnostic criteria.

Sleep disturbances as transdiagnostic phenomena

Sleep disturbance is suggested to have an etiological link to several psychiatric phenomena through different pathways (Harvey et al., 2011). Firstly, sleep has a close bidirectional relationship with *emotion regulation*. Studies show that sleep disturbances strongly increase negative mood, and that emotional arousal in turn may disturb sleep (Franzen, Siegle, & Buysse, 2008; N. A. Hamilton, Catley, & Karlson, 2007; Li, Wu, Gan, Qu, & Lu, 2016). Consequently, a vicious cycle between sleep disturbances and emotion regulation may arise. The concept of insomnia as a state of early mental distress contributing to a cascade of causal relations that gradually develop into diagnosable levels of anxiety, depression and psychosis, is outlined and illustrated by van Os (van Os, 2013).

Secondly, there is evidence for a shared genetic basis between sleep disturbances and psychiatric symptoms. Genes known to be important in the generation and regulation of circadian rhythms (clock genes) have been linked to several psychiatric disorders. For instance, overlap in genetic and environmental causes of sleep disturbance and psychotic symptoms (paranoia) has previously been found in a study of twins (Taylor, Gregory, Freeman, & Ronald, 2015).

Thirdly, both the *serotonergic and dopaminergic systems* are involved in many psychiatric disorders because of their impact on core processes including cognition, emotion, motor function and motivation. The sleep/circadian systems are connected with these systems in an intricate and complex manner (Harvey et al., 2011). Fourth, the *stress response system* constitutes another biological system that closely interacts with the circadian system and several psychiatric disorders (more details in 1.3.3). Taken together, this indicates that the high levels of co-occurrence between sleep disturbance and several psychiatric disorders could be based on shared biological mechanisms and suggests that sleep disturbances are a transdiagnostic feature (Harvey et al., 2011) .

The frequency of sleep disturbances in severe mental disorders

1.2.6.1 Sleep disturbance in schizophrenia

Sleep disturbances are frequent across a broad range of psychiatric disorders (Winokur, 2015). *Insomnia* is the most studied sleep disturbance, and prior research indicates that insomnia is both

common and severe in schizophrenia (Freeman, Pugh, Vorontsova, & Southgate, 2009; Reeve, Sheaves, & Freeman, 2019). Studies applying objective measures of sleep disturbances by use of polysomnography have validated several of the findings based on subjective reports, further confirming that sleep-onset insomnia and difficulty maintaining sleep are characteristic sleep patterns of insomnia (Kamath, Virdi, & Winokur, 2015). These sleep disturbances persist regardless of medication status and illness phases (first episode, acute exacerbation or chronic stage) (Monti et al., 2013). Cumulated research further suggests that insomnia plays an important role in the onset of psychosis and is regarded a prodromal sign of exacerbations (Benson, 2015; Chemerinski et al., 2002; Davies, Haddock, Yung, Mulligan, & Kyle, 2017; Zanini et al., 2013).

Several other types of sleep disturbances are also common. Although significantly less studied, hypersomnia, or symptoms of hypersomnia such as excessive daytime sleepiness, is found in 24% to 31% of people with schizophrenia treated with antipsychotics (Lieberman et al., 2005; Sharma, Dikshit, Shah, Karia, & De Sousa, 2016). Moreover, there are indications that circadian rhythm disturbance may be more common in people with severe mental disorders compared to the general population (Wulff et al., 2012), yet there are surprisingly few studies of delayed sleep phase in schizophrenia.

1.2.6.2 Sleep disturbance in bipolar disorders

Sleep disturbances are listed as a diagnostic criterion for mania, depression and mixed episodes in bipolar disorder in DSM-IV (American Psychiatric Association, 2013) and sleep disturbances are also common during the inter-episode period (Geoffroy et al., 2015). Although rates vary between studies, up to 70% of patients report a clinically significant sleep disturbance in inter-episode periods (Harvey et al 2005), including both insomnia and hypersomnia. (Kaplan et al., 2011). Moreover, reduced need for sleep is the most common prodromal symptom of manic episodes (Jackson, Cavanagh, & Scott, 2003). Importantly, changes in sleep pattern represent a warning sign before new mood episodes of both polarities (Kaplan & Harvey, 2013).

Furthermore, circadian dysfunction has been suggested an underlying pathophysiologic mechanism in bipolar disorder (Alloy, Ng, Titone, & Boland, 2017; Harvey, 2008). Higher rates of delayed sleep phase is found in persons with bipolar disorder compared to controls (Giglio et al., 2010) , and findings from a longitudinal study (Robillard et al., 2016) suggest that sleep fragmentation in young people with mood disorders may be predictive of subsequent worsening of manic symptoms.

In summary, the previous studies of sleep disturbances in schizophrenia and bipolar disorder are relatively small in sample size, and mainly focus on one type of sleep disturbance within a specific disorder, indicating a need for broader focus in larger cross-diagnostic samples.

1.2.6.3 Clinical correlates of sleep disturbances

Sleep disturbances have been associated with a wide range of negative outcomes including reduced quality of life, suicide attempts, cognitive deficits, poorer functioning, impaired physical health and higher relapse rates of mood episodes and in maintenance and exacerbation of psychotic symptoms (Benson, 2015; Davies et al., 2017; Reeve, Sheaves, & Freeman, 2015; Ritsner, Kurs, Ponizovsky, & Hadjez, 2004). Although these relationships can be bidirectional, findings suggest that sleep disturbances affect several areas of functioning in people with severe mental disorders.

1.2.6.4 Factors that may influence sleep

Several factors influence sleep and circadian functions. As previously described, insomnia, hypersomnia and delayed sleep phase are related to both age and gender. Importantly, medication used in treatment for severe mental disorders affect neurotransmitter systems that play an important role in sleep regulation. Antipsychotic, anticholinergic, and anti-adrenergic medications have broad effects on sleep (Benson, 2015; Krystal, Goforth, & Roth, 2008; Monti, 2016). Indeed, both improvement of sleep quality and disruption of the sleep wake cycle may result from use of these medications (Kamath et al., 2015). As these effects are more pronounced with long-term administration, studying sleep in different treatment stages is crucial (Davies et al., 2017). Moreover, alcohol and substance abuse and dependency is common in severe mental disorders, and may also influence sleep quality and symptoms (Benson, 2015). Weight gain is associated with sleep

disturbances and is also a common and challenging side effect of several frequently used medications (Hung, Liao, Wu, Lee, & Lane, 2014). Taken together, several clinical factors highly relevant in severe mental disorders may exert influence on sleep. However, most studies exclude participants with comorbid alcohol and drug abuse or have too small sample sizes to adequately control for the potential influence of these factors.

1.2.6.5 Unanswered questions regarding sleep disturbances in severe mental disorders.

Although sleep disturbances are prominent features of both schizophrenia and bipolar disorder, large-scale studies on the type and frequency of sleep disturbances across severe mental disorders compared to healthy controls, are lacking. Previous studies are limited in sample sizes, and mainly focus on one type of sleep disturbance in one specific disorder. Since the planning of this thesis in early 2015, several studies of insomnia have emerged in disorder-specific studies, particularly in schizophrenia. However, there is still a large knowledge gap regarding hypersomnia and delayed sleep phase. Moreover, little is known about sleep disturbances at different stages of treatment, about the relationship between sleep disturbances and clinical symptoms and functioning, or how this relationship may be influenced by age, gender, recent alcohol and drug use, history of alcohol or drug dependency, use of medications with sedative effects and weight (Body Mass Index (BMI)). Last, but not least, there is a need for more knowledge about commonalities and differences in sleep disturbances across schizophrenia and bipolar disorder.

1.3 Cognitive functioning in severe mental disorders

Cognitive functioning is a term referring to multiple mental abilities including general intellectual functioning, attention, psychomotor speed, learning, memory and executive function. Executive function is an umbrella term covering several higher-order cognitive functions that are used in goal directed tasks (working memory, planning, fluency and set-shifting) and in suppression of contextual and emotional distractors (inhibition and interference control). In the literature on severe mental disorders the term *neurocognitive functioning* is often used for the same purpose, indicating that these are tasks linked to specific regions of the central nervous system. Throughout this thesis the

term cognitive functioning will be used, with a focus on cognitive functions that are impaired in severe mental disorders.

Schizophrenia was initially conceptualized as “dementia praecox”, indicating deterioration in cognitive abilities in young adults. Today, a large body of literature demonstrates marked impairments in multiple cognitive domains in schizophrenia. Attention, memory and executive functions are among the most severely impaired domains (Gur, 2011; Heinrichs, 2005; Heinrichs & Zakzanis, 1998; Menkes, Armstrong, Blackford, Heckers, & Woodward, 2019). Also in bipolar disorder cognitive impairments are widely reported, particularly in many of the same cognitive domains as in schizophrenia; i.e. attention, processing speed, verbal memory, and executive functioning (Menkes et al., 2019; Samamé, Martino, & Strejilevich, 2014). The heterogeneity in cognitive impairment is, however, considerable, both between and within diagnostic categories (Lewandowski, 2018). However, the current consensus in the field is that overall cognitive functioning is more impaired in schizophrenia than in bipolar disorder, also in the early stages of the illness (Menkes et al., 2019).

Cognitive impairments are present both during acute psychotic and affective episodes, and during stable, inter-episode periods, implying that they are trait- rather than state specific. Indeed, cognitive impairment has been viewed as a core feature of schizophrenia for a long time, and more recently also of bipolar disorder (Barch, 2009).

Importantly, cognitive impairment is shown to be a strong predictor of poor functional outcome (Green, Kern, Braff, & Mintz, 2000) and a major contributor to inadequate everyday functioning commonly seen in severe mental disorders, particularly poor occupational functioning (Christensen, 2007; Lystad et al., 2016). To date, no specific therapeutic agent has been found to enhance cognitive functioning. Mild to moderate positive effects have been reported for some antipsychotics. These effects are, however, not sufficient to be considered clinically meaningful and could be secondary to symptomatic improvements (Vreeker, van Bergen, & Kahn, 2015). Cognitive remediation therapy has,

nevertheless, demonstrated promising treatment results. In combination with psychosocial interventions, cognitive remediation therapy is shown to improve everyday functioning (Harvey & Bowie, 2012; Wykes, Huddy, Cellard, McGurk, & Czobor, 2011). Cognitive remediation therapy may be considered refined behavioral treatments for cognitive impairments, and emphasizes that the cognitive improvement that follows treatment should be manifested in everyday life and/or quality of life to be considered successful (Harvey & Bowie, 2012; Wykes et al., 2011).

1.3.1 Sleep and cognitive processes

Theories holding that there is a functional link between sleep and cognition, particularly learning and memory, are based on the extensive overlap between sleep mechanisms and the neurophysiology of these cognitive processes (Poe, Walsh, & Bjorness, 2010). During a cognitive process such as e.g. attention or working memory, neural oscillations and synchronization among different brain regions occur and form a dynamic cognitive network that temporally synchronize these brain regions into a functional unit. The synchronization of these brain regions occurs at all stages (wakefulness through the different stages of sleep). Each stage of sleep is associated with various degrees, frequencies and extent of brain areas involved that aid facilitation of important learning and memory processes (Poe et al., 2010). Indeed, a wide range of studies have documented that compromised sleep leads to impaired cognition in both persons with insomnia and otherwise healthy persons (Chee & Chuah, 2008; Horne, 1993; Van Dongen, Maislin, Mullington, & Dinges, 2003). Sleep disturbances are frequent in severe mental disorders, as are impairment in cognitive processes that are dependent on sleep. Consequently, sleep disturbances may contribute to cognitive impairments in severe mental disorders, although this is an area with limited research.

Sleep disturbances and cognitive impairment in severe mental disorders

The majority of studies investigating sleep disturbances and cognitive impairments in schizophrenia have measured sleep objectively, primarily by use of polysomnography, electroencephalography or actigraphy. Together these studies suggest a link between sleep microarchitecture and cognitive impairment. More specifically, a systematic review of studies in early psychosis (Davies et al., 2017)

points to a possible relationship between sleep architecture and performance on attention tasks, but without a consensus across studies. More clear results are found for memory, with a specific link between sleep spindle abnormalities and overnight memory consolidation in chronic schizophrenia (Baandrup, Christensen, Fagerlund, & Jennum, 2018; Ferrarelli & Tononi, 2017; Manoach et al., 2010; Pocivavsek & Rowland, 2018; Wamsley et al., 2012).

In the bipolar disorder field, studies of sleep disturbance and cognitive impairment is based on a mix of subjective and objective measures of sleep. Studies applying subjective measurement have found disrupted sleep to predict social cognition and working memory (Russo et al., 2015), and greater total sleep time variability to predict poorer performance on tasks measuring working memory and verbal learning (Kanady, Soehner, Klein, & Harvey, 2017). Objective studies using actigraphy link sleep disturbances to attention and processing speed (Bradley et al., 2018) and verbal memory (Robillard et al., 2016). Taken together, there are indications that sleep disturbance in severe mental disorders may contribute to cognitive impairments. However, most studies are small in sample size and larger studies are needed.

1.3.3 Factors that may influence sleep and cognition

Some of the factors influencing risk of sleep disturbances, including age, gender, diagnostic group (schizophrenia or bipolar disorder), recent use of alcohol or drugs, a history of alcohol or drug dependency, the use of medication with sedative effects, and BMI, as well as current positive, negative, depressive and manic symptoms, are also of relevance to cognitive functioning. Associations between sleep disturbances and cognitive impairment could thus be mediated or confounded by these factors.

1.3.4 Unanswered questions regarding sleep and cognition

In general, sleep disturbances have been overlooked as a potential contributor to cognitive impairment in severe mental disorders. Previous studies suggest an association, but few studies have investigated the subjective experience of the most prevalent sleep disturbances, and there is little consensus across studies as to what cognitive domains are impaired. Thus, knowledge about how

different types of sleep disturbance are related to cognition is limited, as is the knowledge of whether this relationship is different between schizophrenia, bipolar disorder or healthy controls. The sample sizes of previous studies have been too small to investigate the influence of potential confounding factors. Therefore, in search of more efficient treatment options, large-scale studies investigating the relationship between sleep disturbance and cognitive functioning across severe mental disorders are required.

1.4 Childhood trauma in severe mental disorders

There is controversy regarding how to define psychological trauma within different fields of research (Gibson, Alloy, & Ellman, 2016). Distinctions have also been made between the age when the traumas occurred, whether traumas thought to be of interpersonally intrusive/abusive character (e.g. physical abuse) from other negative life events such as e.g. parental maladjustment (Hovens et al., 2012). Other distinctions are based on whether the traumatic event was intentional (e.g. sexual abuse) or non-intentional (e.g. motor vehicle accident), or whether it was interpersonal or accident based (Haahr et al., 2018). The focus of this thesis is however childhood trauma defined as an experience of physical, sexual and emotional abuse, and/or physical or emotional neglect, without further distinctions.

Childhood trauma is one of the most documented environmental risk factors for the development of a severe mental disorder (Varese et al., 2012). Depending on study methodology and subtype of trauma, the overall odds of developing a severe mental disorder or positive psychotic symptoms when having experienced a traumatic life event, ranges from 2.78 to 11.50 (Janssen et al., 2004; Varese et al., 2012). Also, childhood trauma is linked to more severe clinical manifestations of severe mental disorders, including earlier age of onset, comorbid disorders, cognitive deficits, treatment resistance, earlier and more frequent hospitalizations, increased risk of suicide attempts and substance abuse (Aas, Henry, et al., 2016; Etain et al., 2013; Mohammadzadeh, Azadi, King, Khosravani, & Sharifi Bastan, 2019). Childhood trauma is associated with more severe manic, depressive and psychotic symptoms in bipolar disorder (Agnew-Blais & Danese, 2016; Etain et al.,

2013) and with more severe depressive symptoms in schizophrenia (Aas, Andreassen, et al., 2016; Kelly et al., 2016; Sahin et al., 2013). It is suggested that being exposed to childhood trauma makes the individual prone to development of a mixture of anxiety, affective, and psychotic symptoms that cut across different severe mental disorders (van Nierop et al., 2014). Thus, the downstream consequences of childhood trauma are not disorder-specific, rather they have transdiagnostic effects and represent an array of symptoms common to several severe mental disorders.

Several studies point to specific trauma subtypes being especially important for certain symptom dimensions. For instance, sexual abuse has been linked to hallucinations and neglect has been linked to paranoia (Bentall et al., 2014). The sum of studies, however, indicates that the relationship between childhood trauma and psychosis is independent of trauma sub type. Therefore, the experience of childhood trauma itself is suggested to be more important than any given specific sub type of trauma in terms of clinical outcome in severe mental disorders (Gibson et al., 2016).

Childhood trauma and sleep disturbance

After exposure to a traumatic event, sleep is often severely, but transiently disrupted. Such sleep disturbances may, however, also be long-lasting. A wide range of sleep disturbances are thus frequently seen as sequelae of trauma exposure both in the short- and the long term (Lavie, 2001; Mysliwiec et al., 2018). Moreover, a recent review of retrospective cohort-studies showed that exposure to childhood trauma is associated with insomnia symptoms, nightmare-related distress and sleep apnea in adulthood (Kajeepeta, Gelaye, Jackson, & Williams, 2015). Yet, there is only one study linking childhood emotional abuse to poor sleep quality in bipolar disorder (Aubert et al., 2016) and one study investigating the joint influence of childhood trauma and sleep disturbance on psychotic-like experiences in students (Andorko et al., 2018). This clearly indicates that the relationship between childhood trauma, sleep disturbance and clinical outcome is not sufficiently studied in severe mental disorders.

Possible pathways from childhood trauma to sleep disturbances in severe mental disorders

Childhood trauma is suggested to cause prolonged neurobiological alterations leading to vulnerability to a later development of a wide range of mental disorders. However, these specific developmental trajectories are not fully clarified (Agorastos, Pervanidou, Chrousos, & Baker, 2019). Dysregulation of the stress response system has been suggested a putative mechanism involved in development of stress-related disorders, including severe mental disorders. The sleep/circadian system is another pathway that may link childhood trauma and later clinical symptoms (Agorastos et al., 2019). The sleep/circadian system synchronizes the stress system, generating a circadian rhythmicity. Disruption of this rhythmicity (often referred to as chrono disruption) causes imbalance of biological systems that in turn may have short- and long-term pathophysiologic effect (Zelinski, Deibel, & McDonald, 2014). In this vein, sleep disturbances may contribute to maladaptive stress regulation; further increasing vulnerability to the development of severe mental disorders (Meerlo, Sgoifo, & Suchecki, 2008). However, there are no prior studies investigating the possible mediating effects of sleep disturbances on the relationship between childhood trauma and clinical outcome in severe mental disorders. Further supporting an interplay sleep disturbance and stress regulation are findings from genetic studies, showing sleep disturbances to be associated with altered CLOCK gene expression in humans, which vitally affects neurobiological response to stress (Ackermann et al., 2013).

Unanswered questions regarding sleep disturbances and childhood trauma in severe mental disorders

The frequency of childhood trauma and sleep disturbances is high in severe mental disorders. Yet, there is a lack of studies investigating their co-occurrence across different severe mental disorders, and whether specific subtypes of childhood trauma might be associated with certain types of sleep disturbances. Furthermore, extensive research illustrates important relationships between childhood trauma and sleep disturbance, and between sleep disturbance and psychotic symptoms. However, whether sleep disturbance mediates the relationship between childhood trauma and severity of psychotic symptoms and poorer functioning in severe mental disorders, remains unknown.

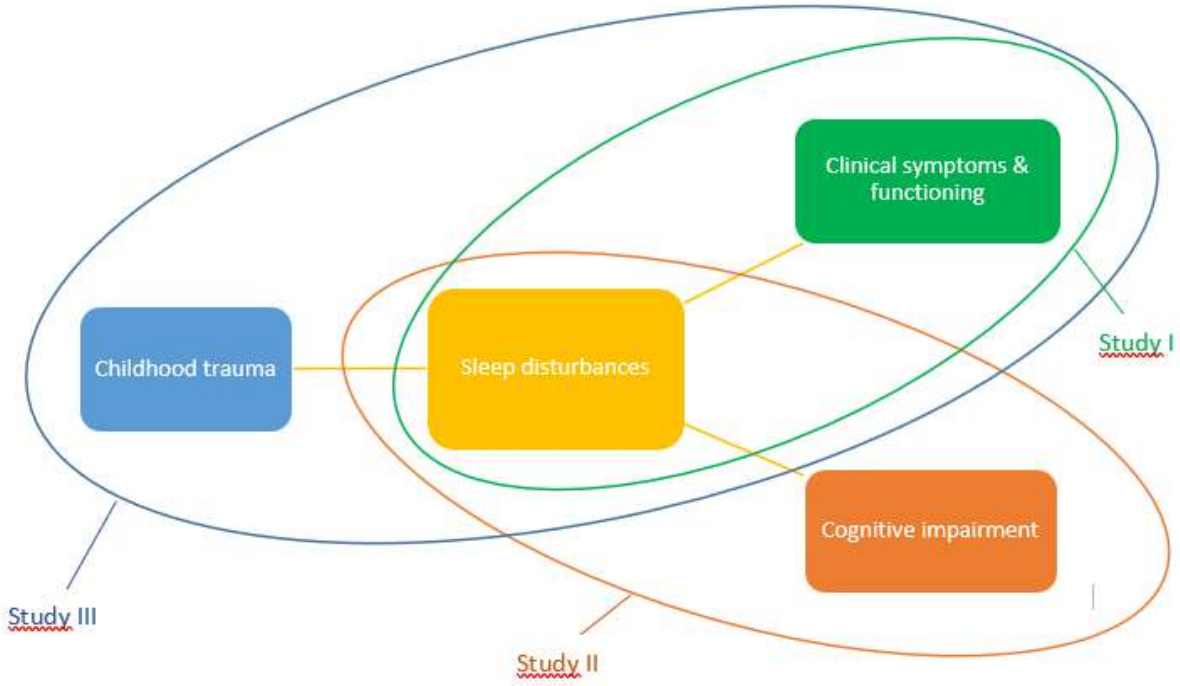
2 Aims

The primary aim of the present study was to investigate if sleep disturbances are related to clinical features in severe mental disorders, and whether an association is transdiagnostic.

The first aim was to record the type and occurrence of self-rated sleep disturbances (insomnia, hypersomnia and delayed sleep phase) in and across severe mental disorders, compared to healthy controls. We then investigated the frequency of the different sleep disturbances across different stages of treatment (first treatment and previously treated patient groups). Finally, we explored the relationship between sleep disturbances and clinical symptoms and functioning while adjusting for potential confounding factors (study I).

The second aim was to investigate the relationship between self-rated sleep disturbances and cognitive impairments in and across severe mental disorders, adjusting for potential confounding factors. We also wanted to investigate whether this relationship varied between different sleep disturbances, and if the relationship between sleep disturbances and cognition differed in severe mental disorders compared to healthy controls (study II).

The third aim was to investigate the relationship between self-rated sleep disturbances and childhood trauma. We also wanted to test if sleep disturbance could be a mediator of an association between childhood trauma and severity of clinical symptoms and poorer functioning in severe mental disorders, adjusting for potential confounding factors (study III). See figure below for visualization of overall study model.



3 Methods

3.1 Design

The three studies included in this thesis are all part of the ongoing Thematically Organized Psychosis (TOP) Research Study at the Norwegian Centre for Mental Disorders Research (NORMENT) in Oslo, Norway. NORMENT is a Centre of Excellence funded by the Research Council of Norway. The aims of the Centre are to better understand the underlying mechanisms of severe mental disorders and to find answers as to why some people develop perceptual disturbances, delusions, depressive and manic phases. The present research project is a naturalistic, cross sectional study of the two main diagnostic categories included in the TOP study; schizophrenia spectrum disorders and bipolar disorders and fits well within the overall aim of the Centre as it investigates the role of sleep disturbances in severe mental disorders.

The Centre is organized as a collaboration between the University of Oslo, the University of Bergen, Oslo University Hospital and Haukeland University Hospital, the University of Oslo being the host institution. Clinical participants in the research study were recruited consecutively from psychiatric in-patient and out-patient units in Oslo. Patient representativity is considered excellent as all individuals with mental health problems in Norway receive public mental health care within their

catchment area. Random selection of healthy control participants from the same catchment areas are ensured by using national statistical records. Healthy control participants were contacted by letter with an invitation to participate. All participants were given thorough information about procedures and the study protocol before they gave written informed consent. The study was approved by the Regional Committee for Medical Research Ethics and the Norwegian Data Inspectorate.

3.2 Procedure

The present study is based on the TOP protocol; including data on sleep disturbances, clinical symptoms and functioning, cognitive performance and childhood trauma. All clinical participants were in treatment (as an in-patient or out-patient), during the study period. Based on symptoms compatible with either schizophrenia spectrum disorders or bipolar disorders diagnosis, clinical participants were referred for assessment from their respective treatment units. Clinical psychologists or medical doctors that had received diagnostic training by completing a three-month education program, carried out the clinical assessment. Supervision by experienced Consultant clinical psychologists or Psychiatrists was established on a regular basis, as well as a monthly clinical supervision meeting in which difficult diagnostic cases were discussed. Assessment of sleep disturbance and childhood trauma was part of the broader clinical assessment. Cognitive assessment was administered no more than two weeks after the clinical assessment to ensure concurrence of clinical symptoms. Clinical psychologists with training in standardized neuropsychological testing carried out the cognitive assessment. Experienced Consultant neuropsychologists provided supervision. After the assessments were completed, reports were sent to the treatment units. Healthy controls were randomly drawn from Statistics Norway and contacted if they responded to an invitation letter. They were screened for exclusion criteria (neurological disorders, head injuries and a history of severe mental disorder including first- and second-degree relatives) via a phone call using the Primary Care Evaluation of Mental Disorders (PRIME-MD) (Spitzer, Kroenke, & Williams, 1999).

Those who met the inclusion criteria participated in a broader personal assessment, including assessment of sleep disturbances, childhood trauma and cognitive functioning.

3.3 Study samples

A subset of the current study sample was included in two previous studies (Steinan et al., 2016; Steinan et al., 2016a). These studies included clinical participants (N=309 and N=223, respectively) with bipolar disorder type I and II, and investigated frequency, clinical and demographic correlates of sleep disturbances in bipolar disorder.

In all studies we examined whether the relationship between sleep disturbance and different outcome measures differed across schizophrenia spectrum and bipolar disorders (study I and II) and if the relationship between sleep disturbance and childhood trauma differed between these two diagnostic categories (in study III). Comparisons to healthy controls were conducted in study I and II. For an overview of distribution of diagnostic subgroups and recruitment period, see appendix 3.

In study I we investigated sleep disturbances across treatment duration, dividing clinical participants into two groups; *first treatment* patients (n=431) and *previously treated* patients (n=626). *First treatment* was defined as less than one year of adequate treatment for the disorder in question at study baseline. *Adequate treatment* was defined as a) mood stabilizers or antipsychotic medication in adequate dosage for >12 weeks or b) admission to a psychiatric ward designed for treatment of severe mental disorders. All other clinical participants were defined as *previously treated*.

Exclusion criteria applied for all three studies included head injury needing hospitalization, neurological disorder, comorbid obstructive sleep apnea or restless legs syndrome and IQ below 70. Exclusion criteria were evaluated as part of clinical and cognitive assessment outlined in the methods section. For study I and III participants outside the range of 18-65 were excluded. In study II the age range was narrowed down to 18-60 due to the inclusion of cognitive test performance, which is shown to be sensitive to older age. All participants also had to have Norwegian as their first language or have completed all compulsory schooling in Norway to ensure a valid cognitive test performance.

To secure a representative clinical sample we did not exclude clinical participants with recent (past two weeks) substance or alcohol intake, or with a prior history of alcohol or substance use disorders. Substance abuse was, however, an exclusion criterion for the healthy control sample.

3.4 Measures

Clinical assessment

Assessment of lifetime diagnosis was completed based on the Structural Clinical Interview for DSM-IV Axis I Disorders (SCID I, module A-E) (First, Spitzer, Gibbon, & Williams, 1995) supplemented by information from medical records, and information from close relatives if needed. Current symptoms were assessed with the Positive and Negative Syndrome Scale (PANSS) (Kay, Fiszbein, & Opler, 1987), the Inventory of Depressive Symptoms – Clinician rated scale (IDS-C) (Rush, Gullion, Basco, Jarrett, & Trivedi, 1996) and Young Mania Rating Scale (YMRS) (Young, Biggs, Ziegler, & Meyer, 1978). PANSS, IDS-C and YMRS were used somewhat differently in the tree studies included in this thesis, depending on the aims and research questions of each study.

PANSS is an interview-based assessment of symptom burden the past 7 days, in which 30 items are scored from 1-7 with higher scores indicating more severe symptomatology. PANSS is originally subdivided into three categories; positive symptoms (7 items), negative symptoms (7 items) and general symptoms (16 symptoms). However, a five-factor model was implemented by Wallwork (Wallwork, Fortgang, Hashimoto, Weinberger, & Dickinson, 2012) capturing the different symptom dimensions more precisely; the *positive factor* includes items P1-delusions, P3-hallucinations, P5-grandiosity and G9-unusual thought. The *negative factor* includes N1-blunted affect, N2-emotional withdrawal, N3-poor rapport, N4-passive/apathetic social withdrawal and G7-motor retardation. The *disorganized/concrete factor* includes P2-conceptual disorganization, N5-difficulty in abstraction and G11-poor attention. The *excited factor* includes P4-excitement, P7-hostility and G8-uncooperativeness. The depressed factor includes G2-Anxiety, G3-Guilt feelings and G6-Depression. Because the latter factor also consists of items capturing anxiety this is referred to as the *depression/anxiety factor* in this thesis. Additionally in study III, we assessed current illness phase by

stratifying participants with schizophrenia into being psychotic or in symptomatic remission, using internationally standardized criteria (Andreasen et al., 2005). Current remission was conceptualized based on scores below 4 on the PANSS as follows: positive symptoms (P1-delusions, G9-unusual thought content, P3-hallucinations), disorganized symptoms (P2-conceptual disorganization, G5-mannerisms/posturing), and negative symptoms (N1-blunted effect, N4-social withdrawal, N6-lack of spontaneity). Thus, all participants with schizophrenia who had a score of 4 or above on any of these items were regarded psychotic.

IDS-C was used to measure current depressive symptoms in study II and III. This is a scale with 30 items, scored from 0-3. Importantly, as further described in the next section, the IDS-C is used to conceptualize and rate the sleep disturbances in this thesis. In study II, depressive symptoms were used as a potential confounding factor. Therefore, to avoid conflicting use of rating scale scores in that study, the sleep items (item 1-4) were extracted from the total depression score. In study III, current depression was part of describing the study sample, defined by an IDS-C total score equal or above 14.

To assess current manic symptoms, we used the YMRS, consisting of 11 items rated from 0-4 with higher scores indicating more severe symptoms the past two days. As with the depressive symptoms assessed with IDS-C, YMRS was used differently in studies II and III; in study II manic symptoms were used as a potential confounding factor. In study III it was applied to describe the frequency of mania in the study sample, defined by a total score equal to or above eight.

Level of functioning was assessed with Global Assessment of Functioning Scale-Split version – function score (GAF-F) (Pedersen & Karterud, 2012). This scale is used to evaluate functioning the prior week on a scale ranging from 0-100. Contrary to all other symptom scales applied, lower scores here indicate poorer functioning.

All clinical participants also went through a physical examination completed by a medical doctor. This included assessment of blood pressure and heart rate, examination of heart, lungs and the abdomen,

a brief neurological examination and assessment of height and weight for calculation of BMI. Moreover, clinical participants were questioned about comorbid disorders including substance abuse, excluding those reporting obstructive sleep apnea or restless legs syndrome.

Information about recent (past two weeks) intake of alcohol (number of units) and/or illegal drugs (times used) were obtained based on clinical interview and medical charts. Lifetime history of alcohol or drug abuse or dependency was based on DSM-IV substance related diagnoses. Current use of psychotropic medication was also obtained through clinical interview and medical charts. Medication with sedative effects were classified as follows: all sedatives and antipsychotics, antidepressants and mood stabilizers that had sedation marked as a main or major side-effect in The Norwegian Pharmaceutical Product Compendium (Felleskatalogen AS, 2018). We inspected their known modes of action on neurotransmitters implicated in inducing sleepiness (histaminergic/muscarinergic). Appendix 4 lists all medication that were classified as medication with sedative effects for the current thesis.

Assessment of sleep disturbances

IDS-C, a part of the standard clinical assessment in the TOP protocol contains four sleep items; difficulty falling asleep (item 1; Sleep Onset Insomnia), difficulty maintaining sleep (item 2; Mid-Nocturnal Insomnia), early awakening (item 3; Early Morning Insomnia) and hypersomnia (item 4; Hypersomnia). Each item is rated on a four-point Likert scale (0-3), with higher scores indicating more subjective sleep disturbance. Report is based on the subjective experience of sleep the past 7 days. The items reflect *symptoms* that are part of the diagnostic criteria in ICDS-3 and DSM-IV-TR, and thus represent symptoms of sleep disturbances. However, prior studies have validated these items as measures of insomnia and hypersomnia, and shown them to adequately predict clinical diagnoses of sleep disorders (Gruber et al., 2009; Kaplan et al., 2011; Soehner, Kaplan, & Harvey, 2014a; Sylvia et al., 2012). Different combinations of scores on these items are used to conceptualize and rate the following three sleep disturbances, emphasizing that these conceptualizations represent *symptoms of sleep disturbances*, and not diagnostic categories.

1. **Insomnia** corresponds to; a) a score of ≥ 2 on *Sleep Onset Insomnia* (more than half the time one uses a minimum of 30 min to fall asleep); b) a score of = 3 on *Mid-Nocturnal Insomnia* (more than half the time, one wakes up more than once per night and stays awake for 20 min or more); **or** c) a score of ≥ 1 on *Early Morning Insomnia* (more than half the time, waking up happens more than 30 min before one needs to get up). In addition, a score of = 0 on the *Hypersomnia* item (sleeps no more than 7-8 hours a night, without naps) was a prerequisite.

   Insomnia total score corresponds to the sum of item 1. *Sleep Onset Insomnia*, item 2. *Mid-Nocturnal Insomnia* and item 3. *Early Morning Insomnia.*

2. **Hypersomnia** corresponds to a score of ≥1 on the *Hypersomnia* item (sleeping up to 10 hours per day) with no evidence of Insomnia.

3. **Delayed sleep phase** corresponds to a score of ≥ 3 on *Sleep Onset Insomnia* (more than half the time, one uses more than 60 minutes to fall asleep), and a score of ≥ 1 on the *Hypersomnia* item.

4. **Any sleep disturbance** corresponds to a score over cut-off on any one of the sleep disturbances described**.**

Cognitive assessment

Two different neuropsychological test batteries were administered over the study period. Battery I was administered before year 2012 and constitutes a standardized test battery shown to be sensitive to cognitive impairments in severe mental disorders (Simonsen et al., 2010). The part of the battery covering executive functions is based on the Delis-Kaplan executive function system (D-KEFS) (Delis, Kaplan, & Kramer, 2005). Battery II was administered to participants included in the study from 2012 to 2018 and is based on the MATRICS Consensus Cognitive Battery (MCCB) (Nuechterlein et al., 2008). We merged the two batteries and formed the following cognitive domains: processing speed, verbal learning, verbal memory, attention and executive functions; the latter including verbal

fluency, working memory, inhibition and flexibility. If the two batteries contained overlapping tests they were merged directly. If the tests were different but tapped the same cognitive functions they were merged in the following way: we calculated z-scores, using a reference group of 1094 healthy controls from the whole study period as basis, and then merged the z-scores. For a detailed overview, see table 1 in study II.

Processing speed was measured with the Digit Symbol-Coding test from the Wechsler Adult Intelligence Scale III (WAIS-III) (Wechsler, 2003) or Symbol Coding test from the Brief assessment of Cognition in Schizophrenia (BACS)(Keefe et al., 2004). In both tests the task is to link a number from 1 to 9 to a specific symbol, based on a key, however the tests have slightly different design. In the Digit Symbol-Coding test from the WAIS participants are given a sheet of paper on which a line of *numbers* appears above a line of blanc boxes to be filled with the corresponding symbols, based on a given key. In the Symbol Coding test from the BACS the lines are opposite; a line of *symbols* appears above a line of blanc boxes to be filled with the corresponding numbers based on a given key. Within 120 seconds (for the Digit Symbol-Coding test from the WAIS-III) and 90 seconds (for the Digit Symbol-Coding test from the BACS) participants are expected to fill in as many corresponding symbols/numbers as possible.

Verbal learning was measured with the California Verbal Learning Test (CVLT)(Delis, Kramer, Kaplan, & Ober, 2004) or the Hopkin´s Verbal Learning Test (HVLT)(Benedict, Schretlen, Groninger, & Brandt, 1998). In the CVLT verbal learning task participants are read a list of 16 words five times and asked to repeat as many of the 16 words they can remember after each reading. A total score is based on the sum of correct words over the 5 trials. In HVLT verbal learning a list of 12 words are read 3 times, and the total score is based on the sum of correct words over the 3 trials.

Verbal memory was also measured by the CVLT or the HVLT. The task in both CVLT and HVLT is delayed free call and involves remembering as many of the previously read words 20 minutes after the last list was read out loud. The number of correct responses equals the score.

Attention was measured by the Digit Span Forward and Digit Span Backward from the WAIS-III in both batteries. Random digits are read out loud and the task involves remembering an increasing number of digits, both forward and backwards. Each sequence of digits corresponds to a given level of difficulty, and for each level of difficulty the participant is given two attempts and may earn two points. The total score is the sum of total correct responses.

Executive functions

Verbal fluency was measured by the Verbal Fluency Test (using the category fluency task) from the D-KEFS or the Category Fluency Test from the MCCB. In both batteries the task is to name as many words (belonging to the category animals) as possible in one minute. The only difference between the batteries is that the D-KEFS is followed by a repetition of the task with words belonging to the category boys' names. The total score is the sum of correct responses.

Working memory was measured by Letter-Number Sequencing test from WAIS-III or the Letter-Number Span from MCCB. Participants are read an increasing number of digits and letters and the task is to first sort the digits in ascending order, and then the letters in alphabetical order. The total score is the sum of total correct responses.

Inhibition was measured with the Color-Word Interference Test from D-KEFS in both batteries. The inhibition score corresponds to the third condition in this test. The task is to name the color of the ink in the written words; however, these are incongruent (i.e. the word red is written in blue ink). The score is represented by the time needed to fulfill the task.

Flexibility was also measured by the Color-Word Interference Test from D-KEFS in both batteries, using condition 4. The task involves alternating between naming the color of the ink of the written words when they appear without a frame and reading the actual words (not the ink color) when they appear with a frame. The score is represented by the time needed to fulfill the task.

In all scores except for inhibition and flexibility, higher scores reflect better performance. Current IQ was measured by with the Wechsler Abbreviated Scale of Intelligence (WASI) (Wechsler, 2007)

Assessment of childhood trauma

To assess childhood trauma we used a Norwegian version of the Childhood Trauma Questionnaire (CTQ) (Aas et al., 2012; D. P. Bernstein et al., 2003). CTQ is a self-report questionnaire consisting of 28 items scored from 1 to 5 on a Likert scale, with higher scores indicating more frequent traumatization. The 28 items are divided into 5 subscales of trauma; emotional abuse, physical abuse, sexual abuse, physical neglect and emotional neglect. A previous study (Larsson et al., 2013) has shown CTQ to have good internal consistency across psychotic disorders in the TOP sample, with an overall internal consistency of 0.86, and for the subscales: emotional abuse, 0.86; physical abuse, 0.82; sexual abuse, 0.91; emotional neglect, 0.88; and physical neglect, 0.65. We also applied cut off scores based on the work of Bernstein & Fink (David P. Bernstein & Fink, 1998), dichotomizing each subscale into “no trauma exposure” (corresponding to none or mild exposure) versus “trauma exposure” (corresponding to moderate to severe exposure).

3.5 Statistical analyses

All analyses were conducted using the Statistical Package for the Social Sciences (SPSS), version 24 for study I, and version 25 for study II and III. Preliminary analyses were conducted to examine the distribution of variables. Descriptive statistics were obtained using proportions, standard deviations, means, medians or range according to measurement level and distribution. Some variables had missing data. These were addressed in each study by footnotes below the descriptive tables. We chose the *Exclude cases pairwise* option, in which a case was excluded from a given analysis if data was missing for that specific analysis but included in all other relevant analyses with existing data.

For all studies, group comparisons of demographics and/or clinical characteristics were carried out using different analyses depending on whether the variables were categorical or continuous.

We applied t-tests or analyses of variance (ANOVAs) to investigate group differences (between schizophrenia, bipolar disorder and healthy controls, or between severe mental disorders and

healthy controls) for continuous variables, and Chi-square statistics when analyzing categorical variables. We conducted non-parametric tests (Mann-Whitney U Tests) for variables that were not normally distributed (CTQ-based variables). In correlation analyses, Pearson correlation coefficient was applied for normally distributed variables, and Spearman`s rho for skewed distributions. All tests were two-tailed with a significance level set to 0.05.

We addressed the risk of type I error due to the high number of analyses employed in all three studies. In both study I and II we conducted a multivariate analysis of variance (MANOVA). Following a statistically significant MANOVA, separate analyses of covariance (ANCOVAs) were conducted for separate outcomes, using relevant factors as covariates. In study II we also applied a Bonferroni adjustment for outcome measures, setting a *p* value of 0.006 as significance threshold for all ANCOVA analyses. In paper II we also applied a two-way between groups MANOVA to investigate potential differences between schizophrenia and bipolar disorder.

In study III we carried out mediation analyses by using Haye´s PROCESS tool version 3.3 for SPSS (Hayes, 2018). Within this tool we selected model 4 designs with childhood trauma as predictor, sleep disturbance as mediator and the different clinical outcome variables as dependent variables. This analysis allows for exploration of *path a* (from the predictor to the mediator), *path b* (from the mediator to the dependent variable), *path c`* (the direct effect of the predictor to the dependent variable) and *path C* (the total effect of the predictor on the dependent variable) in addition to the bootstrapped indirect effect and its confidence interval. Selection of variables in the model were based on the following: Clinical outcome measures that were significantly correlated with both the predictor (childhood trauma total) and the mediator (sleep disturbance), were selected as dependent (outcome) variables for the mediation model, using a Bonferroni adjustment of the *p* value of 0.008.

The sleep disturbance(s) significantly associated with the predictor variable (childhood trauma total) was entered as a mediator in the model. Calculations of the proportion of the total effect mediated and standardized indirect effects were made. Follow-up analyses were then conducted including

covariates selected based on being significantly associated with either the predictor variable (childhood trauma total) or the sleep disturbance(s) significantly associated with the predictor variable (childhood trauma total).

4 Summary of the results

4.1 Study I: Sleep disturbances in schizophrenia spectrum and bipolar disorders – a transdiagnostic perspective

In a sample of 1057 clinical participants (617 with schizophrenia spectrum disorders and 440 with bipolar disorders) and 173 healthy controls we investigated the type and frequency of three different sleep disturbances in and across severe mental disorders compared to healthy controls. We also investigated the frequency of these sleep disturbances across treatment history, as well as the relationship between any sleep disturbance and clinical symptoms and functioning while adjusting for possible confounding factors.

We found a high percentage of any type of sleep disturbance across all groups: 78% of participants in the schizophrenia group, 69% of participants in the bipolar disorder group and 39% of healthy controls. Any type of sleep disturbance was significantly higher in schizophrenia spectrum compared to bipolar disorder. Insomnia was the most frequent sleep disturbance across all groups, reported in ½ of both schizophrenia and bipolar disorder, and in ⅓ of the healthy controls. Hypersomnia presented the largest difference in frequency between clinical groups (28%) and healthy controls (3%). Delayed sleep phase was reported in 11% of the schizophrenia group, in 4% of the bipolar group, but in none of the healthy controls.

When analyzing factors that might influence sleep disturbances, we found that younger age was associated with any sleep disturbance, hypersomnia and delayed sleep phase. Recent substance use was associated with lower frequency of any sleep disturbance, hypersomnia, and delayed sleep phase, whilst substance abuse/dependency was associated with a higher frequency of any sleep disturbance. Recent use of alcohol and a history of alcohol dependency was only associated a higher

insomnia frequency. Use of medication with sedative effects was associated with higher frequency of any sleep disturbance and hypersomnia. Gender and BMI were not associated with any of the sleep disturbances.

The only sleep disturbance related to differences in treatment history was hypersomnia, with a significant interaction effect between treatment history and diagnostic group related to risk of hypersomnia, also significantly influenced by medication with sedative effects. Higher frequency of hypersomnia was found in previously treated schizophrenia and in first treatment bipolar disorder.

Participants with any sleep disturbance had overall more severe symptoms and poorer functioning than participants without any sleep disturbance. Follow-up analyses further showed that participants with any sleep disturbance had significantly more negative and depressive/anxiety symptoms, as well as poorer functioning than participants without any sleep disturbance, also after adjusting for age, diagnostic group, history of drug dependency and medication with sedative effects.

4.2 Study II: Do sleep disturbances contribute to cognitive impairments in schizophrenia spectrum and bipolar disorders?

In this study we had a sample of 797 clinical participants (457 with schizophrenia spectrum disorders, and 340 with bipolar disorders) and 182 healthy controls. We explored the relationship between sleep disturbances and cognitive impairments both in and across severe mental disorders, adjusting for the influence of potential confounders. We also investigated whether the relationship to cognitive impairments varied between the different sleep disturbances. Lastly, we explored if the relationship between sleep disturbances and cognition differed between severe mental disorders and healthy controls.

The results showed that clinical participants with any sleep disturbance had overall poorer cognitive performance compared to those without any sleep disturbance. Further analyses of the eight separate cognitive domains revealed that clinical participants with any sleep disturbance performed

significantly poorer on processing speed and inhibition compared to those without any sleep disturbance. These analyses withstood adjustments for covariates including age, diagnostic group, positive and negative symptoms and medication with sedative effects.

Results from the analyses of potential differences in the relationship between any sleep disturbance and cognition between schizophrenia and bipolar disorder showed no significant overall interaction effect between any sleep disturbance and diagnostic group. Thus, the association between sleep disturbance and cognition was found to be similar across schizophrenia and bipolar disorder.

Analyses of the different sleep disturbances and cognition revealed main effects of both insomnia and hypersomnia (compared to those without) on both processing speed and inhibition, but no main effect of delayed sleep phase.

Separate analyses of the relationship between any sleep disturbance and cognition were conducted in healthy controls. These analyses revealed no significant overall or specific domain-related difference between those with and without any sleep disturbance.

4.3 Study III: Sleep disturbance mediates the link between childhood trauma and clinical outcome in severe mental disorders

In this study the sample consisted of 766 participants with severe mental disorders (418 with schizophrenia spectrum and 348 with bipolar disorders). We explored the relationship between sleep disturbances and childhood trauma and investigated whether sleep disturbance mediates the relationship between childhood trauma and severity of clinical symptoms and poorer functioning, also examining the influence of potential confounding factors.

Having a history of childhood trauma was found in half of the study sample. There was no significant difference in frequency of any sleep disturbance between those with or without childhood trauma experiences. However, a significantly higher frequency of insomnia was reported in those with childhood trauma experiences compared to those without. Around one fourth (26%) of the sample reported the experience of both childhood trauma and insomnia. For hypersomnia, the findings were

in the opposite direction; those with childhood trauma experiences reported significantly less hypersomnia compared to those without childhood trauma experiences. There were no differences in frequency of delayed sleep phase in participants with and without childhood trauma experiences. Follow-up analyses conducted to investigate possible differences between schizophrenia and bipolar disorder, showed that in both diagnostic groups only insomnia was significantly more frequent in those with childhood trauma experiences compared to those without.

Results for the analyses of the different childhood trauma subtypes and the different sleep disturbances showed that *childhood trauma total*, *physical abuse, emotional abuse and emotional neglect* were significantly higher in participants with insomnia compared to those without, but significantly lower in those with hypersomnia compared to those without. There were no significant differences in the level of sexual abuse and physical neglect between participants with or without either insomnia or hypersomnia. Analyses of participants with and without delayed sleep phase revealed no differences in the level of childhood trauma total or any of the childhood trauma subtypes. Whilst the magnitude of *childhood trauma total*, *physical abuse, emotional abuse and emotional neglect* were significantly higher in participants with insomnia compared to those without in schizophrenia, the magnitude of *emotional abuse* was the only childhood trauma subtype found to be significantly higher in participants with insomnia compared to those without in bipolar disorder.

As insomnia appears to be frequent in participants with childhood trauma experiences and is associated with three childhood trauma subtypes, insomnia was selected as the possible mediator in the mediation model.

In terms of clinical outcome, positive, depressive/anxiety symptoms and functioning were significantly associated with both childhood trauma total and insomnia total. Three separate mediation analyses were therefore conducted to investigate if insomnia total mediated the effect of childhood trauma total on positive and depressive/anxiety symptoms and functioning, respectively. Statistically significant indirect effect of childhood trauma total via insomnia total were found for all

three clinical outcome measures. These findings withstood after adjustments for covariates, including age, recent intake of drugs and history of drug dependency. Calculations of the proportion of the total effect mediated revealed that insomnia mediated 25% of the effect of childhood trauma on positive symptoms, 26% of the effect on depressive/anxiety symptoms, and 12% of the effect on functioning.

5 Discussion

5.1 Main findings

The main findings from the three studies included in this thesis are discussed in relation to previous and recent research (5.1) and relevant methodological issues (5.2). Furthermore, the clinical (5.3) and transdiagnostic implications of these findings are outlined, before raising the main strengths and limitations of the studies (5.4), as well as outlining directions for future research (5.5).

The frequency of sleep disturbances in severe mental disorders

In the first study, we found a strikingly high frequency of sleep disturbances across all groups, with 78% in the schizophrenia group, 69% in the bipolar disorder group and 39% in the healthy controls. Our findings are consistent with both previous and more recent studies in schizophrenia (Reeve et al., 2019) and bipolar disorder (Ng et al., 2015), thus adding to a growing evidence base pointing to sleep disturbances as highly prevalent in severe mental disorders.

Not surprisingly, insomnia (reported in almost half of both clinical groups and in around one third of the healthy control group) was the most frequent sleep disturbance. This is in line with established knowledge that insomnia is the most common of sleep disturbances, one of the most prevalent health disorders in the general population and the most frequent sleep disturbance reported in previous studies of schizophrenia and bipolar disorder. Interestingly, our rates of insomnia symptoms in the schizophrenia group were similar to a recent study (Reeve et al., 2019). Notably, this study employed diagnostic assessment, thus stricter criteria, which might suggest that our rates should have been even higher. However, the frequency of our findings is somewhat higher than other

studies investigating insomnia symptoms in schizophrenia samples (Hou et al., 2017), yet similar to other (Batalla-Martin et al., 2020) and also similar to studies using stricter insomnia criteria in studies of bipolar disorder samples (Harvey, Schmidt, Scarna, Semler, & Goodwin, 2005; Kanady, Soehnera, & Harvey, 2015; Ng et al., 2015).

A small percentage of participants with bipolar disorder (4%), and a slightly higher percentage of schizophrenia (11%) reported delayed sleep phase, but none in the healthy control group. Our findings are in line with the few existing similar studies (Bradley et al., 2017; Bromundt et al., 2011; Kanady et al., 2015; Steinan et al., 2016; Wulff et al., 2012), suggesting that people with delayed sleep phase constitute a small but important subgroup in severe mental disorders in need of further investigation.

The largest difference between clinical groups and healthy controls was found for hypersomnia, with 28% in clinical groups compared to 3% in the healthy control group reporting this phenomenon. Thus, our findings suggest that hypersomnia might not be a common sleep disturbance in the general population, but a frequent sleep disturbance in severe mental disorders. To our knowledge, few other studies have directly compared hypersomnia frequency to a healthy control sample (Kaplan et al., 2011). Nonetheless, our findings are in line with the few other existing studies of schizophrenia and bipolar disorders (Harvey, 2008; Kaplan et al., 2011; Reeve et al., 2019; Sharma et al., 2016; Steinan et al., 2016a).

Importantly, medication with sedative effects was found to partly, but not entirely, explain the frequency of hypersomnia. Use of such medication was common (around 50% in both schizophrenia and bipolar disorder), thus there is a great potential for reduction. Moreover, hypersomnia was the only sleep disturbance related to differences in previous treatment history, with a significant interaction effect between treatment history x diagnostic group. A higher frequency of hypersomnia was found in previously treated schizophrenia and in first treatment bipolar disorder, as illustrated in fig. 1, study I. Surprisingly, significantly higher rates of medication with sedative effects were found in

first-treatment bipolar disorder than in first-treatment schizophrenia. As sedative medications can be a factor maintaining hypersomnia, these findings suggest that these medications should be reduced and used with more caution, especially in the early phases of bipolar disorder.

As the frequency of sleep disturbances did not differ across treatment history (except for hypersomnia), our findings suggest that sleep disturbances are core disease characteristic. Because most studies of sleep in schizophrenia has been conducted in older and more chronic samples, this adds valuable information indicating that sleep disturbances are evident early in disease development, yet possibly not treated adequately in early phases.

The cross-sectional design of our study limits the interpretation of these findings. However, further support for the early presence and persistence of sleep disturbances comes from studies in bipolar disorder suggesting sleep disturbances are evident before illness onset (Harvey, Talbot, & Gershon, 2009) and persistent over a 5-year study period (Kanady et al., 2015) and from studies in early psychosis in schizophrenia (Reeve, Sheaves, & Freeman, 2018). Also, research investigating the role of sleep disturbance in individuals with an ultra-high risk for development of psychosis is emerging, pointing to the importance of addressing and treating sleep disturbances early on (Lunsford-Avery et al., 2017; F. Waite et al., 2018; Zanini et al., 2015). Still there is an urgent need for more research on sleep disturbances in the early phases of severe mental disorders, and to firmly establish their potential as an early intervention target (Bradley et al., 2018; Davies et al., 2017).

Except for insomnia, the frequency of the other two types of sleep disturbances (hypersomnia and delayed sleep phase) as well as the frequency of having any one of the three sleep disturbances, were significantly higher in schizophrenia compared to bipolar disorder. Yet, these differences are much smaller than the differences between the two clinical groups and the healthy controls. To our knowledge this is the first study to directly compare different types of sleep disturbances across severe mental disorders, and adds to a growing interest in establishing sleep disturbances as transdiagnostic features (Harvey et al., 2011; Meyer et al., 2020).

Also important in this context is the fact that different ways of measuring sleep disturbances make direct comparison across studies challenging. A more uniform way of measuring sleep disturbance would be an improvement. However, there is little doubt that several different types of sleep disturbances are highly prevalent across severe mental disorders and merit clinical attention.

The relationship between sleep disturbances, clinical outcome and cognition

In study I and II we investigated the link between sleep disturbances and different clinical outcomes (clinical symptoms and functioning in study I, and cognition in study II). One of the overall main findings of the current thesis is that participants with any sleep disturbance had significantly more severe negative and depressive/anxiety symptoms in addition to poorer functioning, compared to those without any sleep disturbance. These findings are in line with previous (Gruber et al., 2009; Reeve et al., 2015) and more recent studies (Bradley et al., 2017; Reeve et al., 2019; Slyepchenko et al., 2019) in both schizophrenia and bipolar disorder, and adds to multiple lines of evidence suggesting that sleep disturbances contribute to a range of symptoms common across severe mental disorders. Notably, a major strength of our study in this context is the large sample which allowed us to investigate whether these associations were confounded by age, diagnostic group, history of drug dependency and medication with sedative effects.

As part of establishing potential causal links between insomnia and psychotic experiences, there has been a particular focus on the link to positive psychotic symptoms over the past years (Freeman et al., 2017; Freeman et al., 2015; Reeve, Nickless, Sheaves, & Freeman, 2018; Reeve et al., 2015). This important work has led to a major leap forward for the evidence base of the role of sleep disturbances in causing and maintaining psychotic symptoms, as well as informing clinical practice, particularly regarding sleep treatment in schizophrenia. This research has been timely, as the access to sleep treatments in schizophrenia has been lagging behind the access found in bipolar disorder (Harvey et al., 2015; Kaplan & Harvey, 2013; Steinan et al., 2014)

However, our strongest finding is the association to depressive/anxiety symptoms, not confounded by diagnostic group. Although we cannot infer causality due to the cross-sectional design of the

study, we do argue that prior research has established sufficient evidence to also suggest a causal and reciprocal link between sleep disturbances (in particular insomnia) and mood symptoms such as depression (Harvey et al., 2011; Reeve, Nickless, et al., 2018). Following this line of argument, we maintain that sleep disturbances are not only a transdiagnostic phenomenon, they also have transdiagnostic effects by contributing to- and affecting both psychotic and mood symptoms. Consequently, a transdiagnostic rather than a disorder-specific treatment approach should be encouraged.

The direction of this relationship (from insomnia to psychotic and affective symptoms) is obviously a simplification of the more complex real-world clinical picture. As shortly outlined earlier, insomnia may contribute to the development of gradually increasing anxiety, depressive and psychotic symptoms. This cascade is characterized by bidirectionality, as supported by a longitudinal study modulating symptom pathways over a three-month time period in a non-affective psychotic sample (Reeve, Nickless, et al., 2018).

As sleep disturbances were significantly associated with fluctuating clinical symptoms based on clinical state, we wanted to investigate if sleep disturbances were related to cognitive impairments which are regarded more stable and trait-like. The main finding of our second paper was that sleep disturbances contributed to cognitive impairments in severe mental disorders. More specifically, we found that clinical participants having any sleep disturbance performed significantly poorer on *processing speed* and *inhibition* than those with no sleep disturbance. As prior research in this field is very limited and consists of disorder-specific studies with small sample sizes, the current study adds valuable information by allowing us to show that the associations between sleep disturbances and cognitive impairments are not confounded by age, diagnostic group, positive and negative symptoms or medication with sedative effects.

Our findings that link sleep disturbances to poorer processing speed are in line with a recent study on bipolar disorder (Bradley, Anderson, Gallagher, & McAllister-Williams, 2018). Processing speed is

found to be crucial for functional outcome, important in the prediction of real world functioning in schizophrenia (August, Kiwanuka, McMahon, & Gold, 2012), and also suggested to be the strongest correlate to occupational outcome (Lystad et al., 2016; Reddy & Kern, 2014). Sleep disturbances are common problems associated with workplace dysfunction in the general population (Ishibashi & Shimura, 2020; Rosekind et al., 2010) and this association has also been found in a bipolar disorder study (Boland & Alloy, 2013). Moreover, people with severe mental disorders often struggle with both sleep disturbances and occupational challenges (Christensen, 2007; Lystad et al., 2016). Thus, it is plausible that sleep disturbances contribute to cognitive impairments, which in turn are associated with occupational difficulties, or that sleep disturbances and cognitive impairments act jointly in creating and maintaining functional difficulties related to work in this patient group. This line of reasoning has also been suggested elsewhere (Boland & Alloy, 2013) and should be an area for future research. It is noteworthy that the inhibition measure, like many other executive tasks, also contains a speed component, indicating that the inhibition task to some extent also taps into processing speed.

Surprisingly few other studies have investigated, or found, associations between sleep disturbances and poorer executive functioning in severe mental disorders. This is despite knowledge that the prefrontal cortical networks are especially involved in controlling goal-oriented tasks and in inhibition of distractors (Banich et al., 2009; Pu et al., 2017), are shown to be impaired in schizophrenia (Ellison-Wright & Bullmore, 2009; Pu et al., 2017) and are particularly prone to alterations in circadian rhythms and sleep (Bromundt et al., 2011). The association between sleep disturbances and inhibition is, nevertheless, in accordance with a study with very limited sample size (Bromundt et al., 2011). However, this study linked poorer inhibition to circadian rhythm dysregulation, whereas we found no main effect of delayed sleep phase. A plausible explanation to our lack of findings here is twofold; the delayed sleep phase group was very small (N=64) compared to the insomnia and hypersomnia groups (N= 357 and 228 respectively) and thus may have had insufficient statistical

power. Also, a more thorough measurement of delayed sleep phase could possibly give other results as outlined in the methodology discussion (section 5.2.3).

Significant main effects of insomnia and hypersomnia were found for both processing speed and inhibition. Insomnia and hypersomnia has been linked to cognitive impairment in a few previous studies of bipolar disorder (Kanady et al., 2017; Russo et al., 2015). This illustrates the important point that both an insufficient and an excessive amount of sleep may contribute to cognitive impairment in severe mental disorders. Moreover, these findings are also in line with a large-scale study from the UK biobank (Kyle et al., 2017), in which both short (<7) and long (>9) sleep was associated with poorer performance across several cognitive domains.

Another important finding in study II is that the relationship between sleep disturbances and cognitive impairments were similar in schizophrenia and bipolar disorder, thus adding to our previous findings by suggesting that sleep disturbances have transdiagnostic associations to cognition. We did not find a relationship between sleep disturbance and cognition in the healthy control group. Given the lay man perception that poor sleep affects cognitive performance, this was somewhat surprising. However, there are several possible explanations. Firstly, the healthy control group (N=182) was considerably smaller than the clinical group (N=797) and very few healthy controls had cognitive impairment (2.7% of healthy controls performed 1.5 SD below the mean for processing speed compared to 26.5% in the clinical group). Consequently, poor statistical power may explain the lack of findings. More intriguing is that as the healthy control group was quite high functioning in terms of cognition, this may have provided them with a cognitive reserve making their cognitive performance more robust. Nonetheless, our lack of findings is in accordance with prior large-scale studies (Kyle et al., 2017) and population based studies of insomnia symptoms and cognition in the general population (Goldman-Mellor et al., 2015). In sum, the discrepancy in findings between the clinical and healthy control group may reflect a greater vulnerability in cognitive performance in those with severe mental disorders compared to healthy controls. This is yet another

interpretation emphasizing the need for more clinical attention towards sleep disturbances in severe mental disorders.

Taken together, the main findings from the first and second study underline what seems to be a slowly emerging consensus in the field; that sleep disturbances are related to a wide range of clinical correlates in severe mental disorders and therefore should be an important treatment target.

Sleep disturbance as a mediator between childhood trauma and severity of clinical symptoms.

In our third study we found that participants with a history of childhood trauma more often experienced insomnia symptoms, but not symptoms of delayed sleep phase and *less* symptoms of hypersomnia, compared to those without a history of childhood trauma. The opposite associations for insomnia and hypersomnia may be based on different biological premises; insomnia is associated with physiological, cognitive and affective hyperarousal (Levenson, Kay, & Buysse, 2015), which also is a common response after a traumatic experience. Hypersomnia, however, may be associated with processes that are diametrically opposite, such as disinhibition of sleep induced transmission and reduced activity in wake-promoting neurons (Carbonell & Leschziner, 2017), which preclude hyperarousal.

Our findings of an association between childhood trauma and insomnia are in line with longitudinal (Thordardottir et al., 2016), retrospective (Brindle et al., 2018) and retrospect cohort studies (Kajeepeta et al., 2015) in non-clinical samples, as well as in a clinical sample of depression (Hamilton, Brindle, Alloy, & Liu, 2018). As this is the first study in schizophrenia and across severe mental disorders that investigates the relationship between childhood trauma and sleep disturbances, there is clearly a need for replications. Hyperarousal associated with traumatization may reflect promptness to react to adverse events, which may be adaptive, thus predisposing the individual to more hyperarousal in response to stress/trauma in adulthood. Adults with childhood trauma experience may therefore be more prone to develop sleep disturbances in response to stressful events.

We found that physical abuse, emotional abuse and emotional neglect were statistically significantly associated with insomnia in the total sample. These results were probably driven by the schizophrenia group, as follow-up analyses found significant associations to physical abuse, emotional abuse and emotional neglect in schizophrenia, but only significant associations to emotional abuse in bipolar disorder. There are several puzzling aspects of these findings. Firstly, the differences between schizophrenia and bipolar disorder are surprising, as childhood trauma is a well-established risk factor in both schizophrenia and bipolar disorder. Yet, another study of people with euthymic bipolar disorder also found a significant association between emotional abuse and poorer sleep quality (Aubert et al., 2016), suggesting that emotional abuse might be a particularly important subtype of trauma for sleep disturbance in bipolar disorder. This finding also arguably adds to previous studies suggesting that emotional abuse is a more specific risk factor for bipolar disorder compared to other trauma subtypes (Etain et al., 2010).

Surprisingly, we did not find an association between insomnia and sexual abuse, despite several studies documenting this link in non-clinical samples (Kajeepeta et al., 2015; Lind, Aggen, Kendler, York, & Amstadter, 2016; Steine et al., 2012). In a prior study (Larsson et al., 2013) the internal consistency of the sexual abuse scale in the TOP-sample was calculated (0.91) and came out with the highest correlations of all the sub-scales. Thus, low internal consistency cannot explain lack of association between insomnia and sexual abuse. Neither can the size of the sexual abuse group or gender, as this was checked in follow-up analyses. Taken together, our data cannot explain why we did not find significant associations between insomnia and sexual abuse. However, this may add to a more general picture of the childhood trauma research field. The reasons as to why some sub-types of childhood trauma appears to stand out regarding association to clinical outcome has yet to be unraveled. The research field today is characterized by inconsistent findings, and there are suggestions that dose rather than type of childhood trauma may be of importance (Gibson et al., 2016; Rowland & Marwaha, 2018).

One of the main findings in this thesis is that insomnia partially mediates the effect of childhood trauma on severity of clinical symptoms and functioning. Because childhood trauma has been shown to affect the clinical course in severe mental disorders, with a more persistent and severe illness trajectory, understanding how trauma contributes to illness development is crucial. The identification of insomnia as a significant contributor is thus an important addition to the field and supports our theoretical model. Moreover, this finding may broaden the understanding of how insomnia following childhood trauma interacts with the stress regulatory system in exacerbation of clinical symptoms as the stress response system and sleep/circadian systems are closely intertwined (Neumann, Schmidt, Brockmann, & Oster, 2019). A sleep disturbance may increasingly change the fundamental mechanisms of the brain systems that regulate neuroendocrine function, which is similar to the dysregulation of the stress system in response to childhood trauma, further promoting development of clinical symptoms. Thus, insomnia may be a pathway mediating neurobiological consequences of childhood trauma, a notion also supported by other studies (Landgraf, McCarthy, & Welsh, 2014; Lavie, 2001; Teicher et al., 2017).

Partial (and not full) mediation was found for all the significant outcome measures, and there are obviously other pathways through which childhood trauma may affect clinical symptoms. Several theoretical models have been proposed here, including information processing biases, locus of control, stress sensitivity, negative schemas, and dissociation (Anglin, Polanco-Roman, & Lui, 2015; Bendall et al., 2013; Fisher, Appiah-Kusi, & Grant, 2012; Fisher et al., 2013; Gibson et al., 2014). Although these make intuitive sense, the empirical data to support them are sparse (van Winkel, van Nierop, Myin-Germeys, & van Os, 2013).

Taken together, the co-occurrence of childhood trauma and sleep disturbance is very high (26%) in our sample. Insomnia seems to be the most important type of sleep disturbance in relation to childhood trauma, possibly due to shared mechanism of hyperarousal. Overall, our results highlight the importance of including both childhood trauma and symptoms of insomnia when assessing

severe mental disorders, especially in schizophrenia spectrum disorders. Moreover, our study adds to existing research viewing insomnia as a contributing mechanism in the exacerbation of psychotic symptoms, thus being a potential target for early intervention.

5.2 Methodological issues

The inconsistent findings across studies presented in the previous sections may partly reflect differences in study populations and measurement. As such, findings in the current thesis raises several methodological issues concerning both the study population as well as the measures applied. In the following section we thus first discuss the external validity (representability and generalizability) before the internal validity of the findings is considered.

Study population

All clinical participants in the current three studies are recruited consecutively from naturalistic clinical settings, thus from in-patient and out-patient units across the four largest hospitals in Oslo. The Norwegian mental health care system is publicly funded and provides mental health care to the population in a given catchment area. This system ensures that the study population has a high degree of representativity for people with schizophrenia spectrum and bipolar disorders independent of economic backgrounds. However, all participants gave informed consent and had to be able to sit through several hours of clinical assessment to participate in the study. This precludes the most severely ill participants from entering the study. Also, high functioning individuals might have trouble taking time off work to participate in time-consuming assessments. As such, both the highest and poorest functioning individuals may be underrepresented. There was however considerable variation in the level of clinical symptoms (from symptom free to severe symptoms), in illness duration (from first treatment to long-term illness) and in the use of medications (from unmedicated to significant polypharmacy). Thus, the findings from this thesis are generalizable to a heterogeneous sample of individuals with schizophrenia spectrum and bipolar disorders treated in a mental healthcare setting.

Confounding factors

Unmeasured variables always pose a challenge in medical research as they may influence the results. A critical part of research is therefore to identify factors that may influence both independent and dependent variables and thus confound the association between them. By identifying potential confounders, we can adjust for them in the statistical analyses and thereby evaluate the relationship between the variables of interest more precisely.

The TOP study protocol included a wide range of information, thus making it possible to identify potential confounders influencing the frequency of sleep disturbances and the relationship between sleep disturbances and clinical outcome measures. In the planning of this thesis, effort was made to identify the most important potential confounders of these associations. We identified the following; for study I and III; age, gender, diagnostic group, recent alcohol and drug use, history of alcohol or drug dependency, use of medications with sedative effects and BMI. In study II we included the same possible confounders as in study I and III, additionally including positive and negative symptoms, depressive symptoms and manic symptoms. With an exception of age and gender, most potential confounders were measures of psychopathology, and therefore not relevant in analyses directly comparing clinical participants to healthy controls or in analyses of only the healthy controls. The relationship between these variables and variables of primary interest were tested by Chi-square statistics, t-tests or correlation analyses. Variables found to be significantly associated with both the independent (sleep disturbance) and dependent (clinical outcome measures) were entered as covariates in the multivariate analyses. In study III we tested a theoretical model, including covariates that were significantly associated with either the predictor variable (childhood trauma) or the mediator (sleep disturbance) in follow-up analyses. However, nightmares are common after traumatic experiences and may cause frequent awakening that again may lead to high insomnia scores. Therefore, nightmare is a possible confounder for the association between childhood trauma and sleep disturbance.

In sum, we have systematically controlled for the influence of several confounding factors in our studies. Yet, we cannot rule out that our results may be influenced by other, unmeasured, factors.

Statistical methods

Although an advantage of the studies included in this thesis is the thorough selection and inclusion of potential confounders, it also constrains the choice of statistical analyses and has important consequences for the results. An example of this aspect is the lack of significant associations between any sleep disturbance and positive, exited and disorganized symptoms in the ANCOVA analyses in study I (table 4). In study III, the relationship between insomnia and clinical symptoms was reanalyzed, as part of selecting variables for the mediation model (table 3). In the latter analyses we performed Spearman´s correlations and found that positive and exited symptoms were significantly correlated with insomnia total, whilst disorganized symptoms were at a trend level. The discrepancies in these findings between study I and III illustrates several important aspects. Firstly, the choice of statistical method applied may affect the result substantially. Although there were differences between these analyses other than the statistical methods applied that obviously also might affect the results (e.g. any sleep disturbance vs insomnia total score and slightly different sample size) there is reason to believe that the inclusion of potential confounding factors played a crucial part in tipping the results in the non-significant direction in study I. This being said, the second point is even more important; the evaluation and interpretation of statistical results concerns more than just p-levels above or below the significance threshold. The effect sizes (Partial Eta Squared) of positive, exited and disorganized symptoms in the ANCOVAs are very small and indicate that only 0.1% of the variance in these symptoms is explained by any sleep disturbance. Thus, when evaluating the contribution of any sleep disturbance to positive, exited and disorganized symptoms (whilst adjusting the influence of possible confounding factors), it becomes evident that the findings are very modest and hence not emphasized, despite their respective relationship to insomnia total being significant in simpler analyses in study III.

Assessments

The phenomena that constitutes the focus of the current thesis; severe mental disorders, sleep disturbances, clinical symptoms, cognition and childhood trauma are all complex. Consequently, they are difficult to define, operationalize and measure. Although the measurements applied in the current thesis are standardized, their quality, applicability and administration are crucial for the validity of findings. As described in the methods section, all the measures used in the studies comprised by this thesis are widely accepted, applied across several comparable studies, and their psychometric properties have been evaluated previously. Administration of diagnostic tools have been quality assured through training, calibration and supervision, and the inter-observer reliability of key measures has been found to be satisfactory. Yet, there are some aspects regarding the assessment of sleep disturbance, cognition and childhood trauma that needs further elaboration.

The use of single or multiple sleep items from rating scales originally designed to assess other or broader clinical concepts is frequently seen in the research field (Kallestad et al., 2012). IDS-C has been used to study sleep in mood disorders in several previous studies (Kaplan et al., 2011; Soehner et al., 2014a; Steinan et al., 2016; Steinan et al., 2016a). However, using items from a rating scale originally designed to assess depression to measure sleep disturbances may pose some challenges. Our *symptom* profiles overlap but are not fully compatible with the criteria for the corresponding sleep *disorder diagnoses.* With regards to insomnia, the assessment of daytime dysfunction and duration of symptom constellations is not precise enough for complete diagnostic comparability. The same goes for hypersomnia, which additionally also lacks assessment of excessive daytime sleepiness. However, the sleep items in the IDS-C have been validated as measures of insomnia and hypersomnia symptom severity, have moderate to high positive and negative predictive values for sleep disorder diagnoses made by clinical assessment, and correspond well with sleep diary recordings and actigraphy measures (Gonzalez, Tamminga, Tohen, & Suppes, 2013; Kaplan et al., 2011; Manber et al., 2005; Soehner, Kaplan, & Harvey, 2014b; Steinan et al., 2016; Steinan et al.,

2016a). We thus assume that the validity for the symptom profiles of insomnia and hypersomnia is adequate.

The symptom profile of delayed sleep phase captures those that spend more than an hour falling asleep, and that sleep up to 10 hours per day. This description may, however, lack a level of precision to more precisely capture the phase delay of the major sleep episode, evident by inability to fall asleep and difficulty awakening at a *desired or required time.* We may speculate that a more thorough assessment of delayed sleep phase could have resulted in a higher frequency of this particular sleep disturbance. This reflection is based on clinical observations that delayed sleep phase seems to be a frequent problem amongst especially young people with severe mental disorders. On the other hand, the frequency found does fit well with the few previous studies in this area and supports the notion that the measure has adequate construct validity. Moreover, the timing criteria used to define delayed sleep phase in this study have been shown to have large and statistically significant correlations with actigraphy measures (Boudebesse et al., 2014; Geoffroy et al., 2014; Geoffroy et al., 2015; Kaplan, Talbot, Gruber, & Harvey, 2012; Manber et al., 2005; Steinan et al., 2016). The lack of findings for delayed sleep phase might as well reflect poor statistical power.

The neuropsychological tests used in this study are standardized, widely accepted and overlap with many previous studies in this research field. The merging of the two test batteries were based on corresponding tests, thought to measure the same cognitive domain. However, as each test measures several cognitive functions simultaneously, assigning each test to a specific cognitive domain has been subject to controversy.

Another important aspect regarding measurement is related to the assessment of childhood trauma. Reports of childhood trauma are retrospectively based. Consequently, recall bias might have influenced the reports. Concerns regarding inflating reports of trauma in samples with severe mental disorders have been postulated. However, studies designed to detect this phenomenon have not validated these concerns. Rather, there are indications that childhood trauma amongst people with

psychosis is under-reported, stable over time and in line with other validating reports of abuse (Fisher et al., 2011; Simpson et al., 2018).

5.3 Implications

The findings in this thesis may have implications for how sleep disturbances are related to clinical outcome, for clinical practice and for a transdiagnostic understanding of sleep disturbances.

Clinical implications

First and foremost, the high frequency of sleep disturbances in and across severe mental disorders, together with their association to clinical symptoms, poorer functioning and cognitive impairment, underlines the need for more attention regarding assessment and treatment of sleep disturbances.

Two recent studies found clinicians to be highly aware that sleep disturbances are common in people with severe mental disorders (Barrett et al., 2020; Rehman et al., 2017). The former study was even based on data including the catchment areas from which recruitment was carried out in the studies in this thesis. Nevertheless, the studies found that sleep disturbances are rarely assessed and treated according to guidelines. Rather, information about sleep hygiene and medications such as antihistamines or hypnotics were used despite indications that these treatments have very limited effects (Kallestad et al., 2011; Rehman et al., 2017). Thus, there is an obvious gap between the need for sleep treatments in severe mental disorders and the treatment offered, despite current recommendations that sleep disturbances should be assessed and treated irrespective of other psychiatric comorbidities (American Psychiatric Association, 2013).

Recently there has been a call from user-organizations, demanding that more research findings are translated into clinically useful treatments. The idea of precision psychiatry - to choose “the right treatment for the right person at the right time” – is also taking hold. The clinical implications of this thesis are in line with these emerging ideas. National barriers to implementation of evidence based interventions for treating sleep disturbances such as Cognitive Behavioral Therapy for insomnia (CBTi) and light therapy for circadian rhythm disorders have been identified, and include lack of knowledge about sleep assessment and treatment, beliefs that sleep treatment is too resource

demanding and that patients lack motivation for treatment (Barrett et al., 2020). Yet, studies have shown that these are barriers that we may overcome with more knowledge (Freeman et al., 2015; Sheaves et al., 2017). Thus, educating health personnel, both about sleep assessment and about the ease and effectiveness of treatment, is needed. CBTi is an approved method for treating chronic insomnia consisting of several components, including sleep hygiene, stimulus control, sleep restriction, cognitive techniques and relaxation training. CBTi has shown to significantly improve not only sleep, but also affective symptoms, psychotic symptoms such as paranoia and hallucinations in addition to functioning (Freeman et al., 2017; Harvey et al., 2015; F. Waite et al., 2016; Waite, Sheaves, Isham, Reeve, & Freeman, 2019). Even more importantly, a randomized controlled trial suggests that treatment of sleep disturbance may also improve cognitive functioning (Kanady et al., 2017). The latter is especially important, given that there are few treatment options besides cognitive remediation therapy that effectively target cognitive impairments in severe mental disorders. Thus, it is time to take research into practice and improve sleep health by implementing evidence-based sleep treatment to those in need of it.

Another important clinical implication of the results presented in this thesis is the need for better tailoring of medications. Medications with sedative effects were partly, but not entirely, found to explain the high frequency of hypersomnia. As we also found that the frequency of such medication is high in severe mental disorders, an important clinical implication is to change or reduce this type of medication, which in turn may effectively reduce hypersomnia rates. This is a particularly salient point given the fact that current knowledge regarding efficient treatment options for hypersomnia is scarce.

Because the frequency of medication with sedative effects was significantly higher in first-treatment bipolar disorder compared to first-treatment schizophrenia, better medication tailoring is especially important in early phases of bipolar disorder. Furthermore, poorer performance on all cognitive domains were significantly associated with the use of medication with sedative effects, except for

attention and flexibility. Thus, reducing the use of medication with sedative effects is also important in terms of improving cognitive impairment.

Finally, when treating people with severe mental disorders with childhood trauma experiences, clinicians should be especially aware of the risk for sleep disturbances. Treating insomnia may here be important to reduce the long-term effect of childhood trauma experiences. Also, carefully building the dynamics of childhood trauma into sleep treatment by e.g. addressing and treating nightmares will be important (Sheaves et al., 2016).

Transdiagnostic implications

The majority of studies on mental illness and sleep are disorder specific, meaning that each study is focused on treating one type of sleep disturbance (typically insomnia) within a specific disorder. A major implication of this thesis is, however, that sleep disturbances are transdiagnostic phenomena with transdiagnostic associations to clinical symptoms, dysfunction and cognitive impairments and therefore should be treated accordingly. There are several advantages of viewing sleep disturbances as transdiagnostic phenomena. Importantly, it implies that one may transfer knowledge about sleep disturbances from one diagnostic category to another. If sleep disturbances and symptoms in schizophrenia spectrum disorders are influencing each other (i.e. insomnia and psychotic or depressive symptoms), it follows that interventions for sleep disturbances may improve these symptoms across disorders (Harvey et al., 2011). These arguments are at the core of a novel treatment approach that has been introduced in the period we were planning and executing the studies in this thesis, the Transdiagnostic Sleep and Circadian Intervention (TranS-C) (Harvey & Buysse, 2017). The tranS-C is based on supplementing CBTi with elements from three other evidence-based treatments; interpersonal and social rhythm therapy, chronotherapy and motivational interviewing. With a theoretical perspective on sleep that promotes sleep health, the aim is to promote optimal sleep across psychiatric disorders, in six dimensions; regularity, satisfaction with sleep, alertness (during daytime), timing, efficiency and duration. In this sense sleep health is relevant to all individuals, irrespective of the presence of a clinical sleep disorder or not. However,

although showing promising results (Dong, Dolsen, Martinez, Notsu, & Harvey, 2019; Harvey et al., 2016; Harvey et al., 2015) large-scale evaluation of the approach is needed. Nonetheless, more research into the effects of implementing TranS-C (thus promoting good sleep health) in severe mental disorders is exciting, given the knowledge that poor sleep quality is linked to several areas of compromised health common in severe mental disorders, including cardiac health (Javaheri & Redline, 2017; Ringen, 2020).

In study III we found that sub-types of childhood trauma were differentially linked to insomnia in schizophrenia and bipolar disorder, with several different subtypes of trauma associated in schizophrenia, but only emotional neglect in bipolar disorders. However, more research is needed before we can draw clear implications from these findings.

5.4 Strengths and limitations

A major strength of the present study is the large sample size, with detailed clinical assessment and thorough diagnostic evaluation by use of DSM-IV criteria of all clinical participants. High agreement regarding diagnostic evaluation and high inter-rater reliability for symptom scores strengthen the results. Moreover, the use of a broad neuropsychological assessment battery for all participants in addition to a well characterized healthy control group adds to these strengths with regards to clinical practice.

The large sample size allows for sufficient statistical control for potential confounding factors. The identification, organization and use of these potential confounding factors in analyses also represent a strength compared to other studies in the field.

Moreover, we did not exclude participants with comorbid alcohol or drug abuse. Rather, by controlling for their influence our study findings are more generalizable to clinical settings, as a relatively large proportion of this patient population has a history of comorbid alcohol or drug abuse.

In addition, the thorough classification of medications with sedative effects represents a strength compared to studies that mainly control for all types psychotropic medication or just investigate

unmedicated participants. As the sedation associated with different types of medication varies, an "all or nothing" approach may mask clinically important associations to specific medications.

An overall limitation of the present study is the cross-sectional design, which precludes us from drawing any conclusions regarding causality. Also, symptoms of sleep disturbances should ideally have been assessed by designated scales such as the Pittsburg Sleep Quality Index, the Epworth Sleepiness Scale, or the recently validated Hypersomnia Severity Index (Kaplan, Plante, Cook, & Harvey, 2019). Applying the sleep items of the IDS-C, however, represents a best practice approach. Moreover, using the IDS-C allows for the focus on the three sleep disturbances most frequently observed by clinical practitioners (Barrett et al., 2020; Rehman et al., 2017).

Moreover, we did not use specific screening tools to identify obstructive sleep apnea or restless legs syndrome when evaluation exclusion criteria. Thus, we may not have identified and excluded all individuals with obstructive sleep apnea or restless legs syndrome. All clinical participants did however go through a physical examination as well as an interview in which they were questioned about history of somatic health and comorbidity. Therefore, symptoms of obstructive sleep apnea or restless legs syndrome would most likely be identified, noted and lead to exclusion from the current study.

Moreover, we did not evaluate comorbidity between the sleep disturbances. Prior research suggests that there may be an overlap between insomnia and hypersomnia (Kaplan et al., 2011; Kaplan & Harvey, 2009) and between insomnia and delayed sleep phase (Giglio et al., 2010) in bipolar disorder, as well as a generally frequent overlap between other types of sleep disturbances in psychosis (Reeve et al., 2019).

5.5 Future research

This study covers important questions regarding the frequency and clinical correlates of sleep disturbances in severe mental disorders. However, it also uncovers a wide range of unanswered

questions that should be addressed and may thus aid in guiding future research. Findings from the third study shows that insomnia following childhood trauma significantly exacerbates clinical symptoms. The most important aspects for future research is to establish a firmer evidence base investigating sleep disturbance as a trigger of mood- and psychotic illness episodes in both at-risk individuals and in early phases of disease development, and to identify the potential for sleep disturbance as an early intervention target in severe mental disorders (Bradley et al., 2018).

The recent results from randomized controlled trials have shown promising add-on effects of treating insomnia with CBTi in severe mental disorders (Freeman et al., 2017; Freeman et al., 2015; Harvey et al., 2015; Reeve, Emsley, Sheaves, & Freeman, 2018). Investigating if such effects also may include improved cognitive performance is highly relevant, as indicated by a recent study (Kanady et al., 2017) and in the light of few existing treatment options for cognitive impairments. CBTi is gradually being established as a feasible treatment option in both schizophrenia and bipolar disorders. Chronotherapy refers to several treatment types acting on the central biological clock, including light therapy which shows promising effects for treating depression in bipolar disorder (Gottlieb et al., 2019; Sikkens, Riemersma-Van der Lek, Meesters, Schoevers, & Haarman, 2019). Yet there is a pressing need for more research into treatment for hypersomnia and delayed sleep phase in severe mental disorders.

6 Conclusion

Since the planning of this study in the beginning of 2015, research into sleep disturbances in severe mental disorders has accelerated, with a particular focus on insomnia. The current thesis has made significant contributions to this development, as well as broadening the focus by showing that the three different types of sleep disturbances investigated in this study (insomnia, hypersomnia and delayed sleep phase) are frequent in and across severe mental disorders compared to healthy controls. Moreover, the studies comprised in this thesis found that having any one of these three sleep disturbances is related to higher severity of clinical symptoms, poorer functioning and more severe cognitive impairments in severe mental disorders. These findings add to and extend previous

research emphasizing the negative effects of sleep disturbances in severe mental disorders and indicates that these associations are not based on confounding factors. Furthermore, the studies comprised in this thesis jointly point to sleep disturbance as a transdiagnostic phenomenon, both in terms of frequency and association to clinical outcome.

Insomnia is of particular importance as the most frequent sleep disturbance, and the only sleep disturbance that is significantly more frequent in those with childhood trauma experiences compared to those without. An important finding is the frequent co-occurrence of childhood trauma and insomnia in severe mental disorders, and indications that the negative effects of trauma on clinical symptoms and functioning may be partly mediated through insomnia.

Another important aspect of the current thesis is the light shed on the high hypersomnia rates found in severe mental disorders. This is a poorly studied sleep disturbance in this patient group, and important contributions are made by showing that the frequency of hypersomnia is significantly associated with the use of medication with sedative effects. This finding warrants more clinical attention, such as better drug tailoring in order to reduce hypersomnia rates. An extra focus is required in early phases of bipolar disorder, as the rates of medication with sedative effects were found surprisingly high in this patient group.

Moreover, this study also indicates that delayed sleep phase is present in a small subgroup of severe mental disorders, and that more research on delayed sleep phase with larger samples and more thorough assessment is needed.

In sum, the findings from the current thesis should contribute to heighten awareness about the frequency and negative impact of sleep disturbance across severe mental disorders, and thus also the importance of implementing evidence-based sleep treatment for this patient group. Now people with severe mental disorders depend on clinicians to take action, put sleep disturbance on the clinical agenda and practice what has been preached in this thesis.

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8 Appendices

8.1 Appendix 1

DSM-IV-TR Schizophrenia and Other Psychotic Disorders
- Schizophrenia
- Schizophreniform disorder
- Schizoaffective disorder
- Delusional disorder
- Brief psychotic disorder
- Shared psychotic disorder
- Psychotic disorder due to general medical condition
- Substance-induced psychotic disorder
- Psychotic disorder not otherwise specified (NOS)
A. Criteria – diagnosis of schizophrenia
- Delusions
- Hallucinations
- Disorganized speech (e.g., frequent derailment or incoherence)
- Grossly disorganized or catatonic behaviors
- Negative symptoms, i.e. affective flattening, alogia, avolition, anhedonia

8.2 Appendix 2

DSM-IV-TR Bipolar Disorders
- Bipolar I disorder
- Bipolar II disorder
- Cyclothymic disorder
- Bipolar disorder not otherwise specified (NOS)
A. Criteria – Major Depressive Episode
- Depressed mood most of the day, nearly every day
- Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day
- Significant weight loss or gain
- ***Insomnia or hypersomnia every day***
- Psychomotor agitation or retardation nearly every day
- Fatigue or loss of energy nearly every day
- Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day
- Diminished ability to think or concentrate, or indecisiveness, nearly every day
- Recurrent thoughts of death, recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide
A. Criteria – Manic Episode
- Inflated self-esteem or grandiosity
- ***Decreased need for sleep***
- More talkative than usual or pressure to keep talking
- Flight of ideas or subjective experience that thoughts are racing
- Distractibility
- Increase in goal directed activity or psychomotor agitation
- Excessive involvement in pleasurable activities that have a high potential for painful consequences

8.3 Appendix 3

	Schizophrenia spectrum disorders				Bipolar disorders			Healthy Controls	Recruitment period
	Schizophrenia	Schizoaffective disorder	Schizophreniform disorder	Other psychotic disorders	Bipolar Disorder I	Bipolar disorder II	Bipolar NOS		
Study I	352	90	43	132	283	130	27	173	2003 - January 2018
Study II	260	60	37	100	216	103	21	182	2003 - December 2018
Study III	223	30	30	104	223	110	25	-	2003 - May 2019

8.4 Appendix 4

Name of drug	Anxiolytic	Sedative/ Hypnotic	Anti-histamine	Anticonvulsant /antiepileptic	Anti-depressant	Anti-psychotic
Diazepam (Valium, Vival, Stesolid)	x	x		x		
Oxazepam (Sobril)	x	x				
Nitrazepam (Apodorm, Mogadon)		x		x		
Zolpidem (Stilnoct)		x				
Zoplicone (Imovane)		x				
Midazolam		x		x		
Chlomethiazole (Heminevrin)		x		x		
Alimemazine (Vallergan)		x	x			
Melatonin (Circadin)		x				
Trimipramine (Surmontil)					x	
Mitrazapine (Remeron)					x	
(Mianserine) Tolvon					x	
Chlorprotixene (Truxal)						x
Levopromazine (Nozinan)						x
Olanzapine (Zyprexa)						x
Quetiapine (Seroquel)						x
Clozapine (Leponex)						x

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Sleep disturbances in schizophrenia spectrum and bipolar disorders – a transdiagnostic perspective

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ABSTRACT

Background: Sleep disturbances are prevalent in severe mental disorders but their type and frequency across diagnostic categories has not been investigated in large scale studies.
Methods: Participants with Schizophrenia spectrum disorders (SCZ, (N = 617)), Bipolar disorders (BD, (N = 440)), and Healthy Controls (HC, (N = 173)) were included in the study. Sleep disturbances (insomnia, hypersomnia and delayed sleep phase) were identified based on items from the Inventory of Depressive Symptoms – Clinician rated scale. Clinical symptoms were assessed with the Positive and Negative Syndrome scale and level of functioning with the Global assessment of Functioning scale.
Results: The rate of any sleep disturbance was 78% in SZ, 69% in BD and 39% in HC. Insomnia was the most frequently reported sleep disturbance across all groups. Both diagnostic groups reported significantly more of any sleep disturbances than HC ($P < 0.001$). Having a sleep disturbance was associated with more severe negative and depressive symptoms and with lower functioning across diagnostic groups ($P < 0.001$, $\eta^2 = 0.0071$). Hypersomnia was the only sleep disturbance associated with previous treatment history.
Conclusion: Sleep disturbances, including insomnia, hypersomnia and delayed sleep phase, are frequent in SCZ and BD, and associated with more severe clinical symptomatology across diagnostic groups. This suggests that sleep disturbance is a clinically relevant transdiagnostic phenomenon.

1. Introduction

Sleep disturbances are frequent across a wide range of mental disorders [1]. Not only are sleep disturbances a distressing symptom in itself, but has been suggested as a putative mechanism for causing and maintaining symptoms and functional difficulties [2]. However, the type and frequency of sleep disturbances have not been investigated across the main diagnostic categories of severe mental disorders, Schizophrenia Spectrum Disorders (SCZ) and Bipolar Disorders (BD). Thus, there is a need for large scale studies investigating whether sleep disturbance is a transdiagnostic phenomenon in psychotic disorders.

There are several types of sleep disturbances, but descriptive studies mainly focus on insomnia. Insomnia is the most common sleep disturbance and one of the most prevalent health disorder in the general population, with prevalence rates varying from 4%–48% [3]. Different types of insomnia, including problems falling asleep and staying asleep, are also the most commonly reported sleep disturbances in severe mental disorders [4,5]. Far less attention has been given to hypersomnia; a sleep disturbance characterized by prolonged nocturnal sleep, excessive daytime sleepiness and unrefreshing naps [6]. Systematic prevalence studies are lacking, but hypersomnia is estimated to be present in 0.02–0.07% of the general population [7], in contrast to around 30% in studies of SCZ and BD populations [8,9].

Hypersomnia may be related to abnormalities in the circadian organization of the sleep-wake cycle. Delayed sleep phase (DSP) is, however, the most commonly occurring circadian misalignment. DSP consists of a phase delay in relation the desired time for sleep, accompanied by trouble falling asleep or waking at the time of desire, whilst sleep itself is reported to be normal [10]. The prevalence of DSP in the general population is not well known; however one population-based study found a prevalence of 0.17% [11]. The comorbidity between DSP and severe mental disorders is high, especially for mood disorders, and of considerable theoretical interest since circadian dysregulation has been proposed as one of the mechanism underlying BD [12,13]. They are also the most recognized early symptoms of mania [14]. As sleep

Abbreviations: DSP, delayed sleep phase; SCH, Schizophrenia; BD, Bipolar Disorder; HC, Healthy Controls; FT, First-Treatment; PT, Previously Treated.

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disturbances also often appear in the prodromal phase of psychotic disorders, they are suggested to be involved in the pathophysiology of psychosis [15] and in exacerbation of psychotic symptoms [16]. Sleep disturbances in severe mental disorders have also been linked to lower quality of life, suicide attempts and poorer clinical and cognitive functioning, as well as higher relapse rates of mood episodes [4,17–21]. Despite the potentially wide-ranging negative effects of sleep disturbances in severe mental disorders, the use of formal sleep assessments and evidence-based treatment is rare [22,23]. Increased awareness of the frequency and magnitude of sleep disturbances among people with severe mental disorders might aid professionals to recognize the importance of sleep disturbance as a specific treatment target.

Many factors may influence sleep quality. Insomnia is more common in women and increases with age [3], whilst hypersomnia and DSP are more prevalent in the young [6,10]. Comorbid alcohol and drug abuse may influence both sleep quality and symptoms [4]. Antipsychotics, anxiolytics, hypnotics or sedatives also have effects that may both improve sleep quality, influence sleep architecture or cause disruption of the sleep wake cycle [24]. These effects are more likely to occur after long-term use; emphasizing the importance of studying sleep at different stages of treatment [17]. Weight gain, a frequent and problematic side effect of many medications, is also associated with sleep disturbances [25] and may increase the susceptibility for additional sleep disturbances such as obstructive sleep apnea. We lack studies of how these factors can mediate or moderate sleep disturbances in severe mental disorders due to small sample sizes in previous studies.

1.1. Aims of the study

We thus aim to determine the type and frequency of self-reported sleep disturbances in patients with schizophrenia spectrum disorders and bipolar disorders compared to healthy controls, and between previously treated and first-treatment patient groups. We also aim to explore the relationship between sleep disturbances, clinical symptoms and functioning, with adjustment for the possible influence of age, gender, recent alcohol and drug use, history of alcohol or drug dependency, use of medications with sedative effects and weight.

2. Materials and methods

2.1. Participants

One thousand and fifty-seven participants with severe mental disorders (SCZ n = 617, BD n = 440) and 173 healthy controls (HC) were recruited from the larger 'Thematically Organized Psychosis (TOP) Research Study' at the Norwegian Centre for Mental Disorders Research (NORMENT) in Oslo, Norway. To be included in the current study all participants had to have data on sleep disturbances. Patients were recruited from 2003 to 2018 and healthy controls from 2017 to 2018. In the SCZ group, 352 had a diagnosis of schizophrenia, 90 were diagnosed with schizoaffective disorder, 43 with schizophreniform and 132 had other psychotic disorders. In the BD group, 283 had bipolar I disorder, 130 had bipolar II disorder and 27 had bipolar NOS. Participants with less than one year of adequate treatment at study baseline were classified as first-treatment participants, 278 with SCZ and 153 with BD. Adequate treatment is part of the inclusion criteria and is defined as a) mood stabilizers or antipsychotic medication in adequate dosage for >12 weeks or b) admission to a psychiatric ward designed for treatment of psychotic disorders. The remaining participants (339 with SCZ and 287 with BD) were classified as previously treated. Exclusion criteria for all participants included history of hospitalized head injury, neurological disorder, obstructive sleep apnea, restless legs syndrome, IQ below 70 and age outside the range of 18–60 years. Exclusion criteria were assessed as part of a thorough physical examination by a physician including history of somatic health, height and weight (BMI), which both clinical participants and healthy controls underwent. Healthy controls were drawn from the population register in Oslo and Akershus. They were an screened with interview about severe mental illness symptoms and the Primary Care Evaluation of Mental Disorders [26] and excluded if they or their first degree relatives had a lifetime history of severe psychiatric disorders (DSM-IV axis 1 disorder), or if they met criteria for alcohol or drug abuse/dependency during the last 6 months. SCZ and BD participants were not excluded because of alcohol or drug abuse/dependency to ensure a representative clinical sample. All participants gave written informed consent. The study was approved by 'The Regional Committee for Research Ethics' and 'The Norwegian Data Inspectorate'.

2.2. Demographics and clinical characteristics

All clinical assessment was completed by trained medical doctors, psychiatrists or clinical psychologists. Clinical participants were diagnosed with the Structural Clinical Interview for DSM-IV (SCID-I) [27]. Symptoms were measured with the Positive and Negative Syndrome Scale (PANSS) using Wallwork's five factor model [28]. High score on the PANSS is indicative of more severe current symptoms. The current level of depressive symptoms was measured by the PANSS depressive factor (Wallwork) including the following items; G2 Anxiety, G3 Guilt Feelings, and G6 Depression Posturing. Global functioning was measured with Global Assessment of Functioning Scale-Split version – function score (GAF-F) [29]. Based on clinical interview and medical charts, information about current alcohol or drug use (the number of units of alcohol and use of illegal drugs past two weeks) and current use of psychotropic medication (type of medication(s) and dose of antipsychotics, antidepressants, antiepileptics and/or lithium) and was obtained. We defined the following as "medication with potential sedative effects", based on their mechanisms of action and reports of having sedation as a main effect or as a major side-effect: 1) All substances marked as sedatives. 2) Antipsychotics, antidepressants and mood stabilizers where sedation is marked as a major side effect in their description of action (based on information given in The Norwegian Pharmaceutical Product Compendium) [30]. 3) By checking their known moods of action on neurotransmitters involved in promoting sleepiness (histaminergic/muscarinergic) such as e.g. quetiapine and olanzapine. Lifetime history of alcohol or drug abuse or dependency was based on DSM-IV substance related diagnoses.

2.3. Sleep disturbances

Sleep disturbances in both clinical groups and HC were obtained as part of the clinical assessment using the Inventory of Depressive Symptoms – Clinician rated scale (IDS-C) [31]. IDS-C comprises four sleep items; difficulty falling asleep (item 1), difficulty maintaining sleep (item 2), early awakening (item 3) and hypersomnia (item 4). All items are scored from 0 to 3 with higher scores indicating higher level of disturbance. IDS-C has been used in several studies to identify different subtypes of sleep disturbances; the items have been validated as measures of insomnia and hypersomnia severity and have shown predictive value in clinical diagnoses of sleep disorders [19,32–35]. Based on the sleep items from IDS-C we use the following definitions of sleep disturbances [8,13], pinpointing that our definitions of the different sleep disturbances are to be regarded as symptoms of sleep disturbances and not diagnostic categories.

1. **Insomnia** was considered present if participants had a score of: Sleep Onset Insomnia ≥2 (more than half of the time it takes minimum 30 min to fall asleep), Mid-Nocturnal Insomnia = 3 (more than half the time, one wakes up more than once a night and stays awake for 20 min or more), or Early Morning Insomnia ≥1 (more than half the time, one wakes up >30 before one needs to get up)

as well as scoring zero on the Hypersomnia item (0 = sleeps no >7–8 h a night, without naps).
2. **Hypersomnia** was considered present if participants had a score of ≥1 on the Hypersomnia item (sleeping up to 10 h per day) with no evidence of Insomnia.
3. **Delayed sleep phase** (**DSP**): DSP was operationalized as Sleep Onset Insomnia ≥3(more than half the time, it takes >60 min to fall asleep), and Hypersomnia ≥1.
4. **Any sleep disturbance**: Was considered present if participants scored over cut-off on any of the sleep disturbances described.

2.4. Statistical analyses

We used the statistical package for the Social Sciences (SPSS Inc., Chicago, IL version 24). Chi-square statistics and logistic regression analyses were used to examine the influence of diagnostic categories on the likelihood of specific sleep disturbances (any sleep disturbance, insomnia, hypersomnia or DSP). The risk for sleep disturbances after adjustments for the two diagnostic groups (SCZ and BD) are reported using odds ratios (OR) with 95% confidence intervals (CI). As none of the HCs reported DSP, only diagnostic groups were analyzed for DSP. We explored the possible association between sleep disturbances and demographic/clinical factors (age, gender, medication with sedative effects, recent intake of alcohol and drugs, a history of alcohol or drug dependency, and BMI) that could influence sleep patterns using *t*-tests or chi-square statistics. Most of the demographic and clinical variables were illness specific and therefore not entered as covariates in analyses containing HC. However, their impact on the risk of sleep disturbances in SCZ and BD was investigated in follow-up analyses using multivariate binary logistic regression. Binary logistic regression analyses were also used to examine the influence of treatment history (first-treatment vs. previously treated) and diagnosis on the likelihood of sleep disturbances.

To avoid the risk of type I errors when exploring the relationship between sleep disturbances, clinical symptoms and functioning, the effect of having any sleep disturbance on clinical symptoms and functioning was first investigated by multivariate analysis of variance (MANOVA). Based on a significant MANOVA, the analysis was continued with a series of ANCOVAs with clinical symptoms (Wallwork's five-factor model) and functioning (GAF-F) as dependent variables and "any sleep disturbance" as the main factor. Diagnostic group and demographic and clinical characteristics that were associated with both the sleep disturbance and the dependents in bivariate associations were entered as co-variates. Effect size was calculated by η^2. Unless otherwise stated, a significance level of $P < 0.05$ (two-tailed tests) was employed.

3. Results

3.1. Demographics and clinical characteristics

As shown in Table 1, the SCZ group was significantly younger, included more males and had lower level of education compared to BD and to HC. The SCZ group also reported more drug dependency, used more antipsychotic medication and less mood stabilizers than BD. There was, however, no difference in BMI, alcohol use or use of medication with sedative effects.

3.2. Sleep disturbances in diagnostic groups compared to healthy controls

As illustrated in Table 2, 78% of participants in the SCZ group, 69% in the BD group and 39% of the HC group reported at least one type of sleep disturbance. The frequency of reporting any sleep disturbance was significantly higher in SCZ than BD. For all three groups, the most frequently reported sleep disturbance was one or more types of insomnia. This was experienced in around 1/2 of participants in both diagnostic groups and 1/3 of the HC group, with no difference in the overall insomnia rate between SCZ and BD. Both sleep onset insomnia and mid nocturnal insomnia was also significantly more frequent in the two clinical groups compared to HC. Early morning insomnia was nominally, but not statistically significantly, more frequent in the HC group compared to clinical groups. The most prominent difference between clinical groups and HC was found for hypersomnia (in 3% of HC and

Table 1
Demographic and clinical characteristics of the sample.

	SCZ Spectrum N = 617	BD N = 440	HC N = 173	ANOVA/ Chi-square		
				F/x^2	P	Post hoc
Demographics						
Age, mean ± SD[a]	30.7 ± 9.8	34.0 ± 12.0	34.8 ± 10.1	F = 15.25	<0.001	HC, BD > SCZ | SCZ < HC,BD
Female sex, n (%)	264 (42.8)	262 (59.5)	49 (45.0)	χ^2 = 29.77	<0.001	HC, SCZ < BD
Education in years, mean ± SD[b]	12.3 ± 2.6	13.5 ± 2.4	14.9 ± 2.2	F = 61.39	<0.001	HC > SCZ,BD | SCZ < HC,BD
Clinical variables						
Alcohol units last two weeks, mean ± SD[c]	7.0 ± 21.1	9.7 ± 20.1	–	F = 4.35	0.04	
Drug use last two weeks, yes (%)	56 (9.0)	45 (11.2)	–	χ^2 = 0.39	0.53	
Lifetime alcohol dependency, Yes (%)	86 (13.8)	61 (13.8)	–	χ^2 = <0.01	0.97	
Lifetime drug dependency, Yes (%)						
First-treatment, n (%)	124 (20.1)	57 (13.2)	–	χ^2 = 9.23	0.002	
	278 (45.0)	153 (34.8)	–	χ^2 = 11.25	<0.001	
Medication & somatic variables						
BMI, mean ± SD[d]	26.2 ± 5.2	25.8 ± 4.6	–	F = 1.80	0.18	
Antipsychotics (%)	524 (84.9)	226 (51.5)	–	χ^2 = 140.39	<0.001	
≥2 agents (%)	130 (21.3)	27 (6.1)	–	χ^2 = 45.29	<0.001	
Mood stabilizers (%)	87 (14.0)	237 (53.7)	–	χ^2 = 191.04	<0.001	
≥2 Mood stabilizers (%)	10 (1.6)	26 (5.9)	–	χ^2 = 14.36	<0.001	
Antidepressants (%)	192 (30.9)	149 (33.8)	–	χ^2 = 0.89	0.35	
Anxiolytics/hypnotics (%)	69 (11.3)	39 (8.8)	–	χ^2 = 1.51	0.22	
Medication with sedative effects (%)	343 (55.4)	196 (44.6)	–	χ^2 = 12.54	<0.001	

Mood stabilizer refers to lithium or antiepileptics. SCZ spectrum = schizophrenia spectrum; BD spectrum = bipolar disorder s; HC = healthy controls. BMI=Body Mass Index. [a] 99.7% (n = 1054) of the clinical participants had data on age. [b] 90.0% (n = 951) of the clinical participants completed data on years of education. [c] 98.4 (n = 1040) of the clinical participants had data on alcohol use during the last two weeks. [d] 93.9% (n = 992) of the clinical participants had data on BMI. 63.0% (n = 109) of the HC group had data on age, sex, BMI, and years of education.

Table 2
Frequency and characteristics of sleep disturbances across groups.

Sleep variables	Whole sample (N = 1230)	HC (n = 173) vs. diagnostic groups (N = 1057)				BD (N = 440) vs. SCZ (N = 617)			
		HC	Patients	x^2	P	BD	SCZ	x^2	P
Any sleep disturbance N (%)	857 (69.4)	68 (39.3)	785 (74.4)	85.49	<0.001	302 (68.6)	483 (78.3)	12.50	<0.001
Insomnia (any type) N (%)	556 (45.1)	63 (36.4)	491 (46.5)	6.01	<0.05	200 (45.5)	291 (47.1)	0.30	0.58
–Sleep onset insomnia, N (%)	378 (30.6)	19 (11.0)	358 (33.9)	36.6	<0.001	134 (30.4)	224 (36.3)	3.92	0.05
–Mid nocturnal insomnia, N (%)	142 (11.5)	9 (5.2)	132 (12.5)	7.78	<0.01	59 (13.4)	73 (11.8)	0.59	0.44
–Early morning insomnia, N (%)	294 (23.8)	49 (28.3)	245 (23.2)	2.16	0.141	117 (26.6)	128 (20.7)	4.93	<0.05
Hypersomnia, N (%)	299 (24.2)	5 (2.9)	294 (27.8)	50.19	<0.001	102 (23.2)	192 (31.1)	8.06	<0.01
Delayed sleep phase, N (%)	83 (6.7)	0 (0)	83 (7.9)	14.57	<0.001	17 (3.9)	66 (10.6)	16.57	<0.001

BD = bipolar disorder; SCZ = Schizophrenia; HC = Healthy controls.

28% of clinical groups). Hypersomnia was also significantly more frequent in SCZ compared to BD. No HC reported DSP, but DSP was almost 3 times more common in SCZ compared to BD.

Any type of sleep disturbance, hypersomnia and DSP were associated with younger age. Recent drug use was associated with less hypersomnia, DSP and lower frequency of any sleep disturbance whilst participants with a history of drug dependency had higher frequency of any sleep disturbance. Recent use of alcohol and a history of alcohol dependency was only associated with more insomnia. Use of medication with sedative effects was associated with higher frequency of any sleep disturbance and hypersomnia. There were no associations between gender or BMI and any sleep disturbances. Follow-up analyses showed that the differences between SCZ and BD for any sleep disturbance, hypersomnia and DSP remained significant also when controlling for age, drug use and medication with sedative effects.

3.3. Sleep disturbances and treatment history

Hypersomnia was the only sleep disturbance related to differences in treatment history (Table 3). There was also a significant interaction effect between treatment history and diagnostic group on the risk of hypersomnia, with higher frequency in previously treated SCZ and in first-treatment BD (Fig. 1). Previously treated SCZ participants also used significantly higher doses of antipsychotic medication and mood stabilizers (antipsychotics: 91.2% vs 77.2%, mood stabilizers: 19.7% vs 7.2%) and had higher BMI (BMI: 26.9 vs 25.3) than first-treatment SCZ participants. The previously treated BD group, however, used significantly less antipsychotics and medication with sedative effects compared to first-treatment participants (45.7% vs 62.5%, 38.8 vs 55.3%). Follow-up analyses showed that the interaction between treatment history and diagnostic group on hypersomnia was significantly influenced by medication with sedative effects. However, the main effect of diagnosis x treatment history remained significant after controlling for medication with sedative effects, in addition to age and recent drug use.

3.4. Relationship between sleep disturbance and clinical symptoms/functioning

Patients reporting any sleep disturbance had overall more symptoms and poorer functioning than patients without sleep disturbance (MANOVA: F = 13.18, p˜0.001, $\eta^2 = 0.0071$). Follow-up univariate ANCOVAs showed that clinical participants with any sleep disturbance had significantly poorer GAF scores and poorer PANSS negative and depressive factor scores than participants without any sleep disturbance. Of the clinical and demographic factors previously found to be associated with sleep disturbances, younger age was associated with all PANSS symptoms meaures except depression. Having a history of drug dependency was associated with more positive, disorganized and excited symptoms as well as functioning, whilst a history of alcohol dependency was associated with more excited symptoms. The use of medication with sedative effects was associated with more negative symptoms and with poorer functioning.

To rule out potential confounding or mediating effects, diagnostic group, age, medication with sedative effects and history of drug dependency were entered as covariates in the analyses of the association between sleep disturbances and clinical symptoms/functioning across diagnostic groups (Table 4). More severe symptomatology and poorer functioning in patients with any sleep disturbance were still observed after adjusting for covariates.

4. Discussion

To the best of our knowledge, this is one of the largest studies of sleep disturbances across severe mental disorders. We found that the risk of having any sleep disturbance in SCZ or BD was almost twice as high as that reported in HC. This underlines the need to focus on sleep disturbances in severe mental disorders. The most frequently reported sleep disturbance across all groups was insomnia, whilst hypersomnia and DSP were considerably more frequent in both clinical groups

Table 3
Sleep disturbances across treatment history.

	Any sleep disturbance			Insomnia			Hypersomnia			Delayed sleep phase		
	OD	CI	P	OD	CI	P	OD	CI	P-value	OD	CI	P
FT vs PT	0.91	0.60–1.39	0.67	1.36	0.93–2.07	0.12	0.60	0.38–0.94	<0.05	1.29	0.45–3.74	0.64
BD vs. SCZ	1.33	0.85–2.06	0.21	1.36	0.92–2.02	0.13	0.89	0.57–1.37	0.59	3.58	1.36–9.43	<0.05
FT/PT* BD/SCZ	1.50	0.82–2.61	0.19	0.66	0.40–1.11	0.12	2.40	1.36–4.24	<0.01	0.76	0.23–2.48	0.65

FT = First-treatment; PT = previously treated. BD = bipolar disorder, SCZ = schizophrenia disorder; OD = Odds ratio; CI = confidence interval. Table three includes patients only.

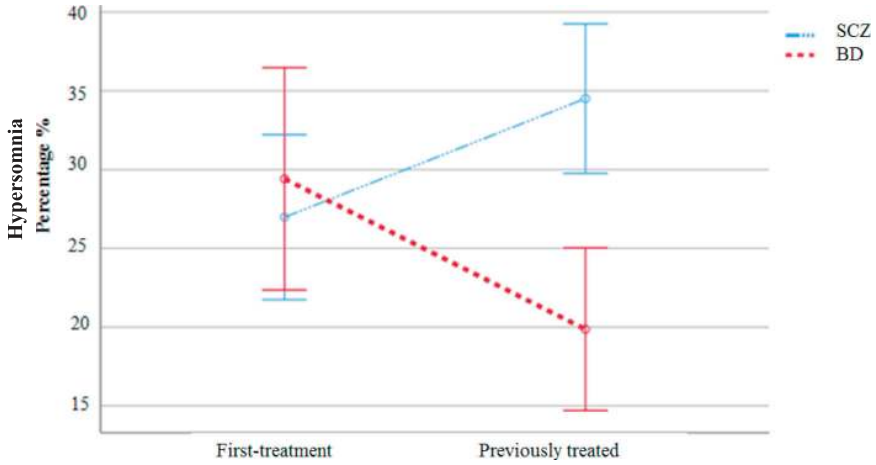

Fig. 1. Interaction between diagnostic groups and treatment history on hypersomnia.

compared to HC. Hypersomnia and DSP were also more common in SCZ compared to BD.

Sleep disturbances were not found to differ in frequency across treatment history, with the exception of hypersomnia, which was more frequent in those with previously treated SCZ and in first-treatment BD. Our study further shows that having a sleep disturbance is associated with more negative and depressive symptoms, and with poorer functioning across SCZ and BD. Age, drug dependency and medication with sedative effects were related to having any sleep disturbance and hypersomnia. Medication with sedative effects influenced the interaction between diagnosis and treatment history in the frequency of hypersomnia, but did not fully mediate the association.

Our findings shows that sleep disturbances are a potential core feature of severe mental illness and supports that sleep disturbances are a transdiagnostic phenomenon. A transdiagnostic perspective implies transfer of knowledge across diagnostic categories and may have important clinical implications, such as tailoring treatment specifically targeting sleep disturbances [36].

The high prevalence of insomnia is of particular importance. Insomnia that is initially occurring secondary to another condition often becomes an independent problem, sharing a reciprocal relationship with the primary disorder [37]. A recent review also suggests that insomnia is associated with increased risk of cardiovascular disease, diabetes, the metabolic syndrome, significant morbidity and increased risk of premature mortality [38]. Although no association to BMI was found in the current study, comorbid insomnia may have additional downstream adverse health consequences in these already vulnerable and exposed diagnostic groups. It is also of interest that half of the HC group reported insomnia, reflecting how frequent the subjective experience of insomnia is in the general population today. Interestingly, several studies indicate that the prevalence rates of insomnia in the general population seem to be rising [39].

Only a handful of previous studies have investigated hypersomnia in BD and SCZ; however, none of them have directly compared the two diagnostic groups to a HC group, or investigated the role of age, medication with sedative effects or drug use in this context. Given the relatively high prevalence of hypersomnia in both SCZ (30.9%) and BD (23.1%), contrasted to the low prevalence in HC (2.9%), it is important to increase clinical awareness of this phenomenon. The finding that hypersomnia is associated with younger age fits well with prevalence studies of hypersomnia in the general population. The hypersomnia is partly, but not entirely, explained by the use of medication with sedative effects. Since around half of the participants in both clinical groups were using this type of medication, a change to other types could be a clinically relevant and potentially effective way of reducing hypersomnia rates.

We only found a small subgroup experiencing DSP in SCZ (10%) and BD (4%), with no occurrence in the HC group. Although the interest in circadian rhythms in patients with SCZ is increasing, there is scarce information concerning the prevalence of DSP. Our study therefore adds valuable descriptive information to the field. The subgroups reporting DSP were younger. A recent review of Alloy, Ng [40] indicates that irregular social rhythms contribute to circadian dysregulation. Individuals with BD are found to exhibit greater social rhythm irregularity compared to HC [41], and may also be hypersensitive to life event-induced social rhythm disruption [42]. These findings, coupled with the frequent shift toward an evening circadian preference often seen in adolescents due to biological changes

Table 4
Sleep disturbances and clinical features across diagnostic groups.

Clinical variables	Any sleep disturbance	No sleep disturbance	ANCOVA		
	Mean ± SD	Mean ± SD	F	P	Partial η^2
PANSS positive	8.5 ± 4.3	7.2 ± 3.6	1.23	0.27	0.001
PANSS negative	11.7 ± 5.5	9.6 ± 4.7	19.33	<0.001	0.02
PANSS disorganized	6.5 ± 2.6	6.1 ± 2.3	0.13	0.72	<0.001
PANSS excited	5.6 ± 2.1	5.4 ± 2.0	0.19	0.66	<0.001
PANSS depressed	8.3 ± 3.2	6.9 ± 2.9	40.16	<0.001	0.037
GAF functioning	47.4 ± 12.7	53.3 ± 14.5	6.36	<0.01	0.006

GAF = Global Assessment of Functioning scale; PANSS = Positive and Negative Syndrome Scale. PANSS was organized after Wallwork's five-factor model (Wallwork et al., 2012). Demographic and clinical characteristics that were associated with both the sleep disturbance and the dependent variable were entered as covariates in the model. *PANSS Negative* was corrected for: age, diagnosis and use of medication with sedative effects (Yes/no). *PANSS Positive*, *PANSS Disorganized and PANSS excited* were adjusted for age, diagnosis and drug dependency. *PANSS Depressed* was corrected for diagnosis only. GAF-F was corrected for: diagnosis, use of medication with sedative effects (Yes/no), and drug dependency. Table four includes patients only.

during puberty [43], underlines the need of more awareness of potential circadian rhythm dysregulation in young people with severe mental disorders.

To this date the majority of research on sleep disturbances in severe mental disorders has been done in older patients with multiple illness episodes. The frequency of sleep disturbances in our study sample does not seem to differ substantially in first-treatment versus previously treated participants, suggesting that sleep disturbances are key disease characteristic independent of treatment history. This finding implies that sleep disturbances are evident early in disease development, and may also indicate that they are not treated adequately at this point. Our finding that medication with sedative effects was significantly higher in first-treatment BD compared to first-treatment SCZ was unexpected. This finding is of clinical importance, suggesting that we need better tailoring of drug treatment in the early phases of bipolar disorder.

One of the main findings of the current study was that clinical participants with severe mental disorders experiencing sleep disturbances had more severe negative- and depressive symptoms, followed by significantly lower functioning compared to clinical participants without sleep disturbances. This is in line with smaller studies ($N < 100$), which found symptoms of insomnia in SCZ to be associated with poorer social and functional outcomes [44] and more severe psychopathology [32,45]. By contrast, better sleep in SCZ has been found to be linked to healthier coping strategies and greater quality of life [44]. Studies of BD patients show that decreased sleep is associated with more severe mood symptoms, poorer daytime functioning and lower life satisfaction compared to those with longer sleep [32]. Our study adds to these findings by showing that the association between sleep disturbances and clinical symptoms are not confounded by clinical diagnosis, age, alcohol or drug use, medication with sedative effects or BMI. Due to the cross sectional nature of our study, we are not able to investigate causality in the relationship between sleep disturbances, severe mental disorders and clinical symptoms. It is thus equally plausible that symptom severity is influencing the quality of sleep, as the other way round. There is however growing evidence indicating that sleep disturbances, particularly insomnia, seem to be causally related to symptoms of severe mental disorders [22,46–48].

Several limitations should be mentioned. The present study relies on definitions of sleep disturbances which categorize them from ratings on an established symptom scale typically used to assess sleep disturbance in symptomatic and remitted depression, rather than the use of formal diagnostic criteria. Our definition of hypersomnia did for example not include daytime sleepiness assessment. Thus, our groups are more precisely regarded as symptoms of sleep disturbances rather than diagnostic categories. This may contribute to higher frequency of reported sleep disturbances. However, compared to other methods of sleep assessment (actigraphy, polysomnography and diagnostic interview for sleep assessment), high levels of reliability and validity of these sleep profiles have been demonstrated in other clinical studies using similar definitions [13,19,32–35,49–54], and are shown to be sufficiently representative of the underlying diagnostic categories [34,55]. Moreover, descriptive studies of sleep disturbances in severe mental disorders are predominantly based on objective sleep measures (e.g. actigraphy, polysomnography). Such methods fail to capture the subjective experience of sleep quality, which is important both in the diagnostic assessment of the sleep disturbances relevant in this study, but also vital for designing better treatment interventions for these diagnostic groups. The time frame used to assess sleep disturbances is 7 days, which may lead to assessment of a more acute rather than chronic sleep disturbance. However, sleep disturbances were found in both first-treatment- and previously treated participants, indicating sleep disturbances as an underlying problem.

No specific screening tool for primary sleep disturbances were given in the assessment of exclusion criteria, therefore we cannot rule out that people with an undiagnosed primary sleep disorder are included in the study. A thorough physical examination in addition to questions about history of somatic health would however most likely pick up on symptoms compatible with OSA and restless legs syndrome, be noted, and the participant thereby excluded. The Bipolar Disorder group is not divided into different phases of illness (manic, euthymic or depressed), although sleep disturbances may vary depending on this. Being one of the main aims, the relationship between sleep disturbances and symptomatology was however measured continuously because this made more sense considering that affective episodes are more common in bipolar disorder and psychotic episodes are more common in schizophrenia spectrum disorders. Moreover, although manic symptoms are not included among the continuous symptoms we investigated, the PANSS excitement factor includes the following items; P4 Excitement, P7 Hostility P7, G8 Uncooperativeness, G14 Poor impulse control. We therefore argue that the PANSS excitement factor can be viewed as a proxy for symptoms of mania.

A considerable strength of this study is the large sample consisting of schizophrenia spectrum disorders, bipolar disorders and HC, assessed with the same protocol across diagnostic groups. The large sample also makes it possible to explore the effects of potentially mediating and moderating factors on sleep disturbances. Moreover, the thorough assessment of medication with sedative effects is a major strength. Few other studies, especially in BD, classify and address the influence of medication with sedative effects on different types of sleep disturbances. Exclusion of patients with alcohol or drug use has constrained representability of clinical samples in previous studies. The differentiation between having a history of alcohol or drug dependency and recent use in our study adds valuable information to the field by showing that recent drug use is associated with less sleep disturbances, whilst having a history of drug dependency is associated with more sleep disturbances. This is of clinical importance because ongoing drug use may partly mask sleep disturbances and be part of an attempt to deal with them.

There are several implications of the present findings. Firstly, that sleep disturbances should be assessed routinely in severe mental disorders. DSM 5 recommends that sleep disturbances no longer should be classified as primary or secondary. This implies that treatment should be tailored, directly targeting the specific sleep disturbance also in severe mental disorders. An important aspect is that sleep and circadian systems are adapted to be responsive to unconditioned environmental stimuli, particularly light, eating and social activities. The neurobiology of sleep/circadian function can thus be modulated non-pharmacologically, such as behavioral and/or light manipulations for sleep and circadian function [36]. Moreover, knowledge about the subjective experience of sleep disturbances in these patient groups show that many patients believe that sleep disturbances are intrinsic to their illness [56,57]. There is a great potential for raising awareness about sleep hygiene; i.e. the importance of physical activity, social rhythms and reduction of caffeine and electronic devices with blue light. Furthermore, several studies on the effectiveness on cognitive behavioral therapy are on the rise, showing that Cognitive-Behavioral Therapy for Insomnia (CBT-I) may be particularly helpful for addressing cognitive and behavioral factors that maintain and exacerbate insomnia [48,58,59].

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Declaration of interest

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ORIGINAL PAPER

Do sleep disturbances contribute to cognitive impairments in schizophrenia spectrum and bipolar disorders?

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Abstract

Sleep disturbances and cognitive impairments are both frequent across psychotic disorders, with debilitating effects on functioning and quality of life. This study aims to investigate if sleep disturbances are related to cognitive impairments in schizophrenia spectrum (SCZ) and bipolar disorders (BD), if this relationship varies between different sleep disturbances (insomnia, hypersomnia or delayed sleep phase (DSP)) and lastly, if this relationship differs between clinical groups and healthy controls (HC). We included 797 patients (SCZ = 457, BD = 340) from the Norwegian Centre for Mental Disorders Research (NORMENT) study in Norway. Sleep disturbances were based on items from the Inventory of Depressive Symptoms—Clinician rated scale (IDS-C). Their relationship with several cognitive domains was tested using separate ANCOVAs. A three-way between-groups ANOVA was conducted to test if the relationship with cognitive impairments varies between different sleep disturbances. These analyses revealed significantly poorer processing speed and inhibition in those with any sleep disturbance versus those without, also after adjusting for several covariates. The relationship between sleep disturbances and cognition was similar across SCZ and BD, and there were significant effects of insomnia and hypersomnia on both processing speed and inhibition. No association between sleep disturbances and cognition was found in HC. Sleep disturbances contribute to cognitive impairments in psychotic disorders. Processing speed and inhibition is poorer in patients with sleep disturbances. Impairments in these domains are related to insomnia and hypersomnia. These findings suggest that treating sleep disturbances is important to protect cognitive functioning, alongside cognitive remediation in psychotic disorders.

Keywords Sleep disturbances · Cognitive impairment · Schizophrenia · Bipolar disorders · Healthy controls

Abbreviations

DSP Delayed sleep phase
SCZ Schizophrenia
BD Bipolar disorder
HC Healthy controls

Introduction

Sleep disturbances and cognitive impairments are frequent in the main categories of psychotic disorders, schizophrenia spectrum disorders (SCZ) and bipolar disorders (BD), with debilitating effects on functioning and quality of life [1–7]. They are both also found to be present irrespective of illness phase, i.e. both during and between mood and psychotic episodes [7–12]. This supports the idea that these two domains may be linked, or more precisely, that sleep disturbances may contribute to cognitive impairments in psychotic disorders.

During the past decade, recognition of the magnitude and wide-ranging negative impact of sleep disturbances in psychotic disorders have increased. Several studies show that almost 80% of people with psychotic disorders experience a sleep disturbance, with insomnia being the most frequent [13–15]. Cognitive impairments are also recognized as core features of both SCZ and BD, however,

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with more severe impairment in patients with SCZ [6] where the level of cognitive functioning on average is one standard deviation below that of healthy controls (HC) [16, 17]. Moreover, cognitive functioning is known as one of the strongest predictors of functional outcome [18]. Even though cognitive remediation techniques seem beneficial [19], current antipsychotics have no documented effect on cognitive impairments, thus there is still need for more efficient treatment options [20, 21]. Finding additional ways of treating cognitive impairments in psychotic disorders is, therefore, required.

The importance of sleep for good cognitive functioning is well known for both healthy persons deprived of sleep [22–26] and otherwise healthy persons with insomnia [27, 28]; with a particularly strong emphasis on the domains of learning and memory [22]. Although seemingly intuitive, the possibility that sleep disturbances contribute to cognitive impairments in psychotic disorders has been largely overlooked, with few studies investigating their relationship. Davies et al. [4] reviewed studies of sleep microarchitecture in SCZ, with results indicating a possible relationship to specific cognitive tasks, especially those tapping into attention. The results were, however, not conclusive. In addition, several studies suggest a relationship between sleep spindle abnormalities and impaired overnight memory consolidation in people with chronic SCZ [4, 29, 30]. A recent study [31] objectively assessed sleep using actigraphy together with a daily sleep log in 46 BD patients and 43 HC [31], in addition to measuring a wide range of cognitive tasks. They found impairments in attention and processing speed confined to BD patients with abnormal sleep patterns. Other studies have found poorer working memory, visual learning, and social cognition in BD patients with poor sleep quality [32], and that higher variability in total sleep time predicted poorer working memory and verbal learning performance in inter-episode BD [33].

A wide range of factors may influence the relationship between sleep disturbances and cognitive impairments in psychotic disorders. This includes age, as the prevalence of hypersomnia and delayed sleep phase (DSP) is higher in young people [34, 35] while the prevalence of insomnia is known to increase with age [36]. Comorbid alcohol and drug abuse may contribute to both cognitive impairment [37, 38] and impaired sleep quality [39]. Sedatives and other medication with potentially sedating effects, such as antipsychotics, antidepressants and mood stabilizers, may influence both sleep quality and architecture or disrupt the sleep–wake cycle [11], and may also affect cognitive performance[40, 41]. Weight gain, commonly seen as a side effect of medications and sedentary lifestyles, is also associated with both sleep disturbances and increased risk of cognitive impairment [42]. Moreover, sleep disturbances are seen in periods with exacerbation of symptoms in SCZ and BD, including mania, positive, negative and depressive symptoms [15, 43, 44], and symptoms may also disturb cognitive performance.

As described above, previous studies in this field have indicated an association between sleep disturbances and cognition in psychotic disorders. Their samples have, however, been too small to evaluate the effect of potential confounding factors. There are also few studies that investigate to what extent associations between sleep disturbances and specific cognitive impairments are disorder specific, or if the same is seen in HC. Elucidating the relationship between sleep disturbances and cognitive functioning is, therefore, required, and may be of crucial clinical importance in search of better treatment options.

Aims of the study

We aim to bridge these knowledge gaps by exploring. (1) The relationship between sleep disturbances and cognitive impairments in a large group of persons with psychotic disorders, while also evaluating the effects of potential confounders (age, gender, diagnostic group (SCZ or BD), positive and negative symptoms, depressive symptoms, manic symptoms, recent intake of alcohol and drugs, a history of alcohol or drug dependency, medication with sedative effects, and weight (BMI)). (2) Furthermore, we aim to investigate if the relationship between sleep disturbances and cognition is different in SCZ or BD, and (3) if there are specific relationships between different sleep disturbances (insomnia, hypersomnia or DSP) and cognitive impairments. (4) Finally, we want to examine if the relationship between sleep disturbances and cognition differs between the clinical group and HC.

Materials and methods

Participants

From the larger 'Thematically Organized Psychosis (TOP) Research Study' at the Norwegian Centre for Mental Disorders Research (NORMENT) in Oslo, Norway, 797 patients with severe mental disorders (SCZ = 457, BD = 340) were recruited from 2003 to 2018, and subsequently, 182 HC were recruited from 2017 to 2018. All participants had to have data on sleep disturbances to be included in the study. Among the SCZ group, 260 had a schizophrenia diagnosis, 60 had a schizoaffective disorder, 37 had schizophreniform disorder and 100 were diagnosed with other psychotic disorders. Among the BD group, 216 were diagnosed with bipolar I disorder, 103 had bipolar II disorder and 21 had bipolar NOS. Clinical participants underwent a thorough physical examination by a physician including assessment of current somatic health, height and weight (BMI). Moreover,

an interview addressing history of somatic health was carried out. Based on this examination and interview, all participants reporting a history of severe head injury (hospitalized), neurological disorder, obstructive sleep apnea (OSA) or restless legs syndrome (RLS) were excluded, as were participants with an IQ below 70 and age outside the range of 18–60 years. All participants had either Norwegian as their first language or received compulsory schooling in Norway to assure valid cognitive test performance. The population register in the counties of Oslo and Akershus was used as basis for random selection of HC. To ensure that none of the HC or their first-degree relatives had a lifetime history of severe psychiatric disorders (DSM-IV axis 1 disorder), they were screened with the Primary Care Evaluation of Mental Disorders and interviewed about severe mental illness symptoms. HC were excluded if they met criteria for alcohol or drug abuse/dependency during the last 6 months. This exclusion criterion was, however, not applied to the clinical participants to establish a representative sample. Informed consent was obtained from all individual participants included in the study. The Regional Committee for Research Ethics' and 'The Norwegian Data Inspectorate' approved the study.

Demographics and clinical characteristics

All clinical assessment was completed by a clinical psychologist, trained medical doctor or psychiatrist. Clinical participants were assessed with the Structural Clinical Interview for DSM-IV (SCID-IV) [45] for diagnostic clarification. Current positive and negative symptoms were rated using the Positive and Negative Syndrome Scale (PANSS) [46]. Current depressive symptoms were rated using the Inventory of Depressive Symptoms—Clinician rated scale (IDS-C) [47]. Because the sleep items in the IDS-C are used as basis to form our definitions of sleep disturbances (specified in Sect. Sleep disturbances) and also are part of measuring current depression, the sleep items are taken out of the sum score to avoid conflicting use of rating scale scores. The Young Mania Rating Scale (YMRS) [48] was used to rate current manic symptoms. Information on current use of alcohol and illegal drugs (the number of units of alcohol and use of illegal drugs past 2 weeks) and current use of psychotropic medication (type of medication(s) and dose of antipsychotics, antidepressants, antiepileptics and/or lithium) was obtained through clinical interview and medical charts. Medication with potentially sedative effects was defined as follows, based on their mechanisms of action and if marked as having sedation as a main or major side effect: (1) All substances marked as sedatives. (2) Based on information given in The Norwegian Pharmaceutical Product Compendium [49], antipsychotics, antidepressants and mood stabilizers with sedation marked as a major side effect in their description of action. (3) By checking their known modes of action on neurotransmitters involved in promoting sleepiness (histaminergic/muscarinergic) such as e.g. quetiapine and olanzapine.

Cognitive assessment

All participants underwent neuropsychological testing completed by a trained psychologist or an assistant trained in standardized neuropsychological assessment. Neuropsychological testing was completed as soon as possible after assessment of symptoms was completed, with a maximum of 2 weeks apart. Participants were tested with either test battery 1 (a standardized test battery described by Simonsen et al. [50]) if included in the study before year 2012, or test battery 2 (based on the MATRICS Consensus Cognitive Battery (MCCB)) [51] if included from 2012 to 2018. To establish the highest possible N to ensure more statistical power, corresponding tests from the two batteries were merged, and formed five overarching cognitive domains as follows (Table 1).

Processing speed measured by digit symbol coding test from the WAIS-III (Battery 1) or brief assessment of cognition in Schizophrenia (Battery 2).

Verbal learning measured by California Verbal Learning Test, total number correct over five trials (Battery 1) or Hopkins Verbal Learning Test, total number correct over three trials (Battery 2).

Verbal memory measured by California Verbal Learning Test, long delay free recall (Battery 1) or Hopkins Verbal Learning Test, long delay free recall (Battery 2).

Attention measured by digit span forward from the WAIS-III (represented in both batteries).

Executive functioning

Verbal fluency measured by category fluency test from D-KEFS (Battery 1) or category fluency test from MCCB (Battery 2).

Working Memory measured by letter–number sequencing test from WAIS-III (Battery 1) or letter–number sequencing test from the MCCB (Battery 2).

Inhibition measured by interference control from color word interference test (represented in both batteries).

Flexibility measured by set shift from color word interference test (represented in both batteries).

To merge the corresponding tests from the two different test batteries, a reference group of 1094 healthy controls from the whole study period was used as a basis for calculating z-scores. The same exclusion criteria as applied for the HC study sample were applied for the reference group. Interference Control and Set Shift from D-KEFS

Table 1 Overview of neurocognitive domains and corresponding tests

Domain/Test	Neurocognitive test battery	Reference group[a] *N*	Mean ± SD	Patients *N*	Mean ± SD	Healthy controls *N*	Mean ± SD
Processing speed	Combined *z* score	1094	0.0 ± 1.0	794	− 1.1 ± 1.2	182	0.0 ± 1.0
Digit symbol coding test from the WAIS-III	1	500	77.2 ± 13.5	640	63.1 ± 16.4	–	–
Brief assessment of cognition in schizophrenia, (digit symbol coding test)	2	596	58.5 ± 9.4	154	48.1 ± 11.0	182	58.5 ± 9.1
Verbal learning	Combined *z* score	1094	− 0.0 ± 1.0	797	− 0.6 ± 1.3	182	0.1 ± 1.0
California verbal learning test, total number correct over five trials/list A total correct	1	500	56.9 ± 9.4	643	51.8 ± 11.6	–	–
Hopkins verbal learning test, total number correct over three trials	2	596	28.5 ± 3.9	154	25.3 ± 5.2	182	28.9 ± 3.9
Verbal memory	Combined *z* score	1094	− 0.0 ± 1.0	776	− 0.6 ± 1.3	182	0.0 ± 1.0
California verbal learning test, long delay free recall	1	500	13.2 ± 2.6	641	11.8 ± 3.3	–	–
Hopkins verbal learning test, long delay free recall	2	596	10.3 ± 1.7	135	9.1 ± 2.3	182	10.3 ± 1.7
Attention	*z* score	1068	− 0.0 ± 1.0	773	− 0.4 ± 0.9	182	0.2 ± 1.1
Digit span forward and backward from the WAIS-III	1 + 2	1068	16.5 ± 3.7	773	14.9 ± 3.4	182	17.1 ± 4.2
Executive functions							
Verbal fluency	Combined *z* score	1094	0.0 ± 1.00	789	− 0.9 ± 1.2	182	0.0 ± 1.1
Category fluency test from D-KEFS	1	501	48.8 ± 8.3	636	41.8 ± 10.4	–	–
Category fluency test from MCCB	2	595	28.61 ± 6.02	153	23.5 ± 6.2	182	28.9 ± 6.4
Working memory	Combined *z* score	1070	0.0 ± 1.0	687	− 0.7 ± 1.0	179	0.2 ± 1.0
Letter–number sequencing test from WAIS-III	1	479	11.4 ± 2.5	535	9.6 ± 2.4	–	–
Letter–number sequencing test from the MCCB	2	593	15.5 ± 2.9	152	13.7 ± 3.0	179	16.2 ± 2.9
Inhibition	*z* score	1088	− 0.0 ± 1.0	775	− 1.0 ± 1.7	181	0.1 ± 0.9
Color word interference test from D-KEFS	1 + 2	1088	48.6 ± 9.7	775	58.4 ± 16.3	181	47.2 ± 8.9
Flexibility	*z* score	1066	0.0 ± 1.0	774	− 0.7 ± 1.5	182	0.2 ± 0.8
Color word interference test from D-KEFS	1 + 2	1066	55.1 ± 11.6	786	63.6 ± 17.4	182	53.3 ± 9.3

[a]Reference group of healthy controls from the whole study period. Two participants were tested with both batteries for which only scores on test battery 1 are included in the combined *z* scores

Color Word Interference test were reversed before z-score transformation.

Sleep disturbances

Information about sleep disturbances in the whole study sample was attained through the clinical assessment, utilizing four items from the (IDS-C); difficulty falling asleep (item 1; Sleep Onset Insomnia), difficulty maintaining sleep (item 2; Mid-Nocturnal Insomnia), early awakening (item 3; Early Morning Insomnia) and hypersomnia (item 4; Hypersomnia). The items are scored from 0 to 3 with higher scores implying the experience of more subjective disturbance. The four sleep items have been validated as measures of insomnia and hypersomnia, and are demonstrated useful in prediction of clinical diagnoses of sleep disorders [1, 52–55]. Moreover, several prior studies [15, 56, 57] have used IDS-C to distinguish subtypes of sleep disturbances, applying the same methods as described below. The four sleep items from the IDS-C are used as basis for defining sleep disturbances as follows, emphasizing that these definitions are to be considered indicative of symptoms of sleep disturbances rather than diagnostic categories.

1. Insomnia was defined as being present when either (a) a score of ≥ 2 on Sleep Onset Insomnia (more than half the time it takes minimum 30 min to fall asleep); (b) a score of = 3 on Mid-Nocturnal Insomnia (more than half the time, waking up happens more than once per night and one stays awake for 20 min or more); or (c) a score of ≥ 1 on Early Morning Insomnia (more than half the time, one wakes up more than 30 min before needing to get up. Moreover, a score of 0 on the Hypersomnia item (sleeps no more than 7–8 h a night, without naps) was a prerequisite.
2. Hypersomnia was defined as being present when participants had a score of ≥ 1 on the Hypersomnia item (sleeping up to 10 h per day) with no evidence of Insomnia.
3. Delayed sleep phase (DSP) was defined as being present with a score of ≥ 3 on Sleep Onset Insomnia (more than half the time, it takes more than 60 min to fall asleep), and a score of ≥ 1 on the Hypersomnia item.
4. Any sleep disturbance was defined as being present when participants scored over cut-off on any of the sleep disturbances described.

Statistical analyses

The statistical package for the Social Sciences (SPSS Inc, Chicago, IL version 25) was used. To test whether there is an overall effect of having any sleep disturbance on cognitive impairments in the patient group, we used a one-way between-groups multivariate analysis of variance (MANOVA) with "any sleep disturbance" as main factor and the eight different cognitive domains as dependent factors. Because MANOVA is sensitive to outliers, Mahalanobis distance was calculated to check for multivariate normality (participants with strange combination of scores across the cognitive domains). Scores exceeding a critical value of 26.13 (obtained using a Chi-square critical value table corresponding to eight dependent variables) were classified as multivariate outliers.

Relevant demographic and clinical factors that could affect both sleep disturbances and cognition (age, gender, diagnostic group, positive and negative symptoms, depressive symptoms, manic symptoms, recent intake of alcohol and drugs, a history of alcohol or drug dependency, medication with sedative effects, and BMI) were explored using t tests, correlations or Chi-square statistics were suitable. Eight separate one-way between-groups' analysis of covariance (ANCOVAs) were then conducted. We applied a Bonferroni adjustment to avoid the risk of type I errors, setting a p value of 0.006 as significance threshold. The demographic and clinical variables with significant bivariate associations to any sleep disturbance and each cognitive domain were entered as covariates.

To investigate whether there is a difference in the relationship between any sleep disturbance and cognitive impairments in SCZ and BD, we conducted two-way between-groups MANOVA, allowing us to test for any interaction effect between any sleep disturbance and diagnostic group status (SCZ or BD). Moreover, to test the effect of each different type of sleep disturbance (insomnia, hypersomnia and DSP) on cognitive impairments, a three-way between-groups ANOVA was completed. Finally, the overall relationship between any sleep disturbance and cognition was explored in HC using one-way between-groups MANOVA, followed by eight separate ANCOVAs, also applying a Bonferroni adjustment of the p value to 0.006. Demographic variables with significant bivariate associations to any sleep disturbance and each cognitive domain were entered as covariates.

Results

Demographic and clinical characteristics

The patient group was both significantly younger and had fewer years of education compared to the HC group, but the gender distribution was similar. Moreover, the patient group had significantly higher frequency of all types of sleep disturbances compared to HC (Table 2).

The relationship between sleep disturbances and cognitive impairments in psychotic disorders

The calculation of Mahalanobis distance revealed that 12 patients and 1 control had scoring combinations identified as multivariate outliers and were, therefore, taken out. Bivariate analyses (data not shown) revealed that higher age was associated with poorer performance on the domains of processing speed, verbal learning, verbal memory, inhibition and flexibility, whilst younger age was associated with having any sleep disturbance. The SCZ group had a significantly higher frequency of any sleep disturbance compared to the BD group (78.3% versus 69.4%) and performed significantly poorer on all cognitive domains. Moreover, amongst the patients reporting any sleep disturbance 60.3% had SCZ and 39.7% had BD. Higher scores on both PANSS positive and negative symptoms were associated with significantly poorer performance across all cognitive domains, as well as with higher frequency of sleep disturbances. Use of medication with sedative effects was associated with higher frequency of sleep disturbances and poorer cognitive performance across all cognitive domains, except for attention and flexibility. The MANOVA showed that patients reporting any sleep disturbance had overall poorer cognitive performance than patients without any sleep disturbance (MANOVA: $F = 2.197$, $p < 0.05$, $\eta^2 = 0.027$). The separate univariate

Table 2 Demographics and characteristics in the total sample

	Patients $N=797$	Healthy controls $N=182$	*T* test/Chi-square	
			F/x^2	*p*
Demographics				
Age, mean ± SD	31.0 ± 10.4	36.3 ± 9.7	106.6	< 0.001
Gender, male *n* (%)	396 (49.6)	88 (48.4)	0.09	0.768
Education in years, mean ± SD[a]	12.8 ± 2.5	14.8 ± 2.0	166.0	< 0.001
Clinical variables				
Insomnia *n* (%)	363 (45.5)	63(34.6)	7.20	< 0.01
Hypersomnia *n* (%)	231 (29.0)	8 (4.4)	48.54	< 0.001
Delayed sleep phase *n* (%)	64 (4.4)	1 (0.5)	13.38	< 0.001
Any sleep disturbance *n* (%)	594 (74.5)	71 (39.0)	85.80	< 0.001
Alcohol units last 2 weeks, mean ± SD[b]	9.1 ± 22.9			
Drug use last 2 weeks, yes (%)	77 (9.7)			
Lifetime alcohol dependency, yes (%)	105 (13.2)			
Lifetime drug dependency, yes (%)	139 (17.4)			
YMRS mean ± SD[c]	4.1 ± 4.8			
IDS-C minus sleepitems (mean ± SD)[d]	13.7 ± 10.2			
PANSS positive (mean ± SD)[e]	12.7 ± 5.0			
PANSS negative (mean ± SD)[f]	13.0 ± 5.8			
Medication and somatic variables				
BMI, mean ± SD[g]	25.9 ± 5.0			
Antipsychotics (%)	565 (70.9)			
Mood Stabilizers (%)	248 (31.1)			
Antidepressants (%)	260 (32.6)			
Anxiolytics/hypnotics (%)	84 (10.5)			
Medication with sedative effects (%)	422 (52.9)			

Mood stabilizer refers to lithium or antiepileptics

BMI body mass index

[a]99.6% ($n=794$) of the patients had data on years of education

[b]98.7% of patients had data on alcohol units last 2 weeks

[c]98.6% ($n=786$) of patients had data on YMRS

[d]Missing items were replaced with 0

[e]99% ($n=789$) of the patients had data on PANSS positive

[f]98.6% ($n=786$) of the patients had data on PANSS negative

[g]95.2% ($n=759$) of patients had data on BMI

ANCOVAs (Table 3), in which age, diagnostic group, positive and negative symptoms and medication with sedative effects were entered as covariates, revealed that patients having any sleep disturbance scored significantly poorer on processing speed and inhibition than patients with no sleep disturbance.

The relationship between sleep disturbances and cognitive impairments across SCZ and BD

No significant overall interaction effect between any sleep disturbance and diagnostic group was found on the two-way MANOVA. This implies that the effect of sleep disturbance on cognition is similar for SCZ and BD.

The effect of insomnia, hypersomnia and DSP

The three-way between-groups ANOVA showed that there were significant main effects of reporting symptoms of insomnia and hypersomnia versus not reporting, for both processing speed and inhibition, whilst no main effect was found for DSP (Table 4). This implies that both insomnia and hypersomnia are important for impairment in these cognitive domains.

The relationship between sleep disturbances and cognition in HC

No significant overall difference between those with and without any sleep disturbance was found for the combined

Table 3 Relationship between any sleep disturbance and cognitive functioning in psychotic disorders

	No sleep disturbance	Any sleep disturbance	ANCOVA[a]		
	Mean ± SD	Mean ± SD	*F*	*p*	η^2
Processing speed	−0.8 (1.1)	−1.1 (1.2)	9.91	< 0.002	0.013
Verbal learning	−0.4 (1.3)	−0.5 (1.2)	1.10	0.294	0.001
Verbal memory	−0.5 (1.3)	−0.6 (1.2)	0.01	0.932	0.000
Attention	−0.3 (1.0)	−0.5 (0.9)	2.11	0.147	0.003
Executive functions					
Verbal fluency	−0.6 (1.3)	−0.9 (1.2)	3.92	0.048	0.005
Working memory	−0.6 (1.1)	−0.7 (0.9)	0.67	0.417	0.001
Inhibition	−0.7 (1.4)	−1.1 (1.6)	7.63	< 0.006	0.010
Flexibility	−0.4 (1.2)	−0.8 (1.4)	5.60	0.018	0.007

[a]Adjusted for age, diagnostic group, PANSS positive and negative and use of medication with sedative effects where relevant

Table 4 Relationship between specific sleep disturbances and cognitive functioning in psychotic disorders

ANOVA	Insomnia			Hypersomnia			Delayed sleep phase		
	F	*p*	η^2	*F*	*p*	η^2	*F*	*p*	η^2
Processing speed	15.43	< 0.001	0.019	6.87	< 0.01	0.009	0.47	0.828	0.000
Inhibition	9.12	< 0.01	0.012	6.05	< 0.05	0.008	0.17	0.679	0.000

cognitive domains in the HC group (MANOVA). When analyzing the eight cognitive domains separately using ANCOVAs and applying a Bonferroni adjustment of the *p* value to 0.006, none of the differences in cognitive domains reached statistical significance. This implies that there is no effect of sleep disturbances on cognition in HC.

Discussion

The overarching aim of the present study was to investigate the relationship between sleep disturbances and cognitive impairments in psychotic disorders. A main finding is that sleep disturbances are related to cognitive impairments in this patient group. More specifically, patients reporting any sleep disturbance perform significantly poorer on processing speed and inhibition than patients without any sleep disturbance. The relationship between sleep disturbances and cognition is, however, not different between SCZ and BD. Insomnia and hypersomnia seem to be the most important types of sleep disturbances in relation to cognitive impairments. Moreover, our study shows that sleep disturbances are not related to cognition in HC. This study stands out by representing the largest investigation of symptoms of sleep disturbances and cognitive impairments in psychotic disorders to this date. Furthermore, the large sample size allows us to examine the influence of multiple confounding variables that few studies have done previously.

The fact that sleep disturbances are associated with cognitive impairments is in line with a previous study of BD [31] and some [29, 30], but not all previous studies of SCZ [58]. An aspect that may explain these divergent findings is the different levels of measurement and various types of sleep assessments applied. While our study captures the subjective experience of symptoms of sleep disturbances, the latter SCZ study investigated sleep microarchitecture using polysomnography. Prior studies have found poor correspondence between self-reported and objective measurement of sleep disturbances, especially in relation to sleep quality, suggesting that they may measure distinct phenomena [59].

Another important finding in our study is that patients reporting any sleep disturbance perform poorer on tasks measuring processing speed and inhibition compared to those without any sleep disturbance, also after adjustment for the influence of age, diagnostic group, positive and negative symptoms, and medication with sedative effects. The finding involving a significant effect of sleep disturbance on processing speed is in line with the previous study of BD [31] and is clinically relevant as processing speed is suggested to be one of the most important cognitive domains for functional outcomes [60–62]. As such, impaired processing speed is a major challenge to this patient group. Although medication with sedative effects did not influence the relationship between sleep disturbance and processing speed, it was significantly associated with poorer performance on all cognitive domains in bivariate analyses, except for attention and flexibility. Over half of the patient group (52.5%) was using these medications. A reduction in use of medication with sedative effects could, therefore, be an important way to improve cognitive performance. This line of reasoning is

supported by prior studies [40, 63] showing that changing or reducing sleep-inducing antipsychotic medication to the lower limit of recommended doses is related to better cognitive functioning, particularly processing speed [64].

Inhibition has previously been linked to circadian dysfunction in patients with SCZ [65]. Although this previous study was very small ($N = 14$), it could suggest that dysregulation of the circadian system (i.e. DSP) might be of importance for predicting cognitive impairment. However, our findings do not support this, as no significant effect of DSP was found on either inhibition or processing speed. This may be due to our DSP group being relatively small compared to the insomnia and hypersomnia groups (64 individuals compared to 357 with insomnia and 228 with hypersomnia after removing multivariate outliers), with the analyses thus having less statistical power. Another aspect is that our sleep measures were not originally designed to assess DSP or other types of circadian dysfunction, thus potentially not being sensitive enough to identify all cases of circadian rhythm dysregulations. Thus, the effect of DSP and other types of circadian rhythm dysregulations on cognitive impairments needs to be further investigated in large studies using a combination of subjective and objective sleep assessments.

Nonetheless, our study found effects of insomnia and hypersomnia on both processing speed and inhibition, which is an important contribution to the field since most previous studies do not differentiate between the sleep disturbances. Insomnia and hypersomnia are characterized by too little and excessive sleep, in contrast to DSP in which the circadian rhythm is delayed rather than necessarily affecting the amount of sleep. The duration rather than the timing of sleep may, therefore, be the driving force of these results. This fits well with findings from the large-scale study from the UK Biobank [66] where poorer performance on reasoning, basic reaction time, numeric memory, visual memory, and prospective memory were associated with both short (< 7 h) and long (> 9 h) sleep durations.

While previous studies indicate an effect of sleep disturbances on cognitive functioning in BD [31], but not in SCZ [58] our findings showed no significant interaction effect between any sleep disturbance and diagnostic group on cognitive domains, thus a similar relationship across SCZ and BD. Moreover, the relationship between sleep disturbances and cognitive impairments remained significant when we entered diagnostic group as a covariate. This suggests that sleep disturbance is a transdiagnostic feature with transdiagnostic effects on cognition.

However, when we investigated the relationship between sleep disturbances and cognition in a HC sample, we found a different relationship compared to that in the clinical sample. In the HC, we neither found a significant overall effect of any sleep disturbance on cognition nor when we investigated the cognitive domains separately. The proportion of HC with any sleep disturbance and cognitive impairment was low (2.7% of HC perform 1.5 SD below the mean on i.e. processing speed compared to 26.5% in the clinical group). This illustrates two important aspects: (1) that the HC group may possess a cognitive reserve making their cognition more robust compared to the clinical group and (2) that poorer statistical power may partly explain the lack of findings. Moreover, as we used a symptom scale designed to assess sleep disturbances in a clinical syndrome, it may also be less suitable to assess sleep in HC. Prior clinical studies [52–55, 57, 67–71] have, however, shown these sleep profiles to have high levels of reliability and validity, and to correspond adequately to the underlying diagnostic categories [1, 55]. The lack of findings is nevertheless consistent with both the large-scale study from the UK biobank [66] as well as other population-based studies of insomnia symptoms and cognition [72]. Thus, we argue that different findings in the patient and HC group might reflect vulnerability in cognitive performance in patients with psychotic disorders.

Several limitations should be addressed. First, using the sleep items from IDS-C to assess sleep disturbances represents a limitation, as this is a rating scale originally designed to evaluate symptoms of depression. As a result, conclusions drawn from this study have to be taken cautiously. Ideally, tests designed to evaluate the specific sleep disorders, such as The Insomnia Severity Index or Epworth Sleepiness Scale would be preferable. However, several other studies [56, 57], including our previous study [15], have used the same methods to define sleep disturbances. We also underline that our definitions of sleep disturbances should be considered as symptoms of sleep disturbances rather than diagnostic categories. Previous studies have nonetheless demonstrated these four sleep items to be adequate in prediction of clinical diagnoses of sleep disorders [1, 52–55]. We also argue that our focus on subjective experience of sleep disturbance is a valuable contribution to this research field which mainly consists of studies linking objective sleep assessments to cognition.

Moreover, as this study had a cross-sectional design, we could not investigate causality in the relationship between sleep disturbances and cognitive impairments. A large body of research, however, underlines how sleep deprivation causally impair neurobehavioral functions [22, 25]. Sleep assessment and neuropsychological testing were not completed the same day due to the large study protocol. As sleep quality may vary from one night to the next, this is a limitation. Furthermore, as the time frame used to assess sleep disturbances was the prior 7 days, there is a possibility that acute rather than chronic sleep disturbances were captured. Self-reported sleep has, however, been suggested to represent chronic sleep patterns [73]. Moreover, a previous study [15] showed that sleep disturbances were frequent across first-treatment

and previously treated patient groups, suggesting that sleep disturbances are persistent. Another limitation is that we did not use specific screening tools for primary sleep disorders when assessing the exclusion criteria. Therefore, individuals having undiagnosed OSA or RLS may not have been identified. Clinical participants, however, underwent a thorough physical examination as well as questions about history of somatic health. As such, symptoms of OSA and RLS would most likely be addressed and thus be excluded.

A considerable strength of the present study is the large sample consisting of SCZ, BD and HC tested with the same two neuropsychological batteries, as well as the diagnostic specification using SCID-I, applied across patient groups. Moreover, we investigated the relationship between sleep disturbances and cognitive impairments across diagnostic groups. To the best of our knowledge, no study has done this previously. Another clinically important strength is the thorough evaluation of medication with sedative effects addressing their relationship to cognitive impairments. We also included and differentiated between insomnia, hypersomnia and DSP, thereby capturing the different nature of sleep disturbances and their effect on cognition, which should be of importance when tailoring treatment in the future.

Our findings that sleep disturbances affect cognitive impairments in psychotic disorders might be of clinical importance. Treating sleep disturbances may have positive add-on effects to cognition; more specifically, it might improve performance on processing speed and inhibition. Whether such improvements will be clinically and functionally significant is only speculative. Given that cognitive impairments in psychotic disorders are strongly linked to poor level of functioning, and the fact that there are few efficient treatment options, this is an area worthy of further investigation. Indeed, prior studies have suggested that sleep disturbance and poor cognitive functioning may act jointly in increasing the likelihood of workplace dysfunction in BD [74]. Therefore, further investigating how these two aspects may interact in maintaining several areas of functional impairment is important.

Conclusion

Taken together, although no direction in the relationship between subjective sleep disturbances and cognitive impairments can be drawn from this cross-sectional study, experiencing sleep disturbance is theoretically more likely to influence cognitive performance in psychotic disorders than the other way round. As our study has found a relationship between the two, more longitudinal research using specific tools to explore sleep disturbances is needed to investigate causality, which should be an area of future research.

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Compliance with ethical standards

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of The Regional Research Committee #2009/2485 and with the 1964 Helsinki declaration and its later amendment.

Conflict of interest The authors declare that they have no conflict of interest.

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III

Psychological Medicine

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Sleep disturbance mediates the link between childhood trauma and clinical outcome in severe mental disorders

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Abbreviations:
DSP: delayed sleep phase; SCZ: schizophrenia; BD: bipolar disorder

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Abstract

Background. The experience of childhood trauma is linked to more severe symptoms and poorer functioning in severe mental disorders; however, the mechanisms behind this are poorly understood. We investigate the relationship between childhood trauma and sleep disturbances in severe mental disorders including the role of sleep disturbances in mediating the relationship between childhood trauma and the severity of clinical symptoms and poorer functioning.

Methods. In total, 766 participants with schizophrenia-spectrum ($n = 418$) or bipolar disorders ($n = 348$) were assessed with the Childhood Trauma Questionnaire. Sleep disturbances were assessed through the sleep items in the self-reported Inventory of Depressive Symptoms. Clinical symptoms and functioning were assessed with The Positive and Negative Syndrome Scale and the Global Assessment of Functioning Scale. Mediation analyses using ordinary least squares regression were conducted to test if sleep disturbances mediated the relationship between childhood trauma and the severity of clinical symptoms and poorer functioning.

Results. Symptoms of insomnia, but not hypersomnia or delayed sleep phase, were significantly more frequent in participants with childhood trauma experiences compared to those without. Physical abuse, emotional abuse, and emotional neglect were significantly associated with insomnia symptoms. Insomnia symptoms partly mediate the relationship between childhood trauma and the severity of positive and depressive/anxiety symptoms, in addition to poorer functioning.

Conclusion. We found frequent co-occurrence of childhood trauma history and current insomnia in severe mental disorders. Insomnia partly mediated the relationship between childhood trauma and the severity of clinical symptoms and functional impairment.

Introduction

Childhood trauma is a well-documented risk factor for the development of severe mental disorders (Varese et al., 2012). In addition, individuals with severe mental illness that have experienced childhood trauma have more severe clinical symptoms than those without childhood trauma experiences (van Nierop et al., 2014). Sleep disturbances, such as subjective experiences of difficulties falling asleep, frequent awakenings, shorter duration of sleep, restless sleep, daytime fatigue and especially nightmares and anxiety dreams, are frequent sequelae of trauma exposure both in the short and the long term (Lavie, 2001). Sleep disturbances are also associated with more severe clinical symptomatology in severe mental disorders including the schizophrenia (SCZ) and the bipolar spectrum (Laskemoen et al., 2019). Thus, sleep disturbance may be a potential mechanism in the pathway from childhood trauma to the severity of clinical symptoms and functional impairment.

Childhood trauma has downstream consequences that include an increased risk of developing a mixture of anxiety, affective, and psychotic symptoms cutting across severe mental disorders (van Nierop et al., 2014). The frequency of childhood trauma in severe mental disorders is high (Church, Andreassen, Lorentzen, Melle, & Aas, 2017; Larsson et al., 2013) and linked to a more severe illness course and outcome, including earlier illness onset, increased risk of suicide attempts, and increased substance misuse (Aas et al., 2016*b*; Etain et al., 2013; Mohammadzadeh, Azadi, King, Khosravani, & Sharifi Bastan, 2019). More severe depressive, manic, and psychotic symptoms are also found in people with bipolar disorder(BD) exposed to childhood trauma (Agnew-Blais & Danese, 2016; Etain et al., 2013), while more severe depressive symptoms are found in people with SCZ exposed to childhood trauma (Aas et al., 2016a;

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Kelly et al., 2016; Sahin et al., 2013). The timing, severity, and duration of childhood trauma exposure are suggested important factors; however, these are poorly studied (Morgan & Gayer-Anderson, 2016). Several studies link specific trauma subtypes to certain symptom dimensions (Bentall et al., 2014; Varese et al., 2012). Yet, no specific trauma-subtype seems to stand out above others. A recent review (Gibson, Alloy, & Ellman, 2016) suggests that the relationship between childhood trauma and psychosis persist irrespective of trauma subtype, and that the experience of childhood trauma itself is the most important factor influencing clinical outcome in severe mental disorders.

Exactly how childhood trauma impacts on later clinical symptoms is however less clear. One possibility is that it causes prolonged neurobiological alterations, rendering the individual susceptible to the development of different mental disorders later in life. The specific developmental trajectories by which this takes place is, however, not fully known (Agorastos, Pervanidou, Chrousos, & Baker, 2019). To date, the majority of research has focused on the alterations of the stress response system as the putative main trajectory into the development of a wide range of mental disorders. More specifically, exposures to high levels of stress during sensitive periods of development in early childhood may over- or under-sensitize the neuroendocrine stress response, thereby inducing developmental disturbances linked to severe mental disorders in adulthood (Meerlo, Sgoifo, & Suchecki, 2008). Other pathophysiological mechanisms that are closely related to the stress response system, including sleep disturbances and circadian dysfunction, are potential mechanisms linking childhood trauma and later clinical symptoms (Agorastos et al., 2019). Both acute and chronic stress affect brain areas regulating sleep, with the potential to cause immediate and enduring sleep disturbance (Duclos et al., 2019; Lavie, 2001; Ouellet, Beaulieu-Bonneau, & Morin, 2015). Indeed, exposure to childhood trauma is associated with several types of sleep disturbances in adulthood, including insomnia symptoms, nightmare-related distress, and sleep apnea (Brindle et al., 2018; Kajeepeta, Gelaye, Jackson, & Williams, 2015). Sleep disturbances may in turn contribute to maladaptive stress regulation; further increasing vulnerability to the development of severe mental disorders (Meerlo et al., 2008).

There is increased recognition of sleep disturbance being involved in the pathophysiology and psychopathology of psychosis (Yates, 2016). Studies have causally linked sleep restriction to the development of psychotic symptoms (Reeve, Emsley, Sheaves, & Freeman, 2018*a*). Also, sleep disturbances are prominent irrespective of illness phase, i.e. both before and during manic and psychotic episodes (Allison & Harvey, 2008; Harvey et al., 2015; Kamath, Virdi, & Winokur, 2015). Moreover, sleep disturbances are associated with more severe positive, negative, and depressive symptoms as well as more severe functional impairment across severe mental disorders (Laskemoen et al., 2019; Reeve, Sheaves, & Freeman, 2015, 2018*c*).

Despite the high prevalence of both childhood trauma and sleep disturbances in severe mental disorders, previous studies have not investigated common links to clinical symptoms of severe mental disorders, with the exception of one study of persons with euthymic phase BD (Aubert et al., 2016). This study found a significant bivariate association between childhood emotional abuse and poorer current sleep quality; however, the association was no longer statistically significant after adjustment for clinical symptoms (suicidal behavior, anxiety, and the use of anxiolytic medication). Another study examined the joint influences of sleep disturbance and trauma on psychotic-like experiences in a sample of otherwise healthy undergraduate students (Andorko et al., 2018), and found that both previous trauma exposure and sleep disruptions predicted psychotic-like experiences. The effect of trauma exposure did, however, not reach the level of statistical significance after correction for sleep disturbances in multivariate analyses. These studies illustrate that the relationship between childhood trauma and sleep disturbance may be confounded by other factors. Age, gender, diagnostic group (SCZ or BD), recent alcohol or drug use, a history of alcohol or drug dependency, medication with sedative effects, or weight are factors previously shown to be related to sleep disturbances, and may also be influenced by childhood trauma. To what extent sleep disturbances mediate the association between exposure to childhood trauma and the severity of clinical symptoms and functional impairment in psychotic disorders has, to best of our knowledge, never been investigated.

Aims of the study

We have previously shown that the frequency of sleep disturbance is high across severe mental disorders (SCZ and BD), and that sleep disturbances are associated with more severe clinical symptoms and functional impairment (Laskemoen et al., 2019). We here investigate the relationship between sleep disturbances (any sleep disturbance and sleep disturbance subtypes) and childhood trauma (any childhood trauma and childhood trauma subtypes). Based on the previous findings of links between sleep disturbances and clinical symptoms/poorer functioning, and between childhood traumas and clinical symptoms/poorer functioning, we examine a theoretical mediation model to test if the relationship between childhood trauma and clinical symptoms/poorer functioning is mediated by sleep disturbances. We also evaluate if this theoretical mediation model is confounded by age, gender, diagnostic group (SCZ or BD), recent alcohol or drug use, a history of alcohol or drug dependency, medication with sedative effects, or weight (BMI).

Materials and methods

Participants

The current study is part of the Thematically Organized Psychosis (TOP) Research Study at the Norwegian Centre for Mental Disorders Research (NORMENT) in Oslo, Norway. This study includes 766 participants with psychotic disorders (SCZ = 418, BD = 348), recruited between 2003 and 2019. In the SCZ group, 223 participants had an SCZ diagnosis, 61 had a schizoaffective disorder, 30 had a schizophreniform disorder, and 104 had a diagnosis of other psychotic disorders. In the BD group, 223 participants had a diagnosis of bipolar I, 110 bipolar II, and 25 bipolar NOS. Participants went through a physical examination and interview about somatic illness history and current health status, completed by a medical doctor. Based on this examination and interview, in addition to consultation of journal notes, participants were excluded from the TOP study if they had a history of head injury needing hospitalization, neurological disorder, and from the current analyses if they had a known primary sleep disorder (based on self-report) such as restless legs syndrome or obstructive sleep apnea. Having IQ below 70 and age outside 18–65 years were also part of the general exclusion criteria, determined based on the information from neurocognitive assessments and clinical interviews. Participants with recent intake of drugs or alcohol, or with a history of drug or alcohol

abuse or dependency, were not excluded to ensure a representative sample. Yet, all had to be abstinent (not visibly intoxicated, or affecting clinical presentation) at the time of interviews and testing. All participants gave written informed consent after being given thorough information about the study protocol and procedures, and the study was approved by 'The Regional Committee for Research Ethics' and 'The Norwegian Data Inspectorate'.

Demographics and clinical characteristics

For diagnostic evaluation, all participants were assessed with the Structured Clinical Interview for DSM-IV (SCID-IV) (First, Spitzer, Gibbon, & Williams, 1995). The Positive and Negative Syndrome Scale (PANSS) (Kay, Fiszbein, & Opler, 1987), applying Wallwork's five-factor model (Wallwork, Fortgang, Hashimoto, Weinberger, & Dickinson, 2012), was used to assess current symptom levels using the factors PANSS positive, PANSS negative, PANSS disorganized/concrete, PANSS excited, and PANSS depressed. As the PANSS depressed includes the items G2 Anxiety, G3 Guilt Feelings, and G6 Depression Posturing, we have in the current paper used the more precise label 'PANSS depression/anxiety' factor. Current illness phase was stratified into those with and without psychosis in participants with SCZ-spectrum disorders and those with and without depression and mania in those with BDs. Current psychosis or symptomatic remission was defined according to the internationally standardized criteria (Andreasen et al., 2005), in which remission requires scores below 4 on the following PANSS items: positive symptoms (P1-delusions, G9-unusual thought content, P3-hallucinations), disorganized symptoms (P2-conceptual disorganization, G5-mannerisms/posturing), and negative symptoms (N1-blunted effect, N4-social withdrawal, N6-lack of spontaneity). Consequently, those scoring 4 or above on any of these items were considered to be psychotic. Current depression was defined using Inventory of Depressive Symptoms – Clinician-rated scale (IDS-C) (Rush, Gullion, Basco, Jarrett, & Trivedi, 1996), with a total score equal to or above 14. We used the Young Mania Rating Scale (Young, Biggs, Ziegler, & Meyer, 1978) with a total score equal to or above eight to define current mania. Those that neither met criteria for current depression or mania were defined as currently euthymic. To assess the level of functioning, we used the functioning subscale of the split-version of the Global Assessment of Functioning Scale (GAF-F) (Pedersen & Karterud, 2012). Clinical interviews and medical charts were used to gather information on recent use (past 2 weeks) of alcohol and illegal drugs (number of units for alcohol and number of times used for any relevant drug), as well as the current type(s) of use of psychotropic medication (antipsychotics, anxiolytics/hypnotics, antidepressants, antiepileptics, and/or lithium). All psychotropic medication that had sedation marked as a main or major side-effect in The Norwegian Pharmaceutical Product Compendium (Felleskatalogen, 2018) were classified as medication with sedative effects. To further enhance this dichotomized classification of psychotropic medication having sedative effects/not, we evaluated their known modes of action on neurotransmitters involved in promoting sleepiness (histaminergic/muscarinergic) such as e.g. quetiapine and olanzapine.

Childhood trauma

To assess traumatic experiences in childhood, we applied the Norwegian version of the Childhood Trauma Questionnaire-Short Form (CTQ-SF) (Bernstein et al., 2003). This self-report questionnaire comprises 28 items rated on a five-point Likert scale ranging from 1 (never true), 2 (rarely true), 3 (sometimes true), 4 (often true) to 5 (very often true) forming five subscales; emotional abuse (EA), physical abuse (PA), sexual abuse (SA), physical neglect (PN), and emotional neglect (EN) in addition to the total trauma score. We used these childhood trauma data both as a continuous variable and as variables dichotomized into 'no trauma exposure' (none or mild exposure) *v.* 'trauma exposure' (moderate or severe exposure), based on the cut-off scores recommended by Bernstein and Fink (1998).

Sleep disturbances

Rating of sleep disturbances was based on the four first items from the IDS-C (Rush et al., 1996); difficulty falling asleep (item 1; Sleep Onset Insomnia), difficulty maintaining sleep (item 2; Mid-Nocturnal Insomnia), early awakening (item 3; Early Morning Insomnia), and hypersomnia (item 4; Hypersomnia). The items are rated on a four-point Likert scale (0–3) in which higher scores represent more subjective disturbance based on sleep experience over the past 7 days. IDS-C has been used in several prior studies to differentiate between – and conceptualize – sleep disturbances (Laskemoen et al., 2019; Steinan et al., 2016*a*, 2016*b*). These four sleep items have also been validated as the measures of insomnia and hypersomnia, and have been shown to adequately predict a clinical diagnosis of sleep disorders (Gruber et al., 2009; Kaplan, Gruber, Eidelman, Talbot, & Harvey, 2011; Soehner, Kaplan, & Harvey, 2014; Sylvia et al., 2012). In line with previous studies (Laskemoen et al., 2019; Steinan et al., 2016*a*, 2016*b*), we define the following sleep disturbances based on the IDS-C (reminding that these definitions represent current symptoms of sleep disturbances and are not diagnostic categories).

(1) **Insomnia** corresponds to: (a) a score of $\geqslant 2$ on *Sleep Onset Insomnia* (more than half the time it takes minimum 30 min to fall asleep); (b) a score of = 3 on *Mid-Nocturnal Insomnia* (more than half the time, waking up happens more than once per night and one stays awake for 20 min or more); or (c) a score of $\geqslant 1$ on *Early Morning Insomnia* (more than half the time, one wakes up more than 30 min before needing to get up). In addition, a score of = 0 on the *Hypersomnia* item (sleeps no more than 7–8 h a night, without naps) was a prerequisite.
(2) **Insomnia total score** corresponds to the sum of item (1) *Sleep Onset Insomnia*, item (2) *Mid-Nocturnal Insomnia*, and item (3) *Early Morning Insomnia.*
(3) **Hypersomnia** corresponds to a score of $\geqslant 1$ on the *Hypersomnia* item (sleeping up to 10 h per day) with no evidence of insomnia.
(4) **Delayed sleep phase (DSP)** corresponds to a score of $\geqslant 3$ on *Sleep Onset Insomnia* (more than half the time, it takes more than 60 min to fall asleep), and a score of $\geqslant 1$ on the *Hypersomnia* item.
(5) **Any sleep disturbance** corresponds to a score over cut-off on any of the sleep disturbances described**.**

All of the above conceptualizations of sleep disturbances are dichotomized variables with the exception of insomnia total score which can be measured continuously.

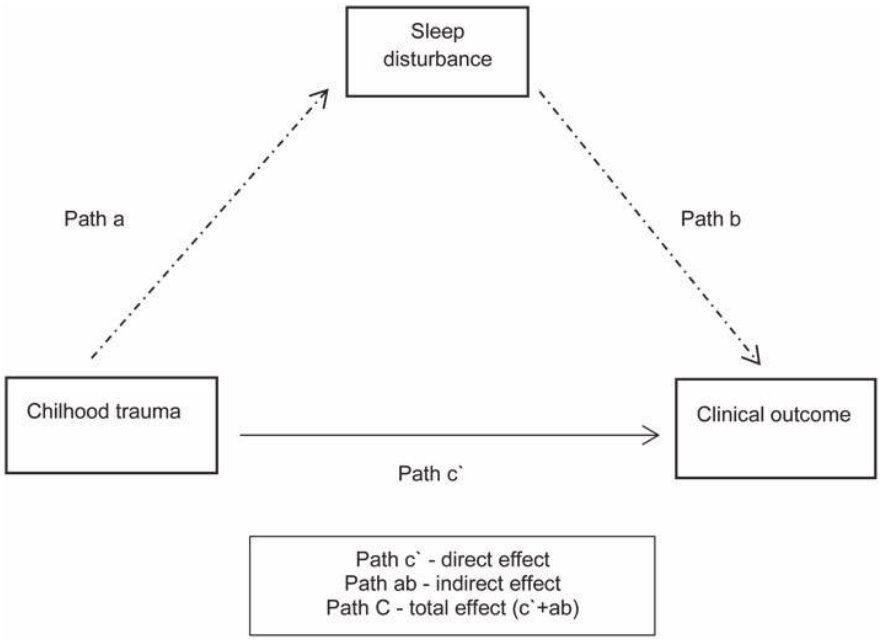

Fig. 1. Overall model.

Statistical analyses

Statistical analyses were performed using The Statistical Package for the Social Sciences (SPSS INC, Chicago, IL, USA, version 25). We first examined the frequency of the different sleep disturbances (any sleep disturbance, insomnia, hypersomnia, and delayed sleep phase; dichotomous variables) amongst participants with and without childhood trauma (dichotomous variables) using χ^2 statistics. We then conducted follow-up analyses, repeating the same analyses separately for the SCZ and BD groups. Secondly, the differences in the reported magnitude of childhood trauma subtypes (assessed as continuous variables) between those with and without the different sleep disturbances (insomnia, hypersomnia, and delayed sleep phase; dichotomous variables) were examined with Mann–Whitney *U* tests due to skewed distributions of childhood trauma data. Follow-up analyses were conducted repeating the same analyses separately for the SCZ and BD groups.

For our third research aim, we examined whether the presence of a sleep disturbance mediated the relationship between childhood trauma total score and clinical outcome, using the following approach to select variables for the model (see Fig. 1). We first examined *path c*, calculating *Spearman's correlations* between the predictor variable (childhood trauma total) and the clinical outcome-dependent variables (PANSS positive, negative, disorganized, excited, depressive/anxiety, and GAF-F). Childhood trauma total was chosen as a predictor variable for several reasons. The relationship between childhood trauma and clinical outcome has been shown to persist regardless of trauma type. Furthermore, the amount of trauma exposure is suggested to be important (Gibson et al., 2016). Lastly, partitioning out a specific trauma sub-type would mean losing statistical power. Secondly, focusing on *path b*, correlations between the mediator (sleep disturbance) and the clinical outcome-dependent variables were calculated. Clinical outcome measures that were significantly correlated with both the predictor (childhood trauma total) and the mediator (sleep disturbance) at a Bonferroni-adjusted *p* level (0.05/6 clinical outcome measures = new *p* value 0.008) were selected as dependent (outcome) variables for the mediation model.

Based on findings from our second aim, the sleep disturbance (s) found to be significantly associated with the predictor variable (childhood trauma total) would then serve as a mediator in the model. We conducted mediation analyses based on *regression analyses*; applying Haye's PROCESS tool version 3.3 for SPSS. We used model 4 designs, in which total childhood trauma score was set as a predictor, sleep disturbance was set as a mediator, and the different clinical outcome variables were set as dependent variables, respectively. We examined *path a* (from the predictor to the mediator), *path b* (from the mediator to the dependent variable), *path c'* (the direct effect of the predictor to the dependent variable) and *path C* (the total effect of the predictor on the dependent variable) as well as the bootstrapped indirect effect and its confidence interval, using 5000 bootstrap samples. We calculated the proportion of the total effect mediated (in percentage) as the ratio of the indirect effect to the total effect, as well as the partially standardized indirect effects.

Lastly, follow-up analyses were conducted including covariates significantly associated with either the predictor variable (childhood trauma total) or the sleep disturbance(s) found to be significantly associated with the predictor variable (childhood trauma total).

Results

Demographics and clinical characteristics

An overview of demographic and clinical characteristics for the total sample is shown in Table 1. As seen under *clinical variables* and *current illness phase*, the majority of participants were currently symptomatic.

The frequency of sleep disturbance in those with and without childhood trauma

As illustrated in Table 1, 50% of the total sample had experienced childhood trauma. The frequency of *any sleep disturbance* was not significantly different in those with childhood trauma experiences (78%) and those without (73%) ($\chi^2 = 2.45$, $p = 0.118$). However,

Table 1. Demographics and clinical characteristics in the total sample

	Total sample $N = 766$	Childhood trauma	No childhood trauma
Demographics			
Age, mean ± S.D.	30.9 ± 10.6	31.6 (10.6)	30.1 (10.6)
Gender, male *n* (%)	384 (50.1)	178 (48.8)	192 (52.2)
Education in years, mean ± S.D.	13.9 ± 3.1	13.5 (3.2)	14.3 (2.9)
Childhood trauma *n* (%)[a]	365 (49.8)		
Physical abuse *n* (%)[b]	92 (12.1)		
Sexual abuse *n* (%)[c]	122 (16.3)		
Emotional abuse *n* (%)[d]	208 (27.7)		
Emotional neglect *n* (%)[e]	209 (28.0)		
Physical neglect *n* (%)[f]	167 (22.1)		
Clinical variables			
Insomnia *n* (%)	344 (44.9)	188 (51.5)	143 (38.9)
Hypersomnia *n* (%)	231 (30.2)	96 (26.3)	125 (34.0)
Delayed sleep phase *n* (%)	58 (7.6)	27 (7.4)	30 (8.2)
Any sleep disturbance *n* (%)	575 (75.1)	284 (77.8)	268 (72.8)
Alcohol units last two weeks, mean ± S.D.	6.5 ± 12.8	6.9 (14.0)	6.3 (11.4)
Drug use last two weeks, mean ± S.D.	0.4 ± 2.0	0.5 (2.3)	0.3 (1.8)
Lifetime alcohol dependency, yes (%)	97 (12.7)	57(15.6)	37 (10.1)
Lifetime drug dependency, yes (%)	128 (16.7)	72 (19.7)	52 (14.1)
PANSS positive, mean ± S.D.	8.0 ± 4.0	8.5 (4.2)	7.5 (3.8)
PANSS negative, mean ± S.D.	11.1 ± 5.3	11.0 (4.9)	11.1 (5.6)
PANSS disorganized, mean ± S.D.	6.3 ± 2.6	6.4 (2.7)	6.2 (2.5)
PANSS excited, mean ± S.D.	5.5 ± 1.9	5.6 (2.0)	5.3 (1.8)
PANSS depression/anxiety, mean ± S.D.	7.9 ± 3.0	8.6 (3.1)	7.3 (2.8)
GAF-F, mean ± S.D.	50.1 ± 13.9	47.5 (12.5)	52.6 (14.6)
IDS-C total, mean ± S.D.[g]	17.4 (11.3)	20.1 (11.5)	15.1 (10.7)
YMRS total, mean ± S.D.[h]	3.7 (4.5)	4.4 (4.7)	3.1(4.4)
Current illness phase[i]			
Schizophrenia-spectrum disorders, $n = 418$			
Psychotic *n* (%)	297 (72.1)	157 (76.2)	126 (67.0)
Remission *n* (%)	115 (27.9)	49 (23.8)	62 (33.0)
Bipolar disorders, $n = 348$:			
Depressed *n* (%)	189 (55.4)	95 (62.1)	87 (49.7)
Manic *n* (%)	50 (14.4)	29 (18.6)	20 (11.3)
Euthymic *n* (%)	131 (38.5)	46 (30.1)	79 (45.4)
Medication and somatic variables			
Antipsychotics *n* (%)	523 (68.3)	237 (64.9)	262 (71.2)
Mood stabilizers *n* (%)	219 (28.6)	107 (29.3)	104 (28.3)
Antidepressants *n* (%)	228 (29.8)	117 (32.1)	96 (26.1)
Anxiolytics/hypnotics *n* (%)	75 (9.8)	44 (12.1)	28 (7.6)
Medication with sedative effects *n* (%)	354 (46.2)	169 (46.3)	169 (45.9)

PANSS, Positive and Negative Syndrome Scale. PANSS was organized after Wallwork's five-factor model; GAF-F, Global Assessment of Functioning scale; BMI, body mass index. Mood stabilizer refers to lithium or antiepileptics.
[a]95.7% ($n = 733$) of the participants had data on childhood trauma.
[b]99.1% ($n = 759$) of the participants had data on physical abuse.
[c]97.5% ($n = 747$) of the participants had data on sexual abuse.
[d]98.0% ($n = 751$) of the participants had data on emotional abuse.
[e]97.4% ($n = 746$) of the participants had data on emotional neglect.
[f]98.7 ($n = 756$) of the participants had data on physical neglect.
[g] = 95.2 ($n = 729$) of the participants had data on IDS-C total.
[h] = 99.5 ($n = 762$) of the participants had data on YMRS total.
[i] = Current illness phase is based on cut-off scores from PANSS items, IDS-C, and YMRS.

Table 2. The relationship between childhood trauma subtypes and different sleep disturbances in severe mental disorders (Mann–Whitney *U* test)

	Insomnia			Hypersomnia			Delayed sleep phase		
	Median Insomnia *N* = 344	Median no Insomnia *N* = 422	Statistics	Median Hypersomnia *N* = 231	Median no Hypersomnia *N* = 535	Statistics	Median DSP *N* = 58	Median no DSP *N* = 708	Statistics
Childhood trauma total	40.0	38.0	*U* = 52 813.50 *z* = −3.39 *p* = 0.001	38.0	40.0	*U* = 46 063.50 *z* = −2.72 *p* < 0.01	38.0	39.0	*U* = 17 355.00 *z* = −0.00 *p* = 0.999
Physical abuse	5.0	5.0	*U* = 62 990.00 *z* = −3.18 *p* < 0.001	5.0	5.0	*U* = 55 018.00 *z* = −2.29 *p* < 0.05	5.0	5.0	*U* = 19 704.00 *z* = −0.45 *p* = 0.655
Sexual abuse	5.0	5.0	*U* = 64 928.00 *z* = −1.8 *p* = 0.072	5.0	5.0	*U* = 56 587.00 *z* = −1.01 *p* = .312	5.0	5.0	*U* = 19 483.00 *z* = −0.15 *p* = 0.882
Emotional abuse	10.0	9.0	*U* = 57 187.50 *z* = −4.26 *p* < 0.001	8.0	10.0	*U* = 50 591.50 *z* = −3.32 *p* < 0.001	10.0	9.0	*U* = 18 756.00 *z* = −0.65 *p* = 0.514
Emotional neglect	11.0	10.0	*U* = 61 418.00 *z* = −2.53 *p* < 0.01	10.0	11.0	*U* = 53 263.00 *z* = −1.99 *p* < 0.05	11.0	11.0	*U* = 18 794.00 *z* = −0.14 *p* = 0.890
Physical neglect	7.0	6.0	*U* = 65 805.00 *z* = −1.66 *p* = 0.098	6.0	7.0	*U* = 56 890.50 *z* = −1.23 *p* = .221	7.0	7.0	*U* = 19 654.50 *z* = −0.38 *p* = 0.707

the frequency of insomnia was significantly *higher* in those with childhood trauma experiences (52%) *v.* those without (39%) ($\chi^2 = 11.84$, $p = 0.001$), with 26% of the total sample reporting the occurrence of both childhood trauma experiences and insomnia. In contrast, the frequency of hypersomnia was significantly *lower* in those with childhood trauma experiences (26%) compared to those without (34%) ($\chi^2 = 5.11$, $p < 0.05$). The frequency of DSP did not differ significantly between participants with (7%) and without childhood trauma experiences (8%) ($\chi^2 = 0.15$, $p = 0.703$). Follow-up analyses showed that for both SCZ and BD, insomnia was the only sleep disturbance that was significantly higher in those with childhood trauma experiences compared to those without (SCZ: 52% *v.* 39%, $\chi^2 = 6.87$, $p < 0.01$; BD: 49% *v.* 38%, $\chi^2 = 4.66$, $p < 0.05$).

The magnitude of childhood trauma subtypes and different sleep disturbances

As illustrated in Table 2, the level of *childhood trauma total*, *physical abuse*, *emotional abuse*, and *emotional neglect* were significantly higher in participants with insomnia compared to those without; while significantly lower in those with hypersomnia compared to those without. The level of *sexual abuse* and *physical neglect* were not significantly different between participants with or without insomnia or hypersomnia. There was no difference between participants with and without DSP for childhood trauma total or any of the childhood trauma subtypes.

Follow-up analyses showed that in the SCZ group; *childhood trauma total*, *physical abuse*, *emotional abuse*, and *emotional neglect* were significantly higher in participants with insomnia compared to those without; whilst *childhood trauma total*, *physical abuse*, and *emotional abuse* were significantly lower in those with hypersomnia compared to those without. In the BD group, only *emotional abuse* was significantly higher in participants with insomnia compared to those without, whilst significantly lower in those with hypersomnia compared to those without.

This shows that insomnia is common in participants with childhood trauma, and in the context of *physical abuse*, *emotional abuse*, and *emotional neglect*. Insomnia was therefore chosen as the mediator in the analyses of the relationship between childhood trauma and clinical outcome, used as a continuous variable labeled '*insomnia total*'. The relationship between the predictor (childhood trauma total) and the mediator (insomnia total) (path a) was re-stated in a significant bivariate correlation (Spearman's $\rho = 0.196$, $p < 0.001$).

Testing the theoretical model; sleep disturbance as a mediator between childhood trauma and clinical outcome

Relationship between insomnia total, childhood trauma total, and clinical outcome

Both *Childhood trauma total* and *Insomnia total* were significantly associated (using a threshold of 0.008) with PANSS positive and PANSS depressive/anxiety, as well as GAF-F (Table 3). Consequently, further mediation analyses were conducted separately for PANSS positive, PANSS depressione/anxiety, and functioning GAF F.

Table 3. The relationship between sleep disturbance, childhood trauma, and clinical outcome in severe mental disorders (Spearman's correlations)

	PANSS Positive	PANSS Negative	PANSS Disorganized/concrete	PANSS Excited	PANSS Depression/anxiety	GAF-F
Childhood trauma total	$r = .142$ $p < 0.001$	$r = -0.003$ $p = 0.934$	$r = 0.019$ $p = 0.620$	$r = 0.097$ $p = 0.01$	$r = 0.256$ $p < 0.001$	$r = -0.180$ $p < 0.001$
Insomnia total	$r = .216$ $p < 0.001$	$r = .114$ $p < 0.01$	$r = 0.068$ $p = 0.062$	$r = 0.105$ $p < 0.01$	$r = 0.339$ $p < 0.001$	$r = -0.158$ $p < 0.001$

GAF, Global Assessment of Functioning scale; PANSS, Positive and Negative Syndrome Scale. PANSS was organized after Wallwork's five-factor model.

Table 4. Insomnia as a mediator in the relationship between childhood trauma and clinical outcome (total effect, direct effect, and indirect effect)

	Total effect, estimate (S.E.), p value	Direct effect, estimate (S.E.), p value	Indirect effect, bootstrap confidence interval	Partially standardized indirect effect	Proportion mediated % (ab/C)
PANSS positive	0.9684, (0.2925) $p = 0.001$	0.7228, (0.2904) $p = 0.0130$	0.1158–0.4039	0.0613	25%
PANSS depression/ anxiety	1.2307, (0.2188) $p < 0.001$	0.9139, (0.2085) $p < 0.001$	0.1614–0.4896	0.1042	25.7%
GAF-F	−5.1711, (0.9948) $p < 0.001$	−4.5423, (0.9948) $p < 0.001$	−1.0996 to −0.2563	−0.0455	12%

Insomnia total as a mediator in the relationship between childhood trauma and clinical outcome

Three separate mediation analyses were conducted to evaluate whether the effect of childhood trauma total on PANSS positive, PANSS depression/anxiety, and GAF-F, respectively, was mediated by insomnia total. As none of the confidence intervals contain zero, there is a statistically significant indirect effect of childhood trauma total via insomnia total for all three clinical outcome measures (Table 4). Insomnia mediated 25% of the effect of childhood trauma on PANSS positive, 26% of the effect on PANSS depression/anxiety, as well as 12% of the effect on GAF-F.

Spearman's correlations, t test, or Mann–Whitney U tests were conducted to evaluate the bivariate associations to covariates [age, gender, diagnostic group (SCZ or BD), recent alcohol or drug use, a history of alcohol or drug dependency, medication with sedative effects, or weight (BMI)], data not shown. Lower age was significantly correlated with insomnia total ($r = -0.071$, $p < 0.05$) and higher age with childhood trauma total ($r = 0.117$, $p < 0.005$). Higher recent intake of drugs was significantly associated with higher insomnia total score ($r = 0.120$, $p < 0.01$), whilst having a history of drug dependency was significantly associated with higher childhood trauma total ($U = 32\,042.5$, $p < 0.05$). Consequently, age, recent intake of drugs, and history of drug dependency were included as covariates in the three separate follow-up mediation analyses. After adjusting for these covariates, the indirect effect of childhood trauma total via insomnia total for all three clinical outcome measures remained statistically significant from zero.

Discussion

This is the first study on severe mental disorders to show that people with a history of childhood trauma more often experience symptoms of insomnia than those without a history of childhood trauma, and that insomnia is a significant mediator of the effect of childhood trauma on the severity of positive symptoms, symptoms of depression/anxiety, and poorer functioning.

Whilst insomnia is significantly more frequent in participants with childhood trauma, the opposite is the case for hypersomnia. These differences in associations could be based on different biological underpinnings of the two sleep disturbances. Insomnia is characterized by physiological, cognitive, and affective hyperarousal (Levenson, Kay, & Buysse, 2015), a theoretically plausible consequence of trauma exposure. The disinhibition of sleep-induced transmission and reduced activity in wake-promoting neurons that may be seen in hypersomnia (Carbonell & Leschziner, 2017) is possibly less likely to be a consequence of trauma-related stress response. Consequently, childhood trauma and hypersomnia might not share common underlying mechanisms; indeed, a state of hyper-arousal would prohibit hypersomnia.

Although the relationship between childhood trauma and sleep disturbance primarily has been investigated in the general population, our finding of an association between total childhood trauma and insomnia fit well with a review of retrospective cohort studies (Brindle et al., 2018). Also, in a recent study of young individuals with a history of depression (Hamilton, Brindle, Alloy, & Liu, 2018), childhood emotional neglect was found to predict insomnia symptoms. This is in line with our findings that three subtypes of childhood trauma (*physical abuse*, *emotional abuse*, and *emotional neglect*) were significantly associated with insomnia in the total sample, most likely driven by the associations in the SCZ group. For BD, we mainly found associations to emotional abuse. We have identified one other study of severe mental disorders in this area (Aubert et al., 2016), showing a significant association between *emotional abuse* and poorer sleep quality in euthymic persons with BD. In the latter study, the authors decided to adjust for clinical aspects, including anxiety and use of anxiolytic medication as potential confounders, i.e. not considering the possibility that sleep disturbances could mediate the association between trauma and clinical symptoms. Taken

together, this supports the idea that *emotional abuse* might be an especially salient trauma subtype in BD.

The existing studies of sleep and trauma in clinical samples (Aubert et al., 2016; Hamilton et al., 2018), including the current, have not found any association between sexual abuse and insomnia. This is in contrast to the studies of non-clinical samples (Kajeepeta et al., 2015; Lind, Aggen, Kendler, York, & Amstadter, 2016; Steine et al., 2012). Our data have no indications of why. However, studies suggest distinct trauma subtypes differentially affect biological stress responses (Kuhlman, Geiss, Vargas, & Lopez-Duran, 2015), and thus may interact with underlying vulnerabilities in different ways. In this vein, different trauma subtypes may also affect sleep disturbances differently.

Our finding that insomnia partially mediates the relationship between childhood trauma and the severity of positive symptoms, depression/anxiety symptoms, and dysfunction lends support to our proposed theoretical model. The findings have implications for understanding how stress impacts on the severity of psychosis, and could imply that sleep disturbances following childhood trauma interact with the stress regulatory system further exacerbating clinical symptoms. This line of reasoning is supported by recent knowledge about the relations between activities of the stress response system and the circadian system (Neumann, Schmidt, Brockmann, & Oster, 2019). Dysregulations of both systems may progressively change the underlying properties of brain systems that regulate neuroendocrine function, and thus play an important role in the development of stress-related disorders, potentially creating a vicious circle. Indeed, sleep disturbances following trauma exposure have been suggested as a core pathway mediating the neurobiological consequences of this exposure (Landgraf, McCarthy, & Welsh, 2014; Lavie, 2001; Teicher et al., 2017). Furthermore, recent studies support that insomnia is a contributory factor in the development of psychosis (Freeman et al., 2017; Reeve et al., 2015, 2018*a*), and that the relationship between insomnia and psychotic experiences is mediated by negative affect, such as anxiety and depression (Reeve, Nickless, Sheaves, & Freeman, 2018*b*). Our findings thus suggest that insomnia in persons exposed to childhood trauma could be one of the driving forces behind worsening of clinical symptoms and functional impairment in severe mental disorders.

In addition to these theoretical aspects, the current study has several clinical implications. Firstly, it identifies a large subgroup of patients with co-occurring childhood trauma and current insomnia, and advocates routine assessment of both childhood trauma and sleep disturbances in clinical practice. Moreover, the suggestion that insomnia could be causally related to the severity of clinical symptoms and functional impairment in this subgroup supports the importance of treating insomnia to improve psychotic symptoms (Freeman et al., 2017). Despite growing evidence that cognitive-behavioral therapy for insomnia is feasible, acceptable, and effective also in psychosis (Freeman et al., 2017; Waite et al., 2016), formal assessment and recommended interventions for sleep disturbances are rarely used in clinical practice (Rehman et al., 2017).

Some methodological limitations should be addressed: Our data are cross-sectional, limiting our possibility to infer on causal associations. Sleep disturbances are based on items from a rating scale primarily designed to assess depressive symptoms (IDS-C). The four sleep items applied have nevertheless been found valuable in the prediction of diagnoses of sleep disorders (Gruber et al., 2009; Kaplan et al., 2011; Soehner et al., 2014; Sylvia et al., 2012) and have been used in previous studies (Laskemoen et al., 2019; Steinan et al., 2016*a*, 2016*b*). As nightmares are common symptoms of trauma, and might cause frequent wake-ups that may lead to high insomnia scores, nightmare disorders should ideally have been assessed. Our measure of childhood traumas is a questionnaire based on retrospective trauma experience, thus recall bias may have influenced the reports. However, evidence of systematic recall bias in the reports of retrospective trauma has not been found in previous studies designed to detect this phenomenon (Edwards et al., 2001).

Conclusion and future directions

This is the first study to identify a large sub-group (26%) of people with severe mental disorders having both childhood trauma experiences and current insomnia symptoms. Importantly, this study provides evidence of a theoretically based mediation model, showing that insomnia partly mediates the association between childhood trauma and the severity of clinical symptoms and functional impairment across severe mental disorders. Longitudinal studies are now needed to disentangle the relationship between childhood trauma, sleep disturbance, and clinical outcome, employing both subjective and objective measures of sleep disturbances. As the current study may suggest a causal trajectory from childhood trauma experiences via insomnia to the severity of clinical symptoms, future studies should also investigate whether the combination of childhood trauma experience and insomnia might represent cumulative risk factors for the development of severe mental disorders. Insomnia could thus be a treatment target in at-risk individuals.

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Ethical standards. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

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