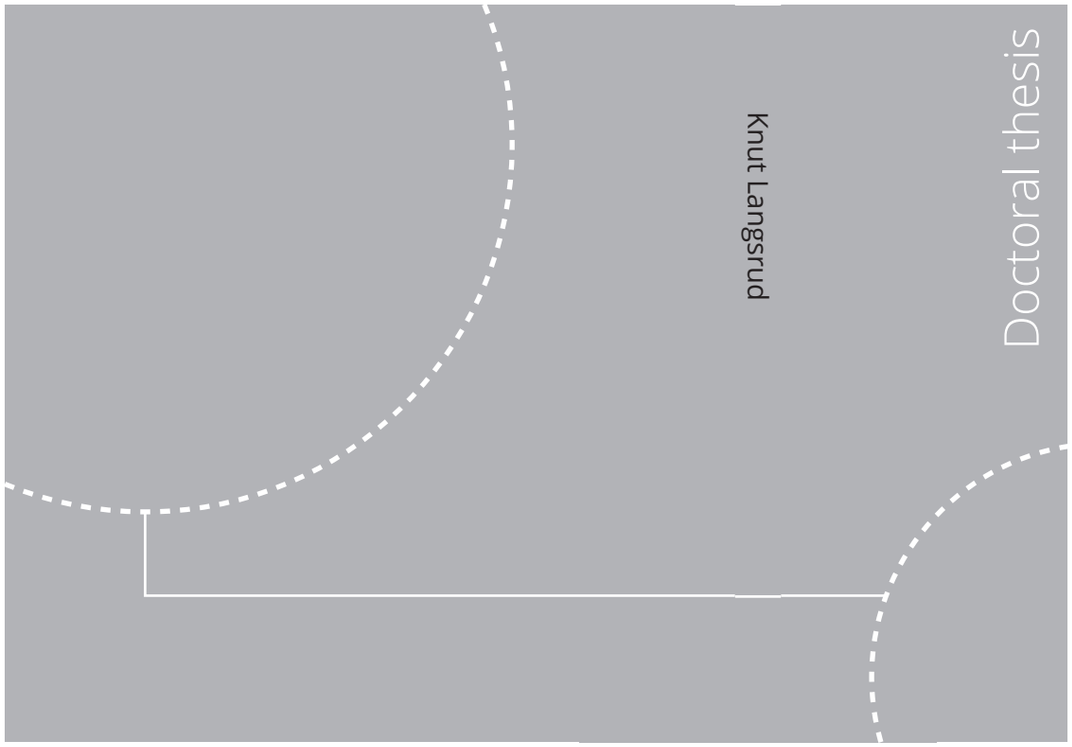

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Hvordan nattesøvn påvirker atferd neste dag hos pasienter ved et psykiatrisk sykehus

Denne avhandlingen beskriver sammenhengene mellom nattesøvn og atferd de neste dagene blant to grupper av pasienter som ble behandlet ved Divisjon Psykisk helsevern, St Olavs hospital: Polikliniske pasienter med forsinket søvnfase syndrom og akutt innlagte pasienter på intensiv-avsnittene i vår avdeling.

God søvn er en essensielt for oss alle, og søvnforstyrrelser kan ha negative helsemessige konsekvenser som vektoppgang, sukkersyke, forkortet livslengde og redusert kognitiv fungering. Vi mangler likevel kunnskap om hvordan søvnforstyrrelser påvirker atferden neste dag hos våre pasienter.

Hos pasienter med forsinket søvnfase syndrom (ekstreme B-mennesker) undersøkte vi sammenhengen mellom søvn om natten og vansker med oppvåkning og kognitiv funksjon neste dag. Flere av pasientene våknet ikke av en vekkerklokke på 104 dB som tilsvarer lydnivået på nattklubb eller et stort idrettsarrangement. Alle var i REM søvn (en søvnfase med hurtige øyebevegelser) og ikke i dyp søvn som forventet. Pasientene med forsinket søvnfase syndrom gjorde det dårligere på kognitive tester om morgenen enn om kvelden.

Hos 135 akutt innlagt pasienter på psykiatrisk intensivavsnitt undersøkte vi om søvn lengde eller endring i søvn lengde mellom to påfølgende netter var relatert til aggressiv atferd neste dag, hvor lenge pasienten var innlagt på intensivavsnittet, samt om målene på søvn kunne bedre mulighetene til å forutsi aggresjon. Både stor forskjell i søvnlengde mellom to netter og kort søvnlengde var knyttet til aggressiv atferd eller voldelige hendelser neste dag. I tillegg var det en sammenheng mellom kort søvnlengde første natt, og stor forskjell mellom søvnlengde natt en og natt to, og lange opphold. En skala utviklet for å forutsi aggresjon og vold i sykehusavdelinger (BVC - Brøset Violence Checklist), blir noe bedre om en legger til et mål for søvnvansker.

Både søvnlengde og variasjon i søvnlengde mellom to netter er relatert til pasienters atferd neste dag. Funnene kan ha betydning både for hvordan en gir behandling ved forsinket søvnfase syndrom, og hvordan en legger opp behandlingen i psykiatriske intensivavsnitt.
Veileder: Professor Gunnar Morken. Biveileder: Professor Arne Vaaler

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Acknowledgments

Denne avhandlingen har gjennom mange år vært mitt lille «private» prosjekt, noe jeg til stadighet har kommet tilbake til mellom det kliniske arbeidet og andre større forskningsprosjekter. Prosjektet har fått hvile og modne gjentatte ganger og over lengre perioder. For de som har stått ved siden av har nok det vært frustrerende. Mange har involvert seg, og uten dem hadde nok dette blitt liggende til evig hvile for flere års siden.

At ting har tatt tid, skylde ikke mangel på muligheter, min sjef ved Østmarka Pål Sandvik har gitt meg frie hender til å styre selv. Og en spesiell takk til mine kollegaer for «good will» til å være borte fra klinikken og for alle «oppmuntrende» kommentarer under veis. Så takk til St Olav hospital.

Mine veiledere Professor og Direktør Gunnar Morken og Professor Arne Valler har trofast holdt trykket oppe, uavhengig om jeg jobbet med dette eller ikke. Når den ene var sliten, oppgitt eller oppfatt, tok den andre over. De har vært avgjørende for at prosjekter i det hele tatt kom i gang, for at det fikk en vinkling som har gjorde arbeide interessant for andre enn bare meg og for at det hele skulle komme til en avslutning.

Takk til NTNU som har gitt veilederne tid og som har vært tålmodige med meg underveis, og latt meg ta forskerkursene to ganger. Og takk til NTNU og St Olav for låne av andre ressurser når jeg trengte det, spesielt skal nevnes professor Tom Palmstierna og den alltid tilstedeværende Cüneyt Güzey.

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Samarbeid med nevrofysiologiene professor Trond Sand og min barndomsvenn Morten Engstrøm har vært berikende. En stadig påminning om hvor mye kunnskap en kan besitte, og hvilket detalj og presisjonsnivå som er nødvendig om en vil opp noen hakk i forsknings verdenen.

Mine døtrer, Julie og Silje er voksne, har flyttet ut og klarer seg godt uten meg. De har nok lidd mere under all tiden jeg har brukt på min kliniske jobb, enn på det akademiske. Men kunnskap om å skrive artikler, prosjektbeskrivelse ol. som jeg har tilegnete meg under veis, har de gladelig tatt i mot og forhåpentlig også kommet dem til gode.

Ja, min kone Elizabeth har rett. Hadde hun ikke startet som PhD stipendiat, hadde jeg aldri blitt ferdig. At hun har arbeidet strukturert, systematisk og planmessig med sitt PhD prosjekt hjemme, på skrive turer til Spania og under oppholdet i Australia, smittet over, i perioder. Nok til at jeg fikk fremgang på mitt arbeid. Selv om jeg har konkurranse instinkt, så var nok ikke dette en likeverdig konkurranse, jeg var nærmest bloddopet med et stort team rundt meg, som bistod umiddelbart når jeg ønsket, mens hun stilte til start uten høydeopphold og støtteapparat. Desto større ble gleden da hun kommer i mål noen uker før meg.

Takk til alle som er nevnt og ikke nevnt, som har bidratt og støttet meg i mitt «private» prosjekt.

List of papers

Paper I

Difficult morning awakening from rapid eye movement sleep and impaired cognitive function in delayed sleep phase disorder patients.

Brandy Solheim, Knut Langsrud, Håvard Kallestad, Alexander Olsen, Bjørn Bjorvatn, Trond Sand.

Sleep Medicine 15 (2014) 1264–1268

Paper II

Sleep patterns as a predictor for length of stay in a psychiatric intensive care unit.

Knut Langsrud, Arne E. Vaaler, Håvard Kallestad, Gunnar Morken.

Psychiatry Research 237 (2016) 252–256

Paper III

Sleep at night and association to aggressive behaviour; patients in a Psychiatric Intensive Care Unit.

Knut Langsrud, Håvard Kallestad, Arne Einar Vaaler, Roger Almvik, Tom Palmstierna, Gunnar Morken.

Psychiatry Research 263 (2018) 275–279

Paper IV

The Predictive Properties of Violence Risk Instruments May Increase by Adding Items Assessing Sleep

Knut Langsrud, Arne Vaaler, Gunnar Morken, Håvard Kallestad, Roger Almvik, Tom Palmstierna, Ismail C. Güzey.

Frontiers in Psychiatry 10 (2019) 323 (doi: 10.3389/fpsyt.2019.00323)

Acronyms and Abbreviations

ANOVA	analysis of variance
AUC	area under the curve
BDI	Beck Depression Inventory
BVC	Brøset Violence Checklist
CCPT II	Conners' Continuous Performance Test (second edition)
CI	confidence interval
CPT	continuous performance test
DASA-IV	Dynamic Appraisal of Situational Aggression – Inpatient Version
dB	decibel
DLMO	dim light melatonin onset
DSM-V	Diagnostic and Statistical Manual of Mental Disorders (fifth edition)
DSPD	delayed sleep phase disorder
DSWPD	delayed sleep-wake phase disorder
EEG	electroencephalography
Hit-RT	hit reaction time
ICD-10	International Classification of Diseases (version 10)
ICSD-2	International Classification of Sleep Disorders (second edition)
IQR	interquartile range
iqRGC	intrinsically photosensitive retinal ganglion cells
MEQ	Horne–Östberg Morningness Eveningness Questionnaire
NICE	The National Institute for Health and Care Excellence
NREM	non-rapid eye movement
PICU	psychiatric intensive care unit
PSG	polysomnography
REM	rapid eye movement
ROC	receiver operating characteristic
SCN	suprachiasmatic nuclei
SD	standard deviation
SOAS-R	Staff Observation Aggression Scale-Revised
SWA	slow wave activity
SWS	slow wave sleep
TST	total sleep time

Summary

This thesis explores the associations between sleep at night and behaviour the next day in two patient samples from a defined catchment area admitted to the Department of Psychiatry, St Olav's University Hospital: outpatients with delayed sleep-wake phase disorder (DSWPD) admitted to the specialist clinic for patients with sleep disorders, and inpatients acutely admitted to the psychiatric intensive care units (PICUs).

Sleep is an essential function for all animals, including humans. Disruption of sleep patterns and lack of sleep affect our functioning and behaviour. Lack of sleep has numerous effects, ranging from deterioration in performance on more complicated cognitive tasks to being associated to a number of somatic health problems, such as increased weight, diabetes, and decreased life expectancy. The associations between sleep and daytime functioning are complex and bidirectional.

Among outpatients with DSWPD and acute psychiatric inpatients admitted to PICUs, disturbed sleep and challenging behaviour is common. The impact of sleep disruptions on behaviour the next day is seldom studied.

This thesis aimed to study the awakening threshold and changes in cognitive function after awakening in DSWPD patients. Additionally to study the effects of sleep duration or night-to-night variations in sleep duration on length of stay and observer-rated aggressive behaviours in acutely admitted psychiatric patients, and finally to investigate whether the predictive properties of a violence risk instrument predicted aggressive incidents more precisely if a sleep variable was added to it.

Methods

Paper one reports data from nine patients with DSWPD and nine sex- and age-matched healthy controls who stayed in the sleep laboratory for one night. They were examined with polysomnography and completed the continuous performance test (CPT) in the afternoon and immediately upon waking. An alarm clock was activated at 07:00 with sound intensity increasing from 72 to 104 dB.

Paper two reports data from 135 patients consecutively admitted to a PICU. Papers three and

four report data for 50 of these admissions. The nurses registered the time the patients were sleeping, aggressive behaviours using the Brøset Violence Checklist (BVC), and aggressive incidents using the Staff Observation Aggression Scale-Revised (SOAS-R).

Results

In all patient groups we found wide variability in sleep duration between individuals.

Three of the patients with DSWPD did not wake up at the alarm sound of 104 dB. The three patients were in rapid eye movement (REM) sleep. On the CPT test, patients with DSWPD had longer reaction times in the morning than in the afternoon.

In the acutely admitted subgroup of patients with schizophrenia, sleep duration the first night correlated negatively with the length of stay. For the whole group of patients, the difference in sleep duration from night one to night two were correlated with length of stay. Short sleep duration the first night correlated with aggressive behaviour the next day. During the stay, large absolute differences in sleep duration between two consecutive nights correlated with aggressive behaviour the next day, and short sleep duration was associated with violent incidents. The violence risk instrument BVC appeared to predict aggressive incidents more precisely when a sleep variable was added.

Discussion

We found that patients with DSWPD struggle to wake up with an alarm clock. These patients were in a period of REM sleep, rather than in the expected period of slow wave sleep (SWS). Their reported drowsiness in the morning was supported by a neuropsychological test.

Among the acute psychiatric patients in the PICUs, we found large variations in sleep duration between individual patients, as well as large intra-individual lack of stability in sleep duration. The lack of stability in sleep duration, and the magnitude of the night-to-night variations of the first nights predicted the length of stay in the PICU. These factors were also associated with threatening behaviour and aggressive incidents. Assessments of sleep disorders may increase the value of psychometric instruments designed to predict the imminent risk of violence in psychiatric inpatients.

The studies had a limited number of participants. There were also limitations in the designs and measures used. Thus, the results should be interpreted with caution. The two-process

model theory of sleep regulation may be useful when comparing studies, interpreting results and seeking new treatments.

Supervisors: Professor Gunnar Morken and Professor Arne E. Vaaler.

1. Introduction

In psychiatric hospitals, many patients struggle with sleep problems. Sleep is monitored as an indicator of both the severity of the illness and the effectiveness of the treatment. This thesis explores the associations between sleep at night and behaviour the next day in two patient samples from a defined catchment area admitted to the Department of Psychiatry, St Olav's University Hospital: outpatients with delayed sleep-wake phase disorder (DSWPD) admitted to the specialist clinic for patients with sleep disorders, and inpatients acutely admitted to the psychiatric intensive care units (PICUs).

1.1 Psychiatry and sleep

Sleep problems are both frequent [1-8] and associated with hospitalization in populations of patients with psychiatric disorders [3]. The relationship between sleep problems and psychiatric disorders seems to be bidirectional, indicating that if a patient has one of the conditions, then there is an increased probability of developing the other compared to patients having neither of the conditions [9]. Treatment of one of the conditions may also improve the other [10-12]. Some psychiatric disorders and sleep problems may therefore have shared, underlying pathogenic mechanisms [6, 13]. Up to 70% of patients with DSWPD have a psychiatric disorder [5], and up to 70% of patients in psychiatric acute wards have sleep problems [4, 8].

The treatment of sleep problems has not always been a main focus in psychiatric care [2, 6, 14]. Sleep problems have often been regarded as secondary to psychiatric disorders. This attitude has changed in the last 5 to 10 years. Many patients regard sleep as one of their main problems. Treatment outcomes may be improved if treatment of sleep problems is integrated with treatment of the specific psychiatric disorder [2, 6, 9, 14, 15]. Psychiatric acute wards and intensive care units have been organized to support sleep, with fixed times for sleep, fixed times for meals, and control of activity and light [16].

1.2 Sleep

Based on behavioural observations, sleep is regarded as an essential function for all animals, including humans. During sleep important cognitive functions take place like transference of information from short- to long-term memory [17]. There are circadian variations in the secretion of hormones such as melatonin, growth hormone and cortisol [18]. Decomposition

products in the brain are removed during sleep as part of the brain recovery process [19-21]. Sleep also has effects on cellular functions and gene expression [22], and recently a relationship between circadian clocks, sleep and neurodegeneration was described [23].

The mechanisms of sleep are complex. In 2017, the Nobel prize in Physiology or Medicine was awarded to J. Hall, M. Rosbash and M.W. Young for their discoveries of the molecular mechanisms that control circadian rhythms [24].

Disruption of sleep patterns or lack of sleep affect our functioning [7, 25-29]. Lack of sleep causes deterioration in performance on more complicated cognitive tasks [25, 26, 29], and it is associated with a number of somatic health problems such as increased weight, diabetes [27, 30, 31], and decreased life expectancy [32]. Disruption of sleep patterns and lack of sleep thus have an impact on several bodily functions [27, 28]. The opposite also occurs; somatic functions, mental processes, and external sensory and emotional stimuli have an impact on our sleep [33, 34]. Thus, our health and functioning seem to be affected by a bidirectional interaction between sleep and behaviour [35].

1.3 The two-process model of sleep regulation

In 1982, Borbély proposed a theoretical framework intended for sleep research. The aim was to understand the alternation between sleep and wakefulness with a two-process model of sleep regulation: the interaction between a homeostatic process and a circadian process [36]. The two-process model has become the most important model of sleep regulation, and it has gradually gained scientific support [6, 37, 38].

The homeostatic process (S) represents sleep debt. It increases during wakefulness and declines during sleep. In the clinic it is often called “sleep pressure” and seen as the drive for sleep. A marker for the homeostatic process is slow wave activity (SWA) during non-rapid eye movement (NREM) sleep. The homeostatic process is shown to be associated to levels of adenosine in the brain [36, 37].

The circadian process (C) reflects the rhythmic variation of sleep propensity when people are sleep deprived. It also reflects the rest–activity cycles when humans are living in an environment in the absence of time cues. It is normally entrained to day and night. The main circadian clock of the body is found in the suprachiasmatic nuclei (SCN). It is central to the

circadian process. It is marked, among other factors, by circadian variations in core body temperature and melatonin secretion [36, 37].

Sleep is triggered when the homeostatic process is near the upper boundary, and awakening is triggered when it is near the lower boundary. The circadian process oscillates the boundaries.

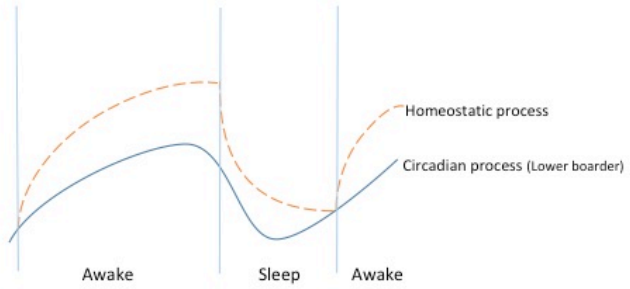

Figure 1. Sketch of the oscillation of the circadian process, the increase of the homeostatic process when awake and decrease at sleep, and the model of interactions between the two processes which regulate sleep [39].

Originally, it was presumed that each of the two processes were regulated separately. Borbély's framework regarded the homeostatic process as a sleep-dependent process, while the circadian process was considered a sleep-independent process that did not interact with the environment [36]. There is increasing evidence for an even more dynamic and complex regulation of sleep, with bidirectional interactions between the homeostatic and the circadian processes [6, 34, 37, 40]. In studies of forced desynchronization of the circadian rhythm (fixed sleep times with a schedule many hours shorter or longer than the circadian rhythm), it was found that the amplitude of several neurobehavioral functions, such as cognition, was modulated by the homeostatic process [41]. Other studies show that sleep pressure after sleep deprivation reduces clock function and the phase shift capacity of light [40, 42]. It was also found that the circadian process modulates the homeostatic process. The level of SWA in sleep is not simply a function of previous wake duration, but also of the time of day one wakes up [43]. Finally, studies have shown that both the circadian and homeostatic processes interact on molecular/genetic levels. Clock gene expression depends significantly upon prior sleep-wake history [44].

1.3.1 Peripheral circadian clocks and drugs effects on sleep regulation

There are "circadian clocks" in most cells of the body. Under normal circumstances they are orchestrated by the SCN [45]. These peripheral circadian clocks can operate desynchronized from the main circadian clock; for example, initiated by changes in the sleep-wake cycles [37]. Eating patterns, metabolism and drugs such as amphetamines seem to change the sleep-wake cycle independent of the homeostatic or circadian processes. These mechanisms or processes are not completely integrated in the model by Borbély [6, 37].

1.3.2 The effects of light on sleep regulation

A theory about the direct environmental effects of light on the central circadian pacemaker in the SCN was described before the two-process theory was presented [46]. The direct effects of light on the circadian pacemaker in the SCN were later documented. Light was found to be the most important environmental "zeitgeber" (time giver or synchronizer) [38].
The effects of light on the sleep – wake cycle depend on the timing of the light. Exposure to light before the low point of core body temperature circadian rhythm (nadir) delays the circadian phase, while light after the nadir of body temperature advances the circadian phase. The effects of light on the circadian phase seem to decrease with increasing distance to the nadir of body temperature [6, 47].

Specialized receptor cells, intrinsically photosensitive retinal ganglion cells (iqRGC), inform the SCN about exposure to light [48]. These cells do not provide visual information. They are primarily sensitive to light at < 530 nm ("blue light") [49]. Light at night inhibits melatonin secretion [23]. Wearing blue-blocking glasses or being in a blue-depleted environment can create "virtual darkness". This has similar effects to total darkness on melatonin onset and counteracts the effects of light at night [50, 51]. Light can also, via the iqRGC, have a direct impact on mood [48]. The effects of light on mood might use a different pathway from retina to brain than the SCN pathway [52].

1.3.3 The effects of darkness on sleep regulation

Artificial light from computers or mobile phones in the evening can delay people's sleep phase [53, 54], while the absence of artificial light can advance the sleep phase. Camping tours in the mountains is an example of non-exposure to artificial light described in the literature [55].

In the treatment of patients with DSWPD, both wearing blue-blocking glasses ("virtual darkness") in the evening [56] and receiving bright light in the morning advance or amplify the circadian phase [5, 57].

Patients acutely admitted with mania and treated with darkness or by wearing blue-light blocking glasses ("virtual darkness") at night, seem to improve faster and be discharged earlier from hospital compared to patients who are not exposed to darkness or virtual darkness [6, 58, 59]. Patients with depressive disorders may improve faster if they receive bright light in the morning [6, 60].

1.3.4 The significance of the two-process model

According to the two-process model, many factors can affect sleep due to interactions with the circadian- and homeostatic processes. Examples are environmental factors, including exposure to light and our usual way of daily living [37, 61, 62]. This also has implications for research. Circadian rhythms in studies may differ depending on whether the participants go to work or school that regulate the sleep – wake patterns, or do not have any regular activity during the day [63, 64]. Many psychoactive medications affect sleep; antipsychotics might influence sleep pressure [65], lithium influences circadian rhythms [66] and amphetamines disturb sleep [67]. Inpatient stays can influence both the homeostatic and circadian processes by regulating the time for sleep, the fixed time for waking up, activity and exposure to light according to ward routines. The homeostatic processes will be influenced both by improving and disturbing sleep [37, 61]. Clinical settings, participants and pharmacological cultures differ between countries and complicate comparison between studies.

1.4 Sleep and Measurements

1.4.1 Measures of sleep duration

The gold standard polysomnography (PSG) [7, 68, 69] includes electroencephalography, electro-oculography, electromyography, electrocardiography, oximetry and oro-nasal airflow. From the PSG, it is possible to get a histogram that illustrates both rapid eye movement (REM) sleep and different types of NREM sleep through the night. PSG data collection, analysis and interpretation are expensive and resource demanding. PSG is therefore less available, usually only used for a single night, and in clinical practice used only on strict indications. In inpatient units, such as psychiatric acute departments and PICUs, PSG

equipment can be a potential risk to the patient's safety. In these settings, there is also a need to monitor sleep repeatedly as an indicator of treatment effect. However, because PSG is usually not an alternative, simpler methods such as actigraphy, radar sensors and observations by the staff can be used.

Actigraphs are several types of electronic devices recording minor and major body movements [68, 70]. Smart-watches and smart-phones often have integrated actigraphs. However, the quality of the actigraphs and software in these items varies, and they are often not satisfactory for sleep assessments in research [70]. Actigraphs measure movements and thus indirectly measure sleep. In spite of this limitation, it is regarded as the best objective measure of sleep in many clinical settings [71, 72]. The advantages of actigraphs are the objective measurements and the ability to measure over long time periods. Actigraphs are cheap, and can also give additional important information about levels of activity during the day [73]. Radar sensors to measure movement is under development. Sleep can probably be estimated accurately with this technique [74, 75].

In hospitals, there are traditions and routines for the observation of sleep by nurses [76-78]. There are studies indicating that such observations have satisfactory correlations with PSG and actigraphy data [68, 72, 79-81]. However, the methods have limitations including lack of standardization [78], and patients lying without movements in the bed while being awake. The routine also has the obvious disadvantage that the patients can be disturbed by the observation. Thus, it may be questioned if the observation of sleep by nurses may be regarded more as an observation of behaviour than of sleep.

Self-reports with sleep diaries are frequently used in outpatient settings [82]. The patients fill in the form every morning indicating when and how they slept the previous night. This method is regarded as adequate for the treatment of insomnia or circadian rhythm disorders [69]. In research, the methodological weaknesses are the sensitivities for sleep misperception and the clinical state of the patients [83-85].

1.4.2 Measures of circadian rhythms

Precise measures of the circadian rhythm can only be done using very elaborate protocols, either in a time-isolation environment in dim light or by using a forced desynchronized protocol. For most studies this is not feasible or necessary [6, 37, 86].

In clinical practice and most experiments, circadian rhythms are measured from the sleep-wake processes. Circadian rhythms are the results of our endogenous circadian clocks being influenced by homeostatic processes and by environmental contributions, including exposure to light and our usual patterns of daily living. Measures of circadian rhythms can be made continuously or repeatedly over a period of time to capture oscillation. In theory, it is possible to use any neuroendocrine, physiological, psychological or cellular functions that oscillate with circadian rhythms: body temperature, hormones such as melatonin, cortisol, and so on [6, 37, 86].

In the last decade, melatonin has become the most used marker for circadian rhythms, and it is regarded by many as the optimal marker [86, 87]. Melatonin can be measured in any body fluid, although saliva is most frequently used. The saliva test is sensitive to contamination from food and drinks. Dim light melatonin onset (DLMO) is often the preferred melatonin measure because it can be done before sleep [86, 88]. It is possible to use a defined threshold level of melatonin (often > 4 pg/ml) for estimating the circadian rhythm. Since melatonin production is inhibited by light, the measure is done in dim light, often less than 10 lux. Conducting an accurate melatonin test is demanding and it is thus less useful in the clinic. There seems to be a phase relationship between the melatonin and the sleep midpoint (midpoint between sleep start and wakening). The sleep midpoint is easily measured, and can be useful in clinical practice [86].

Body temperature has circadian variations with a distinct nadir a few hours before wake up time [6, 86]. In older experiments, an anal probe was used for continuous recording of temperature [47], but for obvious reasons, other methods, such as continuous measures of skin or inner ear temperature, are more acceptable to patients. It is also possible to swallow a capsule that measures the temperature in the gut.

An actigraph or a sleep diary measured over a minimum of a week, can measure the circadian rest–activity cycle [6, 86]. These methods are less expensive and easier ways to measure the circadian rhythms and therefore more frequently used in clinical practise. However, these methods are probably more influenced by daily living than the DLMO.

Questionnaires such as the Horne–Östberg Morningness Eveningness Questionnaire (MEQ)

are often used for assessing the preference of circadian rhythms (chronotype) [89]. Questionnaires of chronotype seem to correlate with the DLMO [90] and results from actigraphy [91]. However, responses in questionnaires are subjective, influenced by what the participants believe to be preferred sleep-wake habits, and probably also more influenced by daily living than the DLMO.

New studies have explored the possibility of estimating circadian rhythms by analyses of cellular circadian processes in blood samples [87].

1.4.3 Sleep duration

Sleep duration changes through life and usually declines in adulthood [62, 92, 93]. A common assumption is that mean sleep duration in the general population has declined in recent decades. A study conducted over a 50-year period with objective measures of sleep duration could not confirm this [94]. Sleep duration around 7 hours is common among healthy adults [62]. Less than 6 hours and more than 9–10 hours of sleep duration are often associated with health risks [62, 64, 95]. A study from Denmark found that 3% of the women and 8% of the men had sleep durations less than 6 hours, while 17.5% of the women and 20.2% of the men slept for 9 hours or more [64].

Sleep duration in patients with DSWPD is normal, in the range of 6–8 hours, and does not usually differ from controls [57, 96]. This is consistent with the diagnostic criteria in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-V) [97] and the International Classification of Sleep Disorders, Second Edition (ICSD-2) [98]. Patients with DSWPD are expected to have normal sleep duration if allowed to choose their preferred schedule.

We have found no published studies of sleep duration in acute or emergency psychiatric populations. In patients with affective disorders, decreased need for sleep is one of several possible criteria for mania, but is not obligatory. In a population of outpatients, Gruber found a correlation between short sleep duration and increased mania severity scores [99].

Between the affective episodes, patients with bipolar disorder have demonstrated both longer [71], and unaltered sleep durations compared with healthy controls [84]. However, a meta-

analysis from 2015 found that the mean sleep duration seems to be longer for patients with bipolar disorder than for healthy controls [100].

At discharge from a psychiatric hospital in Germany, the patients completed a questionnaire about their sleep during their hospital stay. Patients with schizophrenia reported a mean sleep duration of 7.7 SD ± 1.6 hours, while 8% reported sleeping for less than 6 hours and 2% for more than 10 hours [1]. Others have reported longer sleep duration among stable outpatients with schizophrenia compared to healthy controls [101]. In a large population of patients with schizophrenia, also including inpatients in acute psychiatric settings, an association was found between sleep duration of less than 6 hours and substance use [102].

Reduced sleep duration has been associated with increased severity and more symptoms both in schizophrenia and bipolar disorder [8, 99, 103, 104].

1.4.4 Variability of sleep duration

In the last 10 years, a limited number of studies describing intra-individual variability in sleep duration between nights have been published [105, 106]. Among college adolescents, intra-individual variability in time in bed and sleep onset latency were associated with negative mood (composite of self-reported depression and anxiety) [107]. Great intra-individual variability of total sleep time is related to poor subjective sleep quality and well-being [108]. Whether lack of stability in sleep duration has any negative impact on health parameters has not been clarified [61, 105, 106, 109].

In a general population, the intra-individual variability of sleep duration over a period of 14 days was found to be around 1 hour [61, 110]. In a population-based study of Hispanics high variability in sleep time, defined as SD > 1.5 hours, was found in 34% of participants who slept for less than 7 hours, 22% who slept for 7–9 hours, and 27% who slept for 9 hours or more [111].

In a study using actigraphy, Burgess found that patients with DSWPD had significantly more variability in total sleep time than healthy controls [96].

We have found no published studies describing intra-individual variability of sleep duration in populations from psychiatric acute or emergency services. In euthymic bipolar disorder

outpatients, some studies indicate that patients have greater night-to-night variability in sleep duration than healthy controls [71]. This is also confirmed by a 2015 meta-analysis [100]. In stable outpatients with schizophrenia, the intra-individual variability in sleep was found to be two to three times greater compared to a healthy control group [101].

In patients with schizophrenia and bipolar disorder, increased intra-individual variability of sleep duration is associated with increased severity and more symptoms [99, 103, 104].

1.4.5 Circadian rhythms

Our circadian rhythms and the battle to stay in harmony with the 24-hour day/night shifts affect us all [35]. For many people, bedtime and wake-up time vary during the week due to our commitments [112]. The preferred and most comfortable, habitual wake-up time on days off can give an impression of a person's chronotype. The morning type prefers to wake up early and functions best in the morning, while the evening type prefers to go to bed late and functions best in the evening [113]. The chronotype in an individual changes through life [112]. In children, the morning type is most prevalent, in adolescents, evening type is most prevalent, and in older adults, morning type is again most prevalent [112, 114].

DSWPD is regarded as a syndrome with delayed sleep-wake phase. It is the most frequent circadian rhythm disorder [5, 115]. In a Norwegian study using clinical assessments with sleep diaries, 0.17% of the adult population had such extreme delayed sleep phases that they could not keep up with the 24-hour rhythm and sleep at the desired time to function well [116]. They were defined as having DSWPD. A more recent study based on self-report found that 8.4% of high school students in Norway could possibly have DSWPD [117]. The changes in our society in recent decades, such as having more light and activity in the evening, may contribute to this large difference in the prevalence of DSWPD. However, the differences may also at least partly be explained by methodological differences in the studies, such as differences in populations, measures used, and definitions of DSWPD [5].

In a study of 40 patients admitted in acute crises to a psychiatric hospital, it was found that 11 (27.5%) were morning, 16 (40%) were intermediate and 13 (32.5%) were evening chronotypes [76]. Depressive disorders are associated with the evening chronotype, and evening chronotype may also be a trait marker of bipolar disorder [118-120]. However, others still claim that there are too few studies to conclude about possible associations between

bipolar disorder and specific chronotypes [100]. Many clinically stabilized outpatients with schizophrenia are described to have irregularities in their sleep-wake cycles [121-123], but the associations with chronotypes are less clear [67].

In patients with schizophrenia and bipolar disorder, circadian disturbances may be associated with more symptoms [8].

1.5 Sleep at night and behaviour the next day

Changes in behaviour, brain function and cognition are common after disturbed sleep [25, 26, 28, 29]. Based upon our clinical experience, patients with DSWPD themselves and their relatives complain about the patients' difficulties in waking up. The relatives observe that the patients are cognitively affected, or "slow" in the morning.

In acute psychiatric populations in PICUs, sleep is monitored daily both to give an indication of the severity of the illness and as a measure of possible improvements of the condition. Deterioration of the illness may indicate increased risk of aggression, a common and serious behavioural problem in acute and emergency psychiatry [124].

1.5.1 DSWPD, threshold of awakening and cognition in the morning

Inability to wake up at a desired and socially acceptable time is one of the criteria for the diagnosis of DSWPD. However, studies that examine the threshold of awakening by external stimuli among these patients is lacking.

According to Borbély and the two-process theory, "slow wave sleep (SWS) is a deeper form of sleep and therefore a high arousal threshold must be expected". This is supported by experiential data [36]. Studies have explored awakening from sound pollution, such as door slamming, gun firing [125], or trains passing at night [126]. Most sound levels have been less than 70 dB, and the awakening thresholds from the different sleep stages could not be established [125, 126]. The studies on awakening thresholds are mostly old and focused on healthy subjects. The studies mainly show that auditory awakening thresholds are higher in SWS than in REM sleep, and the awakening thresholds seem to increase after sleep deprivation [127]. A more recent study found that DSWPD patients frequently are in deep sleep in the morning when many of them need to get out of bed to go to school or work, usually between 6 and 8 a.m. [88]. We have however, found no published studies examining the awakening thresholds in patients with DSWPD.

Cognitive functions in humans are influenced by the homeostatic process, the circadian process and sleep inertia. Sleep inertia is a transitory impairment in cognitive and sensory-motor performances after awakening. It improves in the first hours of wakefulness. Patients with evening chronotypes seem to have more long-lasting problems with sleep inertia than those with morning chronotypes [128, 129].

Confusion, difficulty in focusing and problems with concentrating are common symptoms upon morning awakening in DSWPD [97]. There are only a few published studies examining cognition in patients with DSWPD. In a recent study, no difference in cognitive function between healthy controls and patients with DSWPD was found [130]. The cognitive test was conducted approximated 2 hours after the wake-up time in the weekends. This is assumed to be more concurrent with the circadian rhythm of the person than a forced awakening time that allows the person to reach school or work. A Norwegian randomized controlled treatment study in patients with DSWPD, found that treatment with bright light and melatonin improved day time cognitive function [131]. There is a lack of studies on difficulties in awakening and its effects on cognitive function in the morning in patients with DSWPD.

1.5.2 Aggression in acute psychiatry

In Norway, acute psychiatric wards are traditionally divided into an ordinary area and a psychiatric intensive care unit (PICU) area [132]. The PICUs are used for patients in need of intensive observations and/or containment of challenging behaviours. The PICUs often consist of a sitting room, bathroom, toilet and a limited number of patient rooms. The principles of treatment in Norwegian PICUs are similar to what the international literature calls “open area seclusion”. The goals for the intervention are improvement of symptoms through reduction of sensory and emotional stimuli, and control of behaviour based on containment of the person [132, 133]. In their studies on a PICU, Vaaler et al found no support for the traditional beliefs that sparsely decorated interiors reduce symptoms and aggressive behaviour [134], but found that segregation in a PICU may have favourable effects on aggressive incidents [16]. Patients in these studies are among the patients included in Paper 2 in this thesis.

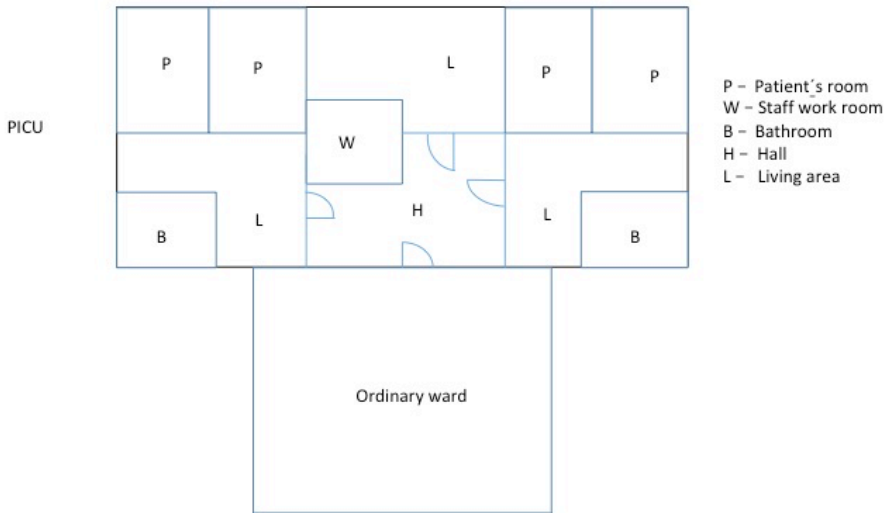

Figure 2. Sketch of a psychiatric intensive care unit (PICU) area.

Violence and aggression, according to the NICE guidelines [135], refer to a range of behaviours or actions that can result in harm, hurt or injury to another person, regardless of whether the violence or aggression is expressed physically or verbally, the physical harm is sustained, or the intention is clear.

Aggression is a natural behaviour, but seldom regarded as a positive and adequate response neither in society nor in psychiatric wards [124, 133, 136, 137]. It is a complex response based on the person's biological factors, such as brain functions or dysfunctions, impulsiveness and cognitive capacity. It is influenced by the person's experiences and learning earlier in life. Aggression can be triggered by social settings, such as involuntary admittance to hospital and/or another person's attitudes. In psychiatric departments, aggression is often triggered by the use of psychoactive drugs, and/or the presence of psychiatric symptoms, such as psychosis and agitation [136-140]. In studies the different measures of aggression vary from self-reports of feelings or thoughts [141, 142], to observations of violence or aggressive incidents [136, 143, 144].

In acute and emergency psychiatry, aggressive behaviour is a major challenge with negative consequences for patients and staff [124, 135, 136, 143, 145, 146]. It is found that one out of

five patients admitted to an acute psychiatric unit may commit an act of violence, 75-100 % of the nurses have been assaulted by patients, and annually one-third of the total nursing costs are connected to managing violence and aggression [135, 145, 147]. Predicting aggressive incidents is important in order to implement preventive measures for specific patients [124, 133, 148, 149]. A number of risk factors for violence have been described [135, 145, 150, 151], as previous violence, personality disorders, impulsivity or instability, substance abuse, major mental illness, lack of insight, future stress situations, unrealistic planning, and lack of support.

The psychometric instruments developed for prediction or risk assessment of violence, as HCR-20 [152] and V-Risk 10 [153], are based on such risk factors. However, in the acute setting these instruments have limitations. They often require more information than available in an acute admission, or the time frame for the prediction may be weeks, months or years ahead, not pin-pointing the next hours or day as desired in an acute ward [135, 147, 154].

The risk factors described in these previous studies vary with the studied population and the setting of the studies. Risk-assessment instruments based upon these risk factors have limited accuracy in acute and emergency psychiatry [135, 155-159].

In highly selected populations with the time frame for assessment as short as a day, there are developed checklists and short questionnaires [135] based on the nurses' observations of behaviour. Examples of instruments for the short-term prediction of violence are the Dynamic Appraisal of Situational Aggression – Inpatient Version (DASA-IV) [160, 161], and the Brøset Violence Checklist (BVC) [162, 163].

None of the instruments for the short-term prediction of violence based on observed behaviour include sleep as a variable. The nurses in a PICU usually observe sleep, if the patient moves, or communicates verbally or non-verbally through the night. As an observation of behaviour, it has thus similarity to the items of the instruments for short time prediction of violence as the BVC.

In a systematic review of the existing literature on sleep and aggression, the authors conclude that the larger part of the literature supports a correlation between subjective poor sleep and irritability, hostility and aggression [164]. Although sleep disturbances seldom result in physical aggression, the risk might increase in vulnerable individuals [164]. Studies of sleep and aggression are limited, and the interpretation of the results is difficult because of the lack of standardization of definitions and measures of aggression and sleep. The interpretation is

also complicated by the mix of studies from different clinical and non-clinical settings [142, 144, 164-166].

There is a lack of studies on the associations between sleep at night and aggression the next day in psychiatric acute and emergency wards. Assessments of sleep could possibly improve our ability to predict imminent violence.

1.6 Research questions and Aims

The overall research question of the thesis was how does observed sleep disturbances' impact behaviour and functioning the next day in patients admitted to a psychiatric clinic.
In clinical samples and by using assessment that are in daily clinical use, to study how sleep disturbances influence cognitions, length of stays in PICU and occurrence of aggressive behaviour. Finally, to study if items assessing sleep improve short-term prediction of violent and threatening incidents in the PICU.

Paper I: The aims were:

- to quantify the awakening threshold in DSWPD patients with an alarm clock
- to compare changes in cognitive function between time of awakening and the evening in patients with DSWPD and healthy controls
- to assess whether problems with awakening are associated with a specific sleep stage (SWS in particular).

Paper II: The aims were:

- to explore whether sleep duration of a single night, or night-to-night variations in sleep duration over the first two nights predict length of stay in the PICU
- to compare sleep duration and night-to-night variations in sleep duration among patients with schizophrenia, mania or other psychiatric disorders in the PICU.

Paper III: The aims were:

- to explore whether sleep duration, or night-to-night variations in sleep duration in the PICU are associated with observer-rated aggressive behaviour and aggressive incidents the next day

- to test whether sleep duration the first night after admittance, or night-to-night variations of sleep duration between the first two nights are associated with aggressive incidents later in the patient's stay.

Paper IV: The aim was:

- to investigate whether the predictive properties of the BVC increase by adding a variable assessing sleep.

2. Methods

All four papers in this thesis are based on data from studies of sleep and behaviour in patients admitted to the Department of Psychiatry, Østmarka, St Olav's University Hospital, Trondheim, Norway. In Paper I, we recruited patients referred to the "Sleep clinic". This is a research-oriented, outpatient clinic focusing on insomnia and circadian rhythm disorders, with about 200 patients referred each year. The data were collected at the Sleep laboratory, Department of Neuromedicine and Movement Science, Norwegian University of Science and Technology (NTNU), in co-operation with the Department of Neurology and Clinical Neurophysiology, St Olav's University Hospital.

Papers II, III and IV are based on data from inpatients acutely admitted to the PICUs at the acute psychiatric wards at the Department of Psychiatry. Norwegian psychiatric inpatient services are publicly funded, catchment-area based and available to everyone. All patients (≥ 18 years) in the catchment area in need of acute psychiatric inpatient services are referred to this department. Referrals to other psychiatric hospitals only take place if the patient temporarily resides outside the catchment area at the time of admittance.

2.1 Paper I

2.1.1 Participants

Nine of 37 patients in the outpatient sleep clinic who fulfilled the DSM-IV (307.45) diagnostic criteria for circadian rhythm sleep disorder [167], and the ICSD-2 criteria for DSWPD [98] were included in the study. The nine patients were asked to participate because they stated clearly that they were difficult to wake in the morning. The sample consisted of four males and five females with a mean age of 22.5 years (SD ± 2.2, range 18–25 years). Subjects with coexisting major health problems, such as impaired hearing, severe somatic or psychiatric disorders, other sleep disorders or regular use of psychoactive drugs in the last 4 weeks, were excluded.

Nine healthy subjects were recruited after posting an announcement on the University's homepage and local campus boards. The controls consisted of four males and five females with a mean age of 23.3 years (SD ± 2.4, range 18–28 years).

2.1.2 Procedure

Physicians with experience in the treatment of sleep disorders diagnosed the patients by using a semi-structured interview before inclusion. The assessment battery consisted of Morin's Insomnia Interview Schedule [168] with the screening questions for psychiatric disorder from the Structured Clinical Interview for the DSM-III-R [169], and description and diagnostic criteria from the ICSD-2 [98].

The participants completed 14 days of sleep diary, 7 days of actigraphy, and a home PSG to minimize the "first-night effect" of PSG before the experimental night. On the intervention day, the participants arrived at the sleep laboratory at 14.00. They first completed the Conners' continuous performance test (CCPT II) at 15.00, and afterwards the psychiatric and sleep-related questionnaires. At 18.00, the light was dimmed to < 200 lux. From 19.00 to bedtime at midnight, sampling of saliva was done hourly for melatonin testing. The alarm clock was activated at 07.00. The starting sound level was set at 72 dB, increasing by 2 dB at equal intervals (sound active for 4.4 seconds with 5-second intervals) to a maximum of 104 dB after 3 minutes. The procedure stopped when the patient woke up. The participants who did not react during the procedure were woken up by the staff in the laboratory. They also recorded time and dB value. Six minutes after waking up, the participants completed the CCPT II test, with identical instructions as the day before.

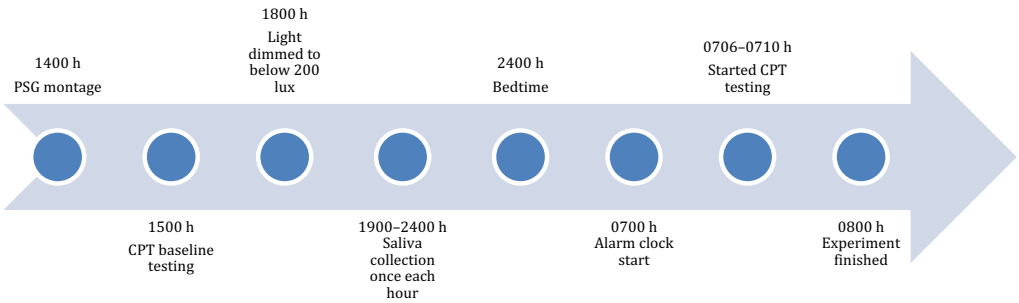

Figure 3. Procedure for the experimental night (made and provided by Brandy Solheim).

2.1.3. Assessments

Actigraphy

The participants carried actigraphs (AW4, CamNtech Ltd, Cambridge, UK) that recorded movements, acceleration, light exposure, and 30-second epochs with medium sensitivity for 7 days. We used sleep start and sleep end for analyses.

Polysomnography

The participants slept in a standard hospital bed within a shielded video-PSG laboratory. A Somnoscreen 10-20 monitor (SOMNOmedics GmbH, Randersacker, Germany) using a standard PSG montage with electroencephalography electrodes, electro-oculography electrodes, an O_2 finger sensor, electromyography electrodes, a nasal airflow sensor and an oro-nasal thermistor, were used. Video and sound were recorded continuously. Polysomnograms were analysed by a blinded, certified clinical neurophysiologist, according to standardized criteria [170] using Domino software version 2.5.0.

Melatonin

Two samples of ≥ 2 mL salvia were collected, placed in a refrigerator at 4 °C within 10 minutes after collection, and later placed in a freezer at < –20 °C. The samples were analysed with the Non-Extraction Melatonin Saliva enzyme-linked immunosorbent assay kit, supplied by IBL International GmbH (Hamburg, Germany).

The samples taken at 20.00, 21.00 and 22.00 were used to calculate baseline levels of melatonin. Melatonin secretion onset was defined if concentrations measured at 23.00 or 24.00 were either more than twice the baseline value, or baseline +2.5 standard deviations (SD) [171]. Delayed melatonin onset was presumed if concentrations had not reached one of the cut-off values at 00.00.

Sleep diary

In a graphic sleep diary, the participants shaded (or did not shade) 24 small rectangular boxes, each representing 1 hour of the day. The sleep diary was completed 14 days prior to the experimental night.

Self-report questionnaires

The Horne–Östberg Morningness Eveningness Questionnaire (MEQ) is a 19-item questionnaire assessing preference of circadian rhythm and chronotype [89]. The MEQ has four or five possible response options on each item giving a scoring range of 16–86.

The Beck Depression Inventory (BDI) is a 21-item rating scale assessing the degree of depressive symptoms. It has four possible responses from 0 to 3 on each item, giving a scoring range of 0–63 [172].

Continuous performance test

The CCPT II [173, 174] was used to assess cognitive function. For 14 minutes, the letters A–Z were each presented for 250 milliseconds on a computer screen. The letters were presented in a pseudorandom fashion with inter-stimulus intervals varying between 1, 2 and 4 seconds. The letter X was presented 36 times. It was defined as the non-target. Letters other than X were presented 324 times. These letters were defined as targets. The participants were instructed to press a button as quickly as possible whenever a target was presented. Measures were:

- Hit-RT: Mean reaction time for pressing a button after a target (letter other than X) was presented on the screen (mean time for correct responses).
- Commission errors: Number of times a button was pressed after the non-target (letter X) was presented on the screen (number of failures to withhold a response).
- Omission errors: Number of times a button was not pressed after a target (letter other than X) was presented on the screen (number of failed responses).

2.1.4. Data analysis and statistics

The main variables were: CPT Hit-RT evening–morning difference; alarm clock level upon awakening; and sleep stage on awakening. Subjects who did not wake up before the alarm reached 104 dB were analysed at 105 dB. Subjects who were awake at 07.00 were analysed at 71 dB.

Each of the three CPT performance measures (Hit-RT, commission errors, omission errors) were analysed with ANOVA tests with groups (patients, controls) and time (afternoon, morning) as fixed factors. In the case of statistically significant main or interaction effects, planned simple contrasts were performed.

The PSG, actigraphy, questionnaire, and sleep diary variables were analysed with non-parametric Mann–Whitney *U*-tests or Wilcoxon signed rank tests. Differences in proportions were tested with a standardized normal deviate. For exploratory correlation analyses within the patient group, non-parametric Spearman's rho was used. A significance level of $p < 0.05$ was applied.

2.2 Papers II, III and IV

2.2.1 Setting

The Department of Psychiatry, Østmarka, had a catchment area of 140,000 inhabitants from both the city of Trondheim (50%) and the rural areas (50%) in Sør-Trøndelag County at the time of the study. About 700 inpatients over 18 years of age were admitted each year.

The hospital had two acute wards, each consisting of an ordinary ward area and a PICU area. The PICU was used for containment of the most behaviourally disturbed patients. The PICU consisted of two separate wings, each with a sitting room, bathroom, toilet and two single patient rooms.

The PICU had allocated nurses who were with the patients and observed them continuously, or at 3–30-minute intervals, depending on the state of the patient. The patients received treatment as usual, including medication. The PICU patients were segregated from other areas of the department. The patients were expected to stay in their rooms and sleep between 22.30 and 07.30, and they were encouraged to come to breakfast at 08.30.

2.2.2 Participants

The participants were all patients admitted to one of the two PICUs. To be included in the study the patients had to stay at least one night. PICU-1 included patients in two periods of 4 and 5 months. PICU-2 included patients in one period of 6 months. This period overlapped with the second period of PICU-1.

Paper II presents data from patients admitted to both PICUs. One patient was excluded due to severe dementia. Patients with multiple admittances were only included once.

Papers III and IV present the same set of data from PICU-2. Some individuals were admitted and included more than once in these studies.

Subgroups of patients

Diagnoses were made in accordance with the ICD-10 diagnostic criteria for research [175], and agreed at a weekly consensus meeting in the department. A minimum of two experienced specialists in psychiatry and/or clinical psychology took part in the meetings. At least one of them had personally examined the patient. Patients with a main or secondary diagnosis from F20 to F29, (Chapter Schizophrenia, schizotypal and delusional disorders) were defined as patients with schizophrenia. Patients with a main or secondary diagnosis from F30.0 to F31.2 were defined as patients with mania.

Paper II analyses a population of patients dominated by patients with a main diagnosis of schizophrenia or mania. These diagnostic groups were compared with the rest of the patients, who were defined as having other psychiatric disorders.

Paper III analyses a population of patients dominated by a main diagnosis of schizophrenia. They were compared with the rest of the patients, who were defined as having other psychiatric disorders.

2.2.3 Procedure

The patients in need of acute psychiatric inpatient care were admitted to the closed acute ward with the most available beds. The physician on duty, together with the nurses, evaluated functioning, symptoms and behaviour and decided whether the patients should be treated in an ordinary, closed ward or in the PICU. Based on the state of the patient, the physicians on duty or the therapists on the ward decided whether the patients were to be observed continuously or at 3–30-minute intervals [16, 176]. Discharge from the PICU occurred following a joint decision among the staff in the ward after taking into account levels of symptoms, general functioning and behaviour. There were no written criteria for admittance or discharge in the PICU [16].

Measures of sleep, aggressive behaviour and aggressive incidents were recorded as part of the routine, clinical practices in the wards. Brief training of the nursing staff was provided as part of the routines in the unit.

The nurses in the PICU registered the time patients were observed to sleep both in the medical

records and in a separate sleep diary. The nurses observed the patients at least every 30 minutes throughout the night, often more frequently, either by opening the door into the patient's room, or by staying in the same room as the patient. The staff was instructed to record if a patient was considered "to be sleeping" according to their own clinical judgement.

The nurses registered BVC three times daily after being with the patients for 1 hour in the morning, afternoon or night. Nurses who witnessed threatening or aggressive incidents registered them with the SOAS-R [177, 178].

2.2.4. Assessments

Sleep

The sleep diary consisted of a column for each 24 hours and a square for each 30 minutes (Appendix 1). The sleep duration in a day was defined as observed sleep from 12 noon to 12 noon (paper II-IV).

Due to the possible significance of variability of sleep [61, 106, 109], the absolute difference in sleep duration between two nights was defined as a measure of variability (paper II-IV). Therefore, the absolute value of both longer and shorter sleep duration was used as a measure of variability. Due to short stays in the PICUs (i.e. median 3 days) we measured between two consecutive days. This measure is easy to implement in the clinic.

The absolute difference between the night with the longest and the night with the shortest sleep duration was calculated. Data for the first three nights and the first seven nights are reported (Paper II).

The variables for sleep duration and night-to-night variations in sleep duration between two nights were categorized, and they defined a combined variable called "sleep disturbance" on a 0–2 scale (Paper IV):

	0 points	1 point	2 points
Sleep duration	≥ 6 hours	4–6 hours	≤ 4 hours
Night-to-night variations in sleep duration	≤ 2 hours	2–4 hours	≥ 4 hours

The item “sleep disturbance” was constructed in this manner due to several reasons. To be compatible with checklists assessing short term risk of violence (for instance the BVC), a categorical scale was chosen. To retain the dimensional aspect of sleep a three-points scale was chosen. The scale should also be easy to implement in daily clinical practice.
The boundaries of the scale were chosen based on the association between sleep and psychiatric symptoms reported in the introduction of the thesis. Sleep duration less than 6 hours seems to be associated with health risks [64]. Mean sleep duration of psychiatric patients are often found to be equal or longer than healthy subjects [1, 100], while the intra-individual variability in sleep duration of 1 hour in the general population [61, 110] is somewhat longer in stabilized psychiatric out-patients [71, 101].

Sleep disturbance was defined as: (Sleep duration + Night-to-night variation in sleep duration)/2. For the first night of admission, the points from sleep duration were used to calculate sleep disturbance.

BVC

The Brøset Violence Checklist (BVC) is a six-item checklist of behaviours that predict imminent aggressive incidents in psychiatric inpatients (24-hour perspective) [162, 163] (Appendix 2). BVC is easy to use, has been extensively tested and has good psychometric properties [135]. The nurses on the ward rate whether six different behaviours are present or not: Being confused, irritable, boisterous, verbally threatening, physically threatening and/or attacking objects. Each item is scored 1 if present or 0 if not, giving a scoring range of 0 to 6. The BVC sum score is often categorized in three groups to recommend when preventive measures should be taken; small risk of violence (0), moderate risk of violence (1–2) and high risk of violence (> 2). The BVC is usually assessed three times daily. In the present study, we used the highest of the morning or the evening scores [159, 179].

BVC-Sleep

In Paper IV, we reported data for a mixed variable to predict aggression called BVC-sleep. This variable is the sum of the sleep disturbance scores for one night, and the highest scores of the morning or the evening scores in BVC from the next day. The BVC-sleep has a scoring range of 0 to 8.

SOAS-R

Aggressive incidents were recorded by the nurses with the SOAS-R [177, 178] (Appendix 3). The SOAS-R is a widely used instrument to record violent incidents in mental health care settings, and it rates both the nature and severity of aggressive incidents. SOAS-R consists of five columns: provocation, means, target, consequences for victims and measures taken to stop aggression.

2.2.5. Data analysis and statistics

Statistical analyses were performed using SPSS 21-24 for MAC. An alpha level of < 0.05 was employed. The data are reported as means and standard deviations (SDs), medians and interquartile ranges (IQRs). Categorical data were analysed with chi-square tests or Fisher's Exact tests. Normally distributed data were analysed with Student's *t*-tests or ANOVA, data not normally distributed were analysed with Mann–Whitney *U*-tests, and correlations with Spearman's rank coefficient (Spearman's rho). In Paper IV, the sleep variables sleep duration, night-to-night variations and sleep disturbance were defined before the calculations, and receiver operating characteristic curve (ROC curve) and area under the curve (AUC) with confidence intervals (CIs) were used to analyse the variables' ability to predict aggressive incidents. No missing data replacements were used.

The sample size needed was not calculated before the study started. Previous studies could not give an estimate of results and the included number of patients was based on the capacity of the department.

2.3 Ethics

The studies were all approved by the Regional Committee for Medical and Health Research Ethics, Central Norway.

In Paper I, the patients were included after an ordinary consultation. All participants were at least 18 years old. They gave a written, informed consent to participate. The treatment of DSWPD was delayed by 2 weeks due to the procedures of the study. This was not expected to have any effects on treatment outcomes. The participants in the study received a small amount of money to cover their extra costs.

All the data used in Papers II, III and IV were collected as part of ordinary, routine clinical practice in the department.

3. Results

Paper I

Difficult morning awakening from rapid eye movement sleep and impaired cognitive function in delayed sleep phase disorder patients.

Brandy Solheim, Knut Langsrud, Håvard Kallestad, Alexander Olsen, Bjørn Bjorvatn, Trond Sand.

Sleep Medicine 15 (2014) 1264–1268

Abstract

Objectives: Difficult awakening is a key symptom of delayed sleep phase disorder (DSPD), but no studies have quantified awakening thresholds in a sleep laboratory. This study assessed whether cognitive function was impaired after awakening and whether difficult awakening was associated with specific polysomnographic features such as slow wave sleep stage N3.

Methods: Nine patients with delayed sleep phase disorder (DSPD) and nine sex- and age-matched healthy controls were included. Polysomnography was performed at our university hospital from midnight. An alarm clock was activated at 07.00 with sound intensity increasing from 72 to 104 dB. Participants performed a continuous performance test (CPT) the previous afternoon and immediately upon awakening.

Results: Three DSPD patients and zero controls did not wake up to the maximum 104 dB alarm sound; all three patients were in rapid eye movement (REM) sleep when the alarm clock went off (difference in proportions, $p = 0.047$). In patients, CPT reaction time was prolonged in the morning compared with the afternoon [analysis of variance (ANOVA) interaction, $p = 0.01$]. DSPD patients made more omission errors than controls regardless of the time of the day (ANOVA main effect, $p = 0.046$).

Conclusion: Difficulty awakening from slow wave sleep was not observed. A subgroup of DSPD patients may have a severe problem waking up from REM sleep. DSPD patients may also have had a state-like impairment in cognitive function in the morning and a trait-like impairment not depending on time of day, compared with normal sleepers.

Paper II

Sleep patterns as a predictor for length of stay in a psychiatric intensive care unit.

Knut Langsrud, Arne E. Vaaler, Håvard Kallestad, Gunnar Morken.

Psychiatry Research 237 (2016) 252–256

Abstract

Objectives: Systematic evaluations of the relationship between sleep patterns and length of stay in psychiatric intensive care units (PICUs) are lacking. The aims of the present study were to explore whether sleep duration or night-to-night variations in sleep duration the first nights predict length of stay in a PICU.

Methods: Consecutive patients admitted to a PICU were included (N = 135) and the nurses registered the time patients were observed sleeping.

Results: In the three first nights, the mean sleep duration was 7.5 (± 3.2) hours. Sleep duration the first night correlated negatively with the length of stay for patients with schizophrenia. The mean difference in sleep duration between nights one and two was 3.3 (± 3.0) hours and correlated with length of stay for the whole group of patients, but especially for patients with schizophrenia.

Conclusion: Patients of all diagnostic groups admitted to the PICU had pronounced intra-individual night-to-night variations in sleep duration. Stabilizing night-to-night variations of sleep duration might be a major goal in treatment.

Paper III

Sleep at night and association with aggressive behaviour; patients in a psychiatric intensive care unit.

Knut Langsrud, Håvard Kallestad, Arne Einar Vaaler, Roger Almvik, Tom Palmstierna, Gunnar Morken.

Psychiatry Research 263 (2018) 275–279

Abstract

Objectives: Evaluations of associations between sleep at night and aggressive behaviour in psychiatric intensive care units (PICUs) are lacking. The aims were to explore whether sleep duration or night-to-night variations in sleep duration correlated with aggressive behaviour and aggressive incidents the next day and through the whole admission period.

Methods: Forty patients with 50 consecutive admissions to a PICU were included (521 nights). Nurses registered the time patients slept, aggressive behaviour with the Brøset Violence Checklist (BVC) and aggressive incidents with the Staff Observation Aggression Scale-Revised (SOAS-R).

Results: At admission, short sleep duration the first night correlated with aggressive behaviour the next day. Admissions with violent incidents had a median of 4.0 hours difference in sleep between nights one and two, compared with 2.1 hours difference for the rest of the admissions. During the stay, large absolute differences in sleep duration between two nights correlated with aggressive behaviour the next day and short sleep duration was associated with violent incidents.

Conclusion: Short sleep duration and night-to-night variations in sleep duration were both associated with increased risk for aggression in PICUs. This observation might help to predict and prevent aggressive incidents.

Paper IV

The Predictive Properties of Violence Risk Instruments May Increase by Adding Items Assessing Sleep.

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Abstract

Background: The psychometric instruments developed for short-term prediction of violence in psychiatric inpatients do not include variables assessing sleep. Disturbances in sleep may precede aggression in this setting. We investigated whether adding information on sleep improved the predictive properties of the Brøset Violence Checklist (BVC).

Methods: The study population consists of all patients admitted to a psychiatric intensive care unit (PICU) over a 6-month period who were hospitalized for at least one night (n = 50). Sleep observed by staff (521 nights), behaviour assessed with the BVC (433 days), and aggressive incidents recorded by the Staff Observation Scale-Revised (n = 14) were included in the analysis.

Results: The ability of the BVC to predict aggressive incidents improved from AUC_{ROC} 0.757 to AUC_{ROC} 0.873 when a combined sleep variable including both sleep duration and night-to-night variations of sleep duration was added to the BVC recordings. The combined sleep variable did not significantly predict aggressive incidents (AUC_{ROC} 0.653, $p = 0.051$).

Conclusions: A sleep disturbance variable improves the predictive properties of the BVC in PICUs. Further studies of sleep duration, night-to-night variations in duration of sleep, and aggression are needed.

4. Discussion

4.1 Discussion of Methods

4.1.1 Participants

The present thesis is based on data from different groups of highly selected patients admitted to the Department of Psychiatry, Østmarka. The patients were all suffering from disorders having major impact on their lives. The patients in the clinic were admitted only after a physician's referral (usually the patient's GP).

The patients in study I were a selected group from the outpatient clinic specializing in sleep disorders. The patients who stated that they had problems with waking up were asked to participate. Many of the included patients had marginal work or social functioning, while participants with DSWPD in other sleep studies have usually been recruited from schools or universities.

The patients in study II-IV were acutely admitted to a PICU. They belonged to the group of acute patients with the most disturbed behaviours. Patients with psychiatric disorders recruited to clinical studies are usually outpatients or inpatients from rehabilitation departments with longer stays.

The results from the present studies may thus not be generalized to other groups of patients with DSWPD or psychiatric disorders recruited from other patient groups.

The patients in study I had higher scores on the BDI than the controls, indicating a higher burden of depressive symptoms. We cannot exclude the possibility that this has affected the results. Depressive episodes are associated with changes in sleep patterns and cognition [180]. In the clinical examination before the study, none of the patients were considered to be in need of treatment for depression. In healthy adolescents, Baum found that sleep restriction was associated with impairment of mood [28]. Murray found an association between depressive symptoms and circadian misalignment in patients with DSWPD [181]. Bei found an association between intra-individual variability of time in bed, sleep onset latency and negative mood among adolescents going to secondary college [107]. This may explain the BDI scores in our patients. We cannot exclude the possibility that the patients and the controls differed on other, unmeasured parameters than circadian rhythm and depression, which might have affected sleep, awakening and cognition.

The broad inclusion in Papers II, III and IV implies that the study populations were diagnostically heterogeneous, but representative for the total population admitted to PICUs.

The small sample size and large variations within the group of patients limited the opportunity to detect differences between the patients and the controls in paper I, and between sub-populations among patients in paper II-IV.

4.1.2 Design

All studies were conducted with patients in unfamiliar environments that differ from their habitual surroundings. There was no adjustment of sleep time before inclusion in the studies, and the sleep time in the studies were not adjusted to the participants' circadian rhythm. This may have had an impact on the results.

In paper I we attempted to control the environmental factors to ensure non-biased data. However, the consequence of this is a restricted and unfamiliar laboratory setting.
Paper II-IV was conducted in a clinical setting as naturalistic as possible, but unfamiliar to most of the patients. The daily routines, staff and treatments were unaltered during the collection of data. Naturalistic studies in acute and emergency psychiatric populations are scarce and thus highly needed. However, in a daily clinical setting, many factors can interact with sleep and behaviour, such as medication, restrictions of behaviours, timing of lights being turned on and off for each patient, and interactions with other patients and nurses. We were not able to control or record all these factors. Other factors that might affect the patients' behaviour and course of illness such as multiple prior admissions, pharmacological treatment, compliance with treatment, and levels of symptoms were not recorded.
The stimulation-deprived milieus in the laboratory and PICUs may have influenced the participants to go to sleep earlier. It is a possibility that this has had an impact on the participants, and a greater impact on the patients than the controls in paper I. It may also have had a different impact on patients from the different diagnostic groups in paper II-IV. The assessments of sleep duration may have been affected by these factors. Thus, the results must be interpreted with some caution.

Bedtime in the laboratory was 24.00 to 7.00. Patient with DSWPD can seldom fall asleep at 24.00. Thus, a difference in total sleep time on the experimental night between patients and controls was expected.
Bedtime in the PICU was 22.30 to 7.30. The patients were encouraged to come to breakfast at 8.30, and to avoid daytime napping. Thus, the circadian rhythm of the wards may be unusual

for the patients and take some time to adjust to. The fixed bedtimes may have affected the results in the studies.

The light in the laboratory was dimmed to less than 200 lux. It is a matter of debate whether DSWPD patients are more sensitive to evening lights than controls [115, 182]. Thus, the influence of the light on the results might have been different on the patients than on the controls [182]. However, taking into consideration the more recent information about the inter-individual variability in sensitivity to night light, and that melatonin suppression can occur at less than 30 lux, we would have chosen to dim the light more in the study [182, 183]. There was no evening dimmed light in the PICU, and the PICU had large windows directed to the east. The inter-individual differences in sensitivity for evening light [183] may vary between the different diagnostic groups studies.
The inter-individual effects of lights may have affected the findings in the studies.

In paper I participants stayed in the laboratory for only one night. Hence, we could not ascertain with our design whether the CPT findings were related to short sleep duration or to DSWPD itself. A second night in the laboratory with CPT measurements after longer sleep durations would have been appreciated. However, the lack of correlation between Hit-RT difference and total sleep time (TST) suggests that short sleep time could not explain the observed difference. A more recent study has similar findings [184].

The participants in paper I had sleep diaries, and we collected data from actigraphy for the same period. There were no restrictions on behaviour or sleep in the days before the test. The patients may have acted differently than the controls before the experimental day, and this may have influenced the results of the study.
We have no records of sleep before admission to the PICU for the patients in paper II-IV. The sleep before the studies may have affected the results.

4.1.3 Measures

The measures used in the papers are all used on a daily, clinical basis in the hospital.

The chosen objective measures of sleep were polysomnography (PSG) in paper I, and nurses' observation in paper II-IV. Sleep observations have lower reliability than assessments with

polysomnography (PSG) or actigraphy. However, observations of sleep have had satisfactory correlations with PSG and actigraphy in some studies [72, 79-81].
In paper II-IV the staff was instructed to record if a patient was considered "to be sleeping" according to their own clinical judgement. Some patients were observed intermittently, and periods awake might have been missed. Some patients may also have been disturbed in their sleep by the nurses' intermittent observations. Observational data also has the weakness of being a manual procedure with the opportunities for errors in documentation, information being forgotten before it is written down, observations forgotten when nurses are disturbed by patients needing urgent help, and observations being given a lower priority when new staff came on shift. The observation of sleep was not standardized [78], which is a weakness in the study. Nevertheless, we believe that the nurses' frequent observation of sleep is acceptable as a measure of sleep duration, and it is the standard measure in clinical practice in PICUs [76]. PSG is expensive and impossible to use in a PICU because of security requirements. A number of patients in PICUs cannot not be exposed to actigraphs or similar electronic devices due to ethical reasons. A possibility in future research is to use more advanced surveillance technology that is not in direct contact with the patient, but instead is installed in the building.

In paper II-IV, other measures, such as the start and end times of sleep were not analysed.

We are not aware that any standardization of measuring intra-individual variability in sleep duration between nights have been published neither for research nor clinical practice. In paper II-IV we chose the simple measure variation; the differences between the night with the longest and the night with the shortest sleep duration among a chosen number of nights. We chose to use the absolute value to capture variability. We have also chosen to use variability between two consecutive nights as a measure. It can be argued that this is change and not variability. Acute and emergency psychiatry is special with patients having short stays indicating fast improvements in symptoms, behaviour and function. Thus, assessing and evaluating changes in sleep from day to day has clinical importance as well as being practical and reasonable.

The sleep variables for sleep disturbance in Paper IV were defined before the calculations. It is possible that different categorizations of sleep disturbances may improve the prediction of aggressive incidents and give different results.

Nurses' observations of sleep at night is for natural and practical reasons regarded as a measure of sleep. However, it can also be seen as a measure of behaviour, to what extent the patients communicate verbally or non-verbally, move or in other way seem to be awake. We did not have any inter-rater reliability measures of observed sleep prior to inclusions. This is difficult to conduct in a PICU. In theory, two different members of staff could individually have entered the room, observed the patient, and recorded separately with a possibility to calculate an inter-rater reliability. A problem would be that more staff members would be going in and out of the room. This may disturb and wake up the patient. An intention with the study was to conduct it in a natural setting.

The BVC is a psychometric instrument designed for short-term prediction of violence. It consists of six items of observed behaviour: being confused, irritable, boisterous, verbally threatening, physically threatening, and/or attacking objects. Paper III reports the use of the BVC as a measure for observed aggressive behaviour. Behaviours such as verbal threats, physical threats, and/or attacking objects are usually regarded as obviously aggressive incidents. Categorizing behaviours such as being confused, irritable or boisterous as aggression may not be as obvious. However, large multicentre studies from Finland have documented that confused and disorganized behaviour is the leading cause of the use of seclusion or physical restraints [185]. In the present study, the BVC was scored after the nurses had been with the patients for at least one hour. In addition, the scorers usually had access to reports from the rest of the staff. However, it is still possible that some incidents of aggressive behaviour may not have been recorded.

Underreporting of aggressive incidents is an ongoing challenge in psychiatric facilities. In clinical studies, staff and researchers have a special focus on the problem. It is therefore reasonable to believe that underreporting of SOAS-R incidents is limited in the present study. However, we cannot rule out the possibility that some incidents were missed [186]. If incidents were not registered, the results in Papers III and IV would have been affected.

In paper I, CCPT II was chosen as the cognitive test partly because it is relatively simple and straightforward, can be repeated, and is used in the hospital. It was chosen also because it would reflect attentional difficulties that are often reported by patients upon awakening with sleep inertia, and it has been used in previous DSWPD work [131]. It measures only a part of a person's cognitive performance; vigilance, impulsivity, sustained and focused attention

[174]. As with all available neuropsychological tests, the CCPT II is sensitive to motivation, and caution is needed in the interpretation of its scorings.
Cognitive tests are difficult to use in a PICU due to the extent of the patients' symptoms, reduced function and challenging behaviours. If such tests had been part of the research protocol, a major part of the patients had to be excluded. The most affected patients in PICUs are not able to give reliable responses in a satisfactory manner. Thus, cognitive tests were not used. However, if cognitive tests had been used on a minor subpopulation, they may have given important knowledge about the associations between sleep and behaviour next day in PICUs.

4.1.4 Statistics

The main aim of the thesis was to examine associations between sleep and behaviour. The chosen statistical observation-unit of the studies is a 24-hour period; a night with the following day. The 24-hour period is frequently used in clinical practise were each day is seen as a separate observation. The method reported in paper 3 and 4 is a replication of the validation study of BVC by Almvik et al (2000) [187].
In controlled studies of short time prediction of violence, a single day is often regarded as an independent observation [133, 159, 188]. Studies of short time prediction of violence using statistics for multiple measures, do not seems to get different results [158, 188]. Some patients may be represented with several days, others with just one day. The regular PICU patients are dominated by acute crises, challenging behaviour, polysubstance abuse, polydrug use and multiple psychiatric and somatic conditions. The consequences are that a single patient may have very different symptoms, behaviour and function from one day to the next during the single admission, or from one admission to another. This is the reason for regarding single days as individual observations in this context. Paper III and IV are based on data where some patients had multiple admissions. However, it is also possible to regard independent patients and not independent admissions, as cases. This will have consequences for the number of partakers in the study, and it may influence the results.
The use of 24 hour period as the statistical unit, and to allow multiple admissions may be regarded as a violations to the assumption of independence of the observations the statics presupposes [189]. However, we regard that the rapid changes in symptoms in individual patients make the choices taken in the studies as reasonable.

The main aims of paper III and IV were to examine associations between the observed sleep and aggressive behaviour the next day, with the ultimate purpose to improve risk assessments. The aims of the studies were not to find causes for aggressive behaviours, but rather to find indicators for risk of violent behaviours in the immediate future. The studies had a limited number of participants, thus the number of covariates that could be used in analyses is very limited [190]. It is not obvious which covariates that would be relevant [135]. Thus, no covariate or cofounders were used in the analyses in paper III and IV. This may be regarded as a weakness of paper III and IV. But on the other hand, with this design of analyses, findings will be relevant for the day-today clinical practice.

In paper III no adjustment for multiple testing was performed. Adjustment for multiple testing are debated [191, 192]. There is a risk that some of the results are by chance and not true associations. Alternatively, if adjustment for multiple testing had been done, one may miss true associations.

Missing data is a problem in all naturalistic studies and in clinical practice. We chose not to replace missing data. In relatively small studies the effects of missing data on the results is unclear [193].

4.2 Discussion of results

4.2.1 Awakening threshold

Three of the nine patients with DSWPD could not be waken by an alarm clock with a sound intensity of 104 dB. They were all in REM sleep. The controls were all awake in the morning or woke up with a sound intensity of ≤ 78 dB. In the patient group, the wake-up threshold did not correlate with PSG-findings or circadian variables, but there were associations with increasing depressive symptoms and declining amount of REM sleep.

With the study design having a fixed bedtime and forced wake-up time, the patients had shorter total sleep time than controls. According to the two-process model, the patients may have higher sleep pressure at the time of forced wake up, which might explain the differences in ability to wake up to a high intensity sound. Because no differences in correlations between wake-up threshold and PSG or circadian variables were found for the patients, it is less likely that short sleep time explains the differences between the two groups.

Subclinical depressive symptoms are often found in patients with sleep disorder as insomnia, and the depressive symptom improve after treatment of the sleep disorder [194]. The correlation with depressive symptoms may indicate that changes in brain function due to depressive symptoms, the circadian disorder or both can contribute to the changes in the sleep/arousal system.

In accordance with the theory for sleep regulation and the results of earlier studies, we expected that the patients would have more SWS in the morning, and that any problem with waking should correlate with this. To our surprise, all three patients who were unable to wake up from an alarm clock sound of 104 dB, were in REM sleep. In the laboratory on the test night, the patients started to sleep earlier than their usual habit and therefore had less time awake before sleep. According to the two-process model, with a shorter time awake, one expects lower sleep pressure, and with low sleep pressure, less SWS. This can explain the finding that the patients had less deep sleep than controls. It may also have reduced the chances of finding SWS in the morning. Based on the interactions between the homeostatic process and the circadian process, we can speculate that a change in the homeostatic process may have contributed to the results.

Former studies have indicated that, in general, it is easier to wake up from REM sleep than SWS. However, it has been found that sleepwalkers need auditory stimuli of higher intensity to wake up in REM than in NREM sleep [127]. Adolescents need higher intensity auditory stimuli than adults to wake up [195].

In a more recent study, we confirmed that patients with DSWPD are more difficult to wake than controls, and that patients in REM sleep have a higher wake-up threshold than patients in NREM sleep [196].

4.2.2 Cognitive function after awakening

The patients' afternoon CPT Hit-RT was faster compared to the controls, and faster than their own morning Hit-RT. These findings support the patients' self-report of "sleep drunkenness" in the morning, and the hypothesis that the patients' cognitive function is reduced after waking up. Even though it was not indicated in our data, we cannot totally exclude the possibility that reduced TST and SWS may have contributed to these results. The patients had shorter sleep time, which can give higher sleep pressure in the morning. Increased sleep

pressure and short TST can affect cognition, and attention seems to be especially vulnerable [25, 26, 29].

Studies of cognitive function in individuals with different chronotypes have similar findings: morning-types perform better in the morning and evening-types perform better in the afternoon [33, 197, 198]. Thus, to be waken up in different phases of the circadian rhythm may have an impact on cognitive performance. Cognitive performances seem to oscillate with the circadian rhythm [129]. Individuals with evening chronotype report more "sleep drunkenness" during the working-day (waking up early), but not during week-ends (habitual sleep-wake schedule) [199]. The participants with the evening chronotype had longer sleep inertia when waking up after 8 hours of sleep in a laboratory than participants with the early chronotype [33]. It cannot be excluded that sleep inertia and waking from different phases of the circadian rhythm can explain some of our results [128]. However, the present study has only tested forced waking.

In a more recent study, we confirmed the findings that the patients' cognitive function was reduced, particularly upon forced wake up, but the study also documented reduced CPT performance compared with controls upon habitual waking up [184]. In a study from 2019 Saxvig et al found that young persons with DSWPD performed poorer on a cognitive test than control persons in the morning [200].

4.2.3 Sleep duration and night-to-night variations

We found a large variation in sleep duration between groups of patients admitted to the PICU, and a large intra-individual night-to-night variation in sleep duration among the same patients. Moreover, the magnitude of these night-to-night variations the first two nights predicted the length of stay in the PICU, primarily among patients with schizophrenia. It was also a negative correlation between sleep duration the first night and length of stay in the PICU, mainly among patients with schizophrenia. This indicates that lack of night-to-night stability in duration of sleep is a marker of an instable and severe phase of the illness, especially in schizophrenia.

The mean sleep duration over the first 3 days was 7.5 hours, with a wide standard deviation (SD) (more than 3 hours) demonstrating large differences in sleep duration between the patients. Even though the mean sleep duration of 7.5 hours was approximately the same as the

general population [201, 202] and outpatients with schizophrenia or bipolar disorders [101, 104, 203, 204], the SD are much wider among the patients in the PICU.

We expected to find shorter sleep duration in mania compared with the other two patient groups, but we found no such differences. A possible explanation is that patients with mania who are admitted to PICUs, often use psychopharmacological medications prior to admittance. In the present study these medications were not sufficient to treat the manic symptoms in this highly selected patient group. However, the medications might have had some effects on sleep.

The intra-individual night-to-night variations of sleep duration were wide in all patient groups. The mean difference between the longest and shortest sleep duration for the patients that stayed at least 1 week was 7.1 hours. Bauer found that sleep changes of more than 3 hours indicated an imminent mood change among bipolar disorder outpatients [205]. The intra-individual night-to-night variations were wider than found in outpatients with bipolar disorder [99]. A number of studies indicate that the degree of sleep distortions seems to correlate with symptoms in outpatients [104, 121, 203, 205, 206], so it is not surprising that the patients in PICUs have wide variations in sleep duration both inter- and intra-individually.

The patients in PICUs are acutely admitted. Usually there is a lack of knowledge regarding their sleep-wake patterns, the homeostatic process or the circadian process prior to admittance. The majority of patients have also used psychoactive substances affecting sleep [207, 208]. In the context of the two-process model, the large variability of sleep duration found in the first days might be regarded as a sign of many patients being in desynchronized states at admission. The patients with the most disturbed sleep-patterns stay longer in the PICU, and they also have the most disturbed behaviour, including aggression.

During the inpatient stay, the patients must adapt to a fixed, circadian rhythm-like structure through the day with regulation of light, rest, activity, and timing of meals. They receive medications that interact with sleep pressure at fixed time intervals. The impact of this possible mismatch between the patients' and the hospital's sleep-wake rhythm is uncertain, but it may have contributed to the results in the present study.

The wide intra-individual variations in sleep duration, the wide variations in sleep duration

between patients, and to some extent the short sleep duration in individual patients, seem to be associated with exacerbations and more symptoms, as well as length of stay in the PICU. This might indicate that lack of stability is more a marker of the conditions of patients admitted to the PICU than short nights.

Psychiatric hospitals encourage regular circadian rhythms and the accumulation of sleep pressure. New technology make it possible to enhance the patients sleep-wake pattern by adjusting the light in the wards [209, 210] and measure sleep without waking up the patients [74, 75].

4.2.4 Sleep at night and aggressive behaviour the next day

As reported in Paper III, short duration of sleep and large night-to-night variations in duration of sleep were both associated with next-day aggressive behaviour and aggressive incidents throughout the stay. In the published paper analyses based on the 50 admissions is reported. If only the 40 single patients are used in the analyses, the association between sleep and aggressive behaviour is still preserved (Appendix 5). The results might indicate that sleep duration or night-to-night variations in sleep duration are factors that increase the risk of aggressive behaviour in PICUs. Interventions that aim to improve and stabilize sleep patterns might reduce aggression. Aggressive behaviour is complex, and it is a result of several factors other than sleep [139]. However, sleep may contribute to aggression. Some earlier studies support a relationship between sleep and aggression. Studies on the association between sleep duration and aggression have been inconclusive [164]. Intra-individual variability in sleep time seems to be associated with sleep quality [108], and sleep quality has been associated with aggression in different populations [142, 166].

We found that short sleep duration on the first night was associated with higher levels of aggressive behaviour the next day, especially among patients with schizophrenia. A high night-to-night difference in sleep duration at the start of the admission was associated with aggressive incidents during the whole stay, measured by SOAS-R. At admission to acute and emergency psychiatric facilities, there is often limited clinical information about the patient. Analysing sleep patterns for the first one or two nights might improve the evaluation of the clinical status and improve planning of short- and long-term treatment and care.

Shorter sleep duration was found before days with aggressive incidents compared to days

without aggressive incidents. The absolute difference in sleep duration between two nights was associated with higher BVC scores the next day, and especially for patients with diagnoses other than schizophrenia. An implication of this finding is that the staff must be aware of the lack of stability in sleep patterns and circadian rhythms in more extended stays in the PICU. This may reduce risk of aggression and improve treatment. Due to large intra-variability in sleep duration, changes or instability in both sleep pressure and the circadian process are expected. According to studies of the two-process model of sleep regulation, both sleep pressure and circadian process influence cognition [129]. Changes in cognitive function may also contribute to aggressive behaviour.

Kamphuis [164] speculates that the relationship between sleep deprivation and context-inappropriate aggressive responses is mediated by loss of behavioural inhibition regarding negative emotional experiences or circumstances. Patients admitted to an acute psychiatric ward are particularly exposed to such experiences. The ward is closed, many patients are involuntarily admitted, and restrictions may be placed on freedom, behaviour, daily routines, smoking and the use of cellular telephones [145]. According to the two-process model [36] and earlier studies, short sleep time gives high sleep pressure [37, 211]. Increased sleep pressure and short TST can affect cognition, and attention seems to be especially vulnerable. This makes the patients vulnerable to misunderstanding their situations. Thus, our findings of relationships between sleep duration and aggressive behaviour could be associated with both clinical characteristics of the patient population and the inpatient setting [139].

The different items on the BVC revealed a pattern where short sleep duration and night-to-night variations of sleep duration were associated with different types of behaviour. Short sleep was associated with irritability and boisterous behaviour, whereas large night-to-night variations in sleep duration were associated with confusion and threatening behaviour.

4.2.5 Sleep as a predictor of aggressive incidents

Paper IV reported that adding items to assess sleep further increased the predictive properties of the BVC. Neither short duration of sleep nor high night-to-night variations in the duration of sleep predicted aggressive incidents at the same level as BVC scores alone.

When the sleep duration and variability of sleep duration between two nights were combined, a close to significant area under the curve (AUC_{ROC} 0.653, $p = 0.051$) was found. In Paper III,

it was found that sleep duration and variability of sleep duration were to some extent associated with aggressive incidents in different ways. By adding night-to-night variations [105] to sleep duration, we may better assess disturbances in sleep. This difference is difficult to explain from the two-process model of sleep regulation. It may be that sleep duration is more influenced by sleep pressure, while variability of sleep duration is mainly influenced by the circadian rhythm. Thus, the combination of both sleep duration and variability of sleep duration gives a more accurate assessment of the disturbance. However, the present data are not sufficient for us to draw conclusions on the topic.

The ability of BVC to predict aggressive incidents (AUC_{ROC} 0.757, $p = 0.001$) in our study was somewhat lower than or comparable to earlier studies [212-214]. By adding the variable for sleep, the prediction of aggressive incidents improved (AUC_{ROC} 0.873, $p < 0.001$). The improvement was at a comparable level to an earlier study that added visual analogue scale ratings of subjective perception of risk for a physical attack to the BVC [213]. Even a marginal improvement in predicting aggression might be of value for patients and staff [213, 215]. This provides support for an association between sleep disturbances and aggression. There is a need for more studies on sleep duration, intra-individual variability of sleep duration and aggression.

4.2.6 Results across the papers

The papers report associations between sleep at night and behaviour. The different behaviours, cognitive affections, length of stay or aggressive incidents, can all be regarded as complex phenomena. If sleep is only a marker, a mediator or a causal explanation of the observed phenomena cannot be answered by the studies.

It can be hypothesized that the morning cognitive impairment found in patients with DSWPD can be regarded as an association between cognition and sleep disturbances in general. This can provide a possible explanation to the association between sleep disturbances and behaviour found in paper 2-4. Impaired cognition with more confusion and misunderstanding that lead to irritation and aggression, contribute to behaviours that are difficult to handle, and longer stays in the PICUs.

It is further possible to hypothesize that the association between sleep and aggression found in paper 3, can be applied to the findings reported in paper 1. It is to be expected that an irritated person would struggle to maintains focus in a quite boring cognitive test, where she or he for

15 minutes is supposed to press or not press a bottom according to what letter that is presented. It is reasonable to believe that patients with DSWPD are more irritable in the morning. This is a frequent statement from the parents in the clinic. This may explain why DSWPD patients have decreased performances in the cognitive test.

Clinical populations from psychiatric department and sleep regulations

The two-process model theory of sleep regulation may be useful when doing clinical sleep-related research in general, treat patients with sleep disorders, compare different sleep studies, interpret results, or seek new treatments. According to the two-process model of sleep regulation, variations in sleep length are due to changes in the homeostatic process, the circadian process or the interaction between them. However, the validity of the model for the patient groups with extreme symptoms, lack of function, unexpected reactions, and challenging behaviour, is more uncertain.

Patients admitted to psychiatric departments are heterogenous. They are usually suffering from a multitude of psychiatric-, somatic-, psychological and socioeconomical problems. Many suffer from substance abuse, and polypharmacy is frequent [119, 216].

The patients included in this thesis were highly selected patients from a clinical setting, in many ways extreme with altered brains functions. For patients with temporary changes in brain function it is probable that the model of sleep regulation still is insufficient to explain the sleep disturbances in these populations. However, this does not mean that they cannot improve by treatment of sleep. It is for instance increasing evidence that light exposure can restore sleep, and improve the recovery of brain structures, functions and cognition in patients with mild traumatic brain injury [217].

The aetiology of DSWPD is unknown. There is some evidence that patients with DSWPD are more sensitivity to evening light [182], and as reported in paper I some patients did not wake up by 104 dB from REM sleep. These findings indicate that these patients may have altered brain functions. In the clinic these patients report improved function in the morning and having less difficulty with waking up after treatment.

In the PICU population different diagnostic groups of patients are admitted due to symptoms induced by temporary changes in brain function [218]. These changes are triggers for acute psychiatric symptoms and temporary, cognitive dysfunctions. The temporary changes in brain function may all at different levels be related to changes in sleep patterns.

Patients with organic brain may develop acute psychiatric conditions dominated by rapidly changing, polymorphous psychiatric symptoms, challenging behaviour and temporary, cognitive dysfunctions. This is frequently seen in populations of patients with complex partial seizure disorders [219] or patients with temporary, cerebral hyperactivity disorders [220]. Lack of sleep is one of the most important triggers for these conditions [221].
Similar psychiatric symptoms and temporary cognitive dysfunctions may develop in patients with substance use disorders in all phases of the disorder; when being acutely intoxicated, suffering from symptoms of withdrawal, or being in a psychotic state like delirium [222]. A wide range of substances can develop these disorders like alcohol, amphetamines and GHB. The different substances and phases of the use induce sleep problems.
Similar symptoms may develop in patients with catatonia [223]. Patients in severe catatonia lack sleep. They may further deteriorate into life-threatening conditions dominated by autonomous symptoms like tachycardia, hypertension, and hyperpyrexia. These patients frequently have global insomnia. The main treatment is benzodiazepines inducing sleep.
Patients in severe depressive episodes have cognitive dysfunctions and they lack sleep. Global insomnia is a warning sign for imminent suicidal behaviour. Induction of sleep reduces suicidal intention [224].
Thus, in the PICU population the main symptoms in acute conditions indicate a bidirectional relationship between development of psychiatric symptoms / temporary cognitive dysfunctions, and changes in regulation of sleep. In the extreme cases autonomous life-threatening instability may develop [225].

For the extreme group of patients in this thesis, it may not only be changes in the homeostatic process or circadian process or the interaction between them, but rather organic dysfunctions that induces an instability in the factors that express and regulate sleep.

The present studies have a limited number of participants, and as reported there are limitations in the designs and measures used. Thus, interpretation of the results should be made with caution. There is a need for larger and better designed studies controlling for confounders to test the causality between sleep and behaviour in the extreme psychiatric hospital populations. The finale goal must be randomized controlled studies that test if specific treatments of sleep improve cognition, decrease aggression and improve recovery.

4.3 Concluding remarks

Sleep is an essential function, and disruption of sleep affect our functioning and behaviour. The relationship between sleep problems and psychiatric disorders seems to be bidirectional. Sleep problems have been regarded as secondary to the psychiatric disorders, but this attitude has changed in the last 5–10 years.

The diagnostic systems DSM and ICD are based on consensus in description of clinical symptoms and signs [226]. The diagnostic systems have been based on self-reports of feelings and experiences by patients, combined with observations from the clinicians [227]. Thus, the systems have mainly been designed less emphasised on pathophysiology. In all revisions of the DSM-system from the launch of DSM-III, it has been explicitly stated that the present categorization is due to lack of biological measures. The Research Domain Criteria (RDoC) project has the aim of creating a framework for research where new data from clinical neuroscience and genetics are integrated [228].

The present thesis documents the problems in the current categorization. The diagnostic systems DSM and ICD consider each diagnosis as a distinct entity. The categorization of each patient included in the present studies must be unsatisfactory since they usually suffer from multiple problems. Somatic problems, brain disorders and substance use are very frequent in hospital populations.

The diagnostic entities in the classification systems are not consistent when regarding specific symptoms. Patients having problems with sleep pose special challenges. The clinical criteria for major depressive episodes include for instance both increased or decreased sleep [227]. The RDoC introduces a new system to assess impairments in different brain systems. It classifies on the basis on behavioural and neurobiological measures that are dimensional in nature [227]. The present thesis indicates that sleep may be such a dimensional measure.

4.4 Clinical implication of the findings

- Certain DSWPD patients may need manual awakening in addition to an alarm clock, at least in the early stages of treatment.

- In the treatment of patients with DSWPD, the procedures around awakening should be simple and take into account the possible reduced cognitive capacity of patients in the morning.

- The night-to-night variability in sleep should be targeted in the observation and treatment of patients in PICUs.

- Preventing violent incidents in the PICU is important, and one of the targets for treatment may be sleep distortions.

5. Main Conclusions

- A subgroup of patients with delayed sleep-wake phase disorder (DSWPD) could not be awakened by an alarm clock with a sound intensity of 104 dB.
- DSWPD patients may have impairment in cognitive functions in the morning.
- Difficulty awakening from slow wave sleep was not observed. A subgroup of DSWPD patients may have had severe problems waking up from REM sleep.
- For patients with schizophrenia admitted to the psychiatric intensive care unit (PICU), sleep duration on the first night was correlated negatively with the length of stay. The mean difference in sleep duration between nights one and two was correlated with length of stay for the whole group of patients, but especially for patients with schizophrenia.
- For patients with schizophrenia, mania and other disorders admitted to the PICU, mean sleep duration was normal and equal, but all patient groups had pronounced intra-individual night-to-night variations in sleep duration.
- For patients admitted to the PICU, large absolute differences in sleep duration between two consecutive nights correlated with aggressive behaviour the next day, and short sleep duration was associated with violent incidents.
- Admissions in PICU with violent incidents during the stay had a larger difference in sleep duration between nights one and two than the rest of the patients.
- Adding a sleep disturbance variable can improve the predictive properties of a short-term risk assessment scale such as the BVC.

6. References

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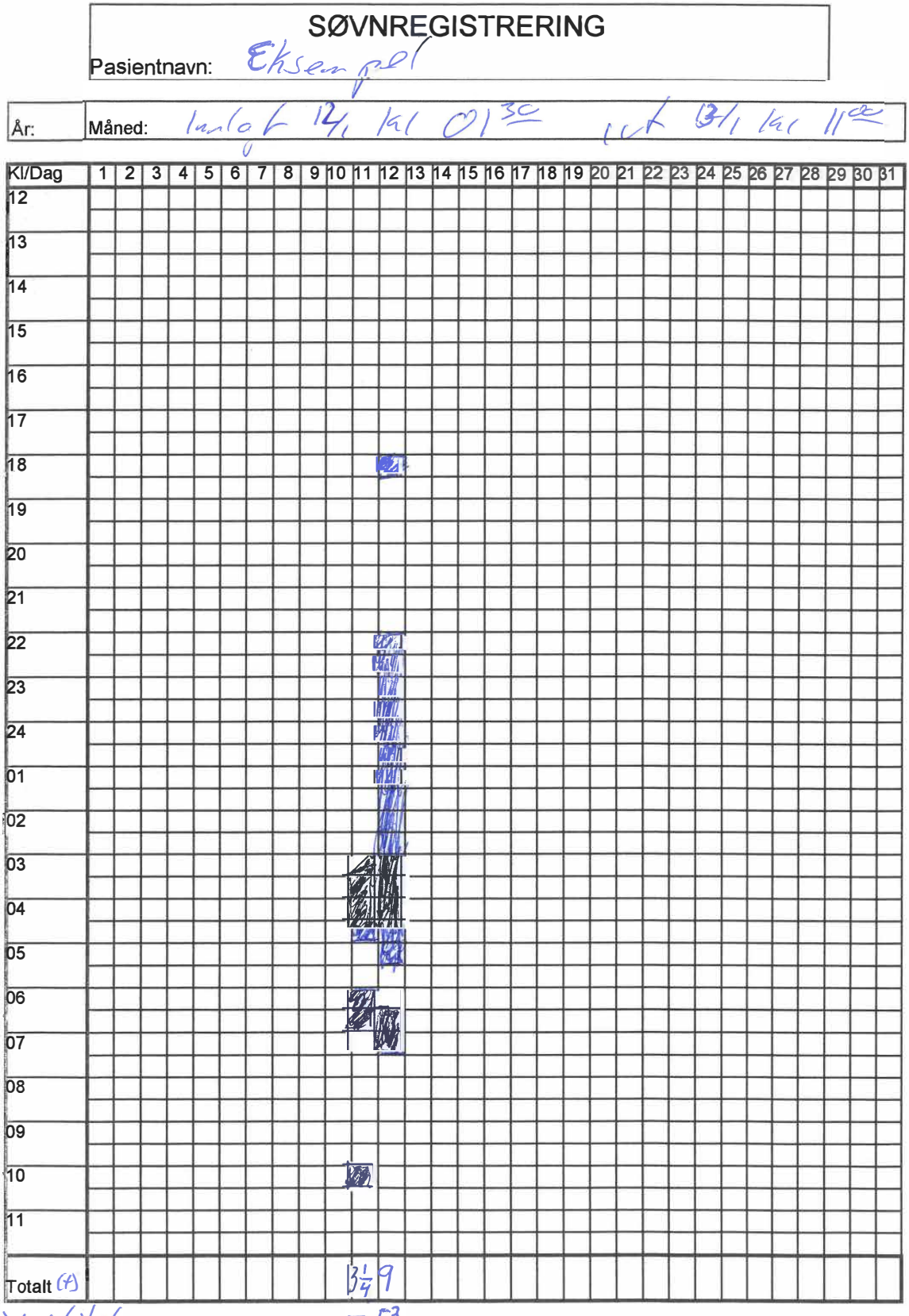
7. Appendix

1. Sleep diaries
2. BVC
3. SOAS
4. Paper 2; Scatterplot of correlations in Table 4
5. Recalculated main results of paper III

Appendix 1. Sleep diaries



SØVNREGISTRERING

Pasientnavn: Eksempel

År: Måned: Innlagt 12/1 kl 0130 Ut 31/1 kl 1100

Kl/Dag	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31
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Variabilitet – 5¾

Appendix 2. BVC

Brøset Violence Checklist (BVC); Pasienten skåres ved hvert skift av f.eks primærpleier senest to timer etter starten på skiftet. Se forøvrig veiledning i prosjektmappe. Fravær av symptom/atferd gir 0 poeng, observert endring i eller tilstedeværende atferd skåres med 1 poeng. F.eks er pasienten vanligvis forvirret vil dette gi skåre 0, men øker forvirringen gis skåre 1. Totalskåre (SUM) er summen av en vertikal kolonne.

Pasientdata

Prosjektnr.: Uke nr.:

Innkomst, ...dag den / 2000			
	Dag	**Kveld**	**Natt**
Forvirret			
Irritabel			
Støyende atferd			
Verbale trusler			
Fysiske trusler			
Slag, spark etc mot gjenstander			
SUM			
Signatur			

Dag , ...dag den / 2000			
	Dag	**Kveld**	**Natt**
Forvirret			
Irritabel			
Støyende atferd			
Verbale trusler			
Fysiske trusler			
Slag, spark etc mot gjenstander			
SUM			
Signatur			

Dag , ... dag den / 2000			
	Dag	**Kveld**	**Natt**
Forvirret			
Irritabel			
Støyende atferd			
Verbale trusler			
Fysiske trusler			
Slag, spark etc mot gjenstander			
SUM			
Signatur			

Dag , ...dag den / 2000			
	Dag	**Kveld**	**Natt**
Forvirret			
Irritabel			
Støyende atferd			
Verbale trusler			
Fysiske trusler			
Slag, spark etc mot gjenstander			
SUM			
Signatur			

Dag , ...dag den / 2000			
	Dag	**Kveld**	**Natt**
Forvirret			
Irritabel			
Støyende atferd			
Verbale trusler			
Fysiske trusler			
Slag, spark etc mot gjenstander			
SUM			
Signatur			

Dag , ...dag den / 2000			
	Dag	**Kveld**	**Natt**
Forvirret			
Irritabel			
Støyende atferd			
Verbale trusler			
Fysiske trusler			
Slag, spark etc mot gjenstander			
SUM			
Signatur			

Dag , ...dag den / 2000			
	Dag	**Kveld**	**Natt**
Forvirret			
Irritabel			
Støyende atferd			
Verbale trusler			
Fysiske trusler			
Slag, spark etc. mot gjenstander			
SUM			
Signatur			

Appendix 3. SOAS

Registreringsskjema For aggressiv atferd **SOAS –R Staff Observation Aggression Scale** - Revised *(Nijman & Palmstierna 1999)*
Til norsk ved Almvik R.., Rør E. ©2000

Pasientdata: Navn:..... Fødselsdato:..... Kjønn:.....	**Utfylt av:**..... Avdeling/Avsnitt:..... Stilling:..... Ansatt siden:.....	Kjønn:..... Alder:.....
Hendelse nr.:	Dato:.....	Klokkeslett:.....

Dette skjemaet skal fylles ut av personalet som har vært vitne til eller involvert i hendelser som kan defineres som aggressive eller voldelige; så som enhver verbal eller non-verbal atferd som kan oppfattes som truende (mot seg selv, andre eller gjenstander), eller fysisk atferd som faktisk medførte fysisk skade (Fra Morrison 1990)
Husk å fylle ut alle data og sett minst et kryss i hver kolonne.

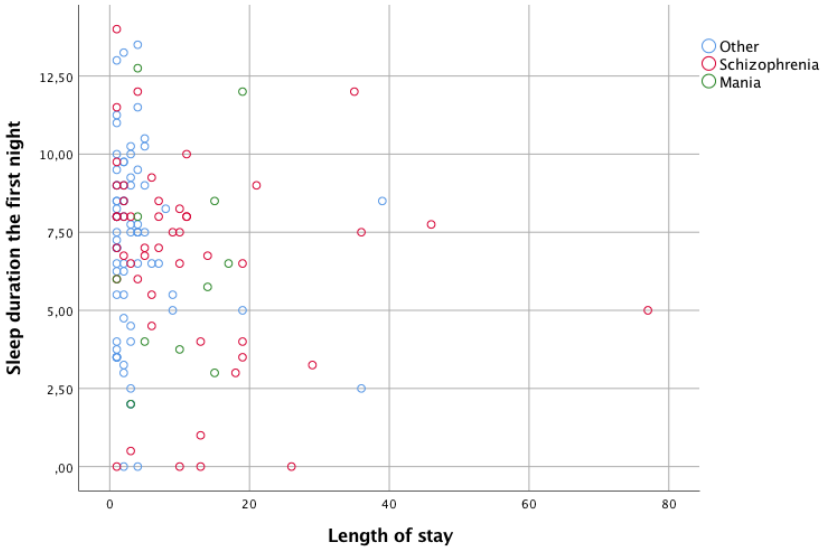
Varselsignaler	**Hvordan begynte aggresjonen**	**Hva brukte pasienten**	**Mål for aggresjonen**	**Konsekvenser av utageringen**	**Hvilke tiltak ble iverksatt**
☐ Ingen observert	☐ Ingen synlig/ forståelig årsak **provosert av:**	☐ Verbal aggresjon	☐ Ingen /Ingenting	☐ Ingen følger **For ting;**	☐ Ingen tiltak
☐ Økt irritasjon	☐ Andre pasienter	☐ Verbal trussel/ drapstrussel	☐ Ting eller gjenstander	☐ Skadet, men brukbar	☐ Snakke med pasienten
☐ Økt forvirring	☐ Hjelp med ADL	**Vanlige ting eller handlinger:**	☐ Medpasient(er) M / K	☐ Skadet, må erstattes **For personer:**	☐ Fjernet fra situasjonen
☐ Økte tegn på angst	☐ Ble nektet noe (eks et gode, aktivitet)	☐ Stoler, inventar e.l	☐ Pasienten selv	☐ Følte seg truet	☐ Skjerming
☐ Verbalt utrykk for sinne	☐ Krav om å ta medisin	☐ Servise, glasstøy, annet	☐ Personale M / K	☐ Smerte < 10 min.	☐ Medikasjon Tbl. /flytende
☐ Kroppslig utrykk for sinne	☐ Krav om å delta i aktiviteter	☐ Spytting	☐ Annen person(er)	☐ Smerte > 10 min.	☐ Medikasjon Injeksjon
☐ Endret psykomotorisk aktivitet	☐ Kommunikasjon/ samtale	☐ Annet; **Kroppsdel:**		☐ Synlig skade	☐ Holdt med makt
☐ Annet;	☐ Uro i avdelingen	☐ Hånd (slag, kilevink e.l)		☐ Behandlings-behov (lettere)	☐ Mekaniske tvangsmidler
	☐ Annet;	☐ Fot (spark)		☐ Behov for legebehandling	☐ Annet;
		☐ Tenner (biting)		☐ Annet;	
		☐ Annet; **Farlige ting eller handlinger:**			
		☐ Kniv/Stikkvåpen skarpe gjenst.			
		☐ Forsøk på kvelning/strupetak			
		☐ Annet;			

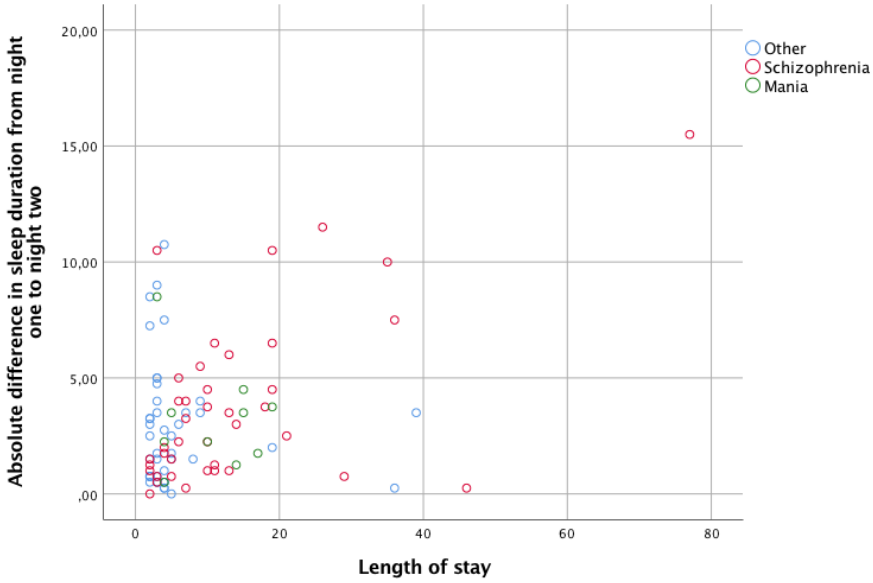
VAS - Visuell Analog Skala

Den voldelige hendelsen var: (avmerk med kryss på streken)

Ikke alvorlig i det hele tatt — Svært alvorlig

Appendix 4. Paper 2; Scatterplot of correlations in Table 4





Appendix 5. Recalculated main results of paper III

Original with 50 admissions, and revised with 40 patients

Table 2

Correlations between sleep duration at night and Brøset Violent Check-list (BVC) the next day, 50 admissions

	Schizophrenia		Other		All	
	r^s	p	r^s	p	r^s	p
Sleep duration the first night	-0.473*	0.041	-0.288	0.145	-0.378	0.010
Absolute difference in sleep duration from night one to night two	0.062**	0.827	0.549	0.055	0.266	ns
Sleep duration, all nights	-0.053	Ns	-0.032	Ns	-0.075	ns
Absolute difference in sleep duration from night to night, all nights	0.104	0.079	0.231	0.021	0.138	0.006

r^s= Spearmans rho

* 19 admission with diagnose Schizophrenia

** 15 admission with diagnose Schizophrenia

Revised Table 2

Correlations between sleep duration at night and Brøset Violent Check-list (BVC) the next day, 40 patients

	Schizophrenia		Other		All	
	r^s	p	r^s	p	r^s	p
Sleep duration the first night	-0.424*	0.116	-0.164	0.467	-0.310	0.062
Absolute difference in sleep duration from night one to night two	0.421**	0.198	0.385	0.174	0.423	0.035
Sleep duration, all nights	0.054	ns	0.100	ns	0.066	ns
Absolute difference in sleep duration from night to night, all nights	0.106	0.139	0.346	0.006	0.161	0.010

r^s= Spearmans rho

* 15 patients with Schizophrenia

** 11 patients with Schizophrenia

Table 3

Length of sleep duration and differences in night-to-night sleep duration in admissions with injuries to staff recorded by Staff Observation Scale- Revised (SOAS-R), compared to admissions without injuries. (50 admissions)

	Injuries			No injuries			
	n	Median	IQR	n	Median	IQR	p
Sleep duration the first night	7	5.5	(4.0-11.25)	43	8.5	(6.0-10.0)	ns
Absolute difference in sleep duration from night one to night two	7	4.5	(3.5-10.0)	29	2.0	(0.625-4.25)	0.020
Sleep duration	15	6.5	(5.0-9.0)	494	9.0	(7.25-11.0)	0.013
Absolute difference in sleep duration from night to night	14	2.25	(1.175-3.5)	439	1.5	(0.75-2.75)	ns

Mann-Whitney U Tests

IQR: Interquartile range

Revised Table 3

Length of sleep duration and differences in night-to-night sleep duration in admissions with injuries to staff recorded by Staff Observation Scale- Revised (SOAS-R), compared to admissions without injuries. (40 patients)

	Injuries			No injuries			
	n	Median	IQR	n	Median	IQR	p
Sleep duration the first night	5	6.5	(4.0-11.625)	35	8.0	(6.0-9.25)	ns
Absolute difference in sleep duration from night one to night two	5	4.5	(3.125-12.75)	21	2.0	(0.625-4.625)	0.057
Sleep duration	9	7.5	(5.75-11.375)	339	8.5	(6.5-10.0)	0.584
Absolute difference in sleep duration from night to night	9	2.5	(0.75-4.0)	298	1.5	(0.75-3.0)	ns

Mann-Whitney U Tests

IQR: Interquartile range

8. Original Papers I-IV

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Original Article

Difficult morning awakening from rapid eye movement sleep and impaired cognitive function in delayed sleep phase disorder patients

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ABSTRACT

Objectives: Difficult awakening is a key symptom of delayed sleep phase disorder (DSPD), but no studies have quantified awakening thresholds in a sleep laboratory. This study assessed whether cognitive function was impaired after awakening and whether difficult awakening was associated with specific polysomnographic features such as slow wave sleep stage N3.
Methods: Nine patients with DSPD and nine sex- and age-matched healthy controls were included. Polysomnography was performed at our university hospital from midnight. An alarm clock was activated at 07:00 with sound intensity increasing from 72 to 104 dB. Participants performed a continuous performance test (CPT) the previous afternoon and immediately upon awakening.
Results: Three DSPD patients and zero controls did not wake up to the maximum 104 dB alarm sound; all three patients were in rapid eye movement (REM) sleep when the alarm clock went off (difference in proportions, $P = 0.047$). In patients, CPT reaction time was prolonged in the morning compared to the afternoon [analysis of variance (ANOVA) interaction, $P = 0.01$]. DSPD patients made more omission errors than controls regardless of time of the day (ANOVA main effect, $P = 0.046$).
Conclusion: Difficult awakening from slow wave sleep was not observed. A subgroup of DSPD patients may have a severe problem waking up from REM sleep. DSPD patients may also have a state-like impairment in cognitive function in the morning and a trait-like impairment not depending on time of day, compared to normal sleepers.

1. Introduction

Delayed sleep phase disorder (DSPD) prevalence among high school students may be as high as 8.4% [1], whereas the prevalence in adults may be as low as 0.17% [2].

Some patients with DSPD report extreme difficulty with waking up in the morning, as they do not react to an alarm clock [3]. Patients may be unable to keep a job or have problems completing education because of absence in the morning [4,5].

Whereas difficult morning awakening is a diagnostic criterion (ICSD-2) and highly disabling symptom in DSPD, research on this phenomenon has not yet been conducted [3]. Specifically, it has not been tested whether patients have a different wake-up threshold compared to healthy controls in the morning. Moreover, no studies have explored potential mechanisms for why these patients have difficulties waking up. Most awakenings in healthy subjects follow a rapid eye movement (REM) sleep period [3,5,6]. On the other hand, awakening from slow wave sleep (SWS) may be difficult, often resulting in confusion and impaired arousal [7]. The difficult morning awakening for patients with DSPD could therefore be related to sleep stage [8].

DSPD patients commonly report poor cognitive function when forced to arise early in the morning. Temporarily impaired cognitive function upon awakening is also a characteristic of sleep inertia (SI) [7,9], and its severity has been related to awakening during slow wave sleep (N3) and after reduced total sleep time (TST) [7,10]. Consequently as DSPD patients have considerable amounts of N3 sleep between 06:00 and 08:00 [8], it may be hypothesized that difficult awakening mainly occurs from N3 in patients with DSPD.

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It has been suggested that SI is primarily associated with low arousal (increased reaction time), whereas SI in the context of sleep deprivation also introduces lapses in vigilance (reduced accuracy) [11]. The continuous performance test (CPT) has the capacity to reliably assess both speed and accuracy [12,13], and measures both sustained and transient cognitive control processes that are subserved by brain regions [14] shown to be particularly prone to SI effects [15].

One aim was to quantify the awakening threshold in DSPD patients with an alarm clock. Another hypothesis was that cognitive function would be reduced upon awakening relative to daytime performance in DSPD patients compared to healthy controls. A third hypothesis was that difficult awakenings would be associated with some sleep stage (SWS in particular).

2. Methods

2.1. Participants

Patients were interviewed by physicians experienced with sleep disorders using a semi-structured interview. Nine patients diagnosed with DSPD were included in the study (four males, five females) (mean age, 22.5 ± 2.2 years; range, 18–25). The included patients met the Diagnostic and Statistical Manual for Mental Disorders, 4th edition (DSM-IV 307.45) diagnostic criteria for circadian rhythm sleep disorder [16] and the ICSD-2 criteria for DSPD [17].

Nine healthy subjects (four males and five females) (mean age 23.3 ± 2.4 years; range, 18–28) were recruited by posting an announcement on the University's homepage and local campus boards.

Subjects with coexisting other major health problems or regular use of neuroactive drugs the last 4 weeks were not included.

The study protocol was approved by the Regional Committee for Medical and Health Research Ethics.

2.2. Procedure

Participants completed a sleep diary for 14 days and wore an actigraph for the last 7 days before polysomnography (PSG) was recorded for two nights. An ambulatory PSG was done first to minimize the 'first-night effect' [18].

The experimental PSG was performed two days after the initial PSG. Participants came to the sleep laboratory at 14:00, took the CPT at 15:00, and completed psychiatric and sleep-related questionnaires afterwards. The light was dimmed to <200 lux from 18:00. Saliva was sampled for melatonin testing every hour from 19:00 to bedtime at midnight. At exactly 07:00 the following morning, an alarm clock was activated. This custom-made tone generator started at 72 dB sound pressure level, increasing by 2 dB at equal intervals (sound active for 4.4 s with 5 s intervals) until the subject was awake or the 104 dB maximum was reached after 3 min. Two standard personal computer speakers (Sony, SRS-Z510) were placed on each side, ~50 cm from the head. The exact time and dB value at which each person reacted were noted. Subjects who did not react at all to 104 dB alarms were awakened manually. Six minutes after awakening the participants took the same CPT test, with identical instructions as the day before.

2.3. Assessments

2.3.1. Actigraphy

The actigraph (AW4, CamNtech Ltd, Cambridge, UK) recorded 30 s epochs for 7 days prior to the experimental night with medium sensitivity. We used sleep start and sleep end for analyses.

2.3.2. Polysomnography

Participants slept in a standard hospital bed within a shielded video-PSG laboratory. A Somnoscreen 10-20 monitor (SOMNOmedics GmbH, Randersacker, Germany) using a standard PSG montage with electroencephalography electrodes (F3, F4, C3, C4, O1, O2, A1, A2 with a Cz reference, and 0.2–35 Hz filter), electro-oculography electrodes (placed 1 cm over/under the left/right lateral canthus), an infrared O_2 finger sensor, two chin EMG electrodes, a nasal airflow sensor and an oro-nasal thermistor were used. Apnea-hypopnea index was <5/h in all participants. Video and sound were recorded continuously (VID65A, HD resolution 2048 × 1536, SOMNOmedics). Polysomnograms were analyzed by a blinded, certified clinical neurophysiologist, according to standardized criteria [19] using Domino software version 2.5.0.

2.3.3. Melatonin

Food or drink was not allowed 30 min prior to each sampling. Five minutes before sampling, the mouth was rinsed with cold water. A piece of Parafilm® (Pechiney Plastic Packaging Company, Chicago, IL, USA) was chewed and two samples of ≥2 mL each were collected and placed in a refrigerator at 4 °C within 10 min. All samples were placed in a freezer at less than –20 °C immediately after midnight and analyzed with the Non-Extraction Melatonin Saliva enzyme-linked immunosorbent assay kit, supplied by IBL International GmbH (Hamburg, Germany).

A melatonin baseline was calculated as the mean value for samples taken at 20:00, 21:00 and 22:00. Normal (early) melatonin secretion onset was defined when a concentration either more than twice the baseline value, or baseline +2.5 standard deviations (SD), was measured either at 23:00 or at 00:00. This cut-off was modified from the 2 SD limit used by Chang et al. [20] in order to account for the observed baseline variability. Delayed dim light melatonin onset (DLMO) was presumed if concentrations had not reached one of the cut-off values at 00:00.

2.3.4. Sleep diary

Participants kept a graphic sleep diary of their subjective experience of sleep timing and duration for 14 days prior to the experimental night. A pencil was used to shade (or leave) 24 rectangular small boxes each representing 1 h of the day. Symbols were inserted for going to bed, lights off, and getting out of bed.

2.3.5. Sleep-related and psychiatric self-report questionnaires

Participants completed self-report questionnaires to assess circadian preference (Horne–Östberg Morningness Eveningness Questionnaire (MEQ) [21], and the Beck Depression Inventory (BDI) [22]).

2.3.6. Continuous performance test

In the present study, Conners' CPT II [23] was used to assess cognitive function. Letters A–Z were presented consecutively on a computer screen for 250 ms each in a pseudorandom fashion for 14 min. Inter-stimulus intervals varied between 1, 2 and 4 s. There were 324 targets (letters other than X) and 36 non-targets (the letter X). Participants were instructed to press a button as quickly as possible whenever a target was presented. Measures were: Hit-RT, mean reaction time for correct responses; commission errors, the number of failed withholdings to non-targets; and omission errors, the number of failed responses to targets.

2.4. Data analysis and statistics

The main variables were: CPT Hit-RT evening–morning difference; alarm clock level upon awakening; and sleep stage on awakening. Exploratory statistical data analysis was performed for the remaining variables.

The value of 105 dB was entered for subjects who did not wake up to 104 dB, whereas a value of 71 dB was entered for subjects who were awake at 07:00.

Separate 2 × 2 repeated measures analysis of variance (ANOVA) was applied for each of the three CPT performance measures (Hit-RT, commission errors, omission errors), with group (patients, controls) and time (afternoon, morning) as fixed factors. In the case of statistically significant main or interaction effects, planned simple contrasts were performed.

Non-parametric Mann–Whitney *U*-test or Wilcoxon signed rank test was applied for PSG, actigraphy, questionnaire, and sleep diary variables. Differences in proportions were tested with a standardized normal deviate. Two-sided $P < 0.05$ was considered significant.

Non-parametric Spearman's rho was used for exploratory correlation analyses within the patient group.

3. Results

Delayed DLMO was confirmed in eight out of the nine patients. Melatonin increased significantly more in controls than in patients (Table 1).

Self-reported MEQ, sleep diary and actigraphy data confirmed a delayed sleep phase in all patients. Patients scored higher on depression than did controls. Based on standard BDI cut-off values (0–9, normal; 10–18, mild; 19–29, moderate; ≥30, severe depression), all controls were normal. Three patients were normal, four mild, and two had severe depression. No significant difference was found regarding diary-reported sleep duration between the two groups (Table 1).

PSG sleep onset latency was longer, total sleep time (TST) was shorter, sleep efficiency (SE) was lower and stage N3 duration was shorter in patients compared to healthy controls (Table 2).

Patients tended to be more difficult to wake up, as quantified through the intensity of the alarm clock sound, but the variation was larger within the patient group and the difference was not significant (Table 2).

Compared to none of the nine controls, three of nine patients failed to wake up from the alarm clock at its highest intensity (104 dB) and had to be manually awakened. All patients who failed to wake up from the alarm clock were in REM sleep at the time of the alarm.

Four patients and three controls were in REM sleep at the time of the alarm. Three out of these four patients compared to none of three controls did not wake up from REM sleep ($P = 0.047$). Patients who failed to wake up from REM ($n = 3$) had significantly less REM percentage (14 ± 5 vs 19 ± 2%, $P = 0.04$) and more stage N1 sleep (35 ± 9 vs 17 ± 12 min, $P = 0.04$) than the other patients ($n = 6$), whereas no significant differences were observed for melatonin (baseline and percent increase) and diary-recorded variables (sleep length, sleep latency, sleep onset hour, and sleep onset hour variability).

CPT performance measures are presented in Table 3. For Hit-RT, there was a statistically significant interaction effect between group and time [$F(1, 16) = 7.76$, $P = 0.013$] (Fig. 1). A planned simple contrast revealed that patients had a statistically significant

Table 1
Sleep diary, actigraphy questionnaire and melatonin data.

Variables	Patients ($n = 9$)	Controls ($n = 9$)	*P*-value[a]
Sleep diary			
Sleep start	01:26 ± 01:03	00:03 ± 00:41	0.004
Sleep end	10:23 ± 01:03	07:55 ± 00:53	<0.0005
Night sleep (h)	7.44 ± 0.69	7.14 ± 0.41	NS
Actigraphy			
Sleep start	01:48 ± 00:47	00:23 ± 00:46	0.003
Sleep end	09:50 ± 1:26	08:05 ± 00:56	0.02
Questionnaires			
BDI	14.7 ± 11.7	2.8 ± 2.9	0.01
MEQ	27.6 ± 6.0	46.8 ± 6.4	<0.0005
Melatonin			
Baseline (pg/mL)	11.0 ± 6.3	9.3 ± 5.7	NS
Percent increase[b]	37 ± 51	137 ± 109	0.01
Delayed DLMO (no.)	8	3	0.02

Values are mean ± standard deviation unless otherwise indicated.
BDI, Beck Depression Inventory; MEQ, Morningness–Eveningness Questionnaire; DLMO, dim light melatonin onset; NS, not significant.
[a] Mann–Whitney *U*- or proportion-difference test.
[b] Maximum increase at 23:00 or 00:00.

Table 2
Polysomnographic data and awakening threshold for the study night recorded from 00:00 to 07:00.

Sleep variable	Patient	Control	*P*-value[a]
TST (min)	333 ± 49	379 ± 22	0.01
SE (%)	82.5 ± 10.7	93.3 ± 5.4	0.01
SOL (min)	41 ± 37	7 ± 7	0.003
N1 (min)	30 ± 13	43 ± 43	NS
N2 (min)	178 ± 31	156 ± 26	NS
N3 (min)	73 ± 16	106 ± 27	0.01
REM (min)	53 ± 19	74 ± 21	NS
Awakening threshold (dB)	85.2 ± 14.9	74.2 ± 2.7	NS

Values are mean ± standard deviation.
TST, total sleep time; SE, sleep efficiency; SOL, sleep onset latency to N1; REM, rapid eye movement sleep; NS, not significant.
[a] Mann–Whitney *U*-test.

Table 3
Summary of CPT measures.

CPT measure	Afternoon (~15:00)	Morning (07:00)
Hit RT (ms)		
Patients	300.6 ± 25.9	326.7 ± 44.3
Controls	347.8 ± 59.6	335.9 ± 56.9
Omission errors		
Patients	3.6 ± 3.9	4.3 ± 4.9
Controls	0.9 ± 0.9	1.1 ± 1.4
Commission errors		
Patients	20.1 ± 9.2	21.8 ± 10.4
Controls	13.7 ± 7.6	13.6 ± 8.6

Values are mean ± standard deviation.
CPT, Conners' Continuous Performance Test II; Hit RT, reaction time.

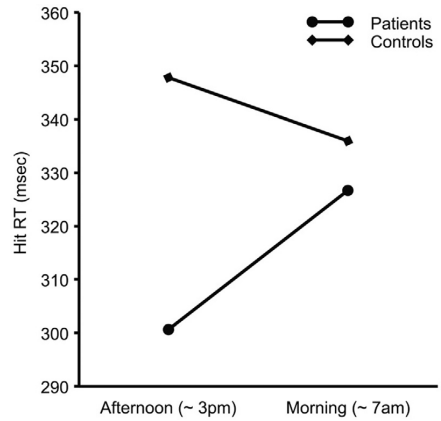

Fig. 1. Conners' Continuous Performance Test II: group (patients, controls) × time (afternoon, morning) interaction for Hit RT [$F(1, 16) = 7.76$, $P = 0.01$]. RT, reaction time.

increase in mean Hit-RT when tested in the morning, relative to that in the afternoon {$F(1, 16) = 7.32$, $P = 0.016$ [95% confidence interval (CI) of difference, 5–46]}. In addition, patients had lower Hit-RT than healthy controls when tested in the afternoon [$F(1, 16) = 4.75$, $P = 0.045$ (95% CI of difference, 1–93)], whereas no statistically significant difference between the groups was found in the morning. Patients generally made more omission errors than controls [main effect $F(1, 16) = 4.69$, $P = 0.046$ (95% CI of difference, 0.06–5.8)]. For commission errors, there were no significant main or interaction effects.

No significant correlations were found within the DSPD group between Hit-RT (afternoon–morning difference) and melatonin increase, diary sleep onset hour, diary sleep length, PSG-TST, SE, and N3. Neither the awakening threshold nor the Hit-RT difference correlated with these variables. Awakening threshold, but not Hit-RT difference, correlated positively with BDI (rho = 0.74, $P = 0.023$).

4. Discussion

Of the nine patients, three could not be awakened from an alarm clock with a sound intensity of 104 dB, whereas all controls either were already awake or woke up from a sound intensity of ≤78 dB. This may point towards a possible dysfunction in sleep/arousal system that may in part explain why some patients seem unable to attend work or school. Awakening threshold did not correlate with either PSG or circadian variables among patients. This suggests that difficult morning awakening may not be a mere reflection of short sleep. A clinical implication is that certain patients may need manual awakening in addition to an alarm clock, at least in the early stages of light treatment before the circadian phase has been shifted.

The trend towards patients being harder to wake up compared to controls was statistically non-significant. This was probably due to a small sample size and large variability within the patient group.

Interestingly, whereas healthy subjects are most likely to wake up from REM sleep [3], all patients who were unable to wake up when exposed to a 104 dB alarm clock sound were in REM sleep. This was contrary to our hypothesis that DSPD awakening problems would be related to slow wave sleep (N3) and suggests a possible REM sleep dysfunction in a subgroup of DSPD patients. This observation seems to be new. To our knowledge, there are no previously reported cases of difficult awakening from REM sleep in the literature.

Current knowledge about REM sleep suggests that 'stimuli incorporation' might be one explanation for the observed difficult awakening. It is not unusual to incorporate external auditory stimuli into a dream [24]. A DSPD subject might then include the sound of an alarm clock into his/her dream, counteracting the expected arousal and awakening. Regrettably, we did not ask patients to recollect dream content in the present study.

The CPT results showed that patients, compared to controls, had increased Hit-RT when tested in the morning as compared to when tested in the afternoon. This supports the hypothesis that the patients' cognitive function is reduced upon awakening. To some extent, this observation may confirm patients' subjective reports of 'sleep drunkenness' when forced to wake up early [17].

No correlation between CPT and PSG or circadian variables was found within the DSPD group. However, reduced TST, reduced SWS, and lower SE may still be contributing factors to the decline in early morning performance when DSPD patients are compared to controls, because the lack of within-group correlation can be explained by a type II error.

DSPD may also affect cognitive function in general, i.e. unrelated to time of day as patients made more omission errors than controls. In addition, patients had faster Hit-RT than healthy controls when tested in the afternoon. These findings suggest that there may be stable trait-like differences between DSPD patients and controls, in addition to the state-dependent change found in relation to Hit-RT.

The high score for depression in our patient group is in agreement with other studies [25,26]. Abe et al. reported that depression is most common in evening chronotypes [26]. Alvarez et al. stated that it is unlikely that depression or personality problems are among the main causes of DSPD [25]. Nevertheless, we observed that high awakening thresholds were associated both with more severe depression and with relatively less REM sleep, suggesting that the possibly interacting effects of depression and sleep structure in DSPD should be investigated further in future studies.

The study has limitations as our sample size was small and the results might not apply to the general DSPD population. A second limitation was that we did not include CPT measurements after a second night with longer sleep durations in patients. Hence, we could not ascertain with our design whether the CPT findings were related to short sleep duration or to DSPD itself. A third limitation was a rather large variability in baseline melatonin recordings. Melatonin was not required for diagnosis, but more stable recordings might improve our ability to detect the effect of the circadian factor on DSPD-related symptoms. We emphasize that our results require independent confirmation and future investigation as there currently is no literature on the subject.

Conflict of interest

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: http://dx.doi.org/10.1016/j.sleep.2014.05.024.

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Sleep patterns as a predictor for length of stay in a psychiatric intensive care unit

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ABSTRACT

Systematic evaluations of the relationship between sleep patterns and length of stay in psychiatric intensive care units (PICUs) are lacking. The aims of the present study were to explore if sleep duration or night-to-night variations in sleep duration the first nights predict length of stay in a PICU. Consecutive patients admitted to a PICU were included ($N=135$) and the nurses registered the time patients were observed sleeping. In the three first nights, the mean sleep duration was 7.5 ($\pm$3.2) h. Sleep duration the first night correlated negatively with the length of stay for patients with schizophrenia. The mean difference in sleep duration from night one to night two were 3.3 ($\pm$3.0) h and correlated with length of stay for the whole group of patients, but especially for patients with schizophrenia. Patients of all diagnostic groups admitted to a PICU had pronounced intra-individual night-to-night variations in sleep duration. Stabilizing night-to-night variations of sleep duration might be a major goal in treatment.

1. Introduction

Normalization of sleep is an important goal in acute psychiatric treatment, but systematic evaluations of the relationship between sleep patterns and length of stay in psychiatric intensive care units (PICUs) are lacking.

In the hospital of the present study, the PICU is a part of the closed acute psychiatric in-patient ward. In the PICU patients with the most disturbed behaviour and severe symptoms are treated, and there is a low patient/ staff ratio. The patient's behaviour and symptoms, including sleep are daily registered as a part of the ordinary clinical practise. To promote sleep there are fixed points in time for eating, activity and sleep in the PICUs. Patients are usually transferred from the PICUs after improvement in symptoms, function and behaviour. Different levels of segregation are used, a treatment method supposed to have effects through control of sensory and emotional stimuli (Hodgkinson, 1985; Vaaler et al., 2011). In addition to pharmacological treatment, the therapeutic milieu in PICUs is organized to manage challenging behaviours. One might expect that sleep is normalized and that length of stay is a parameter indicating the global effects of the interventions.

Among outpatients with schizophrenia and bipolar disorder, increasing night-to-night variations in sleep duration seem to correlate with symptom severity (Gruber et al., 2011; Waters et al., 2011). In bipolar disorder a large mood change is imminent if variation of sleep duration from one night to the next night is more than 3 h (Bauer et al., 2006). Thus, out-patients with severe mental disorders may have large night-to-night variations in sleep, especially in episodes of exacerbation of their illness. Descriptions of night-to-night variations in sleep duration among acutely admitted inpatients are needed both for better monitoring of the status of patients and possible refine treatment interventions.

The aims of the present study were to explore if sleep duration a single night or night-to-night variations in sleep duration the first nights predict length of stay in the PICU. We also wanted to compare sleep duration and night-to-night variations in sleep duration among patients with schizophrenia, mania and other disorders in a PICU.

2. Methods

In this study sleep duration were registered for all inpatients admitted to the PICU at the university hospital.

The Østmarka Psychiatric Department, St Olavs University Hospital, had a catchment area of 140,000 inhabitants from both the city of Trondheim (50%) and the rural areas (50%) in Sør-Trønderlag County at the time of the study. About 700 inpatients above 18 years were admitted each year. Acute admissions to other psychiatric hospitals occurred only when inhabitants temporarily

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resided outside the catchment area. Norwegian acute psychiatric services are public and available to everyone.

The patients were admitted to the one of two closed acute wards with most free capacity. These wards consisted of an ordinary ward area and a PICU area. The PICU was used for containment of the most behaviourally disturbed patients. The patients were admitted to the PICU after assessment from the physician taking into account function, symptoms and behaviour. The therapist in the ward discharged the patients from the PICU after evaluating the patient's, no written criteria for admittance or discharge existed (Vaaler et al., 2006). The PICU consisted of two separate wings with sitting room, bathroom, toilet and two single patient rooms. The patients in the PICU were segregated together with staff, and expected to stay in their rooms and sleep between 22.30 and 7.30. The patients were encouraged to come to breakfast at 8.30 and to avoid daytime napping. The patients received treatment as usual including pharmacological treatment.

In one ward all patients admitted to the PICU in two periods of 4 and 5 months and in the other ward all patients admitted to the PICU in a period of 6 months, were included in the study. All patients who stayed at least one night were included. One patient was excluded due to severe dementia. Patients with multiple admittances were only included once.

2.1. Diagnostic groups

Diagnoses according to ICD-10 diagnostic criteria for research (WHO, 1993) were set in a weekly consensus meeting in the department's staff including the patient's therapist and at least two psychiatrists of whom at least one had personally examined the patient.

The patients with main or secondary diagnosis from F20 to F29 were defined as patients with schizophrenia. The patients with main or secondary diagnosis from F30 to F31.2 were defined as patients with mania. Patients with schizophrenia and mania dominated among patients with a long stay in the PICU and were compared to the rest of the patients defined as other disorders.

2.2. Sleep registrations

The time patients were observed to sleep was registered in a separate sleep diary and in the medical records by the nurses in the PICU. The nurses observed the patients at least every 30 min, often more frequently. The sleep diary consisted of a column for each 24 h and a square for each 30 min. The sleep duration in a day were defined as observed sleep from 12 a.m. to 12 a.m. Sleep registrations started the first night after admission and continued until discharge.

2.3. Variations in sleep duration were defined in three variables, absolute values were used

1. The differences in sleep duration between two nights. 2. The differences between the night with the longest and the night with the shortest sleep duration, A; among the three first nights and B; among the seven first nights (Gruber et al., 2011). 3. The patients were also divided in those with more and those with less than 2.5 h differences in sleep duration between the first and the second nights. The 2.5 h where chosen due to observations by Bauer (Bauer et al., 2006), that the frequency of new mood episodes increased with a three hour or more variation in length of sleep.

2.4. Statistics

Statistical analyses were performed using SPSS 21.0 for MAC. Categorical data were analysed with chi-square tests. Normally distributed data were analysed with Students *t*-test or ANOVA and data not normally distributed were analysed with non-parametric tests. Data were expressed as mean and standard deviations (SD) unless otherwise noted. The significance level was set at $p < 0.05$ (two tailed). The sample size was not calculated before the study started, previous studies could not give an estimate of results and the included number of patients was based on the capacity of the department.

2.5. Ethics

The study was approved by The Regional Committee for Medical and Health Research Ethics, Central Norway.

3. Results

3.1. Description of the sample

In the study 135 patients, 61 females and 74 males, representing 949 nights were included. There were missing data on 12 nights. A description of the patients is given in Tables 1 and 2. Median nights per admission were 3 (min 1, max 77, mean 7.0). More patients with other psychiatric disorders than schizophrenia or mania were discharged after one night and had shorter lengths of stay than patients with schizophrenia or mania (Table 2).

3.2. Sleep duration

Distribution of sleep duration for night one, two and three for all patients are demonstrated in Fig. 1. Sleep duration the first (6.9 ± 3.1 h), second (8.0 ± 3.3 h) or third (8.1 ± 2.9 h) night did not differ between patients with schizophrenia, mania and other disorders (Table 3). Sleep duration the first night did not differ between patients discharged after one night (mean 7.5 ± 2.8 h) and patients that stayed for more than one night (mean 6.7 ± 3.2 h).

3.3. Night-to-night variations in sleep duration

Night-to-night variations in sleep duration are given in Table 3. In the whole sample, the mean absolute difference in sleep duration from night one to night two were 3.3 (± 3.0) h and from night two to night three 2.8 (± 2.6) h. The mean difference between the night with the longest and the night with the shortest sleep duration the three first nights was 4.7 (± 3.5) h and the mean difference between the night with the longest and the night with the shortest sleep duration the seven first nights was 7.1 (± 3.7) h for the whole sample, with no significant differences between the three groups of patients.

Table 1
The number of patients and number of nights in a psychiatric intensive care unit distributed on main diagnostic groups.

	Diagnostic groups	Patients	Nights
	All	135	949
F00–09	Organic mental disorders	11	64
F10–19	Substance abuse	27	61
F20–29	Schizophrenia	49	563
F30–39	Mood disorders	28	190*
F40–99	Anxiety, personality and development disorders	20	71

* F30-31.2 Mania: 11 Patients and 107 nights

Table 2
Descriptive data for the 135 patients admitted to a psychiatric intensive care unit distributed on main diagnostic groups.

	Schizophrenia	Mania	Other	All	*P*
Patients	49	11	75	135	
Discharged after one night	9	1	29	39	0.016*
Discharged after two nights	4	0	14	18	ns
Nights	563	107	279	949	
Length of stay, median (min–max, mean)	7 (1–77, 11.5)	10 (1–19, 9.7)	2 (1–39, 3.7)	3 (1–77, 7.0)	0.000***
Female/male	22/27	8/3	31/44	61/74	0.148*
Age, years (SD)	36.9 (12.3)	46.8 (15.9)	39.1 (17.3)	39.0 (15.6)	0.165**

* Chi square test.
** Anova.
*** Kruskal–Wallis.

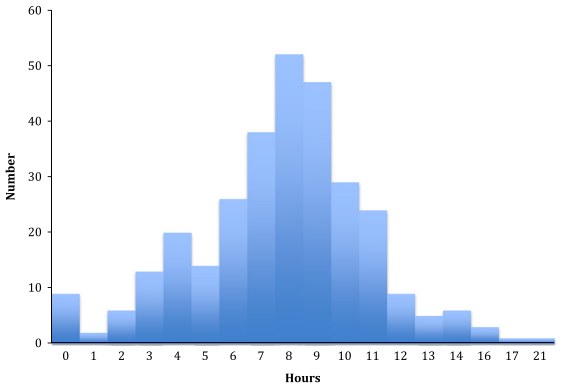

Fig. 1. Distribution of sleep duration the first three nights in a psychiatric intensive care unit: Mean: 7.5 (± 3.2) h.

3.4. Correlations between sleep duration, night-to-night variations in sleep duration the first nights and length of stay in PICU.

Sleep duration the first night correlated negatively with length of stay in PICU for patients with schizophrenia ($r^s = -0.311$, $p=0.029$) and for all patients ($r^s = -0.171$, $p=0.047$). The absolute differences in sleep duration from night one to night two correlated with length of stay in PICU for patients with schizophrenia ($r^s=0.432$, $p=0.005$) and for all patients ($r^s=0.245$, $p=0.018$). See Table 4.

In the whole sample, patients with an absolute difference in sleep duration of 2½ h or more from night one to night two stayed significantly longer in the PICU (median 7, min 2-max 77, mean 11.8 days) than the rest of the patients (median 4, min 2-max 46, mean 7.6 days) (Mann–Whitney *U*-test $p=0.044$). In the group with schizophrenia, patients with an absolute difference in sleep duration of 2½ h or more stayed significantly longer (median 13 min 3-max 77, mean 18.1 days) than the rest of the group (median 5.0, min 2-max 46, mean 9.2 days) (Mann–Whitney *U*-test $p=0.002$).

4. Discussion

We found a large variation in sleep duration between the patients admitted to the PICU and, more importantly, a large intra-individual night-to-night variation in sleep duration among the same patients. Moreover, the magnitude of these night-to-night variations the first nights predicted the length of stay in the PICU, primarily among patients with schizophrenia. There was also a negative correlation between sleep duration the first night and length of stay in the PICU, mainly among patients with schizophrenia. This indicates that lack of night-to-night stability in duration of sleep is a marker of an instable and serious mental illness, especially in schizophrenia. Even if patients admitted to the PICU represented broad diagnostic groups, the long stays and the total number of nights were dominated by patients suffering from schizophrenia or mania.

4.1. Sleep duration

The mean sleep duration the first three days were 7.5 h with a wide standard deviation (more than 3 h) demonstrating large differences in sleep duration between patients admitted to the PICU (Fig. 1). Even if the mean sleep duration of 7.5 h is approximately the same as in healthy populations (Friborg et al., 2012; Oyane et al., 2008), the standard deviations are much wider among the patients at the PICU. The mean sleep duration in the present study was also approximately the same as in outpatients with schizophrenia and bipolar disorder, but with much wider standard deviations (Gruber et al., 2009; Kaplan et al., 2012; Waters et al., 2011; Wulff et al., 2012). The wide variations in sleep duration between patients at the PICU seem to be a marker of acute psychiatric illness.

Shorter sleep durations in mania than in the two other patient groups were expected, but no such differences were found. A possible explanation is that the patients with mania admitted to a PICU often have tried several pharmacological treatments without success before admittance and that in this highly selected patient

Table 3
Sleep variables for 135 patients admitted to a psychiatric intensive care unit distributed on diagnostic groups.

	Schizophrenia		Mania		Other		All		*P*
	Mean	*(SD)*	*Mean*	*(SD)*	*Mean*	*(SD)*	*Mean*	*(SD)*	
Sleep duration, hours									
The first night	6.6	(3.3)	6.6	(3.5)	7.1	(2.9)	6.9	(3.1)	0.616
The second night	8.3	(4.0)	7.8	(3.8)	7.9	(2.6)	8.0	(3.3)	0.808
The third night	8.3	(3.4)	7.3	(2.0)	8.1	(2.6)	8.1	(2.9)	0.622
Absolute differences in sleep duration between two subsequent nights, hours									
Night one to night two	3.8	(3.6)	3.2	(2.3)	2.8	(2.6)	3.3	(3.0)	0.304
Night two to night three	3.2	(2.7)	2.6	(2.7)	2.3	(2.6)	2.8	(2.6)	0.320
Absolute difference between the longest and shortest sleep duration, hours									
The three first nights	5.4	(3.9)	4.2	(2.3)	4.1	(3.2)	4.7	(3.5)	0.245
The seven first nights	7.0	(3.8)	6.5	(3.5)	7.6	(4.2)	7.1	(3.7)	0.872

Anova tests were used.

Table 4
Correlations between sleep duration the first night and absolute differences in sleep duration the two first nights and length of stay in a psychiatric intensive care unit.

	Schizophrenia		Mania		Other		All	
	r^s	*P* value	r^s	*P* value	r^s	*P* value	r^s	*P* value
Sleep duration the first night	−0.311	0.029	0.228	0.500	−0.030	0.797	−0.171	0.047
Absolute difference in sleep duration from night one to night two	0.432	0.005	0.061	0.866	−0.036	0.820	0.245	0.018

r^s = Spearmans rho.

group, the mania symptoms are not reduced even if there is a response to pharmacological treatment on sleep duration. Another possible explanation may be that patients with mania do not only have a diminished ability to sleep, but that they do not give themselves an adequate opportunity to sleep. In the PICU there is a very high degree of external structure and regulation that provides an improved opportunity to sleep.

4.2. Night-to-night variations

The night-to-night variations of sleep duration in each patient were wide in all three patient groups. The mean difference between the longest and shortest sleep duration the first week was 7.1 h and did not differ between the disorders. The variations expressed as standard deviations were wider than found in outpatients with bipolar disorder (Gruber et al., 2011), indicating an association between increased symptoms, reduced general function and lack of stability in sleep duration. Bauer found that sleep changes of more than three hours are late prodromal signs for an imminent mood change among bipolar outpatients (Bauer et al., 2006). It is established that the degrees of sleep distortions seem to correlate with symptoms in outpatients (Afonso et al., 2011; Bauer et al., 2006; Cohrs, 2008; Gruber et al., 2009; Waters et al., 2011), so it is not surprising that the patients in PICU have wide variations in sleep duration both between patients and intra-individually in each patient. Lack of stability of sleep duration from night-to-night seems to be a core feature of increased symptoms and decreased function across several psychiatric disorders. Nearly all patients with a long stay at the PICU suffered from schizophrenia or mania. The authors have no explanation for the apparently higher instability in sleep duration in the schizophrenia group than in the mania group although Wulff speculated that sleep changes among some people with schizophrenia are due to their wide-spread alterations in brain architecture and physiology (Wulff et al., 2010).

4.3. Correlations between sleep duration, night-to-night variations in sleep duration the first nights and length of stay at the PICU.

The length of sleep duration the first nights had a weak negative correlation with the length of stay, i.e. short sleepers had longer stays, the correlation was most evident among patients with schizophrenia. The absolute differences in sleep duration from night one to night two correlated with the length of stay and patients with a night-to-night difference in sleep duration of more than 2.5 h the first two nights had a significantly longer stay than other patients, especially among patients with schizophrenia. This might support that lack of stability more than short nights is a marker of the condition of patients admitted to the PICU.

4.4. Implication for the treatment in PICU

To our knowledge the present study is the first to examine sleep duration and variations in sleep duration from night-to-night among acutely admitted patients in a PICU. The results support an assumption that large night to night variations in length of sleep is a warning sign for extended stay.

Hypnotics and sedatives are often used when patients are hospitalized (Rankin and Brakoulias, 2012) and sleep is one of the most common causes for administrating pro re nata drugs in acute psychiatric wards (Stewart et al., 2012). An awareness of the variations in sleep duration from night to night is important to avoid unnecessary changes in pharmacological treatment based on impressions from only one night.

To our knowledge there are no studies that have described effects of stabilising sleep duration in PICUs.

4.5. Limitations

This study was not designed to explore the influence of homoeostatic and circadian factors on sleep (Borbely, 1982; Waterhouse et al., 2012). Measures of sleep inducing factors as medication, restrictions in behaviour, time of lights being turned on and off for each patient were not recorded. Other factors that can affect patients' course of illness as pharmacological treatment, compliance and symptoms level were not analysed.

In this study we used observed sleep by the nurses as a measure of sleep duration (Van de Water et al., 2011). The gold standard of sleep registration is polysomnography, which is expensive and impossible to use in a PICU. Actigraphy have the resent years been used to give indirect reports of sleep patterns. Observations of sleep have in some studies correlated with results from polysomnography and actigraphy (Ancoli-Israel et al., 1997; Edwards and Schuring, 1993; Fontaine, 1989). We believe that the nurses' observation of sleep duration in the present study is acceptable as a measure of sleep duration.

The number of patients limits the possibility to discover differences between the diagnostic groups, the sexes and age groups. Categorizing substance use disorders, depressive mood disorders anxiety disorders, and personality disorders in to the same group is a limitation.

4.6. Conclusions

The present study shows large variations in sleep duration between individual patients and a large intra-individual lack of stability in sleep duration. Lack of stability in the sleep duration and the magnitude of these night-to-night variations the first nights predicted the length of stay in the PICU and should be treated as a warning sign for an extended stay. Treatment studies of stabilizing sleep in patients with serious mental illnesses in general and more specific in psychiatric intensive care units are warranted.

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Sleep at night and association to aggressive behaviour; Patients in a Psychiatric Intensive Care Unit

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Psychiatry
Inpatients
Risk assessment

ABSTRACT

Evaluations of associations between sleep at night and aggressive behaviour in Psychiatric Intensive Care Units (PICU) are lacking. The aims were to explore if sleep duration or night-to-night variations in sleep duration correlated with aggressive behaviour and aggressive incidents the next day and through the whole admission. Fifty consecutive patients admitted to a PICU were included (521 nights) and the nurses registered the time patients were sleeping, aggressive behaviour with The Brøset Violence Checklist (BVC) and aggressive incidents with The Staff Observation Aggression Scale-Revised (SOAS-R). At admission, short sleep duration the first night correlated with aggressive behaviour the next day and admissions with violent incidents had a median of 4.0 h difference in sleep from night one to night two compared to 2.1 h for the rest of the admissions. During the stay, large absolute difference in sleep duration between two nights correlated with aggressive behaviour the next day and short sleep duration was associated with violent incidents. Short sleep duration and night-to-night variations in sleep duration are both associated with increased risk for aggression in PICUs. This observation might help to predict and prevent aggressive incidents.

1. Introduction

In acute and emergency psychiatry, sleep disturbances and aggressive behaviour are prominent problems with negative consequences for staff and patients (Iozzino et al., 2015; NICE Guideline NG10, 2015; Vaaler et al., 2011). Psychiatric Intensive Care Units (PICUs) are inpatient facilities designed to contain patients with violent or threatening behaviour. Many acute psychiatric wards are divided in ordinary ward areas and PICUs. PICUs usually have a higher staff to patient ratio and better possibilities for observation of patients. It is of interest both to reveal imminent increased risk of aggression based on information about sleep the previous night, and to assess if specific sleep-patterns the first one or two nights after admission might predict aggression or violent incidents during the whole stay.

Behaviour associated with lack of sleep has some similarities with aggressive behaviour; being tense/anxious, angry/hostile, confused, oppositional, irritable and having reduced emotional regulation (Baum et al., 2014). Sleep problems are also highly prevalent among patients who are admitted to PICUs (Langsrud et al., 2016) and could contribute both to aggression and violent behaviour. In a systematic review of the existing literature on sleep and aggression, the authors concluded that the larger part of the literature supports a correlation between subjective poor sleep and irritability, hostility, and aggression (Kamphuis et al., 2012). Although sleep disturbances seldom result in physical aggression, the risk might increase in vulnerable individuals (Kamphuis et al., 2012), such as patients admitted to a PICU. Improved understanding of factors associated with aggression and violent behaviour could identify possible therapeutic targets and prevent aggression. To the knowledge of the authors, there are no studies that have explored the relationship between sleep one night and aggression the next day in acute and emergency psychiatry.

In studies of sleep duration and symptom severity in patients with bipolar or schizophrenic disorders it has been found an association between level of symptom severity and variability of sleep duration (Barbini et al., 1996; Gruber et al., 2011; Waters et al., 2011; Wulff et al., 2012). We have previously reported that length of stay in a PICU correlated with the variability of sleep duration, but not with mean sleep duration (Langsrud et al., 2016). Thus, among psychiatric

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inpatients, the variability or lack of stability of sleep duration may be an important factor contributing to next day aggression.

A wide range of measures of sleep and aggression have been used in previous studies, measures often based on self-rapports of aggression and mean sleep duration or sleep duration of one night (Kamphuis et al., 2012). However, self-reported levels of aggression have a clear potential for bias, particularly in populations with antisocial personality disorder, mania, or psychosis where self-reports might underestimate the level of aggression. Observer-based assessment of aggressive behaviour and aggressive incidents may therefore be more relevant for this patient population.

The aims of this study were to test if sleep duration or variations in sleep duration in the PICU were associated with observer-rated aggressive behaviour and aggressive incidents the next day. We also wanted to test if sleep duration the first night after admittance or night-to-night variations of sleep duration between night one and two were associated with aggressive incidents later in the admission.

2. Methods

The Østmarka Psychiatric Department, St. Olavs University Hospital, had a catchment area of 140,000 inhabitants from both the city of Trondheim (50%) and the rural areas (50%) in Sør-Trønderlag County at the time of the study. About 700 patients above 18 years were admitted each year. Acute admissions to other psychiatric hospitals occurred only when inhabitants temporarily resided outside of the catchment area. Norwegian acute psychiatric services are public and available to everyone.

The acute ward consisted of an ordinary closed ward area and a PICU area. The PICU was used for containment of behaviourally disturbed patients. The PICU consisted of two separate wings. Each wing had a sitting room, a bathroom, a WC and two single patient rooms. The physicians on duty assessed patients at admittance to the PICU. The therapists on the ward discharged the patients after evaluating the patient's symptoms and behaviour, no written criteria existed for indications for admittance or discharge (Vaaler et al., 2006). The patients in the PICU were segregated together with members of the staff, and they were expected to stay in their rooms and sleep between 22:30 h and 07:30 h. Patients were encouraged to come to breakfast at 08:30 h and not sleep during daytime. Depending on the state of the patient, the physicians on duty or the therapists on the ward decided if the patient were observed continuously or with 3–30 min intervals.

All admitted patients that stayed for at least one night in the PICU, during a 6-month period, were included in the present study. Seven admissions with a total of 12 nights were excluded due to missing short time risk assessment (BVC) registrations for the time of admission.

The measures of sleep, aggressive behaviour and aggressive incidents had been used in previous studies and in routine clinical practices at the ward. A brief training of the nursing staff was also provided before start of the study.

2.1. Diagnostic groups

Diagnoses according to World Health Organization´s International Classification of Diseases version 10 (ICD-10) (WHO, 1993), diagnostic criteria for research were set in a weekly consensus meeting at the department where at least two specialists in psychiatry and/or clinical psychology attended. One of these specialists had personally examined the patient.

The patients with a diagnosis from F20 to F29 were defined as patients with schizophrenia. Patients with schizophrenia dominated the admissions in the PICU, and they were compared with the rest of the patients defined as other disorders.

2.2. Sleep

The nurses in the PICU registered the time patients were observed to sleep both in the medical records, and in a separate sleep diary. The nurses observed the patients at least every 30 min throughout the night, often more frequently, through the door or by being in the same room as the patients. The sleep diary consisted of a column for each 24-h period, and a square for each 30 min.

The sleep duration in a day were defined as observed sleep from 12:00 h to 12:00 h. Night-to-night variations in sleep duration were defined in absolute values of the differences in sleep duration between two nights and keyed on the second of the two nights.

2.3. Aggressive behaviour

The Brøset Violence Checklist (BVC) is a 6-item checklist of behaviour that predicting imminent aggressive incidents in psychiatric inpatients (24 h perspective) (Linaker and Busch-Iversen, 1995; Woods and Almvik, 2002). BVC is easy to use, has been extensively tested and has good psychometric properties (NICE Guideline NG10, 2015). The nurses on the ward rate if six different behaviours are present or not: Being confused, irritable, boisterous, verbally threatening, physically threatening, and/or attacking objects. Each item is scored 1 if present or 0 if not, giving a scoring range of $0-6$. The BVC sum score is often categorised in three groups, for recommendations of when preventing measures should be taken; small risk of violence (0), moderate risk of violence ($1-2$) and high risk of violence (>2). The BVC is usually assessed three times daily. In the present study, we used the highest scores of the morning or evening scores (Abderhalden et al., 2008; van de Sande et al., 2011).

2.4. Aggressive incidents

Aggressive incidents were recorded by the nurses with the Staff Observation Aggression Scale-Revised (SOAS-R) (Nijman et al., 1999; Palmstierna and Wistedt, 1987). In the SOAS-R both the nature and the severity of aggressive incidents are rated. The SOAS-R consists of five columns; provocation, means, target, consequences for victims and measures taken to stop aggression. SOAS-R is widely used worldwide to monitor violent incidents in mental health care settings.

2.5. Statistics

The statistical analyses were performed using SPSS version 24 for MAC and an alfa level of < 0.05 was employed. Data were expressed as means and standard deviations (SD) or median and interquartile range (IQR). Categorical data were analysed with Fishers Exact test, normally distributed data were analysed with Student´s *t*-tests, and data not normally distributed were analysed with Mann-Witney *U*-tests and correlations with Spearman's rank coefficient (Spearman´s rho).

2.6. Ethics

The study was approved by The Regional Committee for Medical and Health Research Ethics, Central Norway. All the data used in the study were collected as part of ordinary routine clinical practice in the department.

3. Results

3.1. Characteristics of the sample

The study included 40 patients with 50 admissions, 21 (42%) females and 29 (58%) males and 521 nights. Patients with: Organic Disorders (F00–09) had 6 admissions and 20 nights, substance abuse (F10–19) had 9 admissions and 19 nights, schizophrenia (F20–29) had

Table 1
Descriptive data and sleep variables for 50 admissions to a Psychiatric Intensive Care Unit.

	Schizophrenia	Other diagnoses	All	p
Admissions	21	29	50	
Nights	381	140	521	
Discharged after one night	5	7	12	ns[a]
Length of stay, median (IQR)	7 (2–24)	3 (1.5–6)	3 (1.5–11)	0.034[b]
Female / Male	8/13	13/16	21/29	ns[a]
	Mean (SD)	Mean (SD)	Mean (SD)	
Age, years	37.4 (13.1)	44.8 (19.6)	41.7 (17.4)	ns[c]
Sleep duration, hours				
The first night ($n=50$)	7.7 (3.6)	7.8 (2.7)	7.7 (3.1)	ns[c]
The second night ($n=36$)	10.2 (4.8)	8.4 (2.4)	9.2 (3.8)	ns[c]
All nights ($n=509$)	9.4 (3.0)	8.0 (2.3)	9.0 (2.9)	0.000[c]
Absolute differences in sleep duration from night to night				
Night one to night two ($n=36$)	4.5 (4.4)	2.7 (2.1)	3.5 (3.4)	ns[c]
All nights ($n=453$)	2.0 (2.0)	1.9 (1.6)	2.0 (1.9)	ns

Interquartile range (IQR).
Standard deviation (SD).
[a] Fishers Exact Test.
[b] Mann-Whitney *U*-Test.
[c] Student´s *t*-test.

21 admissions and 381 nights, mood disorders (F30–39) had 13 admissions and 99 nights and the rest (F40–99) had 1 admission and 2 nights. There were missing sleep data on 12 nights and missing BVC data on 78 days. Median nights per admission in the PICU were 3 (IQR 1.5–11.0). A description of the patients is given in Table 1.

3.2. Sleep duration and night-to-night variations in sleep duration

Table 1 shows sleep duration and night-to-night variations in sleep duration for patients with schizophrenia, for other disorders, and for all patients. Sleep duration the first and second night did not differ between patients with schizophrenia and other disorders, but for all nights during the stay, patients with schizophrenia had longer sleep duration than patients with other disorders. There were no differences in the night-to-night variations of sleep duration between patients with schizophrenia and other disorders.

3.3. Aggressive behaviour defined by Brøset Violent Checklist (BVC)

When dividing the 433 BVC records in categories after risk of violence; 355 were defined as small (BVC = 0) risk of violence, 69 as moderate (BVC = 1–2) risk of violence and 19 as high (BVC > 2) risk of violence.

3.4. Sleep duration, night-to-night variations in sleep duration, and aggressive behaviour recorded by BVC

Short sleep duration the first night correlated with higher scores on the BVC the next day ($r^s = -0.47$, $p = 0.04$) for patients with schizophrenia. The same was found for all patients in the study ($r^s = -0.38$, $p = 0.01$), but not for the group of other diagnoses (Table 2). The night-to-night variation in sleep duration the first two nights did not correlate with scores on the BVC the next day, although the group of patients with other diagnoses than schizophrenia had a high correlation value ($r^s = 0.55$, $p = 0.055$) (Table 2).

For all 443 nights, night-to-night variations correlated with BVC the next day for patients with other diagnoses than schizophrenia ($r^s = 0.23$, $p = 0.02$) and for the whole group of patients ($r^s = 0.14$, $p = 0.006$) (Table 2).

Table 2
Correlations between sleep duration at night and Brøset Violent Check-list (BVC) the next day.

	Schizophrenia		Other		All	
	r^s	p	r^s	p	r^s	p
Sleep duration the first night	−0.473	0.041	−0.288	0.145	−0.378	0.010
Absolute difference in sleep duration from night one to night two	0.062	0.827	0.549	0.055	0.266	ns
Sleep duration, all nights	−0.053	ns	−0.032	ns	−0.075	ns
Absolute difference in sleep duration from night to night, all nights	0.104	0.079	0.231	0.021	0.138	0.006

r^s = Spearman´s rho.

Comparing all days with and without a positive score on each of the six items of BVC, sleep duration differed between those with irritation, (median 8.5 h, IQR 6.0–10.125) or not (median 9.25 h, IQR 7.5–11.0), (Mann-Whitney p = 0.047) and being boisterous (median 7 h, IQR 5.5–10.0) or not (median 9.25 h, IQR 7.5–11.125), (Mann-Whitney $p = 0.004$). Night-to-night variations in sleep duration differed between days with confusion, (median 2.5 h (IQR 1.125–3.625) or not (median 1.5 h (IQR 0.75–2.75), (Mann-Whitney $p = 0.002$), and physical threats, (median 3.25 h, IQR 1.5–4.5) or not (median 1.5 h, IQR 0.75–2.75), (Mann-Whitney $p = 0.048$).

3.5. Sleep duration, night-to-night variations in sleep duration and aggressive incidents recorded by SOAS-R

Admissions with aggressive incidents defined by SOAS-R during the whole stay had greater variations in sleep duration from night one to night two (median 4.0 h) compared to admissions without such aggressive incidents (median 2.13 h) (Table 3).

Aggressive incidents recorded by SOAS-R were preceded by short sleep duration the night before the incident (median 7.0 h), compared to days without such incidents (median 9.0 h) (Table 3).

4. Discussion

In this prospective study of patients admitted to a PICU, our main finding was that both short duration of sleep and great night-to-night variations in duration of sleep, were associated with next-day aggressive behaviour and with aggressive incidents during the whole stay at the PICU. This may indicate that sleep duration or night-to-night variation in sleep duration might be an important factor in increasing the risk of aggressive behaviour in populations admitted to PICUs, and that interventions to improve and stabilize sleep patterns might reduce aggression. Earlier studies support a relationship between reduced quality of sleep and aggression, but have been inconclusive about the association between sleep duration and aggression (Kamphuis et al., 2012).

4.1. Sleep the first nights and aggression during the admission

At admission to acute and emergency psychiatry, there is often limited clinical information about the patient. Analysing sleep patterns the first one or two nights might improve the evaluation of the clinical status of the patient and improve planning of both short- and long-time treatment and care. We found that short sleep duration the first night was associated with higher levels of aggressive behaviour the next day, especially among patients with schizophrenia. We did not find the same

Table 3
Length of sleep duration and differences in night-to-night sleep duration in admissions with injuries to staff recorded by Staff Observation Aggression Scale- Revised (SOAS-R), compared to admissions without injuries.

	SOAS-R						
	Injuries			No injuries			
	n	Median	IQR	*n*	Median	IQR	*p*
SOAS-R recorded injuries during admission							
Sleep duration the first night	6	6.0	(4.5–11.44)	44	8.5	(6.0–9.94)	ns
Absolute difference in sleep duration from night one to night two	6	4.5	(3.32–11.38)	30	2.13	(0.69–4.56)	0.042
SOAS-R recorded injuries the day after sleep							
Sleep duration	14	7.0	(5.0–9.19)	495	9.0	(7.25–11.0)	0.033
Absolute difference in sleep duration from night to night	14	2.25	(1.19–3.5)	439	1.5	(0.75–2.75)	ns

Mann-Whitney *U*-Tests.
IQR: Interquartile range.

association between high night-to-night variation in sleep duration the two first nights and aggression the next day, even if there was a high non-significant correlation ($r^s = 0.549$) with BVC score among patients without schizophrenia. Interestingly, such a high night-to-night difference in sleep duration at the start of the admission were associated with aggressive incidents during the whole stay measured by SOAS-R.

4.2. Sleep at night and aggression the next day

Short sleep duration was not associated with the total BVC scores. However, there were shorter sleep durations before aggressive incidents recorded by SOAS-R than before days without such aggressive incidents. The absolute difference in sleep duration between two nights was associated with higher BVC scores the next day for all patients, and especially for patients with other diagnoses than schizophrenia. An implication of this finding is that also during a longer stay at a PICU, the staff has to be aware of lack of stability in the sleep patterns and circadian rhythms of the patients, both to reduce risk for aggression, but also to improve treatment in general.

4.3. Sleep and aggression

Kamphuis et al. (2012) speculated that the relationship between sleep deprivation and context-inappropriate aggressive responses are mediated by loss of behaviour inhibition regarding negative emotional experiences or circumstances. Patients admitted to an acute psychiatric ward are particularly exposed to such experiences: the ward is closed, many patients are involuntarily admitted, and there are restrictions in areas to stay in, smoking, use of telephone, et cetera (Iozzino et al., 2015).

Thus, our findings of relationships between sleep duration and aggressive behaviour could be associated both to clinical characteristics of the patient population and the inpatient setting.

Sleep is a central biological phenomenon. The neurobiological effect of sleep deprivation (Krause et al., 2017) and aggression (Blair, 2016; Weiss, 2012) are complex and possible bidirectional. Some changes after sleep deprivation are also common in person with aggressive and violent behaviour, as altered function of the prefrontal cortex, striatum and amygdala. Also changes in executive functions, impulsivity, risk-taking and sensational seeking behaviour, and negative emotional processing are seen both in sleep deprivation and in aggressive periods. One might speculate that patients admitted to acute psychiatric wards are at risk for increase in aggressive and violent behaviour do to disruptions in sleep patterns. Our study explored the association between sleep and aggression, neurobiological mechanisms which may underlie the behavioural changes occurring during daytime after disruption of sleep patterns should be explored in a PICU population. Such biological mechanisms might differ between diagnostic groups.

4.4. Beyond mean sleep duration, include night-to-night variation

In previous studies of associations between sleep and aggression, the main focus has been on mean sleep duration during an admission or sleep duration one night (Kamphuis et al., 2012). In the present study, night-to-night variations in sleep duration has been analysed in addition to the duration of sleep, it adds new information about the sleep among acutely admitted patients with a high level of symptoms and deviant behaviour.

Moreover, we found a pattern where short sleep duration and night-to-night variations of sleep duration were associated with different types of behaviour. Short sleep was associated with irritability and boisterous behaviour, whereas large night-to-night variations in sleep duration was associated with confusion and threatening behaviour. We also found that patients with schizophrenia and patients with other disorders seemed to react differently to sleep disturbances in the PICU. First, short sleep duration the first night correlated with aggressive behaviour the next day primarily among patients with schizophrenia. Secondly, large night-to-night variation in sleep duration correlated with aggressive behaviour the next day, primarily among patients with other diagnoses than schizophrenia. In sum, these findings indicate that night-to-night variations in sleep duration should be included in further studies (Bei et al., 2016). It is possible to speculate that subgroups like mood disorders highly influenced by circadian rhythms, might be especially vulnerable to lack of stability in sleep duration.

Medication could have influenced both the sleep duration, night-to-night variation in sleep duration and aggressive behaviour, but we have no data enlightening this. The department uses tranquilizers frequently as described in other studies from psychiatric acute and emergency units (Rankin and Brakoulias, 2012; Stewart et al., 2012), and that aggression also are treated with much the same medication in these facilities (Huf et al., 2007; NICE Guideline NG10, 2015; Nielssen et al., 1997). Expert consensus guidelines recommend benzodiazepines as first-choice medication in a number of clinical conditions in acute and emergency psychiatry (Allen et al., 2003). However, sleep problems and aggression are still frequent.

In one study patients admitted to hospital in crises got treatment for sleep problem where discharged 8.5 days earlier than patients that only got treatment as usual (Sheaves et al., 2017). Such treatment might also have an effect on aggressive behaviour. Today the treatment in PICUs supports stabilisation of sleep with daily monitoring and fixed time for meals and sleep. Recent studies of using glasses that block blue light has shown stabilisation of sleep duration and improvement for patients with mania (Henriksen et al., 2016). Chronotherapeutic interventions (Dallaspezia et al., 2015) are suitable for PICUs and might stabilize sleep, and it is important to develop and evaluate such treatments.

4.5. Strengths of the study

A strength of this study is the naturalistic setting and that all admitted patients were included. We used standardized measures for aggressive behaviour that are widely used in clinical practice.

4.6. Limitations

The number of patients limits the possibility to discover differences between the diagnostic groups, gender and age groups. The numbers of aggressive incidents (measured with SOAS-R) were limited.

In this study, we used sleep observed by the nurses as a measure of sleep duration (Van de Water et al., 2011). This has lower reliability than “gold standard” sleep assessment with polysomnography (PSG), or actigraphy. However, PSG is expensive and impossible to use in a PICU. We believe that the nurses’ frequent observation of sleep duration in the present study is acceptable as a measure of sleep duration. Observations of sleep have in some studies correlated with results from polysomnography and actigraphy (Ancoli-Israel et al., 1997; Edwards and Schuring, 1993; Fontaine, 1989). A possibility in future research is to use actigraphs or monitors based on more advanced technology to record sleep, or at least in hospitals, to use standardized observations. However, a number of patients in PICUs can from ethical reasons not be exposed to actigraphs or similar electronic devices. As some patients were observed intermittently, wake periods might have been missed and some patients might have been disturbed from sleep by the nurses’ intermittent observations. More knowledge for specific diagnostic groups, gender and age are needed in future studies.

Measures of sleep inducing factors, such as medication, restrictions in behaviour, time of lights being turned on and off for each patient were not recorded. Other factors that can affect patients' course of illness, such as multiple admissions, pharmacological treatment, compliance and symptoms level were not analysed.

4.7. Conclusion

We found that both short sleep duration and night-to-night variations in sleep duration between two nights were associated with increased aggression among patients in a PICU. Patients with schizophrenia seemed more vulnerable to short length of sleep, while other patients seemed to react more negatively to instability in length of sleep. The findings might improve prediction of aggression and increase focus on treatment of sleep and circadian disturbances in Psychiatric Intensive Care Units.

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The Predictive Properties of Violence Risk Instruments May Increase by Adding Items Assessing Sleep

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Background: The psychometric instruments developed for short-term prediction of violence in psychiatric inpatients do not include variables assessing sleep. Disturbances in sleep may precede aggression in this setting. We investigated whether adding information on sleep improved the predictive properties of the Brøset Violence Checklist (BVC).

Methods: The study population consists of all patients admitted to a psychiatric intensive care unit (PICU) over a 6-month period who were hospitalized for at least one night (n = 50). Sleep observed by staff (521 nights), behavior assessed with the BVC (433 days), and aggressive incidents recorded by the Staff Observation Scale-Revised (n = 14) were included in the analysis.

Results: The ability of the BVC to predict aggressive incidents improved from AUC_{ROC} 0.757 to AUC_{ROC} 0.873 when a combined sleep variable including both sleep duration and night-to-night variations of sleep duration was added to the BVC recordings. The combined sleep variable did not significantly predict aggressive incidents (AUC_{ROC} 0.653, p = 0.051).

Conclusions: A sleep disturbance variable improves the predictive properties of the BVC in PICUs. Further studies of sleep duration, night-to-night variations in duration of sleep, and aggression are needed.

Keywords: prediction, sleep, aggression, violence, psychiatry, inpatients

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INTRODUCTION

Predicting aggressive behavior is important in acute and emergency psychiatry (1, 2). The Brøset Violence Checklist (BVC) has been developed to assess the risk of imminent aggressive behavior in psychiatric inpatients (3–5). It has a short-term perspective (4–6), and it is used in emergency facilities in a number of countries (6–10).

The predictive properties of the BVC have been documented in different psychiatric facilities including acute and emergency departments (6–10). Although the BVC is a successful predictor

Abbreviations: AUC, area under the curve; BVC, Brøset Violence Checklist; CI, confidence interval; PICU, psychiatric intensive care unit; SOAS-R, Staff Observation Scale-Revised; ICD-10, Diagnoses according to World Health Organization's International Classification of Diseases, version 10; ROC curve, receiver operating characteristic curve; SD, standard deviation.

of aggressive behavior, its main focus is the patients' immediate behavior, such as irritability and the display of verbal or physical threats by the patient (3, 4). One variable that has the potential to affect violent behavior directly, which is not included in the BVC, is sleep (11).

Losing sleep may lead to changes in cognitive functions, emotional regulation, and control of behavioral responses (11–13). Although the exact relationship between sleep and aggression is not clear, several studies have indicated an association between them (11). In a study of combat veterans, those who reported sleep duration of less than 6 h had the strongest association between combat exposure and posttraumatic stress, aggression, and risky behavior (14). An inverse association between hours of sleep and aggression has been found in youths (15). In individuals with low-functioning autism, prediction of daytime challenging behavior, including aggression, was strongly driven by sleep variability (16). In an earlier study, we also found an association between disturbance in sleep and aggression the next day in a psychiatric intensive care unit (PICU) (17). We have not found any studies examining whether sleep items or stability of sleep can be used as a short-term predictor of aggression.

The aim of this study was to investigate whether adding items assessing sleep duration and night-to-night variations in sleep duration between two consecutive nights increased the predictive properties of the BVC in a population of patients in a PICU.

METHODS

Setting

The Norwegian psychiatric health care system is publicly funded and catchment-area based. All patients from the catchment area in need of acute psychiatric inpatient services are admitted to the hospital. At the time of the inclusions, the Department of Psychiatry at St Olav's University Hospital had 700 admitted patients (≥18 years) each year from a catchment area with 140,000 inhabitants.

The PICUs in the Department of Acute Psychiatry are separated parts of the closed psychiatric acute wards, and each has a sitting room, eating area, bathroom, and patient rooms. There are always allocated nurses in the PICU. The nurses remain with the patients and observe them continuously or at 3- to 30-min intervals, depending on the state of the patients. Details about the catchment area, hospital, PICU, and the assessments have been published previously (17–19).

All admitted patients that stayed for at least one night in the PICU during a 6-month period were included in the study.

The diagnoses were set according to the World Health Organization's International Classification of Diseases version 10 (ICD-10) criteria for research (20).

Assessments

Sleep Variables

The times the patients were observed to sleep were recorded both in the medical records, and in a separate sleep diary, with one column for each 24-h period and a square for every 30-min block from 12:00 noon to 12:00 noon, by the nurses in PICU. The staff was instructed to record if a patient was considered "to be sleeping" according to their own clinical judgement. The nurses were in the room with the patients or observed them through the door every 3–30 min, depending on the state of the patients.

In calculating the night-to-night variations in sleep duration, the absolute values of the differences in sleep duration between two consecutive nights were used.

To make the sleep items compatible with a checklist and to retain the dimension aspect of sleep, we used a three-point scale rather than the two-point scale used in the BVC. The variables used in analyzing sleep duration, night-to-night variations in sleep duration between two consecutive nights, and the combined variable of both, sleep disturbance, were defined on a 0–2 point scale. Sleep duration for 6 h or more was defined as 0; between 4 and 6 h, 1; and 4 h or less, 2. Night-to-night variations in sleep duration for 2 h or less was defined as 0; between 2 and 4 h, 1; and 4 h or more, 2.

Sleep disturbance was defined as: (sleep duration + night-to-night variation in sleep duration)/2, or only the value from the sleep duration if the patient had only one night of stay.

Brøset Violence Checklist

The BVC is an observer-rated instrument predicting imminent (a 24-h perspective) aggressive incidents among psychiatric inpatients (3, 4). The hospital's staff has experience in the use of this instrument in both daily clinical practice and research (9, 18). After being with the patients for about 1 h on each shift, the nurses rate the six-item checklist of behavior: being confused, irritable, boisterous, verbally threatening, physically threatening, and/or attacking objects. The BVC has a scoring range from 0 to 6. In the present study, the highest of the morning or evening BVC scores was used. When an aggressive incident occurred, only the BVC scores prior to the incident that day were included.

New Brøset Violence Checklist Sleep Score

By adding the sleep disturbance score to the BVC sum score the day after sleep, we calculated a new combined BVC-sleep score with a range from 0 to 8.

Staff Observation Scale

Aggressive incidents were recorded with the Staff Observation Scale-Revised (SOAS-R) (21, 22). The nurses witnessing an incident filled in the form. The SOAS-R captures different aspects of aggressive incidents: provocation, means, target, consequences for victims, and measures taken to stop the aggression.

Statistics

SPSS version 24 was used in the statistical analyses. A p value < 0.05 was employed as significant. Normally distributed data were analyzed with Students' t test. The Mann–Whitney U test was used to analyze data that were not normally distributed. Receiver operating characteristic curve (ROC curve) and area under the curve (AUC) with confidence intervals (CIs) were used to analyze the variables' ability to predict aggressive incidents. No missing data replacement was used (23).

RESULTS

Characteristics of the Sample

A total of 40 patients with 50 admissions and 521 nights were included in the study. Females had 21 admissions and males had 29. The mean age in the sample was 41.7 (SD ± 17.4) years. Patients with a main diagnosis of schizophrenia (F20–29) made up the majority of the admissions ($n = 21$) and nights ($n = 381$). Patients with mood disorders (F30–39) had 13 admissions and 99 nights, patients with substance abuse (F10–19) had 9 admissions and 19 nights, patients with organic disorders (F00–09) had 6 admissions and 20 nights, and 1 patient with other diagnoses (F40–99) had 2 nights.

The mean sleep duration was 9.0 (SD ± 2.9) h and the mean absolute difference in sleep duration from night-to-night was 2.0 (SD ± 1.9) h. The median number of nights per admission in the PICU was 3 (IQR 1.75–11.0). Of the 433 BVC forms, 355 had BVC = 0, categorized as small risk; 69 had BVC = 1–2, categorized as moderate risk; and 19 had BVC > 2, categorized as high risk of violence. Fourteen aggressive incidents (SOAS-R) from six patients were recorded. Sleep data were missing on 12 nights and BVC data were missing on 78 days.

Receiver Operating Characteristic Curve

The ROC analyses can be seen in **Figure 1** and the AUC_{ROC} can be seen in **Table 1**. BVC gave an AUC_{ROC} value of 0.757. The new combined BVC-sleep score gave an AUC_{ROC} value of 0.873, improving the BVC score. Both BVC and BVC-sleep AUC_{ROC} values were highly significant. None of the sleep variables alone gave a significant AUC_{ROC} value.

DISCUSSION

In this prospective study, the BVC was shown to be sensitive in predicting aggressive incidents, and adding sleep disturbance to the BVC scores improved its predictive capacity further. Neither short duration of sleep nor high night-to-night variations in duration of sleep predicted aggressive incidents at the same level as BVC scores alone. As far as we are aware, only a previous study from our group has explored the relationship between sleep and aggression in acute or emergency psychiatry services (17). That study provided support for a possible association between sleep disturbances and aggression. The current study indicates that observations of sleep improve the sensitivity of the BVC.

The BVC is a recommended instrument for the short-term prediction of aggressive incidents. It can also be used as a decision-making tool for seclusion in the PICU (6). In this study, the ability of the BVC to predict aggressive incidents (AUC_{ROC} 0.757, $p = 0.001$) was somewhat lower than or comparable to earlier studies (4, 8, 9), but the prediction of aggressive incidents was improved by adding the variable for sleep (AUC_{ROC} 0.873,

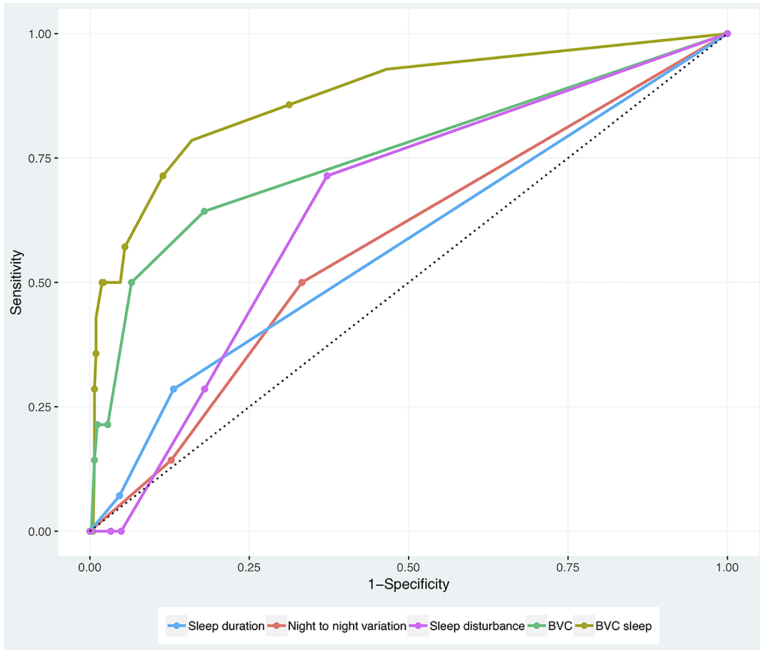

FIGURE 1 | Receiver operating characteristic (ROC) analyses of sleep duration, night-to-night variation in sleep duration, sleep disturbance (combined variable of sleep duration and night-to-night variations), Brøset Violence Checklist (BVC), and BVC-sleep (a combination of BVC and sleep disturbance).

TABLE 1 | Area under the curve (AUC_{ROC}) for sleep duration, night-to-night variation in sleep duration, sleep disturbance (a combined variable of both sleep duration and night-to-night variations), Brøset Violence Checklist (BVC), and BVC-sleep (a combination of BVC and sleep disturbance).

	Missing	AUC	95% CI	Sign[a]
Sleep duration	12	0.575	(0.412–0.738)	0.337
Sleep night-to-night variations	68	0.576	(0.424–0.728)	0.335
Sleep disturbance	18	0.653	(0.520–0.786)	0.051
BVC	78	0.757	(0.601–0.914)	0.001
BVC-sleep	84	0.873	(0.767–0.981)	0.000

CI, confidence interval.
[a]*Null hypothesis: true area = 0.05.*

$p = 0.000$). A study that added Visual Analogue Scale ratings of subjective perception of risk for a physical attack to the BVC (8) improved the BVC at a comparable level.

Adding sleep information to the BVC requires extra effort, especially if the sleep information is not routinely recorded during treatment in the PICU. In the study PICUs, collection of sleep information was a part of the standard treatment protocol and therefore added little to the workload of the staff. Violent behavior is common in acute psychiatric wards. It is found that one out of five patients commit an act of violence, 75–100% of the nurses have been assaulted by patients, and annually one-third of the total nursing costs are connected to managing violence and aggression (1, 2). These high numbers make even a marginal improvement in predicting aggression valuable for patients and staff, in order to improve safety (8, 10).

In the present study, neither sleep duration (AUC_{ROC} 0.575, $p = 0.337$) nor night-to-night variations in sleep duration between two consecutive nights (AUC_{ROC} 0.576, $p = 0.335$) predicted aggressive incidents the next day. When the sleep duration and variability of sleep duration between two consecutive nights were combined in the new sleep disturbance variable, a numerically larger area under the curve (AUC_{ROC} 0.653, $p = 0.051$) was found, but the difference did not reach statistical significance. The reason for this might be the complex nature of aggressive behavior (24), and that sleep duration and night-to-night variability in sleep duration capture different aspects of sleep disturbance when analyzed as isolated predictors. By adding night-to-night variation (25), we may assess disturbances in sleep better than when analyzing sleep duration alone.

Earlier studies suggest that sleep deprivation leads to a complex set of changes such as increased sensitivity to identification of negative stimuli, increased hostile attributions, and loss of inhibition of context-inappropriate responses. Reduced top-down control of emotional signals, poor affect regulation, in addition to decreased emotional intelligence may contribute to the overall aggressive behavior (11–13). These neurobiological changes are complex and may not be captured completely by the BVC's six-item checklist of behavior.

Strengths and Limitations

The naturalistic setting in the PICU, inclusion of all admitted patients from the catchment area, and the use of standardized measures for risk behavior and aggressive incidents are the major strengths of the present study.

The currently used "observed sleep" by the nurses has both strengths and weaknesses (26). It is the standard measure for sleep in most psychiatric departments in daily, clinical practice. It is therefore already implemented. However, the nurse-based observations of sleep may be prone to errors, such as misjudging what has been observed, not noticing when patients may be awake, or being interrupted in the observations, giving reduced report quality. The clinical observation by nurses is not as objective as polysomnography or actigraphy, assessments tools that are not possible to use in the PICUs because of security, cost, and ethical reasons. However, some studies document satisfactory correlations between these different measures (26–28). Another weakness in the study is the lack of registered information on other risk factors for aggression such as involuntary admission, alcohol abuse, and history of violence.

CONCLUSIONS

After adding sleep disturbance to the BVC, an instrument for short-term prediction of violent behavior from inpatients, both the specificity and the sensitivity of the instrument improved. The combined variable of sleep duration and night-to-night variations in duration of sleep (sleep disturbance) seems to have a promising capacity to contribute to prediction. Further studies of sleep duration, night-to-night variations in duration of sleep, and aggression are necessary.

DATA AVAILABILITY STATEMENT

Data are available upon request to the corresponding author.

ETHICS STATEMENT

All the data used in this study were collected as part of ordinary routine, clinical practice in the department. Patients acutely admitted to PICUs have limited capacity to consent in taking part in clinical studies. This is due to the mixture of psychiatric and behavioral challenges. The patients in this study were thus included without giving an informed, written consent. The study including the inclusion procedures was approved by the Regional Committee for Medical and Health Research Ethics, Central Norway.

AUTHOR CONTRIBUTIONS

KL contributed to the planning, data management and analyses, interpretation of the results, and writing. AV, GM, and RA contributed to the planning, interpretation of the results, and writing. HK and TP contributed to the interpretation of the results and writing. ICG contributed to the analyses, interpretation of the results, and writing. All authors read and approved the final manuscript.

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