Blue-blocking glasses as adjunctive treatment for bipolar mania — and exploration of motor activity patterns in serious mental disorders

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Thesis for the degree of Philosophiae Doctor (PhD)
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Tone Elise Gjøtterud Henriksen is a shareholder in Chrono Chrome AS and has received speaker honorarium from H. Lundbeck AS.

Scientific environment

This doctoral thesis is based on work conducted at Valen Hospital and Haugesund Hospital in the Division of Mental Health Care in Helse Fonna, the Division of Psychiatry, Stavanger University Hospital, and the Department of Psychiatry at St. Olavs Hospital, Trondheim.

I was a Doctoral Fellow at the Section for Psychiatry, Department of Clinical Medicine, Faculty of Medicine, University of Bergen, which was the most central scientific environment providing fellowship, supervision, and the PhD program. The work involved collaboration with researchers in multiple disciplines: statistics at the Centre for Clinical Research, Haukeland University Hospital, sleep research and basic research at the Bergen Stress and Sleep Group, Department of Biological and Medical Psychology, Faculty of Psychology and photo physics at the Department of Physics and Technology, Faculty of Mathematics and Natural Sciences, University of Bergen.

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Supervisors

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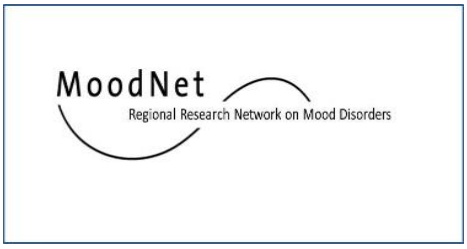
MoodNet
Regional Research Network on Mood Disorders


HELSE FONNA


HELSE STAVANGER
Stavanger University Hospital


ST. OLAVS HOSPITAL
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Preface

The research forming this thesis is based on in-patient samples from three major diagnostic groups in psychiatry: bipolar disorder, schizophrenia and (unipolar) depression. The main emphasis of the thesis is the effect and feasibility of the novel intervention of blue-blocking (BB) glasses for mania in bipolar disorder. Second, the diverse utility of actigraphy is a common theme throughout. Although all papers included in the thesis primarily have aims related to clinical practice (treatment or diagnostic support), the results also enabled the discussion of theories on pathophysiological mechanisms.

The first two papers are based on data from a randomized placebo-controlled trial (RCT) that tested the effects of blocking blue light during a manic episode. In Paper I the aim was to test whether blue-blocking (BB) glasses had an effect on overall manic symptoms as compared with a placebo, and whether this intervention was feasible in the clinic. Primary outcome measures were: clinically rated manic symptoms using the Young Mania Rating Scale (YMRS) and mean motor activity measured by wrist-worn actigraphs [1]. In paper II, the aim was to compare and describe the effects on actigraphy-derived sleep parameters between the two groups: one with the BB glasses and one with the placebo. In paper III, yet another utility of actigraphy data was described; the use of linear and non-linear mathematical analyses for characterizing motor activity patterns of variability and complexity in recordings of 24 h, as well as in morning and evening periods. The aim was to investigate whether it was possible to differentiate between the diagnostic entities of schizophrenia spectrum disorders, mania, and unipolar depression, based on the diurnal activity patterns.

Data for patients and the healthy controls used in papers I and II were derived from the Virtual Darkness as Additive Treatment in Mania (VATMAN) trial [2]. The participants were recruited between February 2012 and February 2015 from Helse Fonna and Helse Stavanger Health Authorities. In paper III, data from healthy controls were also derived from the VATMAN trial, while the patients were recruited

from the Agitation at Admittance to a Psychiatric Acute Department study conducted at Østmarka Hospital in Trondheim. Data were collected from 1st September 2011 to 31st March 2012.

The intervention BB glasses used in the VATMAN trial is an evolvement based on the recent neuroanatomical discovery of the daylight signaling system which is mainly sensitive to blue light, and the dark therapy pilot study and case reports [3]. These two lines of research combined with shift work studies demonstrating the utility of BB-glasses to induce "night mode" in the brain, pawed the way for virtual darkness therapy for bipolar disorders [4-6]. This story will be presented in more detail in Chapter 1.

One of the most frequently occurring terms throughout this thesis is activation. Here, activation refers to generalized activation, as a result of the influence of multiple systems. The arousal system has almost immediate downstream effects on generalized activation, and for most situations and conditions, arousal and activation covary [7, 8]. Actigraphy is a measure of the integrated motor activation and is used as an objective measure of generalized activation [9, 10]. However, strictly speaking, an activity count measured at the wrist or trunk reflects the final executive steps of activation within the locomotor system, which may be disassociated from arousal in extreme hyper-aroused states such as catatonia. However, the patients who participated in the studies included in this thesis were not in the most extreme symptomatic condition; therefore, the interpretation was made that the actigraphy data could serve as a proxy for generalized activation of the brain.

In addition to presentation and discussion of the results from papers I-III, the relevant theoretical and empirical research context is discussed in the thesis. Lastly, a theory on how BB interventions may halt a mania-sustaining feedback loop is presented.

Abstract

Background: There is a need for more effective treatments of bipolar mania. Promising reports of the effects of dark therapy on bipolar disorder symptoms and the discovery of a mainly blue-light sensitive daylight-signaling retinal ganglion cells has resulted in the utility of BB glasses to create a virtual darkness condition for the brain. Changes in activation or aberrant motor activity is present in all serious mental disorders. Actigraphy is a non-invasive and simple means of assessing motor activity, but is still mostly used to assess sleep outcomes. Before the utility of actigraphy can be broadened, there is need for further exploration of daily activity pattern characteristics for the diagnostic entities.

Aims: By means of the Virtual Darkness as Additive Treatment in Mania (VATMAN) trial, we aimed to test the effectiveness and feasibility of BB glasses as an adjunctive treatment for mania compared to placebo glasses. As part of the Agitation at Admittance to a Psychiatric Acute Department Study, we aimed to characterize the motor activity patterns among a new sample of patients with psychotic disorders, and compare these characteristics to the motor activity patterns of patients with affective disorders and with healthy controls.

Methods: Eligible patients for the VATMAN trial (hospitalized with bipolar disorder mania and otherwise fulfilling inclusion criteria) were randomized to receive either BB-glasses or clear-lensed placebo glasses. The glasses were worn as an adjunctive treatment from 6:00 p.m. to 8:00 a.m. for seven consecutive days. Manic symptoms were rated daily using the Young Mania Rating Scale. Motor activity was measured using wrist-worn actigraphs. Feasibility was assessed using a self-report patient experience questionnaire together with the clinical observation of side-effects. Sleep was assessed using actigraphy-derived sleep parameters. In the Agitation at Admittance to a Psychiatric Acute Department study, all hospitalized patients in the acute psychiatric ward in Østmarka Hospital, Trondheim were asked to wear an actigraph for 24 h. The motor activity patterns of patients diagnosed with

schizophrenia and other psychotic disorders were compared to those of patients with mania, motor-retarded unipolar depression, and healthy controls. Linear and non-linear analytical methods were used to describe and compare motor activity variability and complexity (irregularity) for a 24 h period as well as in morning and evening sequences.

Results: Out of 32 randomized patients in the VATMAN trial, 12 patients in the BB-group and 11 patients in the placebo-group were included in the analyses. After seven days, the Cohen's d effect size was 1.86. There was a significant group difference in YMRS scores after three days ($p = 0.042$) and the group difference increased steadily throughout the intervention. Observed side effects included headache in one patient and rapidly reversible depressive symptoms in two patients. Actigraphy-derived sleep outcomes at night five showed significantly higher sleep efficiency, lower motor activity and less minutes of wake after sleep onset in the BB group as compared to the placebo group. Several patients in both groups displayed a 48 h-like rhythm of shorter or disrupted sleep. The schizophrenia spectrum group shared the characteristic of high motor activity variability with the unipolar depressed group, but differed with respect to more irregular (complex) activity pattern in the morning sequence. The schizophrenia spectrum and the mania groups could not be separated using formal statistical analyses, being most similar with regards to high morning activity irregularity. The mania group was the only one to show a blunted morning-to-evening activity fluctuation, while the normal morning-to-evening decline was more preserved in the schizophrenia spectrum group.

Conclusions: BB-glasses were found to be both effective and feasible as an adjunctive treatment for mania. The BB-group showed actigraphy-derived sleep parameters reflecting less activated sleep compared with the placebo-group. The use of actigraphy data to characterize diurnal motor activity patterns, by use of the combination of linear and non-linear analytical approaches, seems to have potential for assessment of symptoms and for diagnostic support.

List of Publications

Paper I

Henriksen TEG, Skrede S, Fasmer OB, Schoeyen H, Leskauskaite I, Bjørke-Bertheussen J, Assmus J, Hamre B, Grønli J, Lund A. Blue-blocking glasses as additive treatment for mania: a randomized placebo-controlled trial. Bipolar Disorders, 2016. 18(3): p. 221-32.

Paper II

Henriksen TEG, Grønli J, Assmus J, Fasmer OB, Schøyen H, Leskauskaite I, Bjørke-Bertheussen J, Ytrehus K, Lund A. Blue-blocking glasses as additive treatment for mania: effects on actigraphy-derived sleep parameters. Journal of Sleep Research, 2020: p. e12984.

Paper III

Krane-Gartiser K [1], Henriksen TEG [1], Morken G, Vaaler AE, Fasmer OB. Motor activity patterns in acute schizophrenia and other psychotic disorders can be differentiated from bipolar mania and unipolar depression. Psychiatry Research 2018: 270: p. 418-425. [1] Shared first authorship

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Abbreviations

ANCOVA	analysis of covariance
ANOVA	analysis of variance
BB	blue-blocking
BD-I	bipolar disorder type I
BD-II	bipolar disorder type II
CI	confidence interval
CRF	corticotrophin releasing hormone
DSM	Diagnostic Statistical Manual
EEG	electroencephalogram
HOMEQ	Horne-Östberg Morningness-Eveningness Questionnaire
HPA	hypothalamic pituitary adrenal
ICD	International Classification of Disease
ipRGC	intrinsically photo responsive retinal ganglion cell
SAD	seasonal affective disorder
SAS	sympathoadrenal system
SCN	suprachiasmatic nucleus
SD	standard deviation
SPAQ	Seasonal Pattern Assessment Questionnaire
SPSS	Statistical Package for the Social Sciences
T3	triiodothyronine
VATMAN	Virtual Darkness as Additive Treatment in Mania
YMRS	Young Mania Rating Scale

Contents

1. Introduction

1.1 The spectra of bipolar disorder and schizophrenia

Bipolar disorders are prevalent in approximately 1 % of the human population worldwide [11]. The illness is associated with increased mortality due to both suicide and comorbid somatic illness [12, 13]. In spite of advances in pharmacological treatments, bipolar I disorder (BD-I) patients are symptomatic for more than 40 % of the time on average [14]. Emil Kraepelin made the distinction between dementia praecox (renamed to schizophrenia by Bleuler in 1911) and manic-depressive illness, based on the mood symptoms and better prognosis of the latter [15]. The modern denomination of bipolar disorder evolved during the 1990s along with a suggestion of a wider bipolar spectrum [16]. Manic-depressive illness originally described large mood swings (including full-blown manic episodes) corresponding to BD-I diagnosis in the Diagnostic and Statistical Manual (DSM-5) [17]. The modern broader bipolar disorder category included a new group of patients with depression-hypomania mood swings, called bipolar II disorder (BD-II) [16]. Hypomania is a milder presentation of manic symptoms lasting less than 1 week. [17]. Although one single manic episode qualifies for a BD-I diagnosis, the recurrence of mood episodes is characteristic [17]. The length of time in stable mood and functioning can vary from many years to almost nil in severe rapid-cycling bipolar disorder [17-19]. For some patients their mood swings low with much time spent in depression and only brief and few glimpses of hypomania. This is typical for BD-II patients, who in spite of less time in hospital may suffer most. Other patients may experience moderate or mild depression, but repeatedly develop full-blown psychotic mania requiring hospitalization. The continuum of presentations regarding polarity, duration, severity, episode-frequency, age of onset, and treatment responsiveness, justifies the proposal of a bipolar spectrum rather than separate categories [16, 20, 21]. This conceptualization is supported by the polygenetic nature of bipolar disorders [22, 23]. In addition, individual epigenetic effects could explain the variety of endophenotypes observed. In a practical sense, the

psychiatrist should ask, “how bipolar is my patient’s affective disorder?” [20, 21]. From the perspective of considering bipolar disorders on a spectrum, the extreme presentation could be rapid cycling BD-I with childhood onset and a significant family history of bipolar disorder. Conversely, the least bipolar affective disorder phenotype could be a late-life single episode of unipolar depression with no family history of bipolarity.

The other main group of the serious mental illnesses is represented by schizophrenia, with a prevalence of 4-7 per 1000 [24]. The current diagnostic category of schizophrenia is notably much broader than dementia praecox described by Kraepelin, which corresponds to the current subcategory of hebephrenic schizophrenia in the World Health Organization’s International Classification of Disease (ICD-10) [25]. Schizophrenia affects cognition, emotion, and behavior, often with detrimental consequences for daily life functioning. Early intervention can improve the outcomes, the basis for which is correct diagnosis [26, 27]. In the prodromal phase, schizophrenia may present with many symptoms in common with depression, which poses a diagnostic challenge [28]. These shared symptoms are social withdrawal, lack of normal emotional reactivity, and loss of motivationally directed behavior and interest [25, 28]. In the context of schizophrenia, these symptoms are called *negative symptoms*, but overlap extensively with the depressive syndrome [17, 25]. *Positive symptoms* of schizophrenia refer to hallucinations and delusions, often accompanied by severe anxiety [17, 25]. Of the most characteristic positive symptoms are bizarre delusions, delusions of thoughts being directly controlled by other people and hearing commenting voices [17, 25]. The voices may command the patient not to tell, a phenomenon that may prolong the diagnostic process. Commenting voices is a core symptom of schizophrenia; however, also patients with affective disorders may experience psychotic symptoms. Depression may present with anger, and psychotic mania may appear similar to schizophrenia with florid positive symptoms [29]. Without the support of valid and reliable objective diagnostic tools, clinicians must still make diagnostic decisions based on the medical history of the patient and

observations of symptoms in clusters and time. This makes the diagnostic process prone to delays and errors, the consequences of which are delayed treatment, greater suffering, and poorer prognosis.

Although the categorization between bipolar disorder and schizophrenia is clinically useful for guiding treatment, the distinction is less clear at a group level [29]. Inflammation is implied as a central factor in in both conditions [30, 31]. Several gene polymorphisms overlap and some patients have symptoms of both bipolar disorder and schizophrenia [29, 32]. These patients constitute the intermediate diagnostic category of schizoaffective disorder [19]. The term schizophrenia spectrum disorders is currently often used in both clinical and research contexts, including in paper III in this thesis [33].

1.2 Biological rhythms and bipolar disorder

Rhythmicity is an inherent trait of all life forms [34]. The most striking feature of bipolar disorder is the rhythmicity of episodes. Some patients demonstrate a clock-like regularity for alternating antipode states [18]. In healthy subjects, the biological rhythms are regular and synchronized both within the organism and to the outer environment [35, 36]. The most well-known biological rhythm is the *circadian* (circa one day) that controls e.g. the body's temperature and melatonin secretion [35, 37]. Biological rhythms with periods longer than one day are called *infradian* (such as monthly or annual rhythms of fertility) [34]. The circadian and annual rhythms are both influenced by the light/dark cycles caused by the Earth's 24-hour rotation around its own axis and the 365-day orbit around the Sun. More recently, a dopamine-driven activity rhythm (which normally has a four-hour period) has been discovered [38]. This is an example of an *ultradian* (shorter than one day) biological rhythm.

Some have argued that bipolar disorder evolved as an adaption to seasonal photoperiods [39]. This theory infers that the bipolar constitution evolved in temperate regions, as an adjustment of function to survive extreme seasons [39]. For a group of

people, members with bipolar traits may have increased the general likelihood of survival. In situations of opportunity, manic excessive energy, initiative, and courage could have promoted the expansion of habitat through warfare or migration [40]. In times of starvation with no escape (such as winter), the depressive syndrome may have promoted survival through decreased energy expenditure while passively awaiting resources (spring) to return. This way, bipolar disorder traits may have served as an evolutionary asset [39, 40].

Circadian dysregulation has long been proposed a central cause of affective disorders [41, 42] Hypotheses relating to internal desynchronization of circadian rhythms in affective disorders (presented more than 40 years ago), are now supported by more recent research findings [41, 43-49]. During affective episodes, the circadian rhythms are desynchronized both in relation to the environmental light/dark cycle, and within the organism [44, 50-53]. Many gene-polymorphisms that are associated with bipolar disorder codes for proteins involved in regulation of the circadian clocks [23, 54, 55]. Commonly used mood-stabilizers and antidepressants affect the rhythmicity of neurons of the master clock (the suprachiasmatic nucleus SCN), and peripheral cell clocks [56, 57]. Moreover, individual chronotype and cellular circadian rhythms have been found to predict lithium response, a finding that clearly illustrates the close relationship between circadian function and bipolar disorder symptoms [58]. However, circadian disruption is not included within the diagnostic clinical syndromes, and exactly *how* circadian dysfunction relates to the mood-syndromes is not fully understood. Until recently, it was not even known whether (and how) variants of circadian rhythms (expressed as morning or evening preference) relate to episode polarity [52]. Most of the studies on the nature of circadian rhythms in bipolar disorder have used cross-sectional designs, subjective reports on morning or evening preference, or activity data as measures of circadian phases among bipolar disorder patients [52, 59]. A majority of studies have found an association between eveningness (evening preference) in depressive episodes as well as in euthymia; however, the findings have not been consistent [53, 59, 60]. Few studies have included manic

patients [52, 59, 60]. With only one exception, there is a lack of recent studies using multiple outcomes including valid measures of central circadian rhythm (such as melatonin) and measures of peripheral circadian rhythms [50]. Furthermore, studies of the transitions between mood-states have been lacking since some rather advanced case-reports from before the millennium [52, 61-64]. One exceptional recent study by Moon et al. examined the transition between states *and* used multiple outcomes for circadian rhythms. The results indicated extremely advanced circadian phases in 21 out of 23 manic patients as measured by fluctuations in cortisol and peripheral clock genes [50]. For the five depressed patients in the study, the same rhythms were delayed [50]. The circadian phases of patients with mixed symptoms were intermediate to those of the manic and depressed patients. For all, the desynchronized circadian rhythms returned to normal along with recovery from the episodes [50]. In spite of the relatively small sample-size, the findings were very consistent. Notably, for both the depressed and manic patients, the central and peripheral circadian rhythms were disassociated from the more stable rest/activity cycles [50]. This indicates that data on rest/activity cycles alone cannot serve a proxy for data on the phase of the circadian rhythm machinery during affective episodes. This observation could explain the inconsistencies in the previous literature on circadian rhythms and chronotype in bipolar disorders, which was most often based on data on rest/activity rhythms [52]. But how may these state-dependent disassociated circadian rhythms mechanistically relate to the mood symptoms and abnormal levels of energy? In recent years, there has been a renewed interest in this basic question that may bring us closer to understanding the origin of mood symptoms and mood switches [65-70]. This topic will be more discussed in Chapter 6.

1.3 The role of light

The circadian rhythm matching the speed of the Earth's rotation is programmed into each separate cell within the body [35]. The intrinsic rhythm is not dependent on external control to maintain the circa 24 h cycle [35]. However, the cell-clocks do need

an external time signal to remain synchronized within the body and to the external time. The synchronizing master-clock is the suprachiasmatic nucleus (SCN), which is a small a part of the hypothalamus located adjacent to the third ventricle of the brain, just above the crossing (chiasma) of the optic nerve [71]. The main signal of time for the SCN is the presence or absence of light [35]. Cells that monitor light (daytime) or darkness (nighttime) are identified as the intrinsically photo-responsive retinal ganglion cells (ipRGC) located in the inner layer of the retina [72-74]. This relatively recent discovery has facilitated the mapping of neural circuits involved in the non-image-forming responses to light [75-78]. However, this term has been subject to criticism for being inaccurate, as the ipRGCs may elicit (some very blurry) visual perception in otherwise blind subjects [79]. The more correct term is therefore *ipRGC-influenced responses to light* [80]. The photo pigment in the ipRGC is melanopsin, which change isomeric form (promoting ipRGC signaling) when absorbing blue light [81, 82]. In addition, ipRGCs receive some light information from rods and cones, which accounts for the green proportion of the ipRGC sensitivity spectrum [83]. This spectrum is the basis for the new light metric *melanopic lux*, which provides information of the daylight signaling property of light sources [80, 84]. When exposed to light with sufficient melanopic lux, the ipRGCs send excitatory signals to the SCN. The SCN responds by conveying daytime-signal to the cells and organs in the body, by suppression of the dark hormone melatonin and via direct innervation [85-87]. In darkness (or more precisely, in the absence of light with shorter wavelengths than 530 nm) signaling from the ipRGCs to the SCN is halted. This allows melatonin production in the pineal gland and the biological night can commence [5, 6].

In addition to merely serving as a time-signal (*zeitgeber*) to the master clock SCN, light is also a direct activator and mood-regulator though neuronal projections independent of SCN involvement [77, 78]. It has not yet been established which mechanism is most important in bipolar disorder: light as a time-cue, a direct activator/mood regulator, or both [3, 88]. Recently, light in the morning is shown also to have neurotrophic effects, an effect not yet studied in bipolar disorder subjects [89].

The spring and autumn peaks of mania is suggestive that *change* in photoperiod is provocative [90, 91]. Furthermore, solar insulation at the latitude of residence and season of birth seems to modulate the course of illness [92-94]. Light supersensitivity has been suggested as a potential trait marker of bipolar disorder, and although some studies have shown contradictory results, other studies have demonstrated deviant light responses in the pupillary reflex, in melatonin output, and in color perception [95-103]. The nature of the proposed light sensitivity in bipolar disorder is not revealed, but recent findings are in support of a supersensitivity in very low light conditions [104-106]. It is likely that some of the experimental research on light sensitivity have been hampered by use of light exposure above the ipRGC saturation threshold [105, 107]. Moreover, commonly used medications in bipolar disorder alter retinal function, which means that effects from medication should be controlled for in future research on light sensitivity in bipolar disorder subjects [108-110].

1.4 Sleep in bipolar disorders

Sleep problems are present in most psychiatric conditions, but only in affective disorders sleep problems (or change in sleep) are defined as part of the diagnostic syndromes. In bipolar disorders, sleep characteristics usually follow the polarity of the episodes. In bipolar depression, the sleep problems can present as insomnia or hypersomnia [111]. But regardless of sleep length, the depressed patients feel unrested. As the mirror image of the depressed state, the manic patient usually experiences a reduced need for sleep and often does not regard few hours of sleep as a problem. It is a common view that short sleep and reduced need for sleep reflects the level of manic symptoms. This understanding is reflected in the construction of the item for sleep (Item 4) of the Young Mania Rating Scale (YMRS) [1]. Consequently, one of the main clinical treatment strategies in the clinic is to promote adequate hours of sleep, with less emphasis on sleep quality or when sleep occurs. However, new data suggests that sleep disturbances for patients with bipolar disorder are best characterized by poor sleep quality and high variability of sleep length, while average total sleep duration

seems to be less affected even during episodes [112-115]. Studies investigating sleep in bipolar disorder patients are generally few and diverse concerning the state of the subjects and outcome measures [59, 116].

Actigraphy is shown to be a valid source of data for sleep outcomes among bipolar disorder patients, although studies of patients in mania are scarce [59, 117]. One study of patients in manic and mixed states found increased daytime sleep, and high inter-daily variability of sleep length, while the 24 h sleep time was less reduced in mania than previously assumed [60]. This suggested that sleep disturbance during mania may relate to hyper-arousal and/or disrupted circadian rhythms rather than an actual reduced need for sleep [60].

The basic mechanistic relationship of mania and sleep disturbances is not fully understood. Altered sleep is an inherent symptom of mania, as well as a mania trigger [118, 119]. Transient misalignment of circadian rhythms both within the organism and in relation to outer light/dark cycles could explain part of the worsening of sleep-problems during bipolar disorder episodes [50]. In the informative paper by Moon et al., the sleep/wake cycles of the manic patients were found to be disassociated from their central and peripheral circadian rhythms in a state-dependent manner. While their cortisol and peripheral clock gene rhythms showed a near 180 degrees deviation from the depressed comparators, both groups' sleep/wake cycles showed little deviation from the normal rhythm [50]. The circadian desynchrony observed in the manic patients resembled the circadian rhythm turmoil and sleep problems occurring during jet-lag, where the sleep schedules are largely controlled by the social rhythm.

1.6 Chronotherapies in affective disorders

Chronotherapies (from the Greek *Khronos*, meaning time; *time(ing)-therapy*) for affective disorders are interventions directed to alter biological rhythmicity by adjusting the function of the time-keeping system, thereby improving affective symptoms [3]. At present, the chronotherapeutic armamentarium consists of five main

approaches, as follows [3]. Clinical application of bright light as a therapy for depression commenced in the early 1980's and is effective for seasonal affective disorders (SAD) as well as for non-seasonal depression [3, 120]. The development of wake-therapy protocols with lasting effects enabled the clinical application of this potent treatment for (otherwise) treatment-resistant depression [3, 121]. Melatonin-agonist as a pharmacological intervention for affective disorders has been the subject of researched since the last millennium, although so far it has shown mixed results [3, 122, 123]. The psychological/behavioral therapies of inter personal social rhythm therapy (IPSRT) and cognitive therapy for insomnia in bipolar disorder (CBTI-BP) was introduced in 2005 and 2013, respectively [124, 125]. These interventions have modest effects as compared with light and wake therapies, and of the behavioral therapies, only IPRST have shown effectiveness during acute (depressive) episodes [3]. However, the behavioral interventions of the chronotherapies have contributed much to the psychoeducational focus on regularity of sleep and daily schedules for preventing bipolar disorder episodes.

Dark therapy is one of the latest developments of the chronotherapies. The idea of using regular periods of darkness as a means of stabilizing mood was suggested by Tom Wehr in 1989 [126]. The rationale was twofold: to stop a vicious circle of sleep problems and mood instability, and to promote circadian regularity by increasing the SCN's sensitivity to light in the morning (after the extended darkness period). In the first reported case of a patient with rapid cycling bipolar disorder treated with a schedule of 14 h darkness and extended bedrest, simultaneous stabilization of mood, sleep, and activity was demonstrated shortly after the procedure commenced [126]. In the following year, similar results were demonstrated for another patient with severe rapid cycling bipolar disorder [127]. The first controlled study on dark therapy for mania was published in 2005 [128]. Acutely admitted bipolar disorder patients in a manic episode were treated with complete darkness from 6:00 p.m. to 8:00 a.m. in addition to treatment as usual (TAU), and the outcome was compared to a group who

received TAU only. The decrease in manic symptoms for the dark therapy group was striking, with a high effect size of 1.6 (Cohen'*s* d) after only three days [128].

Whilst James Phelps first described the concept of exchanging complete darkness with BB glasses in treatment efforts for bipolar disorder outpatients, our VATMAN trial was the first to test the effect of BB-glasses for inpatients in a manic state [4, 129]. Several case reports and studies on effect and feasibility of BB interventions have now been published [130-143]. The majority are pilot studies or the first within each age group or diagnostic category. In spite of relatively small sample sizes, all published studies have described improvement in either psychiatric outcome measures, sleep outcomes, melatonin profile or cognitive performance [130-143]. Since 2016, no new papers have been published on the effect of BB glasses on manic symptoms, although we are awaiting the results from an ongoing controlled study of effects of BB-depleted evening and night light environment (from 6:00 p.m. to 7:00 a.m.) for acutely admitted patients in Trondheim [144].

1.7 Dysregulated activation in mental disorders

Motor activity disturbances in serious mental disorders are evident, ranging from hyper-kinetic states to catatonia [9, 10, 145]. To acknowledge this, the category of sensorimotor systems was added to the Research Domain Criteria (RDoC) framework in 2018 [146, 147]. RDoC is a leading transdiagnostical framework for research on mental disorders developed by the National Institute of Mental Health (NIMH) in the United States, which focuses on neurobiological systems beyond diagnostic categories [148]. Increase in "activity or energy" was added as an additional first rank criterion for manic episodes in the last revision of the DSM-5 [17]. Studies on the association between the separate symptoms of affective syndromes have indicated that activation is a core symptom in mania, and a distinctly different dimension than mood [9].The lack of a clear conceptualization and operationalization of "activity and energy", motivated a comprehensive review of activation in bipolar disorders by Jan Scott et al. in 2017 . Their chosen definition of activation was descriptive, rather than based on

theories of etiology: “1) emerging from underlying physiological change; and 2) measurable in the objectively observed behavior (motor activity) and the related subjective experience of overt behavior (energy)” [9]. Based on 56 studies with objective data on motor activity or subjective energy, two of their main conclusions were: 1) Mean activity is lower in depressed and euthymic patients than in healthy controls and other comparative groups. 2) Patients with mania have higher mean activity than depressed patients, but demonstrate greater difference with regard to more unpredictable and complex activity patterns (according to linear and non-linear mathematical analyses of activity in time series) [9]. This review was restricted to studies on activation in bipolar disorder and relatively few studies have compared activity across diagnostic groups [149-154]. Reduced mean activity seems to be a common finding in hospitalized patients compared to healthy controls [9, 59, 155]. Given the limited information from analyses of mean activity alone, some studies have included analyses on activity variability, as well as applied non-linear mathematical analyses that can inform on degree of chaos/irregularity/complexity of motor activity in time series [150-153, 156-158]. In schizophrenia spectrum disorders, low activity mean is associated with negative symptoms, and irregular motor activity is associated with positive symptoms and agitation [155-157]. Similar to depressive patients, patients with schizophrenia demonstrate higher than normal activity variability, which in combination with low mean activity describes a monotonous activity pattern. The high degree of complexity in activity patterns for patients with schizophrenia is also found in patients in a manic state [158]. Thus, according to previous literature, the schizophrenia spectrum group seem to share motor activity traits with both depressed and manic patients groups.

1.8 Motor activity monitoring in serious mental disorders

The first efforts to monitor motor activity objectively consisted of handwriting analyses, actigraphy case-reports, or case series [18, 159, 160]. The last two decades have seen a growing interest in actigrapy research; however, until recently, most of the

studies have focused on sleep outcomes and fewer have studied diurnal motor activity characteristics [59, 155].

There is an ongoing world-wide effort to collect large-scale actigraphy data to characterize motor activity traits for various diagnostic entities in the Mobile Motor Activity Consortium for Health project (mARCH) [10, 161]. In addition, a large scale number of private consumers wear products with integrated motor activity sensors sending real-time activity information to online suppliers of health services. In contrast to the vast amount of data that is now collected around the world, the science of data-interpretation is less mature.

Other methods have been tested for assessing motor activity in serious mental disorders, such as the human open field[1] paradigm, which involves assessment of exploratory behavior in a novel environment within a limited period [162]. In a study by Perry et al., patients in a manic state demonstrated a characteristic pattern of rapid straight approach, tactile exploration and gathering of objects during the first part of the session. In contrast, patients diagnosed with schizophrenia showed a constant low level of exploration and a reduced approach towards objects. Although this human "open field" paradigm suggested higher diagnostic specificity than the nurse observations, this method is probably not applicable outside a research context in the near future [162]. Radar technology is currently being tested for sleep and safety monitoring of patients in their rooms, and may also be applicable for motor activity supported diagnostics and symptom monitoring in the future [163]. For now, actigraphy is still the most feasible method for obtaining motor activity data in a hospital setting as well as for outpatients.

[1]The human open field paradigm is a human parallel of the rodent open field paradigm for behavioral testing in a novel environment.

2. Aims

2.1 Paper I

The aims of the randomized controlled trial (RCT) were first to test the effectiveness of BB glasses as adjunctive treatment for hospitalized patients in a manic episode, and second, to examine their feasibility of use within in the hospital setting.

The specific aims were as follows:

1) To compare mean YMRS total scores and mean motor activity of the BB group to the outcomes of the placebo group.

2) To investigate the feasibility of use of the BB glasses through a patient satisfaction self-report form and by monitoring side effects.

2.2 Paper II

The aim of this study was to examine the effect of BB glasses on actigraphy-derived sleep parameters, as an adjunctive treatment for hospitalized patients in a manic episode.

The specific aims were as follows:

1) To compare sleep efficiency and mean motor activity of the BB group with the outcomes of the placebo group.

2) To compare total sleep duration, wake after sleep onset, wake bouts, sleep fragmentation, total sleep length, sleep onset, sleep offset, and mid-time sleep of the BB group with the outcomes of the placebo group.

3) To describe sleep pattern observations from patients in a manic state who received treatment with either adjunctive BB glasses or placebo.

2.3 Paper III

The overall aim was to investigate whether the activity patterns of patients with schizophrenia spectrum diagnoses could be differentiated from activity patterns of patients with mania, unipolar depression and healthy controls.

The specific aims were as follows:

1) To describe the 24 h activity patterns and 64 min morning and evening sequences in a new sample of patients with schizophrenia spectrum disorders.

2) To compare the motor activity patterns in the schizophrenia spectrum group to the motor activity patterns of patients with bipolar mania, unipolar depression, and healthy controls.

3. Materials and methods

3.1 Settings

3.1.1 Setting for the Virtual Darkness as Additive Treatment in Mania (VATMAN*)* trial

The patients were recruited from three hospitals and two district hospital centers in southwest Norway at latitudes 58–59 °N from February 1st 2012 to February 15th, 2015.

Recruiting centers

1. Valen Hospital and Folgefonn District Hospital, Valen, from February 1st 2012

(14 patients, 28 healthy controls)

2. Haugesund Hospital and Haugaland District Hospital, Haugesund from August 29th 2012 (5 patients, 12 healthy controls)

3. Stavanger University Hospital, Stavanger from August 20th 2014
(5 patients, 5 healthy controls)

The recruitment was closed at all sites at February 15th 2015.

3.1.2 Setting for the study Agitation at Admittance to a Psychiatric Acute Department study/paper III.

This study was undertaken at Østmarka Department of Psychiatry, Trondheim University Hospital, Norway. During the period September 1th 2011 to March 31st 2012, 280 acutely admitted patients were recruited, and 71 were included in the analyses of Paper III. Data from 28 healthy controls included in the study (recruited in the VATMAN trial, Valen, Haugesund, Stavanger) were sampled in the time period 1th February 2012 to 15th February 2015.

3.2 Study populations

3.2.1 Diagnostic process

3.2.1.1 Diagnostic process for the VATMAN trial

The diagnoses of the patients included in the trial were verified by a specialist in psychiatry, using the Mini International Neuropsychiatric Interview Plus (MINI Plus) for diagnostic support [164]. During the recruitment-period, a new revision of the DSM (the DSM-5, 2013) was published [17]. The criteria for manic episode were amended by adding "increased goal-directed activity or energy" as a second A-criterion, in addition to the previous mood criterion "persistently elevated or irritable mood [17]. Due to the clinical priority of addressing ongoing manic symptom, the diagnostic entity *mixed episode* was replaced by *manic episode with mixed features*, also in the cases where depression and mania symptoms present in same proportions. Consequently, the DSM-5 definition of manic episode has been somewhat broadened since the data-collection for the VATMAN trial.

3.2.1.2 Diagnostic process for the Agitation at Admittance to a Psychiatric Acute Department study

The patients included in this study were diagnosed through an expert consensus meeting of a minimum of three specialists in psychiatry. The criteria for diagnoses were defined by the ICD-10 [25]. All available information was included in the diagnosis decision process, and at least two of the specialists had firsthand information on the patients' history and current state. To select unipolar depressed patients with motor retardation, *the Symptomatic Organic Mental Disorder Assessment Scale (item B)* was used [165].

3.2.2 Inclusion and exclusion criteria for the VATMAN-trial and analyses in Paper I and Paper II

3.2.2.1 Inclusion criteria for the VATMAN trial

For patients the inclusion criteria were as follows:

1) Diagnosis of BD-I with current manic episode. The recruitment of hospitalized patients defined the severity of symptoms at the level of mania, without the need for use of the symptom duration criterion (a minimum of one week of symptoms for manic episode).

2) Aged 18-70 years

3) Ability to comply with the protocol

4) Willingness to participate in the study

5) Delayed written informed consent at discharge

For the non-bipolar controls the inclusion criteria were:

1) Aged 18-70 years

2) Written informed consent

Inclusion criterion for the intention to treat analyses in Paper I

The inclusion criterion was use of BB glasses for a minimum of one evening/night.

Inclusion criteria for the group comparison analyses in Paper II

The inclusion criterion was valid actigraphy recordings both night one and night five.

3.2.2.2. Exclusion criteria

The exclusion criteria for patients were as follows:

1) Inability to comply with the protocol

2) Severe retinal damage, cataract or corneal damage to both eyes

3) Daily use of NSAIDS, beta-blockers, or calcium-antagonists

For the non-bipolar controls the exclusion criteria were:

1) Working night shift

2) Diagnose of bipolar disorder or single manic episode

3) Severe retinal damage, cataract or corneal damage on both eyes

4) Daily use of alcohol, benzodiazepines, NSAIDS, beta blockers, or calcium antagonists.

3.2.3 Inclusion and exclusion criteria for the Agitation at Admittance to a Psychiatric Acute Department study and analyses in Paper III

3.2.3.1 Inclusion criteria for patients

1) Hospitalization at Østmarka acute department

2) Ability and willingness to grant written informed consent

3.2.3.2 Exclusion criterion for patients

Inability to grant written informed consent

3.2.3.3 Inclusion criteria for healthy controls

1) Recruited in the VATMAN trial

2) Aged 18-70 years

3) Written informed consent

3.2.3.4. Inclusion criteria for the analyses in Paper III

1) Diagnosis of a primary psychotic disorder, a manic episode of bipolar disorder, or a (clinically rated) motor-retarded unipolar depression without psychotic symptoms.

2) The presence of valid (near) 24 hour actigraphy recording

3) For the analyses of morning and evening sequences, a 64 minute period of continuous activity (in 1 minute epochs) after 6:00 a.m. and before midnight p.m. respectively

3.2.4 Withdrawal from the studies

All participants could withdraw consent at any time without any given reason before the analysis and publication of the data. The participants were informed of this right both orally at recruitment and in writing in the information and consent form

3.3 Methods

3.3.1 Study designs

3.3.1.1 Design of The VATMAN trial/papers I and II

The VATMAN trial was an effectiveness trial with an RCT design. The trial constituted of two groups of patients who were randomized to use either BB glasses or clear-lensed glasses as placebo condition. In addition, we recruited a non-bipolar control group to serve as a comparator with regards to activity-data and for monitoring of side effects.

3.3.1.1.1 Randomization and masking

The patients were randomized (to receive either BB glasses or placebo) by using folded patches that were manually drawn by secretaries who had no other role in the trial. The study was single-blinded. The patients were blinded for assignment to the

respective group by receiving the same information: the glasses were filtering some part of the spectrum of light and one type of glasses would be compared to the other. No patient observed the other type of glasses during the intervention. The doctors who rated the patients for daily manic symptoms (using YMRS) were not blinded to the assignment, nor were the persons performing the analyses.

3.3.1.1.2 Baseline assessment

Baseline assessment in Paper I included demographical data, clinical characteristics, YMRS scores at day 0 (scored at daytime before the first night of intervention), and mean daytime activity before 6:00 p.m. on day 0. There was no baseline assessment of actigraphy sleep outcomes.

3.3.1.1.3 Interventions

Either BB glasses or placebo clear lenses glasses were used as interventions, worn from 6:00 p.m. to 8:00 a.m. adjunctive to TAU. The glasses could be taken of when going to bed and turning off the light. Intervention and observation were for a period of seven days. The nursing staff were instructed to pay equal attention to all patients and encourage continuous use between 6:00 p.m. to 8:00 a.m. (except when the lights where turned off), regardless of group assignment.

3.3.1.1.4 Treatment as usual

The interventions were purely adjunctive in an otherwise naturalistic clinical setting. Thus, TAU consisted of all usual modalities of treatment for patients in a manic episode, based on individual assessment and decision taken by the treating doctor (who was not involved in the study). The pharmacological TAU is shown in Table 1. In addition, non-pharmacological treatments were used, such as stimuli reduction by use of seclusion.

Table 1. Individual Medications for Patients Assigned to Blue-Blocking (BB) Glasses or Clear Glasses (Placebo) [129]

Patient	Antipsychotics, mean dosage (mg/day)	Anticonvulsants, mean dosage (mg/day)	Lithium, mean dosage (mg/day)	Anxiolytics/Hypnotics/ Sedatives, mean dosage (mg/day)
1[1]	Olanzapine 5.6 Quetiapine 600.0	Valproate 837.5		Diazepam 21.3 Zopiclone 15
2	Quetiapine 200.0			
3		Valproate 3300.0	Lithium sulfate 84.0	Zopiclone 7.5 Alimemazine 40.0
4		Valproate 600		Oxazepam 31.25 Cetirizin 10.0
5	Haloperidol 6.25 Levomepromazine 50.0	Valproate 1537.5		Diazepam 10.0, Zopiclone 7.5
6	Haloperidol depot 50.0 (every 14 days) Chlorpromazine 162.5		Lithium sulfate 119.9	Diazepam 16.3
7	Haloperidol 0.75 Olanzapine 22.5	Carbamazepine 325.0		Diazepam 34.4
8	Olanzapine 20.0 Quetiapine 100.0		Lithium carbonate 1200.0	Oxazepam 17.0 Zopiclone 3.3 Alimemazine 10.0 Cetirizine 10.0
9	Chlorprothixene 123.1 Olanzapine 23.6			Oxazepam 10.0
10	Levomepromazine 6.3 Olanzapine 3.8		Lithium sulphate 166.0	Diazepam 5.0 Melatonin 0.5
11	Aripiprazole 9.0 Quetiapine 30.0 Zuclopenthixol 10.0	Valproate 936.0		Cetirizine 10.0
12[2]	Quetiapine 250.0	Valproate 1200.0		Diazepam 10.0
13	Quetiapine 350.0 Zuclopenthixol 20.0		Lithium sulphate 84.0	
14[3]		Lamotrigine 300.0		
15				Zolpidem 7.5
16	Olanzapine 20.0	Valproate 562.6		
17	Olanzapine 15.0			
18	Chlorpromazine 500.0		Lithium sulphate 166.0	Clonazepam 1.25 Cetirizine 10.0 Promethazine 25.0
19	Olanzapine 6.9 Quetiapine 600.0	Valproate 450.0		
20	Olanzapine 25.0	Lamotrigine 200.0	Lithium sulphate, 192.6	Clonazepam 0.9
21	Aripiprazole 10.0			
22	Chlorprothixene 100.0 Olanzapine 40.0		Lithium sulphate, 249.0	Buspirone 30.0 Clonazepam 2.25
23	Risperidone 0.6	Lamotrigine 162.5	Lithium sulphate 120.8	Alimemazine 3.75 Mirtazapine 24.4
24	Olanzapine 15.0	Valproate 600.0		

[1] Patient 1-11: patients wearing clear glasses (placebo)
[2] Patient 12-24: patients wearing orange glasses
[3] This patient was excluded from the study

3.3.1.1.5 Assessments

Demography, illness characteristics and medical examination

Information on demography (age, sex, education, employment, marital status) and illness characteristics were obtained from interviews and medical journals for each patient. The healthy controls were asked about psychiatric illness and use of medication besides the demographic data. Morning or evening preference and seasonality were assessed using the Horne-Östberg Morningness-Eveningness Questionnaire (HOMEQ) and Seasonal Pattern Assessment Questionnaire (SPAQ) [166-170].

With all subjects, the eyes were examined for transparency using ophthalmoscopy inspection of red reflex, and vision was confirmed by use of a finger-count-test.

Assessment of symptoms

Symptoms of mania were assessed using YMRS, which constitutes of 11 clinician-rated items: 1) Elevated mood, 2) Increased motor activity and energy, 3) Sexual interest, 4) Sleep - duration and subjective need for sleep, 5) Irritability, 6) Speech-rate and amount, 7) Language-thought disorder, 8) Psychotic content of thought, 9) Disruptive or aggressive behavior, 10) Appearance, and 11) Insight [1]. Symptoms were rated daily at the end of each day shift (2:00 p.m.). The ratings were performed by doctors trained in use of the YMRS in consensus with at least one member of the nursing staff (who had attended the patient during the dayshift). Nurse reports were used as supportive information. The assessment period was 24 h, starting at midnight. Motor activity was recorded for the full seven-day observation period by using a wrist-worn actigraph (Actiwatch Spectrum; Philips Respironics, USA) To inform on feasibility, a patient experience self-report form was developed for the trial and consisted of seven statements targeted so that patients could grade their agreement, using a scale response: fully disagree/somewhat disagree/neither disagree nor agree/somewhat agree/fully agree.

Finally, any observed or subjectively reported side effects were noted.

3.3.1.2 Design of the Agitation at Admittance to a Psychiatric Acute Department study/Paper III

This study utilized a cross-sectional design, sampling motor activity data from acutely admitted patients (with diagnoses of schizophrenia spectrum, mania, or unipolar depression with motor retardation) in a 24 h time window shortly after admittance. The 24 h activity data from healthy controls were chosen from a seven- day recording period, based on the presence of 64 min sequences of continuous activity, which was required for the Fourier analyses.

3.3.1.2.1 Assessments

The demographic data on age, gender, body mass index (BMI), diagnosis, and medical treatment were used to characterize the patient samples. For the healthy controls, BMI data was not available. In addition, the HC subjects were interviewed for a medical history of psychiatric illness and current use of medications. Data on wrist movements were sampled by actigraphy as counts per minute (1 min epochs).

3.3.1.2.2 Mathematical computation of data

The data were computed using linear and non-linear mathematical analyses of the data over 24 h and in 64 min sequences for both morning and evening recordings.

In addition to analyses of mean activity, mathematical analyses of variability and complexity (degree of irregularity) were applied:

The standard deviation (SD) in given % of the mean expresses the general variability of the period of interest.

The root mean square successive difference (RMSSD) expresses the difference between successive counts and is a measure of short term variability.

The *RMSSD/SD ratio* provides a measure of the relation between short term and overall variability of the time series.

Three non-linear measures of activity patterns morning and evening sequences (each of 64 min) were applied. Periods of 64 min were selected according to the requirements for Fourier analyses: sequences of continuous activity in potencies of 2 (2-4-8…..64-128). Based on previous experience, the maximum length of these continuous activity sentences was set to 64 min [158].

Fourier analysis is a mathematical method of analyzing frequency patterns in time series. In paper III, this is presented as the relation between the variances in the high and low frequency activity spectra for the patient groups. Higher values indicate relatively higher variance in the high frequency spectrum.

Autocorrelation at lag 1 expresses the correlation between numbers (here activity counts) in successive time series lagged one step further. More simply put, the autocorrelation analyses in paper III was the correlation between successive activity counts. Possible values are one or less, with low values indicating lower correlation and more variable activity patterns from minute to minute.

Sample entropy is the negative natural logarithm of the estimated conditional probability that subseries of a certain length (m) that match point-wise, within a tolerance (r), also match at the next point. It is customary to use $m = 2$ and $r = 0.2$, and these values were also used in this study. Higher values of sample entropy indicate higher complexity of time series, while lower values indicate more regular time series.

3.3.2 Statistical analyses

3.3.2.1 Paper I

Power analysis was based on the outcomes of the dark therapy pilot study, with the power set to 0.8 and a significance level of 0.05 [128]. This yielded an estimated sample size of 21 patients for each group of the RCT. Demographic data, clinical characteristics, and use of medication were presented with descriptive statistics performed using SPSS 22.0 software (IBM Corporation USA) which was presented in tables. For effectiveness testing, mixed linear analyses were used with baseline data as single contrast. The YMRS total score and activity mean were primary and secondary outcomes respectively. The YMRS single items were not subject to statistical testing but were presented graphically with means and 95% confidence intervals (CI) for each day during follow-up. Scores from the patient experience self-report form were presented graphically, and side effects were descriptively reported.

3.3.2.2 Paper II

Prior to the analyses, the raw data were inspected. The main rest interval was set based on significant change in activity supported by light data and nurse reports on times for waking and sleeping. Manual inspection of actigraphy data and use of all available supplementary data is recommended in the context of sleep research [171]. Demographic data, clinical characteristics, and medication treatment were computed using SPSS software 24.0, after adjustment for a change of sample due to three cases of missing actigraphy data. Group differences were analyzed using covariance (ANCOVA) analysis performed at night five and adjusted for outcomes at night one. Group comparison analyses were performed at night five because non-random drop-outs occurred in the placebo-group at nights six and seven. Sleep patterns of interrupted sleep by longer wake periods were not subject to statistical testing but descriptively presented. In both papers I and II, the Actiware 6.0 software (Philips Respironics, USA) was used to calculate activity means (counts/min) for all subjects

before group analyses. In Paper I the analyses were performed using SPSS 22.0 and Matlab 7.1. (MathWorks Inc. USA). In paper II SPSS 24.0 and R.3.5.0. (R team, Austria) were used, whith the graphics produced in Matlab 9.0. [172-175]

3.3.2.3 Paper III

Analyses of variance (ANOVA), one-way, with least significant differences post-hoc test were used for analyses of group differences of means. To test within-group morning-to-evening differences in activity parameters, we used paired sample t-tests. To test group differences (for patients) in morning-to-evening changes in activity parameters, linear mixed model analyses were performed. When controlling for treatment with antipsychotic medications, analyses of covariance (ANCOVA) were performed. For all analyses, the significance level was set to $p \leq 0.05$ and analyses were computed in SPSS software 24.0 [173].

4.0 Results

4.1 Paper I

From 32 randomized patients included in the VATMAN trial, 12 patients in the BB group and 11 patients in the placebo group were analyzed for group differences in YMRS total scores. Both patient groups' mean activity data were compared to the mean activity of 35 non-bipolar controls.

More men than women were recruited to both patient-groups. Those in the placebo group were somewhat older than patients in the BB group (mean ages were 49.8 years and 43.0 years, respectively) and the mean baseline YMRS score was slightly higher for the placebo group (27.0) compared with the BB group (23.4).

The mean decline in YMRS total score for the BB group was 14.1 (95% CI 9.7– 18.5) as compared to the placebo group mean decline of 1.7 (95% CI 4.0–7.39). The group difference and SD corresponded to a Cohen's d effect size of 1.86. The difference was statistically significant after three days of intervention ($p = 0.042$) and after seven days the difference was highly significant ($p = 0.001$). The mean activity in the two analyzed intervals (6:00 p.m.–8:00 a.m. and 8:00 a.m.–6:00 p.m.) was lowest for the BB-group from the second night, compared with both the placebo-group and the healthy control group. Of the YMRS single item scores for the BB group, items 5 (Irritability) and 6 (Speech, rate and amount) reduced most markedly from the first to second day.

The BB group was in receipt of less polypharmacy treatment, expressed as number of different anti-dopaminergic medications and of anxiolytic/sedative/hypnotic medications per patient as shown in Table 1.

Ratings from the patient experience self-report form suggested that that the concept of treatment by use of glasses was well perceived, and a high proportion of the patients in both group stated that they would like to use BB glasses as a treatment in the future if

proven effective. Two patients reported transient depressive symptoms that were relieved by postponing or discontinuing the intervention. These observations corresponded to reports of uncomfortable low energy levels for four participants in the healthy control group, and depressive symptoms were noted as a likely side effect. One patient experienced headache and three healthy controls reported the same. Headache was therefore also noted as a likely potential side effect of the BB intervention.

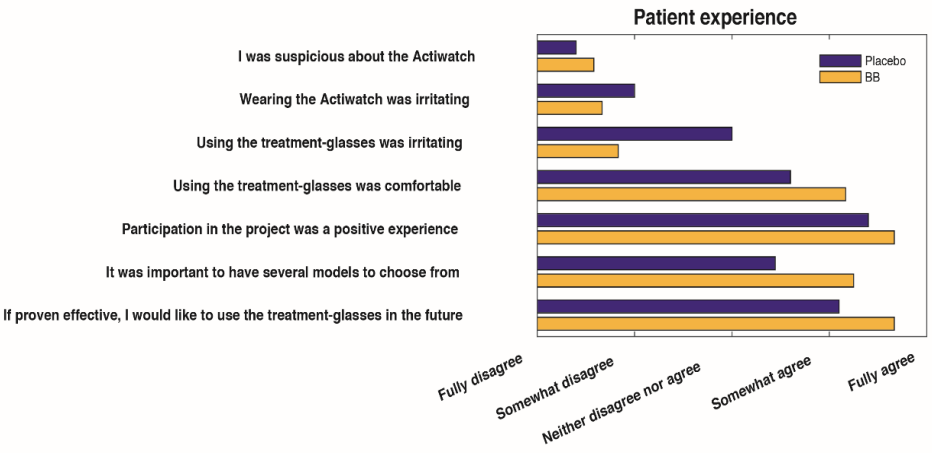


Figure 1. Self-reported patient experience with participation in the VATMAN-trial for patients in the BB group (n = 12) and placebo group (n = 11) [129].

4.2 Paper II

Twenty randomized consenting patients with valid actigraphy recordings night one and night five (10 patients in each group) were included in the analyses of group differences in actigraphy-derived sleep outcomes. The description of nights with longer wake periods included the recordings from 22 patients, which comprised 12 patients in the BB group and 10 patients in the placebo group.

In the 20-patient sample for group comparison analyses in paper II, the demographic variables differed only slightly from those reported in paper I. With regards to morningness/eveningness and seasonality traits in the sample, the placebo group included more morning-type patients with a mean HOMEQ score of 60.4. The BB group scored 52.4, which is in the range of intermediate type. Both groups recorded less than the global seasonality score (GSS) cut-off value of 9 points for sub-SAD, and approximately the same proportion of patients in both groups reported a seasonal variation of 1 h or more for sleep duration. For half of the patients in the BB group (5/10), their intervention occurred during the fall (September–November), whereas participation for patients in the placebo group was more evenly distributed throughout the seasons.

The primary outcome of sleep efficiency (SE) was demonstrated to have increased for the BB group from night one (mean SE 88.1%; 95% CI 82.4%–93.8%) to day five (mean SE 92.6%; 95% CI 89.4%–95.8%). In comparison, SE for the placebo group SE diminished slightly from night one (mean SE 83.4%; 95% CI 71.2%–95.6%) to night five (mean SE 83.1%; 95% CI 75.9 %–90.3%). The difference between the groups at night five, (adjusted for outcomes at night one) was significant ($p = 0.027$). The group difference was also significant for the second primary outcome of mean activity (counts per 30 s) in sleep intervals ($p = 0.007$ at night five). The activity count for the BB group almost halved from night one (20.0; 95% CI 9.1–30.9) to night five: 11.7 (95% CI 5.6–17.8)

By contrast, motor activity increased for the placebo-group from day one: (33.3; 95% CI 0.1–66.6) to day five (47.4; 95% CI 17.5–77.3). Wake after sleep onset (min) mirrored the decline in nightly mean activity for the BB group from night one (60.7; 95% CI 23.6–97.7) to night five (33.5; 95% CI: 19.8–47.1), while for the placebo-group, minutes in wake after sleet onset increased from day one (64.8; 95% CI 14.7–114.9) to day five (79.2; 95% CI: 48–110.3). This difference was also statistically significant ($p = 0.010$). The sleep fragmentation index and wake bouts reduced

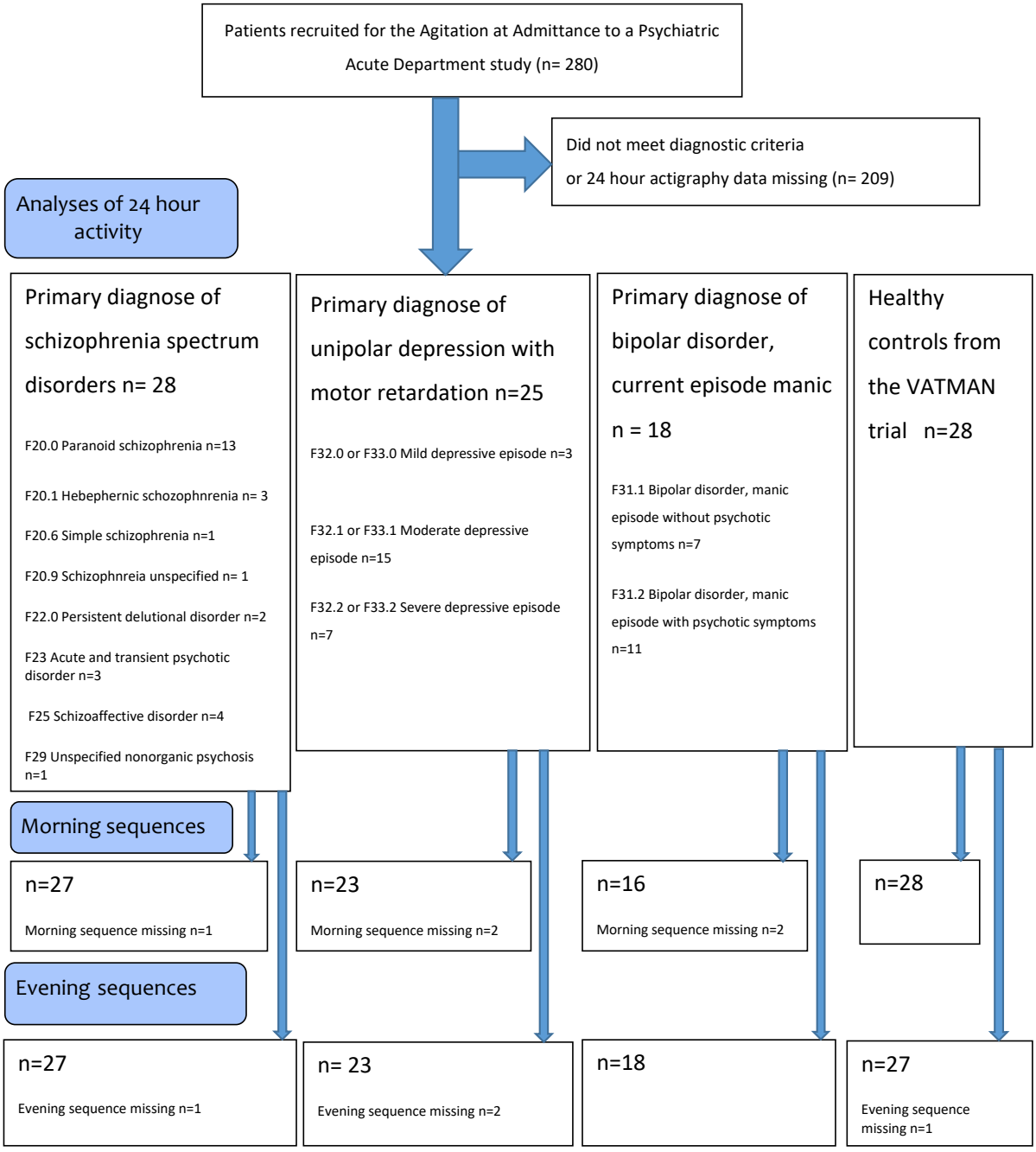
(improved) for BB group and increased (worsened) for the placebo group; however, the differences were not significant. Total sleep time increased by nearly one h for the BB group from day one (6.7; 95% CI 5.5–7.9) to day five: (7.6; 95% CI 6.4–8.8) compared to no change for the placebo-group from day one: (6.3; 95% CI 5.1–7.4) to day five: (6.3; 95% CI 5.3–7.4); however, the difference between the groups was not statistically significant. Sleep-onset, sleep offset, and mid-sleep times showed no group differences at night five.

The patients in the BB-group had fewer nights of interrupted sleep. During five nights of actigraphy monitoring, 29.6% (16/54) of recorded nights for the BB group and 43.8% (21/48) of nights for the placebo group contained 30 min or longer active wake periods. Several patients in both groups demonstrated high variability in wake/sleep timing during the intervention. A characteristic wake/sleep pattern was observed in several patients showing high variability of the sleep interval length. These patients showed either short sleep or interrupted sleep on alternate nights, which gave the impression of a 48-hour rhythm of nights with more disturbed sleep.

4.3 Paper III

Of the total of 71 included patients recruited from the Agitation at Admittance to a Psychiatric Acute Department study, 28 patients were diagnosed with a schizophrenia spectrum disorder, 25 were diagnosed with motor retarded unipolar depression, and 18 had bipolar disorder, current episode manic. In the mania group, 11/18 (60.1%) was diagnosed with “manic episode with psychotic symptoms” (by an error, in paper III it says “nearly 70%”). Trial profile is shown in Figure 2.

Figure 2. Trial profile for Paper III



The mean age for the patient groups ranged from 41.5 for the schizophrenia spectrum group to 51.2 years for the mania group, while the mean age for the healthy control group was 41.7 years. There were no major differences in the distribution of gender or body mass index (not obtainable for healthy control group). The patient groups received a variety of medications with much overlap between the groups. The highest percentage of patients using antipsychotic medication was in the mania group. Antidepressants were most often used among patients in the unipolar depression group; however only by 36% of these patients.

Mean activity

For all patient groups, 24 h mean activity was significantly lower than the mean activity for the healthy control group. The analysis of mean activity in morning periods demonstrated a significantly higher activity for the healthy control group compared to all patient groups but in contrast, there were no significant group differences in the evening periods.

SD/minute in % of mean

In the 24 h SD analyses, the unipolar depressed group showed a significantly higher SD/min (in % of the mean) compared to all other groups, which expressed higher variability of the activity pattern (larger fluctuations from the mean and greater alternation between inactivity and activity) per min. Also in the morning periods the unipolar depressed group demonstrated the highest SD/min, but after adjustment for use of antipsychotic medication the difference compared to the schizophrenia spectrum group was no longer significant.

RMSSD/min in % of mean

In the 24 hour analyses, the unipolar depressed group showed a significantly higher RMSSD/min compared with the mania and healthy control groups. The schizophrenia

spectrum group also exhibited high RMSSD/min which was also significantly higher than for the healthy control group. The pattern of higher RMMSD/min for the unipolar depressed and schizophrenia spectrum groups compared with the healthy control group persisted in the analyses of morning periods, but were absent in evening periods.

RMSSD/SD

In the 24 h analysis, all patient groups showed significantly higher values of RMSSD/SD compared with the healthy control groups. In the morning periods, the schizophrenia spectrum and mania groups similarly showed higher RMSSD/SD than the unipolar depressed and healthy control groups. These differences were more evident (lower p-value) after adjusting for the use of antipsychotic medication.

Sample entropy

In the morning periods, the schizophrenia spectrum and mania groups demonstrated significantly higher sample entropy values than the unipolar depressed group. In evening periods, there were no significant group differences.

Fourier analysis

The schizophrenia spectrum and mania groups demonstrated the highest values which were significantly higher compared with the healthy control group for the morning periods. Also, there was a significant difference in the Fourier analyses between the schizophrenia spectrum and unipolar depressed group in the morning periods, while there were no significant group differences in the evening periods.

Autocorrelation

The morning autocorrelation values for the schizophrenia spectrum and mania groups were similar and significantly lower than for the unipolar depressed and healthy control groups. There were no significant group differences in the evening periods.

Within group analysis of morning-to-evening differences in activity measures

The healthy controls showed a marked decrease in morning-to-evening mean activity and a marked increase in the morning-to-evening SD/min, with both fluctuations being statistically significant. All patient groups demonstrated a lower fluctuation of morning-to-evening decline in mean activity, and a smaller increase in SD as compared to the healthy control group. However, the mania group differed from the other groups by lacking a diurnal fluctuation in these parameters. The schizophrenia spectrum group was the only group showing a significant decline in morning-to-evening sample entropy, which means that the mania and schizophrenia spectrum groups shared the characteristic of high motor activity complexity only in the morning periods. Between the groups, there were no significant differences in morning-to-evening change in activity variables (group by time analyses). Adjustment for use of antipsychotic medications did not alter these results.

5.0 Discussion

5.1 Discussion of main results

5.1.1 Effects of BB glasses on YMRS outcomes, motor activity and sleep

In this first RCT on the effectiveness on BB glasses as adjunctive treatment for patients hospitalized with a manic episode, we found that the effect was rapid, and with a large effect-size. The main finding (a sharp decline of mean YMRS total score for the BB group) was supported by the objective actigraphy data showing abruptly reduced mean motor activity both during daytime and in the 14 h BB interval. The actigraphy sleep outcomes at night five showed significantly higher sleep efficiency, lower mean activity and less minutes of wake after sleep onset for the BB group compared with the placebo group. In all these measures, the placebo group worsened during the first five days of the follow-up.

The placebo group also demonstrated more nights of sleep disrupted by long waking periods. In paper II, this was described as the percentage of nights containing one or more active waking periods lasting 30 min or longer during the first five nights of the intervention. The patients in the placebo group had biphasic or poly-phasic sleep patterns in 43.8% of the recorded nights compared with 29.6% of the nights for the BB group.

The effect measured by change in YMRS corresponded to a Cohens'*d* effect size of 1.86, which was very similar to the effect size of the dark therapy pilot study (1.6). To date, the study by Barbini et al. is the only study with which a reasonable comparison of effects size can be made, as no other controlled studies on BB interventions or (real) dark therapy for patients in a manic episode have been published. However, large effects-sizes have also been found in other studies on the effects of BB interventions (or with protocols including evening light avoidance) for patients with sleep problems [143, 176]. Large effect size increases the likelihood for reproduction in future studies

[177]. Unfortunately, we could not calculate the effect on sleep outcomes in paper II due to a lack of baseline data.

The patients in the BB group demonstrated a uniform pattern of change for several YMRS items. Items reflecting brain activation declined first (Item 5: Irritability, Item 6: Rate and amount of speech). Notably, these are core symptoms of mania [17, 25, 178]. Over the following days of the intervention, there was a decline in item-scores reflecting higher cortical processes: cognition, salience, and valence (Item 8: Content of thought/psychotic symptoms and Item 10: Appearance). The clinical symptoms reflecting decline in activation was supported by actigraphy findings of reduced mean motor activity among the BB group.

The worsening of the sleep parameters indicating increased activation for the placebo group could be an iatrogenic effect of hospital light environments. This interpretation may seem bold. Several environmental factors may counteract sleep within a hospital environment, such as unfamiliar surroundings or sounds, coercion and (temporary) loss of autonomy [179-182]. However, the sole difference between the two groups here was a difference in light exposure. Inspection rounds made at night may cause light flashes [182]. Even short light pulses have the capacity to create circadian responses [183]. Awake patients in a manic state are prone to turn on the light, and these are usually much brighter in hospitals than in the home environment. Light exposure at night (in the hospital) may unintentionally counteract the effect of TAU. I have found no published research on the naturalistic course of manic symptoms and motor activity during the first days of a hospital stay. However, it is a common clinical observation that patients in a manic state may present worsened symptoms during the first days of hospitalization. One illustrative case report of a patient with schizoaffective disorder described a switch to rapid cycling and insomnia after hospitalization. The wearing of sunglasses indoors was interpreted as motivated by delusions, and therefore prohibited. When the patient was able to resume wearing amber and green glasses at home on leave from the hospital, the insomnia improved

within a few days [184]. In our study, several patients spontaneously reported themselves to be particularly light sensitive. Within the usual clinical context, these complaints are prone to be interpreted as the patient's delutional attribution of symptoms to random environmental factors, and as such a demonstration of lack of insight. It is also not uncommon to interpret a transient increase of manic symptoms as a function of psychological decompensation. Our data suggest that the hospital light environment could provoke a worsening of manic symptoms.

Item four (Sleep) of the YMRS is a merge of two dimensions: the subjective need for sleep and total sleep duration. No difference between the groups was demonstrated for this item; however, when we analyzed the actigraphy data, we found significant differences in three outcomes reflecting activated and fragmented sleep. Although the total sleep time for the BB group increased by nearly one hour, there was no statistically significant group difference in the sample overall.

Paper II also contributes to the literature on sleep fragmentation and inter-daily variability of sleep for patients with mania [60, 113]. These recent insights into the characteristics of sleep in mania patients suggest a need for revision of the sleep item of the YMRS. Alternatively, a supplementary sleep measure could be added to the scale. It is clear that Item 4 of the YMRS was not constructed to detect sleep fragmentation or poor sleep quality. Because improved sleep quality may reduce total sleep time, this measure may have particularly low validity during BB interventions. We made this interpretation in a previous case report demonstrating markedly shorter but subjectively deeper and objectively less activated sleep along with full recovery from mania during BB treatment [134].

5.1.2 Feasibility of BB-glasses as treatment for manic patients

The participants generally liked the concept of treatment glasses, as shown in the scores presented in Figure 2. The sample in our study had symptoms in the range of moderate mania (mean). Two otherwise motivated patients were unable to comply

with the protocol due to severe mania and hence very short attention span. Six eligible patients either declined to participate or withdrew consent at the first night. We considered that high levels of manic symptoms influenced their decisions. Only eight women were recruited, (of 24 patients), and several women responded that they found all models of the glasses "ugly". We strived to provide many models to satisfy different style preferences; however, the rather sporty designs of most of the models seemed to be preferred by the men. A majority from both groups agreed with the statement: *It was important to have several models to choose from*. This observation is important for utility, particularly in departments without spectrum-controlled dynamic lighting systems. We observed headaches in one patient and three healthy control participants that were clearly associated with the use of the BB glasses. The headache emerged shortly after the start of use and diminished abruptly after discontinuation. Interestingly, two out of the four affected participants had comorbid migraine. Photophobia during migraine is linked to ipRGC signaling [185]. Depressive symptoms were observed in two patients towards the end of the intervention. The emerging depressive symptoms were reversed within hours of discontinuing use of the BB glasses for one patient and by delaying the start of use to 8:00 p.m. for the other. No patient switched to a severe depressive episode. To date, no other studies have reported of side effects of the BB intervention. In sum, we found that blue-blocking by means of wearable glasses was feasible and safe for moderately manic patients, and the design of the glasses might influence patient acceptance.

5.1.3 Motor activity patterns in affective and psychotic disorders

This might be the first study to compare three diagnostic groups (schizophrenia spectrum disorder, bipolar mania, and unipolar depression) from the same acute ward concerning diurnal motor activity patterns. The motor activity characteristics of this new sample of patients with schizophrenia spectrum disorders replicated previous findings with respect to low mean activity, high variability (in 24 h recordings and morning sequences), and high irregularity of the motor activity [152, 157, 186].

However, there are inconsistencies in the literature about variability of motor activity for patients with schizophrenia, which may relate to the epoch-length, time of day, and length of studied time-series [152, 186].

The schizophrenia spectrum patients shared a high minute to minute variability with the unipolar depressed patients (expressed as high RMSSD/minute) in 24 h and morning sequence analyses, but differed with respect to higher mean activity and higher activity irregularity in the same intervals.

Both the schizophrenia spectrum and mania groups had more irregular activity patterns in morning periods compared with the unipolar depressed and the healthy control groups. This is in line with previous research findings, where high irregularity of activity is trans-diagnostically associated with psychotic symptoms and activated states [152, 157, 158, 165]. Notably, 11/18 of the manic patients in paper III had psychotic symptoms.

The mania group were distinct from the other groups by displaying an abnormally constant level of mean activity throughout the day. The finding of a blunted diurnal motor activity rhythm is in line with previous research showing low circadian amplitudes for patients in a manic state [50, 187]. In contrast, the healthy control group demonstrated a markedly higher morning activity and lower evening activity (38% decline). This normal diurnal activity fluctuation was more preserved in the schizophrenia spectrum and unipolar depressed groups.

We observed a characteristic 48 hour-like pattern of wake/sleep rhythms in both groups. The presence of 48-hour rhythms of mood swings and neuroendocrine fluctuations are reported in several previous case reports, and some of these papers included data on motor activity and sleep length [18, 63, 134, 159, 160, 188]. Because the majority of these reports were published before 1990, these patients were mostly described as manic-depressive or in some cases “unipolar” (but cycling). The latter patients would now be regarded as BD-II patients. Instability in wake/sleep cycles has

also been reported for patients with schizophrenia, but there are no similar reports of 48-hour activity rhythms for this group [113, 189]. This particular activity rhythm may be characteristic of patients on the bipolar spectrum and could have potential as diagnostic support. However, before firm conclusions can be drawn regarding the specificity of 48-hour activity rhythms as a bipolar disorder trait, this phenomenon needs to be transdiagnotically researched.

5.2 Methodological Considerations and Limitations

5.2.1 Paper I and II

5.2.1.1 The samples

In all papers, the patient samples consisted of acutely admitted patients. The public hospital service in Norway allows for elimination of selection bias due to social disparity. In papers I and II the patient groups were diagnosed with bipolar disorder with a current manic episode. Use of the structured diagnostic interview tool MINI + was chosen to optimize the validity of the diagnosis [164]. The inclusion criteria were otherwise broad: an age-span of 18–70 years and written consent. Only near-complete blindness and ongoing withdrawal symptoms prohibited inclusion. This should speak for high generalizability to the BD-I patient group overall. The mean YMRS scores for both groups were in the moderately manic range, and as a rule, the glasses could not be used by the most severely manic patients. Even when severely manic patients seemed motivated to participate, it was most often impossible for them to adhere to the protocol due to fragmented thinking. The absence of the most severely manic patients in the sample (except for one patient) prohibits a firm conclusion on the effect of BB-glasses for patients with YMRS > 35–60. However, non-inclusion of the most severely ill patients may well have resulted in an underestimation of the effect. Due to moderate YMRS scores as a baseline and a rapid decline in symptoms for the BB group, there may have been a flooring effect (scores could not reduce further) in several of the YMRS items before the end of the observation period.

It cannot be ruled out that the BB glasses might have appealed to a certain type of personality among patients. Differences in outcomes related to personality traits, other individual factors, and environmental factors that could possibly affect the outcomes need to be studied with a larger sample. The location of the VATMAN trial (in the southwest of Norway) should also be considered. Latitude and solar insulation seem to influence endophenotypes and the course of illness [92, 93]. The majority of participants in the VATMAN trial were born and raised at a rather extreme latitude (Norway), which may have had an influence on their responsiveness to the intervention. The patients were recruited all year round over three years, but the sample was too small to compare effect by season. One notion contrary to the large effect being related to latitude is the outcome of the dark therapy pilot study, conducted in Italy, which demonstrated similar results [128]. In the future, a comparison of effect according to latitude and season may be possible.

Selection bias from previous knowledge and interest in BB interventions was unlikely. Only two patients were ineligible because of previous knowledge on the possible effect the BB glasses. Due to growing interest in the effects of blue light in the popular science media, the inclusion of patients in the study was terminated in February 2015 because of the risk of a selection bias. Beyond this time, the study design would have been hampered by the systematic exclusion of the best-informed patients.

The healthy controls were recruited from the VATMAN trial. Nearly all (42/45) were employed and as such may have been generally healthier than the normal population. The majority worked in hospital wards and some worked on alternating morning or evening shifts. This may have imposed a bidirectional influence on motor activity; both regularization because of daily obligations, but also more variability due to irregular work hours for some of the participants.

5.2.1.2 Research design

As the first attempt to measure the effect of BB glasses in a sample of manic patients, the RCT design was added to TAU in a naturalistic setting. The resulting study on effectiveness has a high degree of generalizability to the usual setting of clinical treatment for manic inpatients. The design however prohibited a precise effect-estimate due to multiple confounding sources, in particular from variations in TAU.

The choice of lens properties for the BB glasses was based on previous studies demonstrating preservation of melatonin by blocking nearly all light with wavelengths shorter than 530 nm [5, 6] Using the same intervention interval (6:00 p.m. to 8:00) a.m. as well as the adjunctive (to TAU) design optimized the comparative value.

5.2.1.3 Treatment as usual

Differences in medication per TAU are shown in Table 1. Because of the strictly naturalistic design, the medication was adjusted based on a day-to-day assessment of symptoms by the treating doctor who was not involved in the study. This meant that the placebo group was more intensively treated because they were persistently more symptomatic for the duration of the intervention. Conversely, two patients in the BB group were moved to a less-intensive level of care during the observation period. This coincided with a transient increase in YMRS scores. This obvious source of confounding variables was accepted in the planning and conduct of this trail, because a stricter efficacy study with no additional medication would have been unethical (based on there being no preceding studies on the effect of BB intervention for mania patients). In addition, no single TAU works for all patients, and standardized treatment for one week could have delayed improvement for some. However, relocating the less symptomatic patients out of the acute ward could have been avoided, and in this respect, the naturalistic design was somewhat excessive.

5.2.1.4 The placebo

The placebo condition was given much consideration. In 2011, knowledge was still limited on of effects of various qualities of light, and any type of colored lenses could potentially produce physiological effects, thereby serving as an active intervention. On the other hand, it was essential for the study design that patients could perceive the intervention as a potential active intervention. We sought to solve this dilemma by choosing clear placebo glasses and inform the patients in both groups similarly; *the study in which you participate aims to compare the effect of glasses that block different wavelength of light*. This same approach was used in a more recent study involving a BB intervention and a placebo [143]. Very importantly, the nursing staff and treating doctors were instructed to treat both groups the same way concerning reminding them to adhere to the protocol. People in a manic state are more irritable and less socially conforming than their euthymic self; therefore we inferred that the placebo was valid as long as the patients adhered to the protocol. The by-chance event that no patient could observe the other type of glasses on a fellow participant eluded debate with regard to the color of lenses.

5.2.1.5 Randomization and blinding

Allocation to the groups was made simply by the manual drawing of folded patches, performed by someone not otherwise involved in the trial. The groups were similar with respect to medical history and lifetime severity of the illness. The placebo-group was slightly higher in YMRS rated symptoms at baseline and somewhat older than the BB-group; a difference we regarded could not explain the outcomes. In an ideal RCT design, participants and rater are both blinded to the group assignment; however, the VATMAN trial was only single-blinded. As for most other chronotherapeutic interventions, the visibility of the intervention made double blinding practically impossible. This problem together with the countermeasures taken to reduce the probability of rater bias are both thoroughly discussed in Paper I.

5.2.1.6 The validity of measures

The Horne-Östberg Morningness-Eveningness Questionnaire is a validated and commonly-used rating scale for morning or evening preference, translated to Norwegian by Idalill Udnes et al. [166, 170]. The Seasonal Pattern Assessment Questionnaire was first published in 1984 and is widely used for assessing SAD symptoms [167-169]. From this questionnaire, the sub-score GSS is derived, which provides an operational score for assessing SAD symptoms [168].

The primary outcome in the VATMAN trial was YMRS total score. The YMRS is the most widely used mania rating scale, with high validity and substantial interrater reliability [1, 190]. Despite some weaknesses (such as the comprised item 8 that encompasses symptoms from hyper-creativity to grandiosity and hallucinations), by using this we were able to compare our results to the majority of previous studies on mania treatments. Most importantly, this scale was used in the preceding dark therapy pilot [128].

The secondary outcome motor activity (by actigraphy) was added as an objective measure to support the clinical YMRS ratings in Paper I, and as such increased the validity of the findings. To increase the likelihood of patient acceptance, the placement on either wrist was accepted. Placement on either the dominant or non-dominant wrist is equivocal concerning wake/sleep estimates as validated by polysomnography; however, the position of the actigraph may have influenced other activity outcomes [191, 192].

The actigrah device could potentially provoke suspicion, and thereby influence symptoms. To inform on this, a statement regarding the perception of the actigraph device was included in the patient experience self report form. Most patients disagreed to the statements: *I was suspicious about the Actiwatch* and *Wearing the Actiwatch was irritating*. This indicated that the actigraphy-recording did not increase psychotic or manic symptoms.

Actigraphy is regarded as a valid measure of motor activity and as a source of data for wake and sleep, but may overestimate sleep when the subjects are lying quietly but still wake [117, 155]. For the group of patients hospitalized with mania, some medications may have reduced locomotor activity but failed to induce sleep. To reduce error regarding estimated sleep intervals, the raw data was inspected and validated with data regarding lights being switched on and off, and nurse reports on wake and sleep [171, 192]. For the sake of transparency and reproducibility, the rules that were applied for setting manual rest intervals were detailed and published as supplemental material for Paper II.

5.2.2 Paper III

5.2.2.1 The sample

To optimize diagnostic validity, at least three specialists provided a diagnose consensus for each patient (two specialists had thorough knowledge to the patient's history and symptoms). With regard to the generalizability of finings, two aspects require consideration. The unipolar depressed patient group was selected based on clinically assessed motor retardation. As such, the outcomes in motor activity only applied to this endophenotype of unipolar depressed patients. The schizophrenia spectrum group was made very broad. In addition, there were some overlap with affective symptomatology due to the inclusion of the intermediate category of schizoaffective disorder. The finding of no significant differences in motor activity compared to the mania group may be a consequence of the heterogeneity of the schizophrenia spectrum group.

5.2.2.2 Research design

The cross-sectional design was suitable for the purpose of describing and comparing activity patterns of specific diagnostic categories. As such, the study was grounded

within a tradition of descriptive psychopathology advocated by Kraepelin more than 100 years ago [15].

5.2.2.3 Validity of measures

Actigraphy has limitations with regard to monitoring complex movements or local movements that do not involve the limb used for the placement of the recording device [155]. The device may also evoke suspicion with regard to surveillance beyond the presented purpose [155]. However, in the VATMAN trial, (where a majority of the patients had experienced psychotic symptoms), most patients indicated that the device did not make them suspicious.

5.2.2.4 The treatments as a confounding source

The somewhat constrained hospital environment could have contributed to the significantly lower levels of activity over the 24 h period in all patient groups compared with the heathy control group. The finding of low activity mean (even for the mania group), is in line with other research performed in hospital environments [59].

The possible confounding of psychotropic medication was given much consideration. Besides targeting activation and affecting general cortical function, medication may produce side effects involving the motor system, such as tremor or involuntary movements [193, 194]. In modern practice, side effects causing motor disturbance are usually corrected quickly. Here, the question was whether medication was responsible for the group differences. Unsurprisingly, the medication profiles differed somewhat between patient-groups, with main differences being more antidepressants and less antipsychotics prescribed for patients in the unipolar depressed group and more patients using mood stabilizers in the mania group. For the affective disorders in particular, treatment is often aimed at normalizing dysregulated activation. This means activating motor retarded depressed patients and calm those who have manic symptoms; hence, to *reduce* the differences between the groups. We therefore argued

that the differences in the psychotropic medication could not fully explain the results. The literature provides little information on this issue; however, one study identified lower circadian amplitude in a sample of manic patients regardless of their medication profiles [187]. A degree of confounding influence from medication cannot be ruled out, but the fact that we could identify different constellations of activity patterns in a naturalistic environment of ordinary clinical practice argues for real motor activity differences, which the medications could not erase. Lastly, controlling for treatment with antipsychotics did not change the main findings.

5.2 Statistical considerations

The research in all three papers involved relatively small sample sizes prone to type II error (wrongly confirming of the nil hypothesis) due to lack of power. Analysis of actigraphy data is particularly susceptible to this issue because of the inherent large degree of variability.

The demographic variables from patient groups in the VATMAN trial were not tested for statistically significant group differences. Because the procedure of allocation secured random group assignment, a statistically significant difference in demographic variables would be a by-chance event. Group differences in age and YMRS at baseline were regarded as insufficient for explaining the differences in outcomes.

In Paper I, linear mixed model analysis was considered appropriate for the design and purpose of testing the effect of a novel intervention. The linear mixed model allows the inclusion of drop-outs in the intention to treat analyses for each analyzed time point (day) during the trial [195]. This method is conservative, being more likely to underestimate rather than overestimate effects [195].

In Paper II, ANCOVA analysis at night five (adjusted for outcomes at night one) was chosen because of small sample size and no baseline data for sleep parameters. Night five was used as time-point for the analysis because of two drop-outs that occurred after that point. We regarded these drop-outs as a consequences of the patients

receiving placebo intervention rather than the BB intervention. In one case, the patient stopped believing in the placebo, and in the other case the increasingly manic patient demanded discharge from the hospital. At night five, the integrity of the design was still largely intact and the sample sizes were still sufficient for meaningful analysis of the actigraphy data.

Paper III involved multiple analyses and it could be argued that the p-value should have been adjusted accordingly. Despite pre-planned analyses, multiple testing involves an increased chance of statistically significant findings from single analysis. However, the study was exploratory in nature, and the use of multiple mathematical analyses for studying the same phenomenon (such as activity complexity) was a means of increasing the interpretive value.

5.3 Ethical considerations

All studies included in this thesis were conducted in accordance with the Helsinki Declaration, and involved written inform consent from all participants who were allowed to redraw their participation at any time before the analyses [196]. To ensure that the patients had capacity to grant their written informed consent in the VATMAN trial, the full written information and consent was obtained when the patient was no longer in a manic state, as approved by the regional ethical committee (Regional Etisk Komite, REK). This meant that eligible patients were given limited information that was considered sufficient for preliminary decision to participate. If patients agreed to participate, they were then recruited and underwent the protocol; however, the data were not included in the analyses unless written consent was obtained. In the answers to the patient experience self-report form, a clear majority agreed to the statement: *Participation in the project was a positive experience*. This contributed to the general impression that the participation added meaning to the otherwise difficult situation. Also, the participation was voluntary and thereby fully controllable, unlike some other aspects of hospitalization.

6.0 Possible mechanisms

6.1 Activation and motor activity patterns

First, the construct activation needs some elaboration. The definition by Scott et al. was strictly descriptive for the purpose of reviewing the objective evidence for motor activity disturbance in bipolar disorder [9]. The neuronal circuitry underlying normal and deviant activation is complex, and the term has several different aspects involving various neuronal circuits and functions, such as control, periodicity, dynamics and subjective experience of energy [9]. Net activation, as measured by actigraphy from some part of the body, is the result of the interplay between different systems as put by Steele and Mistlberger,"Activity is a slave to many masters" [197]. The arousal system is one of the most powerful of these, and serves as a prerequisite for consciousness [8]. The arousal system enables the individual to respond to stimuli from the environment [198]. If the individual perceives a major threat, the response options are freeze, fight or flight, through activation of the hypothalamic-pituitary-adrenal (HPA) axis and the symphatoadrenal system (SAS) [199]. Neuroanatomically, the system consists of ascending pathways providing sensory input through the medulla to the monoaminergic brain stem nuclei [198]. These nuclei have widespread axonal projections to the cerebral cortex, basal ganglia and forebrain, which–by the expression of the monamines noradrenaline, dopamine, serotonin, histamine and acetylcholine–promote wakefulness, alertness and goal- directed activity [198]. The descending pathways from the hypothalamic nuclei of the forebrain provide multiple homeostatic input to the monoaminergic nuclei, such as the orexin neurons of the lateral hypothalamic nucleus activating the monaminergic nuclei, which promote wakefulness [8]. This pathway is essential in the regulation of wake and sleep [200]. Activation of the arousal system during wake and non-REM sleep increase motor activity, and in particular the tone of posture muscles [198, 200].

The different brainstem nuclei of the arousal system have differential connectivity, and it is beyond the scope of this thesis to detail this extensively; however, some connections need more description. The locus coeruleus, which is central in bipolar disorder, is a hub of the arousal system activating the HPA axis and the sympathetic nervous system, and sensitizes the brain to novel stimuli [201, 202]. According to fMRI studies by Vandewalle et al., blue light stimulus seems to increase the signal from the locus coeruleus [203, 204]. The connectivity from the retinal ipRGCs to the locus coeruleus in the brain stem is not fully mapped; however, the hypothalamic nuclei of the arousal system projecting to the brain stem are extensively innervated by ipRGC projections [75]. The light information from the ipRGCs is in principal sensory (like information on sound, touch, pain, smell and taste) as in the ascending pathway, but same time (day)light signals relay through the hypothalamic nuclei of the forebrain involved in homeostatic control (descending pathway). Given recent insights on the activating effects of light stimuli, input from the ipRGC projections should be considered for inclusion in the schematic of the arousal system in the future [205].

The generalized arousal system can be differently tuned based on genetic variance, as illustrated by differences in sensitivity to stimuli observed in both humans and non-human animals of the same species [8]. Also the net strength of the incoming signal may differ, as seen in conditions involving disturbances in the gating of sensory information such as in schizophrenia and autism [206]. Additionally, internal stimuli contribute to hyper-arousal in some mental illnesses, such as intrusive memories in post-traumatic stress syndrome and hallucinations in schizophrenia [17, 207].

One theory on the function of the generalized arousal system seems particularly useful for translating arousal functions to motor activity patterns [198]. The firing pattern of neurons in the resting state is complex and chaotic, but such a system can mobilize rapidly and facilitate rapid transitions from sleep to wake to goal-directed behavior [198]. Non-linear mathematical methods, as applied in Paper III, are useful for assessing the degree of complexity as in the resting pre-action state [8]. On the

transition to goal-directed activity, the firing pattern in neurons and the corresponding motor activity become regular; a transition which happen abruptly, and is similar to the phenomenon of chaotic molecules in the liquid phase turning into a very orderly solid structure at the critical temperature [8]. As water close to the freezing point, the resting arousal system seems to be tuned to the brink of "criticality", to be ready at all times to take directed action. In the model by Pfaff et al., the threshold from rest to ordered goal-directed activity happens at a certain level of (sufficient) arousal [198]. However, as the same authors mention in a later paper, the optimal level of arousal is *moderate*, as hyper arousal leads to reduced function if a task is complex [8]. The empirical relationship between arousal and performance is called the Yerkes-Dodson law, which is usually presented as a dome, illustrating decrease in performance beyond an optimal level of arousal [208]. This law is particularly applicable for mental disorders that often involve hyper-arousal. Due to transient or chronic cognitive impairment, many tasks may be complex for the brain of a severely manic patient or for a patient with schizophrenia [209]. Hyper arousal prohibiting transition from the pre-action state to the active, goal-directed, ordered state could provide a theoretical explanation for the chaotic and complex motor activity patterns seen in the manic and the schizophrenia spectrum groups in Paper III and in previous literature.

Several studies have reported a correlation between agitation and high activity complexity [157, 158, 165]. Mania usually presents with agitation, and approximately 60% of the manic patients in Paper III had psychotic symptoms. Higher scores for positive symptoms (hallucinations and delusions) and excitement in schizophrenia (which may correspond to agitation in mania) have previously been found to correlate most strongly with high irregularity in activity patterns [157].

Dopamine-dysregulation in the striatum (which is part of basal-ganglia) has been implied in psychosis since the discovery that chlorpromazine had anti-dopaminergic effects [210]. Motor dysfunction in schizophrenia has been linked to abnormal function in the cortico-basal ganglia motor pathways, but also more widespread effects

related to altered glutamatergic transmission and demyelination could affect motor function [145, 155, 210-212]. Dopamine receptors continue to be the main target for most anti-psychotic medications, which are the first line treatments for both acute and chronic psychosis as well as for mania [213]. In sharp contrast to mania, schizophrenia may involve negative symptoms, which refer to lack of initiative, interest and emotional response [25]. These symptoms are also part of the depressive syndrome. For both schizophrenia and depression, lack of initiative and low motivational drive have been linked to frontal cortex dysfunction which is associated with reduced locomotor activity [211, 214]. The similar patterns of high variability and low mean motor activity in the schizophrenia spectrum and unipolar depressed groups could reflect some shared dysfunction in the same frontal cortex circuits, however likely through different mechanisms.

An overarching phenomenon that may influence the motor activity patterns for different diagnostic categories may be the differential interplay between circadian activity rhythms and ultradian (dopamine driven) activity rhythms [38]. Although *ultradian* refers to periods shorter than 24 h, in experimental conditions with increasing dopamine availability (in mice) the dopamine ultradian oscillator (DUO) rhythm is extended from 4 h up to 48 h [38]. In Paper II, we described a 48 h pattern of shorter or interrupted sleep, which was previously reported in several rapid-cycling bipolar disorder subjects [18, 38, 63, 188]. An explanation for this particular pattern could be a dysfunctional 48 h dopamine rhythm that disrupts sleep every second night [215].

Since the DUO is tunable (as observed in an animal model), the DUO period could theoretically range from 4–48 hours in humans as well, which could produce a range of frequencies of DUO activity bursts superimposed on the circadian activity rhythm [38]. When adding dysregulated arousal and circadian desynchronization, this could create the variety of motor activity patterns observed; from reduced or blunted circadian amplitude to abnormally rhythmical activity with increased variability [152-

154]. Even in patients with borderline personality disorder (with symptoms not usually perceived as being related to disturbances of biological rhythms), researchers have recently demonstrated abnormal activity variability as well as 4 h cycles of irritability and negative mood [216, 217]. Disrupted circadian function is associated with more severe symptoms, reduced function and reduced quality of life [105, 218]. Actigraphy could be a useful tool for monitoring effect of interventions directed to restore health-promoting biological rhythm function. However, this dimension first needs to be acknowledged more in research and in practical mental health care.

6.2 The BB intervention's effect on manic symptoms

It was not an aim of the VATMAN trial to study mechanisms; however, the results suggested that the BB intervention targeted some basic mechanism of mania. Without any direct neurobiological outcome measures, the following discussion on mechanisms is based on the temporal changes in the clinically observed symptoms, objectively measured motor activity and subjective feedback from the patients. In addition, preexisting theories and findings from both animal and human studies will be discussed, regarding the effects of light on mood, activation, and the bipolar switch process.

6.2.1 Change in light input to the visual cortex

The BB-intervention imposed an abrupt change in the patient's light exposure in several ways. Firstly, could the change in visual perception from harsh white light to warm orange glow have caused a psychological soothing effect? The BB lenses reduced overall visual brightness, altered color perception to an amber hue, and enhanced contrast-vision. Altered stimulation of the visual cortex and psychological responses cannot be ruled out with regards to contribution to the effects, as opposed to ipRGC-influenced responses. To solve this methodological problem, researchers have developed a method of delivering light-stimuli that looks the same but have different melanopic lux, referred to as metameric light conditions [205, 219]. Objectively (EEG)

measured alertness has been shown to be significantly increased during light exposure with high melanopic irradiances, regardless of the visual perception of color [205]. Clearly, the difference between real darkness and virtual darkness is also considerable concerning visual orientation. We first guessed that the effect observed in the dark therapy pilot study was mediated partly by sensory deprivation and reduced mobility. This consideration was taken into account in the power calculation for the VATMAN trial, as the estimated power was set to 0.8, which was half the effect seen in the dark therapy pilot-study by Barbini et al. [128]. We discovered that the effect of virtual darkness on manic symptoms was similar in magnitude to the effect of real darkness. This is indicative that sensory deprivation was not the main mechanism for the effect of dark therapy, and that avoidance of blue light exposure was a likely major factor. However, the small sample sizes of both studies limits the interpretations based on effect size comparison [220].

6.2.2 Improvement of sleep

We observed increased sleep efficiency and improved sleep maintenance in the BB group. Could improvement of sleep be the mechanism through which the BB glasses had effect on overall manic symptoms? The idea that restored sleep mediates improvement in other affective symptoms (through resynchronization of circadian rhythms), has been proposed in several previous publications and is central to the rationale for application of cognitive therapy for insomnia in bipolar disorder [35, 119, 124, 221]. Restauration of regular sleep was a central first hypothesis for the mechanism for the effect of dark therapy [126, 221]. However, this theory is not supported by strong evidence for the directed mechanistic relationship between restored sleep and circadian resynchronization. Sleep is found to yield a relatively week time signal to the SCN [222]. Based on the results in papers I and II, we cannot answer if improved sleep quality mediated improvement in other manic symptoms, or if improved sleep was a coinciding phenomenon mediated by another factor. Planned

analyses on directed associations between YMRS items and actigraphic sleep outcomes may inform on these questions.

6.2.3 Change in timing and regularity of light signal to the SCN

Restauration of a normal circadian rhythm could theoretically have been involved in the recovery mechanism. Notably, the study by Moon et al. suggested that wake/sleep rhythms for hospitalized manic patients were disassociated from the grossly advanced hormonal and peripheral circadian rhythms [50]. This means that with no other measure than motor activity, we do not have information on the effect of BB glasses on circadian rhythms or whether circadian resynchronization preceded mania recovery. Furthermore, the intervention in our study was probably too short to observe changes in circadian function at a group level. Derived from the findings of Moon et al., the imposition of regular darkness periods from 6:00 p.m. likely caused temporary circadian turmoil that would require some time to resolve. Because of the effect observed after only three days, we surmised that the main mechanism was unlikely mediated by circadian resynchronization. In other samples, it is a consistent finding that BB interventions have the capacity to strengthen circadian amplitude by promoting melatonin secretion [5, 6, 133, 135-137]. Future clinical studies on the effects and mechanisms of BB interventions should ideally include multiple measures of circadian rhythms (both central and peripheral rhythms) and longer observations [50].

6.2.4 Deactivation by decrease in blue-light exposure

Several findings accounted for a primary effect through deactivating mechanisms. Scores in YMRS items most related to activation declined first, followed by items assessing cognitive content and ideation. As such, the actigraphy data was in line with the pattern of the clinically rated symptoms as we observed rapid decrease of mean motor activity in the BB group. Several patients spontaneously reported a calming sensation shortly after starting to wear the glasses. Some reported a sudden awareness

of feeling sleepy or exhausted. The rapid calming effect seemed to encourage adherence to the protocol. With the exception of one patient who developed a headache, none of the patients adhering to one night of BB glasses later dropped out of the study.

The direct activating and mood regulatory effects of light are seen in both human and non-human animals [76, 77, 203, 204, 223]. This challenges the current theoretical basis of the chronotherapies for mood disorders; effects through regularization of circadian processes. On the contrary, the mood regulatory effects of light seem to be independent of circadian regularization. Replicated animal studies have recently demonstrated that mood regulatory projections from the ipRGC simply bypass the SCN and project to the habenula/perihabenuar area, a brain area responsive to changes in light conditions and involved in affective regulation [77, 78, 224]. Conversely, it is reasonable to hypothesize that a halted signaling through these projections (due to the virtual darkness condition) could reduce abnormally high activation and elated mood in humans.

Human fMRI studies have shown general brain activation following blue light exposure, starting within seconds as an increased signal in the hypothalamus and an area interpreted as locus coeruleus [203, 204]. From the brain stem, locus coeruleus produces and administers noradrenaline through widespread projections to the cortex and limbic system [201]. Antidepressants increasing noradrenaline availability are prone to provoke manic episodes [202]. Noradrenaline metabolites in the cerebrospinal fluid and urine are higher in manic subjects than in depressed bipolar subjects or healthy controls [62, 159, 202, 225]. Dopamine is another central monoamine in bipolar disorder pathophysiology and has recently been found to be co-expressed with noradrenaline from the locus coeruleus [213]. As such, the fMRI studies by Vandewalle et al. also yield indirect support of effect of blue-light exposure on dopamine availability [204, 226].

The deactivation hypothesis for the effect of BB glasses during mania conforms well to the results of sleep outcomes in Paper II, which showed rapid effects in outcomes related to activation in the sleep interval and sustainment of sleep. Hubbard et al. suggested a three-process model of sleep regulation that was an expansion from the original two-process model by Borberly et al. In the three-process model, environmental light is added as a third separate process to the sleep homeostat (process S) and the circadian component (process C) [227, 228]. This expanded model provides a good theoretical framework for discussing how the BB intervention could promote more sound sleep. Due to its alerting effects, light at night suppresses the effects of high sleep pressure (process S) [227]. Stimulation of the arousal system contributes to holding the wake/sleep "flip-flop switch" (of the hypothalamus and brain stem) in the position that promotes wake [229]. In addition, light at night suppresses melatonin and delays the circadian rhythm (process C) [227]. Again, our data mostly support deactivating mechanisms that may have increased sleep efficiency through disinhibition of the sleep homeostat factor S.

6.2.5 Do the results contribute to insights in the bipolar switch process?

Shortly after the publication of Paper I, Daniel Kripke sent me his paper on the circadian bifurcation theory [68]. I interpreted his communication as his understanding that our findings were somehow in line with his hypothesis on the manic switch mechanism. In the paper, he described a compelling theory of how a possibly unstable SCN of the BD-I phenotype may switch to a double-speed 12 h rhythm, resulting in a two-peak shallow melatonin rhythm and a resultant excessive brain triiodothyronine (T3) secretion via downstream effects [68]. Elevated brain T3 has the capacity to produce many of the core symptoms of mania [68]. This theory is supported by a human study that found two daily peaks of melatonin in a sample of manic patients [230]. There is a lack of other data on the occurrence of a bifurcated circadian rhythm in humans. However, shallow amplitudes of various circadian rhythms during mania are demonstrated, which could be the result of state-dependent bifurcation [50, 187].

In Paper III, we found a constant mean level of morning and evening activity in the group of manic patients, as opposed to the normal morning-to-evening decline. This blunted diurnal activity fluctuation may as well be an expression of two consecutive 12 h periods [231]. Bifurcation of circadian rhythms can be provoked in hamsters and mice by use of extreme photoperiods [232, 233]. After a few days in constant darkness, the bifurcated rhythm switches back to an ordinary 24 h rhythm. [233]. In the VATMAN trial (similar to in the previous dark therapy case reports and dark therapy pilot study) we imposed regular periods of 14 hour darkness from 6:00 p.m. [2, 126-128]. If the patients' circadian rhythm was 2 x 12 h, the BB glasses may have stopped the day signal for the second day-phase of a bifurcated circadian rhythm and switched the patients back to a regular 24 h rhythm. This interpretation is in accordance with the theory of circadian bifurcation in humans by Daniel Kripke et al. [68]. Moreover, the switch back to a normal circadian rhythm could theoretically happen abruptly and provide an explanation for the rapid effects observed in our study.

6.2.6 The essence of photoperiod

Also involving extreme photoperiods, a breakthrough paper published in 2013 may have brought us closer to resolving the puzzle of affective switch mechanisms. The study by Dulcis and colleagues showed that in response to extreme photoperiods, mature hypothalamic interneurons of adult rats have the capacity to change *morphology*, and as such serve as a mood switch [67]. Later research has replicated the findings, and the neuronal mechanisms are now under further investigation [234-236]. These switching neurons are innervated by ipRGC projections. The long day photoperiod (19 h light (L)/5h dark (D) promoted a predominance of somatostatin expression, whereas the short day (5L/19D) promoted dopamine expression. This process of switching cell morphology required one week of the extreme photoperiod condition to happen. Behavioral testing showed that increased dopamine expression was associated with more running around, less anxious behavior and more risk taking, whereas somatostatin promoted opposite behaviors associated with depressive

functioning. The two cell-types of the switch have an antipode downstream effect on the corticotrophin releasing factor (CRF). Somatostatin increases CRF and corticosterone release in rats. In bipolar disorder, hypothalamic-pituitary-adrenal-axis abnormalities are evident [237, 238]. Interestingly, in several case reports on rapid cycling bipolar disorder, longitudinal monitoring of cortisol metabolites has demonstrated fluctuations in cortisol levels in line with the findings of Dulcis et al. showing lower cortisol-metabolites on days of mania and higher levels during days in depression [159, 188, 239-242]. Dulcis and colleagues infer that the findings in nocturnal animals could easily be translated to diurnal humans, only for humans a long photoperiod would elicit a switch to dopamine expressing cell morphology, suppressed CRF and vice versa. There might still be significant differences in neural function or neural connectivity between rodents and humans prohibiting firm translational conclusions regarding the issue of neuronal switching [243]. However, one post-mortem human study from Scotland demonstrated clear seasonal variation in the number of mid-brain dopamine cells. In five people who had died in the summer, there was a significant and six-fold higher number of cells positive for tyrosine hydroxylase (the rate limiting enzyme for dopamine production), compared to five people who died during the winter months [244]. This first human study on photoperiod-associated differences in dopamine cell expression was clearly in support of the translational value of the animal studies on photo-period-induced transmitter switching.

6.2.7 Manic state—light exposure positive feedback loop

Taken together, results from many lines of clinical research and animal studies support that light is a central environmental trigger of manic episodes [68, 70, 90, 92]. Our data suggest that BB-intervention 6:00 p.m. to 8:00 a.m. alleviates mania and improves sleep, sequentially first through deactivating mechanisms.

Light from electric sources is nearly always present in hospital wards. Patients in a manic state feel rested after a short sleep and are usually active shortly after waking regardless of the hour. It is therefore likely that wake and light exposure as a rule are

coupled for manic patients. The bifurcation hypotheses of Kripke, and the findings of photoperiod-induced switching of hypothalamic neurons imply that all sleep disturbing events could initiate a manic episode in BD-I phenotypes by causing aberrant light exposure and prolongation of the photoperiod [67, 68, 118]. Several researchers have described the likely existence of a mania self-sustaining process, involving poor sleep as both the trigger and sustainer of the manic state [119, 126, 221, 245, 246]. As an alternative common factor, light exposure (caused by wake at night), has previously been suggested by some authors [68, 189]. Nevertheless, this perspective has generally been missing. In the present hypothesis, (blue) light exposure (as a concomitant of wake/non-sleep) is replacing sleep problems (per se) as a causative mania-sustaining factor. Light is a much more potent disrupter of circadian rhythms than sleep-loss in isolation [222]. Light has rapid activating effects as well as transmitter-switching effects [67, 88, 204]. Change in sleep pattern will most often affect light exposure. For example, a 48 h wake/sleep pattern is prone to causing a long photoperiod every other day. An emerging manic state may be fueled by the continued reinforcing feedback loop created by the manic sleep disturbance and the resultant exposure to aberrant light cycles. The BB intervention could be effective by halting a manic state—light exposure feedback loop by providing (virtual) darkness during waking in the biological night.

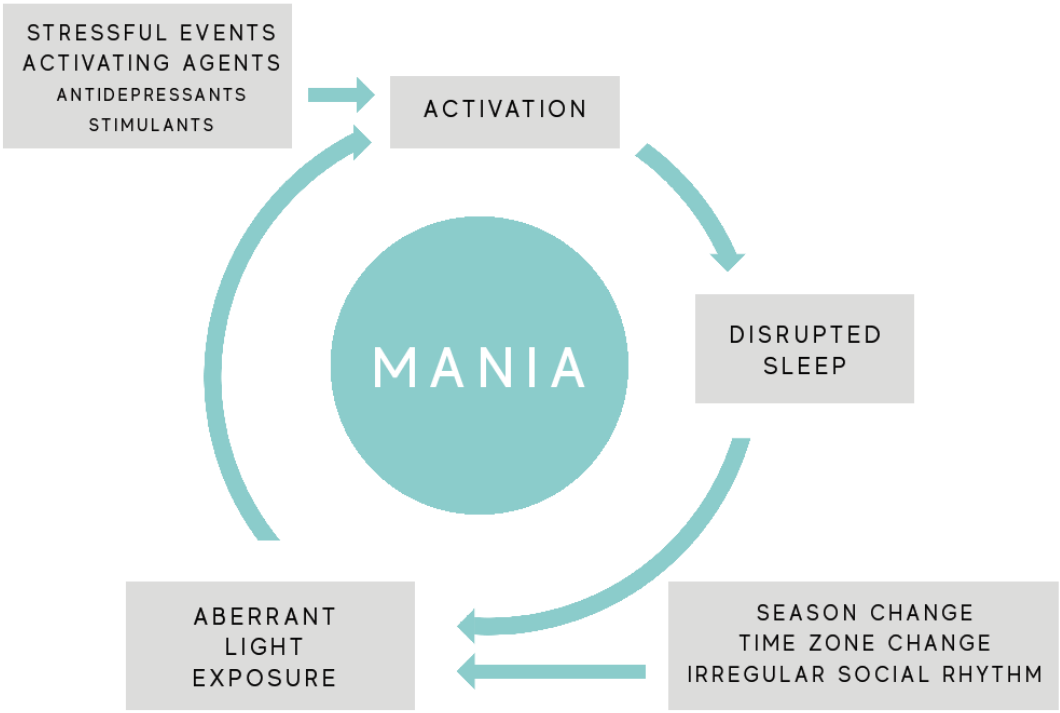


Figure 3A. How stress, activating agents and change in light exposure may initiate a reinforcing mania-sustaining feedback-loop by the interaction of disrupted sleep–more light exposure and activating effects.

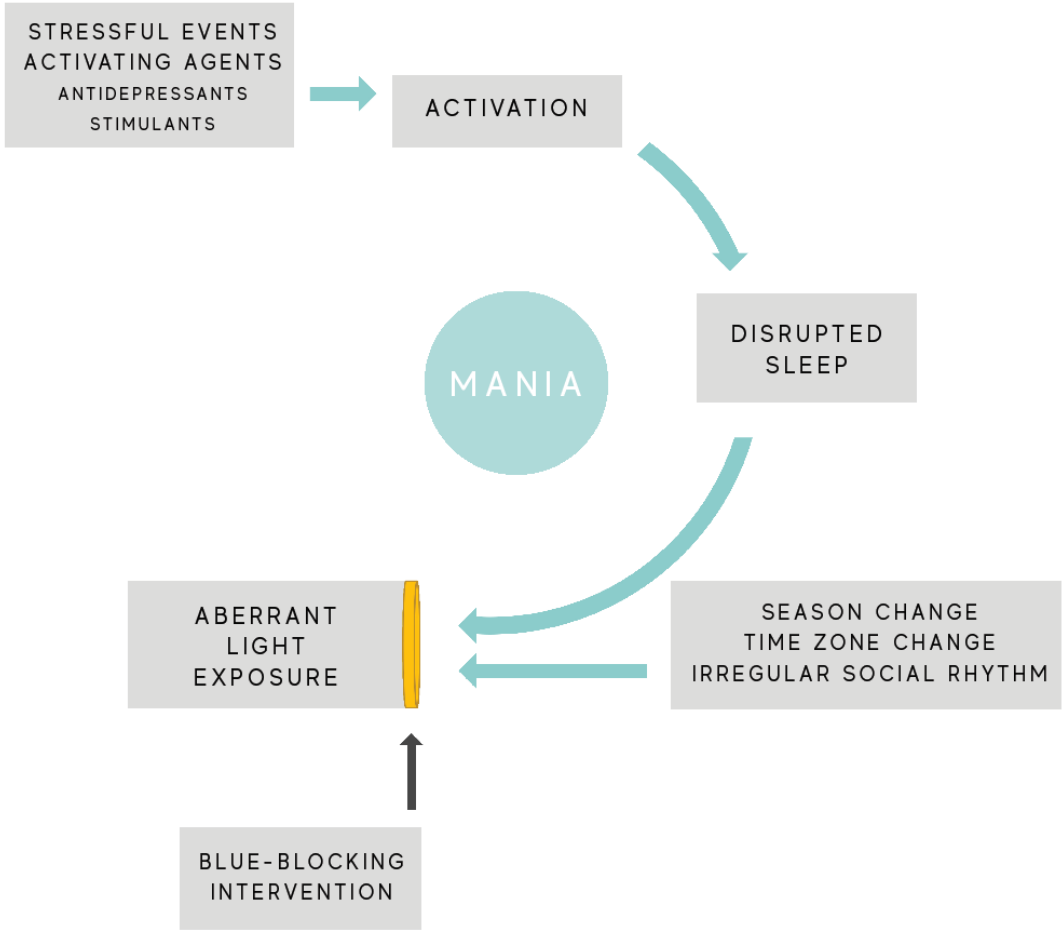


Figure 3B. How the blue-blocking glasses may stop the mania sustaining process by uncoupling wake and activating light-exposure in the evening and night.

7.0 Conclusions and implications

We found that BB-glasses was effective and feasible as an adjunctive treatment for mania. Sleep efficiency was higher and sleep maintenance was better in the BB group than in the placebo group. The rapid and large effect on overall manic symptoms was likely mediated through deactivating mechanisms. The observation time was too short to detect changes in the circadian phase of the wake/sleep patterns. Concerning previous theories on basic pathophysiological mechanisms of mania, the actigraphy findings and observations in papers II and III could support both the circadian rhythm bifurcation theory and influence of a magnified and prolonged dopamine oscillator rhythm. The results in papers I and II, as well as new insights in the effects of light from multiple lines of research, suggest the presence of a manic state—light environment positive feedback loop. The BB intervention may be effective by uncoupling wake from (melanopic) light exposure.

Paper III contributed more evidence for the utility of actigraphy to discriminate between different psychiatric symptoms and diagnostic entities. We replicated previous findings of high activity complexity and high activity variability in the schizophrenia spectrum group [152, 157]. All patient-groups demonstrated reduced morning-to-evening fluctuation in activity; however, for the mania group this rhythm was completely blunted. The diagnostic categories of schizophrenia spectrum disorders, bipolar mania and unipolar (motor retarded) depression all showed different constellations of motor activity patterns which we regard have discriminative potential. The inclusion of analyses on wake/sleep rhythms and circadian function may increase the utility of activity monitoring for diagnostic support and for assessment of treatment response [154, 155].

The results from the VATMAN trial have contributed to local changes in clinical practice both in Norway and abroad, and encouraged more research on effects of hospital light environments [144]. In April 2018, a *Mini Metodevurdering* (evaluation

of evidence, risks, costs, and ethics of a new therapeutic procedure) of *Virtuell mørkebehandling ved bipolar lidelse* (Virtual darkness therapy for bipolar disorder) was published at Folkehelseinstituttet, a governmental source of information on research, treatments and practices [247]. Paper I provided data on effectiveness and side effects (risks). Several Norwegian health authorities have decided to advice on implementing BB interventions in ordinary hospital practices for patients with bipolar disorder in a manic state. Paper I was also included in a recent review on chronotherapies for bipolar disorders from the ISBD Chronobiology Task Force, in which dark therapy (including BB interventions) were recommended as part of the ordinary hospital treatment for bipolar disorder mania [3].

Besides the acute effects on manic symptoms, the BB intervention may change how people with a bipolar constitution perceive themselves. The narrative of having a disorder that involves “hyper-responsiveness” to a natural condition; light, is very different from being a victim of an incomprehensible illness causing meaningless unforeseen mood swings.

Source of data

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BIPOLAR DISORDERS

Original Article

Blue-blocking glasses as additive treatment for mania: a randomized placebo-controlled trial

Henriksen TEG, Skrede S, Fasmer OB, Schoeyen H, Leskauskaite I, Bjørke-Bertheussen J, Assmus J, Hamre B, Grønli J, Lund A. Blue-blocking glasses as additive treatment for mania: a randomized placebo-controlled trial.
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Objectives: The discovery of the blue lightsensitive retinal photoreceptor responsible for signaling daytime to the brain suggested that light to the circadian system could be inhibited by using blue-blocking orange tinted glasses. Blue-blocking (BB) glasses are a potential treatment option for bipolar mania. We examined the effectiveness of BB glasses in hospitalized patients with bipolar disorder in a manic state.

Methods: In a single-blinded, randomized, placebo-controlled trial (RCT), eligible patients (with bipolar mania; age 18–70 years) were recruited from five clinics in Norway. Patients were assigned to BB glasses or placebo (clear glasses) from 6 p.m. to 8 a.m. for 7 days, in addition to treatment as usual. Symptoms were assessed daily by use of the Young Mania Rating Scale (YMRS). Motor activity was assessed by actigraphy, and compared to data from a healthy control group. Wearing glasses for one evening/night qualified for inclusion in the intention-to-treat analysis.

Results: From February 2012 to February 2015, 32 patients were enrolled. Eight patients dropped out and one was excluded, resulting in 12 patients in the BB group and 11 patients in the placebo group. The mean decline in YMRS score was 14.1 [95% confidence interval (CI): 9.7–18.5] in the BB group, and 1.7 (95% CI: −4.0 to 7.4) in the placebo group, yielding an effect size of 1.86 (Cohen's *d*). In the BB group, one patient reported headache and two patients experienced easily reversible depressive symptoms.

Conclusions: This RCT shows that BB glasses are effective and feasible as add-on treatment for bipolar mania.

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Bipolar disorder is a serious mental illness with a prevalence of approximately 1% (1). Bipolar I disorder is characterized by manic and depressive mood swings. Patients in an episode of mania present with symptoms of elevated mood, irritability, increased energy, risk-taking behaviour, sleep disturbances, and changes in thoughts and perception, sometimes to the level of psychosis. Patients with bipolar disorder have the highest suicide rate (20%) amongst all those with psychiatric disorders (2). Manic episodes are associated with a particularly high risk of injury and death from accidents, as well as social, economic and professional damage (3). A full-blown psychotic mania also increases the risk of a subsequent depressive episode (4, 5). Effective treatment of manic episodes is therefore of high clinical importance.

Current treatment of bipolar mania rests heavily on the use of mood-stabilizing and antipsychotic agents, the effects of which are slow in onset. The duration of manic episodes is several weeks on average (6, 7). This fact alone is a strong indication that the current treatment options do not target the most elemental mania-sustaining mechanisms.

Recent research supports the common clinical experience that bipolar episodes are provoked by changes in light conditions (8, 9). Also, there is supporting evidence for seasonality in bipolar disorder, and symptoms of bipolar disorder are closely linked to abnormal circadian rhythms (10, 11).

The light/dark cycle is the strongest synchronizing environmental signal to the 'master clock' of circadian rhythms, the suprachiasmatic nucleus (SCN) located in the hypothalamus. Light through the eye signals daytime to the SCN, which in turn inhibits production of the 'dark hormone' melatonin in the pineal gland (12).

Dark therapy (DT) aims to synchronize circadian rhythms by placing patients with mania in a completely dark room for 14 hours during the night. DT has been described to have striking effects in two case reports and one pilot study (13–15). However, total darkness provides a broad range of sensory deprivation that may cause serious adherence problems, particularly for patients in a manic state.

During the last three decades, a specialized retinal ganglion cell type responsible for detecting and conveying the daylight signal to the brain has been identified and characterized. These cells, termed intrinsically photo-responsive retinal ganglion cells (ipRGCs), contain the blue light-sensitive photopigment melanopsin (16). In addition to direct signalling of the light/dark status of the environment via ipRGC-SCN projections, ipRGCs connect with several other regions of the brain, including the limbic system, striatum and brain stem (16). Aberrant light conditions have been demonstrated to affect mood and cognition both through the fast-acting direct pathways in the ipRGC circuits and indirectly via effects on circadian rhythms and sleep (16).

The fact that a narrow spectrum of light (blue light) constitutes the daylight signal can be exploited in a therapeutic setting. Preventing blue light from entering the eye has been demonstrated to create a state of virtual darkness in the brain. Wearing orange glasses (blue-blockers) in white-light environments (17, 18), or using light during the night-time without wavelengths below 530 nm (19), has been shown to preserve melatonin production, similar to the melatonin profile for subjects in darkness.

In a 21-patient case series describing euthymic patients with bipolar disorder wearing orange glasses in the evening, 50% of the patients reported improved sleep during the intervention (20). Similar findings have been reported in one patient with schizoaffective disorder (21), in one patient with mania (22), and in one patient with bipolar II disorder (23).

In this RCT, we examined the effectiveness and feasibility of blue-blocking (BB) glasses as an add-on treatment in reducing symptoms of mania in hospitalized patients with bipolar disorder. The main hypotheses were: BB is effective in treating manic symptoms and, furthermore, BB is feasible as a treatment for patients in a manic episode. The primary outcome was change in manic symptoms. The secondary outcome was change in motor activity. Finally, the feasibility of BB was assessed through a patient experience self-report form and monitoring of side effects.

Patients and methods

Study design

The study was a multicentre randomized placebo-controlled single-blinded study. Patients were recruited from five hospitals in the south-west of Norway, latitude 58–59′N. Patients were recruited from Valen Hospital and Folgefonn District Hospital from 1 February 2012, from Haugesund Hospital and Haugaland District Hospital from 20 August 2012, and from Stavanger University Hospital from 20 August 2014. Healthy controls were recruited from the same locations and in the same periods of time as the patients. The study was terminated on 15 February 2015.

Eligible patients were those admitted to hospital with manic symptoms and bipolar disorder according to the Diagnostic and Statistical Manual of Mental Disorders, 4th edition, Text Revision (DSM-IV-TR) criteria (24), and aged 18–70 years. Exclusion criteria were previous knowledge of BB glasses, not consenting to participate, daily use of beta blockers, nonsteroidal anti-inflammatory drugs (NSAIDs) or calcium antagonists, and severe eye disease or traumatic injury affecting both eyes. In the case of withdrawal symptoms from any drug or alcohol at the time of admission, the start of the intervention was delayed until withdrawal symptoms had ceased. Recruiting doctors were not involved in the ordinary treatment of the participants. Inclusion criteria for healthy controls were age 18–70 years and written informed consent to participation. Exclusion criteria were diagnosis of bipolar disorder and previous or current night-shift work, and were otherwise the same as for patients. Previous knowledge of BB glasses was not an exclusion criterion for healthy controls.

Data from the literature were scarce with regard to previous trials using DT and nonexistent with regard to BB in patients with mania, making power analysis difficult. Based on the DT study (large effect sizes 0.9–1.6; Cohen's *d*), a power analysis indicated that, for a probability level of 0.05 (two-tailed) and power set at 0.80, 21 patients in each group would be sufficient to detect a significant difference (15).

However, after 3 years of recruitment and with a total number of 24 patients included for the intention-to-treat analysis, inclusion was ended due to the increasing risk of a selection bias because of the growing public awareness of the effects of blue light and BB glasses.

All patients who adhered to the protocol (used the glasses from 6 p.m. to 8 a.m.) for at least one evening, night and early morning were included in the intention-to-treat analysis. One patient in the BB group was excluded from the analysis because of withdrawal symptoms from benzodiazepines at the start of the intervention.

Ethics

The procedures were approved by The Regional Ethical Committee in Norway (REK) and were in accordance with the Helsinki Declaration. REK approved the use of delayed consent for the participating patients. All subjects granted written informed consent after receiving a full description of the study.

Randomization and masking

Included patients were randomly assigned to wearing either orange glasses (BB) or clear glasses (placebo), by use of manual drawing from a fixed number of folded patches. Secretaries not otherwise involved in the trial made the allocation. The participants were masked to group assignment by receiving identical limited information about the purpose of the study: testing the effectiveness of different types of glasses in reducing manic symptoms by blocking different wavelengths of light. No patient observed other patients wearing glasses of a different colour during the trial. Patients did not have access to the internet. The persons assessing day-to-day mania symptoms and analysing the data were not blinded to group assignment.

Procedures

Patients were diagnosed by experienced psychiatrists trained in the use of the Mini International Neuropsychiatric Interview-Plus (25). All patients were physically examined for severe impairment of vision. The BB group wore orange glasses (LowBlueLights.com, University Heights, OH, USA), and the placebo group wore clear-lensed glasses (Uvex, Furth, Germany and 3M, Austin, TX, USA) from 6 p.m. to 8 a.m. for seven consecutive days. The transmittance spectra of the intervention glasses are shown in *Supplementary Fig. 1*. For both groups, the intervention was given in addition to treatment as usual (TAU) (Table 1). Participants were instructed that the glasses could be taken off when turning out the light at bedtime and should be put on if turning on the light before 8 a.m. In both groups, the patients were offered a choice between different models of glasses.

The patients' manic symptoms were scored daily by use of the Young Mania Rating Scale (YMRS) (26) at the time of nurse reports from the day shift (2 p.m.). Doctors trained in YMRS scoring rated all participants and all ratings were performed as a consensus together with at least one trained member of the nursing staff who had attended the patient on the day of assessment. The score for each item was assigned on the basis of the highest level of symptoms, regardless of duration, during the 24-hour interval starting at midnight. If symptoms increased from 2 p.m. to midnight, the score was adjusted by the doctor responsible for the scoring.

By use of a wrist-worn actigraph (Actiwatch Spectrum; Philips Respironics, Inc., Murrysville, PA, USA), motor activity was continuously

Table 1. Individual medications and outcomes for patients assigned to blue-blocking glasses or clear glasses (placebo)

Patient no.	Antipsychotics Mean dosage (mg/day)	Anticonvulsants Mean dosage (mg/day)	Lithium Mean dosage (mg/day)	Anxiolytics/hypnotics/sedatives Mean dosage (mg/day)	Day of study exit	Delta YMRS
Clear glasses (placebo)						
1	Olanzapine 5.6 Quetiapine 600.0	Valproate 837.5		Diazepam 21.3 Zopiclone 15	7	−5
2[a]	Quetiapine 200.0				7	−12
3		Valproate 3300.0	Li sulfate 84.0	Zopiclone 7.5 Alimemazine 40.0	7	0
4		Valproate 600		Oxazepam 31.25 Cetirizin 10.0	1	17
5[a]	Haloperidol 6.25 Levomepromazine 50.0	Valproate 1537.5		Diazepam 10.0 Zopiclone 7.5	7	11
6	Haloperidol depot 50.0 (every 14 days) Chlorpromazine 162.5		Li sulfate 119.9	Diazepam 16.3	7	−1
7	Haloperidol 0.75 Olanzapine 22.5	Carbamazepine 325.0		Diazepam 34.4	7	1
8	Olanzapine 20.0 Quetiapine 100.0		Li carbonate 1200.0	Oxazepam 17.0 Zopiclone 3.3 Alimemazine 10.0 Cetirizine 10.0	6	−15
9	Chlorprothixene 123.1 Olanzapine 23.6			Oxazepam 10.0	7	−7,5
10	Levomepromazine 6.3 Olanzapine 3.8		Li sulphate 166.0	Diazepam 5.0 Melatonin 0.5	7	0
11	Aripiprazole 9.0 Quetiapine 30.0 Zuclopenthixol 10.0	Valproate 936.0		Cetirizine 10.0	5	12
Blue-blocking glasses						
12	Quetiapine 250.0	Valproate 1200.0		Diazepam 10.0	1	−8
13	Quetiapine 350.0 Zuclopenthixol 20.0		Li sulphate 84.0		7	−17
14[b]		Lamotrigine 300.0			2	15
15				Zolpidem 7.5	7	−19
16	Olanzapine 20.0	Valproate 562.6			7	−4
17	Olanzapine 15.0				7	−2
18	Chlorpromazine 500.0		Li sulphate 166.0	Clonazepam 1.25 Cetirizine 10.0 Promethazine 25.0	7	−24
19	Olanzapine 6.9 Quetiapine 600.0	Valproate 450.0			7	−14,5
20	Olanzapine 25.0	Lamotrigine 200.0	Li sulphate 192.6	Clonazepam 0.9	7	−11
21	Aripiprazole 10.0				7	−12
22	Chlorprothixene 100.0 Olanzapine 40.0		Li sulphate 249.0	Buspirone 30.0 Clonazepam 2.25	7	−17
23	Risperidone 0.6	Lamotrigine 162.5	Li sulphate 120.8	Alimemazine 3.75 Mirtazapine 24.4[c]	7	−17
24	Olanzapine 15.0	Valproate 600.0			7	−17,5

Li = lithium; YMRS = Young Mania Rating Scale.
[a]Patients 2 and 5 were administered ibuprofen 250 mg/day. Ibuprofen can affect melatonin production.
[b]This patient was excluded from the analysis because of withdrawal symptoms at the start of the intervention.
[c]Sedation is a recognized side effect of the antidepressant mirtazapine.

recorded for all groups (patients and healthy control subjects). An actigraph contains a piezoelectric accelerometer recording movements in all directions and stores the registered activity count (per defined epoch) in an internal memory unit (27). The patients were monitored during the seven days of intervention. Healthy controls were monitored for a seven-day baseline period without any intervention, followed by a seven-day period of daily BB from 6 p.m. to 8 a.m.

The BB/placebo interval (intervention interval) was defined in the Actiwatch software as lasting from 6 p.m. to 8 a.m. for patients and for healthy controls. The interval without glasses was defined as 8 a.m. to 6 p.m. Based on nurses' reports for patients and self-report forms for healthy

controls, any reported deviation from the protocol was corrected by changing the start and end times of the interval accordingly. If BB glasses were taken off temporarily during the intervention interval, the period of nonuse was excluded, and the remaining interval analysed. Intervals with more than 50% invalid time (activity) were excluded from the analysis. Pre-treatment activity intervals of more than 70 min were included in the analysis.

The feasibility of the intervention was assessed using a patient self-report form developed for the trial. Patients were instructed to rate five statements about the study and the intervention on a five-point scale ranging from 'fully disagree' to 'fully agree'. Additionally, all subjects had the opportunity to add individual comments detailing their experiences in the trial.

Outcomes

The primary outcome was change in the YMRS score. The secondary outcomes were change in motor activity recorded by means of an actigraph and scores from the patient experience self-report form. Side effects were recorded if present.

Statistical analyses

Descriptive statistical methods were used to characterize the sample. The association between treatment and the primary outcome YMRS total score as well as secondary actigraph outcomes was assessed in a linear model with repeated measures, with time, treatment and their interaction as predictors using simple contrasts (all time-points compared with the baseline value). The single items were assessed by graphical methods and means with 95% confidence intervals (CIs) at each time-point. Average activity (counts/min) was calculated for all subjects by use of the Actiware Statistics program. Computation was otherwise performed using SPSS 22 (IBM Corp., Armonk, NY, USA) and Matlab 7.1 (Mathworks, Inc., Natick, MA, USA) and all graphics were produced in Matlab 7.1.

Results

The trial profile is shown in Figure 1. A total of 32 patients were randomized to one of the two groups. Six patients withdrew consent on the first night of the intervention and two were unable to adhere to the protocol, yielding an intention-to-treat group of 24 patients in total, 13 patients in the BB group and 11 patients in the placebo group. Actigraph recordings from 22 patients (12 in the BBT group and 10 in the placebo group) and 35 healthy controls were analysed.

Demographic variables and baseline clinical characteristics for all groups are shown in Table 2. There were more men than women in both patient groups. The pre-treatment mean YMRS score for the control group was 27.0 as compared to 23.4 in the BB group. The healthy control group differed from the patient groups with respect to a more equal distribution of sexes, a higher level of education and a higher level of employment. During the intervention week, pharmacological treatment was less intensive for the BB group than for the placebo group (Table 1); that is, only three of 12 patients in the BB group received two or more different types of antipsychotic drugs as compared to eight of 11 in the placebo group. Only six of 12 patients in the BB group received an anxiolytic, hypnotic or sedative drug, as compared to all patients in the placebo group.

A significant difference in YMRS score change between the BB and placebo groups was apparent after three days of intervention ($p = 0.042$, partial $\eta^2 = 0.222$), and continued to increase throughout the intervention, reaching $p = 0.001$ (partial $\eta^2 = 0.49$) after seven days (Fig. 2). The mean change in total YMRS score after seven days of intervention was 14.1 (95% CI: 9.7–18.5) in the BB group as compared to 1.7 (95% CI: −4.0 to 7.39) in the placebo group. This yielded a Cohen's *d* of 1.86 (*Supplementary Table 1*).

The single YMRS item scores are shown in Figure 3. There was a pronounced and rapid decline in eight out of 11 items in the BB group compared to the placebo group. There was an immediate decline in scores for items 5 (Irritability) and 7 (Language-thought disorder), followed by a stable difference as compared to placebo, while other items showed a progressive decline over the entire time period, for example, items 6 (Speech: rate and amount) and 10 (Appearance). For two of the items showing no change, items 3 (Sexual interest) and 9 (Disruptive and aggressive behavior), both groups scored very low at the start of the intervention. For item 4 (Sleep) there was no change in symptoms between groups.

Actigraph data showed that the average activity counts/min, in the intervention interval 6 p.m. to 8 a. m., was consistently lower in the BB group as compared to the placebo group from the second night of the intervention, although the difference was not statistically significant (*Supplementary Fig. 2*). There was a marked decline in activity from the first to the second night of the

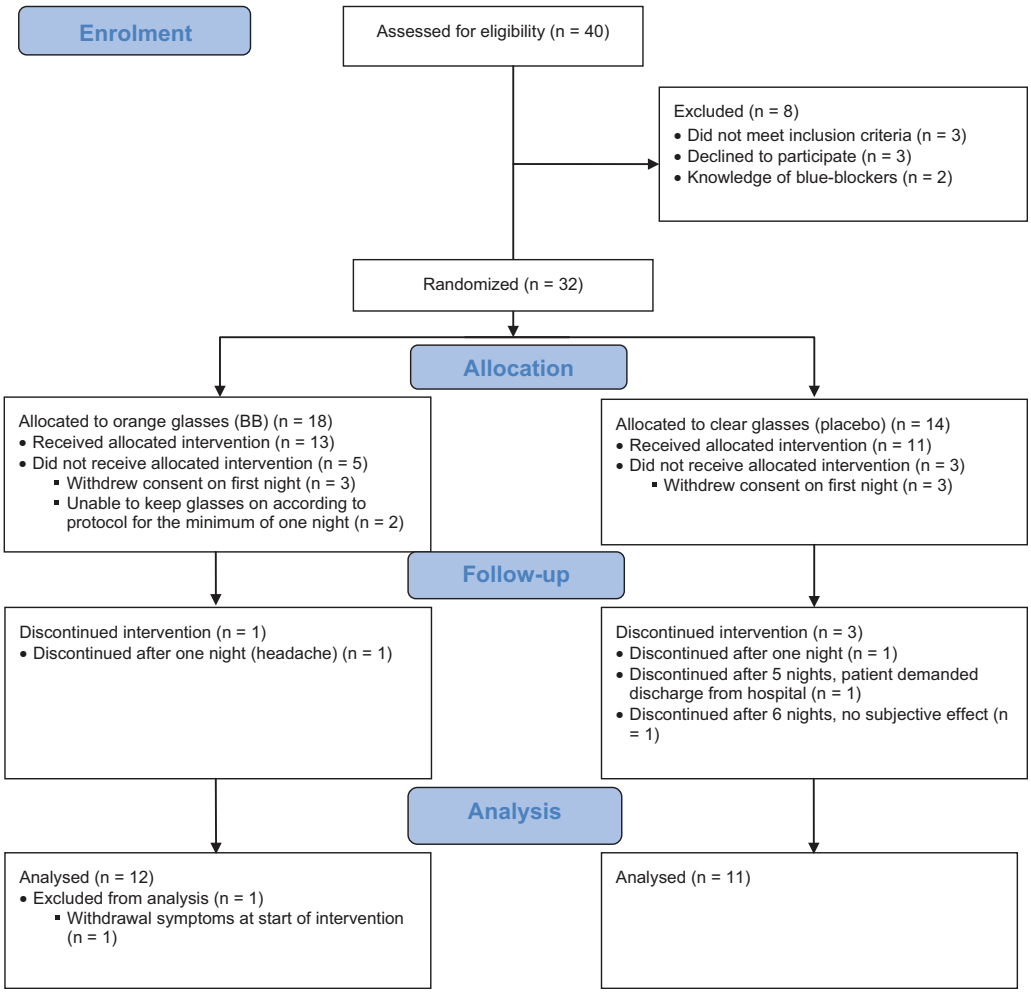

Fig. 1. Trial profile in a randomized controlled trial of blue-blocking (BB) glasses versus placebo glasses for patients with bipolar mania.

intervention in the patient BB group, and compared to healthy controls also wearing BB glasses, the difference was already significant from the first to the second BB interval ($p = 0.018$). Furthermore, for activity during daytime (without glasses), there was a significant difference between the patient BB group and healthy controls on days 2–4, where activity decreased in the patient group and increased in the healthy control group as compared to pre-treatment day 0 (for days 0–2: $p = 0.028$).

Scores from the patient experience self-report form showed that wearing glasses was generally well tolerated by patients in a manic episode (Fig. 4). Patients in the placebo group found the glasses somewhat more irritating than patients in the BB group. In both groups, some patients reported paranoid thoughts regarding the Actiwatch Spectrum device.

With regard to side effects, two patients in the BB group reported emerging depressive symptoms on days 6 and 7, respectively. For one patient, these instantly diminished after a two-hour shortening of the duration of BB by delaying the start to 8 p.m. For the second patient, a break from BB lasting one evening and one night was

Table 2. Characteristics of patients with mania assigned to blue-blocking glasses or placebo and the healthy control group

	Patient group/placebo (n = 11)	Patient group/blue-blocking (n = 12)	Healthy controls (n = 45)
Current episode			
YMRS score at start of intervention, mean (SD)	27.0 (7.1)	23.4 (8.0)	
Psychotic symptoms	9/11	8/12	
Hospitalized against own will	8/11	6/12	
Demographic variables			
Age, years, mean (SD)	49.8 (13.8)	43.0 (11.0)	42.3 (10.8)
Sex, male	9/11	7/12	22/45
Highest level of education completed			
High school	4/11	4/12	6/45
High school/vocational studies	3/11	6/12	7/45
University/higher education	4/11	2/12	32/45
Employment status			
Unemployed	2/11	1/12	0/45
Student	1/11	0/12	1/45
Employed	3/11	6/12	42/45
Retired	1/11	1/12	2/45
Disability benefit	4/11	4/12	0/45
Marital status			
Single	3/11	4/12	
Cohabiting	1/11	2/12	
Married	2/11	3/12	
Divorced	5/11	3/12	
Clinical characteristics from medical history			
Family history[a]	6/10	4/12	
Self-reported age at first affective episode, years, mean (SD)	24.7 (12.1)	23.0 (10.9)	
Age at first psychiatric hospital stay, years, mean (SD)	32.9 (4.0)	31.7 (3.5)	
Duration of illness, years, mean (SD)	22.8 (3.8)	18.0 (3.1)	
Psychotic mania in medical history	10/11	10/12	
Self-reported no. of depressive episodes, mean (SD)	7.2 (2.8)[b]	12.0 (8.0)[b]	
No. of previous psychiatric hospital stays, mean (SD)	7.2 (2.2)	4.6 (1.2)	
No. of psychiatric hospital stays for mania, mean (SD)	7.0 (2.2)	2.9 (0.8)	
No. of psychiatric hospital stays for depression, mean (SD)	0.7 (0.3)	1.0 (0.5)	
Previous suicide attempts	2/11	3/12	
Lifetime medication use			
Antidepressants	2/11	7/12	
Antipsychotics	9/11	10/12	
Anticonvulsants	8/11	9/12	
Lithium	7/11	6/12	
Hypnotics/sedatives	8/11	7/12	
Anxiolytics	4/11	6/12	

SD = standard deviation; YMRS = Young Mania Rating Scale.
[a]Relatives with bipolar disorder, affective/anxiety disorders, psychotic disorders or psychiatric hospital stays.
[b]Data missing for one subject.

followed by a rapid elevation of mood to hypomania on the following day. No patients had a switch to a severe depressive episode during or immediately after the intervention. One patient, with comorbid migraine, reported headache associated with the use of BB glasses, causing dropout on the second night of the intervention. In the healthy control group, three subjects reported headache attributed to BB. One of these reported having migraine. Four healthy control subjects reported uncomfortably low energy and two of these also reported lowered mood that was reversed after the discontinuation of the use of BB glasses.

Discussion

This is the first placebo-controlled RCT examining the effectiveness and feasibility of blue-blocking orange glasses (BB glasses) as an add-on treatment for patients diagnosed with bipolar mania compared to the placebo condition clear glasses. Patients wore glasses from 6 p.m. to 8 a.m. for seven consecutive days, but were otherwise treated as usual.

BB glasses were highly effective as an add-on treatment for patients in a manic episode, with a significant difference in total YMRS score between the BB and placebo groups as early as three days

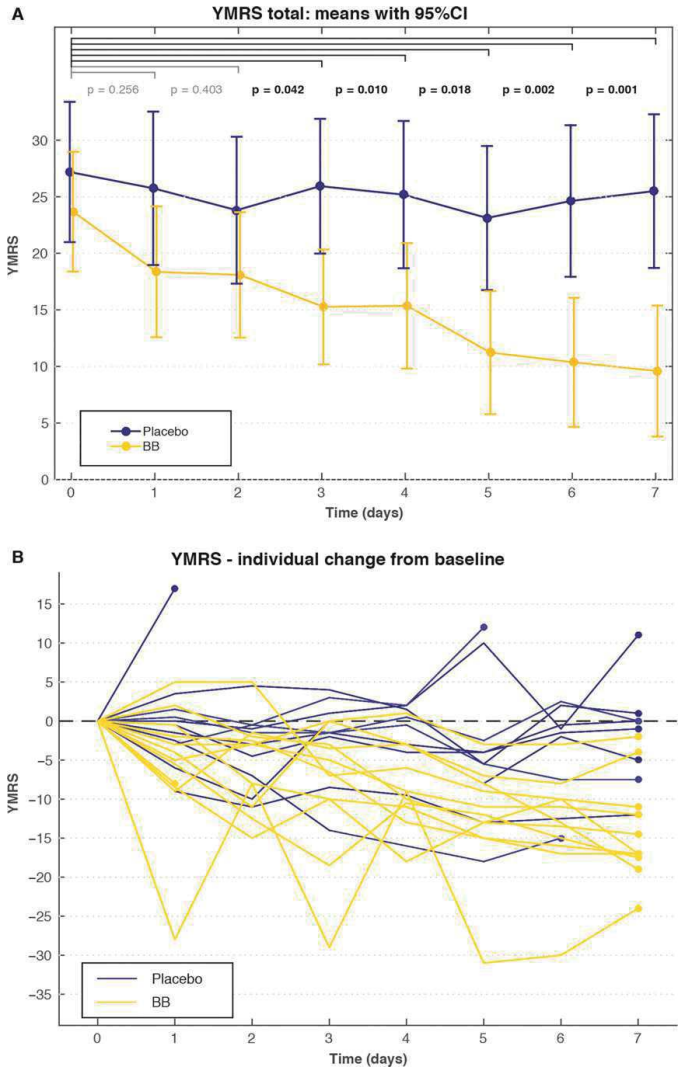

Fig. 2. (A) Young Mania Rating Scale (YMRS) total scores for patients assigned to blue-blocking (BB) glasses (n = 12*) or clear glasses (placebo) (n = 11**). Values are reported as means with 95% confidence intervals (CIs). The p-values are reported for the effect of the interaction (change of treatment effect between baseline and each time-point) in a linear model. (B) Spaghetti plot of YMRS individual scores for patients assigned to BB glasses (n = 12*) or clear glasses (placebo) (n = 11**). *One dropout on day 1. **Three dropouts on days 1, 5, and 6, respectively.

after the start of the intervention. The effect sizes, ranging from 1.05 to 1.86 during the last three days of the intervention, were extraordinarily high, and were strikingly similar to the effect sizes reported in a previous DT study (15). Unlike the outcome in the DT study, we did not find any relationship between pre-intervention duration of episode and outcome (15).

Remarkably, some symptoms of mania (YMRS single item scores) were clearly attenuated after a single night of intervention. This pattern of YMRS single item scores was supported by actigraph recordings showing a significant drop in motor activity in the patient BB group from the first to the second BB interval, as compared to a healthy control group also receiving BB. With regard to

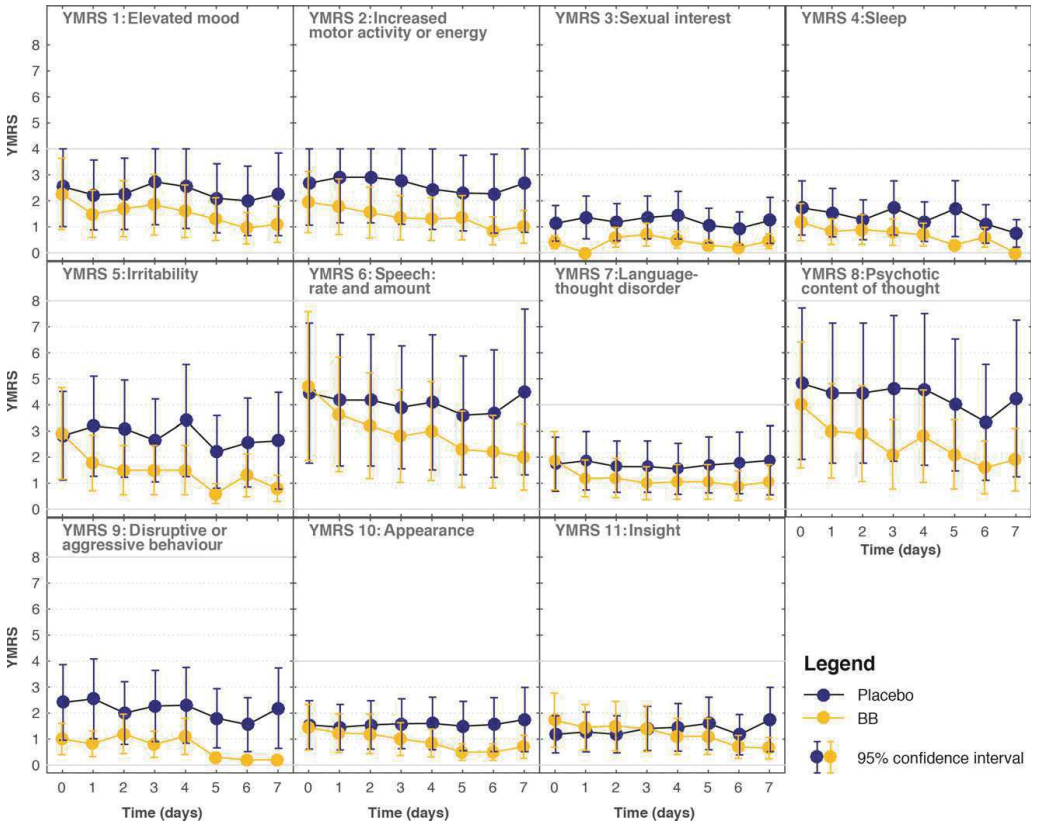

Fig. 3. Young Mania Rating Scale (YMRS) item scores for patients assigned to blue-blocking (BB) glasses (n = 12; one dropout on day 1) or clear glasses (placebo) (n = 11; three dropouts on days 1, 5, and 6, respectively). Values are reported as means with 95% confidence intervals (CIs). Items 5, 6, and 9: scale range 0–8 points; for other items, scale range 0–4 points.

the somewhat surprising finding of no change in item 4 (Total hours of sleep/subjective need for sleep), it has previously been suggested that this item may not be suitable for BB conditions (22).

BB glasses were generally well perceived by the patients, and their use was found to be feasible even for several manic patients with psychotic symptoms. The observed side effects, namely headache and uncomfortably lowered mood and energy, were observed at approximately the same frequencies in the patient BB group and in healthy controls receiving BB. Notably, two of the four individuals reporting headache had previously been diagnosed with migraine. Headache and lowered mood diminished rapidly for all subjects when BB was discontinued.

This study was not double-blinded as the nature of the intervention (coloured glasses) made masking practically impossible. Even if raters had been blinded, it would have been difficult to blind the reporting staff, and patients in a manic state cannot be instructed to withhold information concerning treatment from the rater. To limit the danger of rater's bias, all YMRS ratings were made as a consensus between at least two persons. In our opinion, consensus decisions partially based on observations throughout the 24-hour period were crucial for counteracting the effects of patients' tendency to compose themselves when interacting with a doctor. Ultimately, YMRS ratings were supported by objective actigraph monitoring showing marked decline in motor activity corresponding in time with the drop in YMRS items related to activation.

The sample size was relatively small, but nevertheless sufficient to test the hypothesis. The sample size and naturalistic design may, however, have influenced the precision of the effect size, as illustrated in *Supplementary Table 1* showing the variation of effect sizes during the intervention. In a

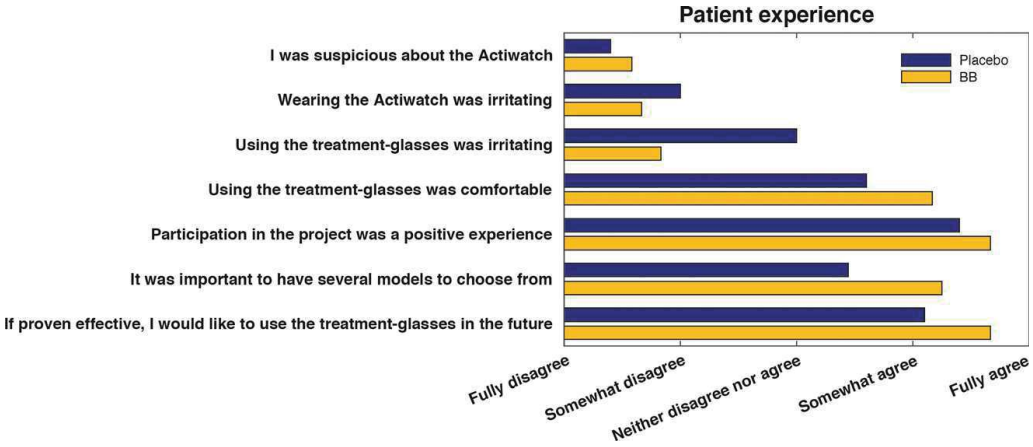

Fig. 4. Self-reported patient experience with intervention and participation in study for the patients assigned to blue-blocking (BB) glasses (n = 12) or clear glasses (placebo) (n = 11).

large sample, a slightly better outcome in the placebo group would be expected and hence somewhat less dramatic effects size than 1.86. Unfortunately, because of the growing awareness of blue light and blue-blockers, it may prove difficult to reproduce this study with the exact same design with a larger sample. The sample size yielded insufficient statistical power for detecting significant differences in average Actigraph-recorded activity between the patient groups.

The slow decline in YMRS score in the placebo group is a disturbing, but not surprising, finding. The somewhat higher age and longer illness duration of the placebo group may have contributed to this. It is, however, well known that acute episodes of mania, even first episodes, respond slowly to TAU (7). It should also be mentioned that our study was performed in a true naturalistic setting with few exclusion criteria, yielding high generalizability for the population of patients with bipolar disorder. Similar study designs are rarely seen in pharmacological efficacy studies, and this issue should be kept in mind when interpreting the YMRS pattern in the placebo group.

In fact, one consequence of the strict naturalistic design was that treatment was continually adjusted according to the patients' clinical state. The potential confounding of less intensive treatment in the improving BB group may have contributed to underestimation of the effect of BB glasses. For instance, due to rapid improvement of symptoms, two patients in the BB group were moved from the acute ward to a local hospital during the intervention. For both patients, transfer was followed by a transient worsening of symptoms. In contrast, no patients in the placebo group were transferred.

Interestingly, in the BB group, YMRS item scores related to increased activation, and actigraph-recorded motor activity, declined before items related to symptoms of distorted thought and perception. This led to the hypothesis that the primary anti-manic effect of BB is deactivation. The mechanisms that may underlie such a relationship have been elucidated through functional magnetic resonance imaging (fMRI) studies, where exposure to blue light, within seconds, activated areas in the brain stem corresponding to the noradrenergic nucleus locus coeruleus (LC) (28, 29). Noradrenergic pathways project from the LC to most of the brain, particularly to the forebrain, and their activation leaves neurons more excitable to novel synaptic stimuli (30). Additionally, the LC activates the hypothalamic-pituitary-adrenal (HPA) axis, which many studies have found to be dysfunctional in bipolar disorder (31). Interestingly, an fMRI study showed that the effect of blue light during an executive task depended on circadian phase and sleep homeostasis (32). Patients in a manic episode are indeed out of their homeostatic balance with regard to rest and sleep as well as circadian rhythmicity (11). Thus, the manic symptoms may be fuelled by blue light via excitatory pathways from the brainstem.

The last few decades have seen growing interest in the role of dopamine in the pathophysiology of mania, and it is not disputed that elevated dopamine levels are reflected in many symptoms of mania (4). However, our findings imply that

changes in cognition and perception during mania (i.e., psychotic symptoms) may be secondary effects of increased activation. This observation is in accordance with the sequence of the developing symptoms during the build-up of manic episodes. Interestingly, the original catecholamine hypothesis proposed that manic symptoms may be caused by high levels of noradrenalin (33). If, however, the dopaminergic drive during mania is secondary to persistently high activity of noradrenergic systems, this could explain the slow onset of overall improvement for patients in a psychotic manic episode, where the current conventional treatment mainly relies on dopamine-blocking agents (4).

The rapid reduction in YMRS item scores related to activation in the BB group gives us reason to state the hypothesis that the anti-manic effect seen during BB treatment is due to silencing of signalling in the ipRGC circuits directly influencing mood and cognition, rather than indirect effects via melatonin secretion, sleep or increased circadian synchrony. A subsequent contribution from impact on melatonin secretion and circadian rhythmicity is very likely, but cannot be confirmed by the present data. In a recent case report describing a patient with bipolar II disorder using BB glasses over 2 weeks, the onset of nocturnal melatonin secretion was advanced by 1 hour 18 min, along with improved mood and relief from anxiety (23). Several other studies have shown preservation of melatonin during BB in light conditions for healthy individuals (17, 18, 34), and in one case report the sleep–wake cycle was rapidly and markedly regularized during BB for a patient in a manic episode (22).

Ultimately, the basic mechanisms underlying the effects of BB in mania need further investigation. Our results are strongly indicative that light, more specifically blue light, is a major environmental factor maintaining bipolar mania through the melanopsin–ipRGC systems. Our results provide a new opportunity for bridging both theoretical and therapeutic gaps related to bipolar disorder. Most importantly, however, this study implies that BB glasses, used in accordance with our protocol, are a safe and efficient intervention for bipolar mania that should be utilized in treatment efforts. In parallel, follow-up studies are needed for replication of findings and refinement of this novel treatment option.

Acknowledgments

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Disclosures

The authors of this paper do not have any commercial associations that might pose a conflict of interest in connection with this manuscript.

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Supporting Information

Additional Supporting Information may be found online in the supporting information tab for this article:

Fig. S1. Transmittance (%) of light versus wavelength (nm) through blue-blocking (BB) glasses and clear glasses (placebo).

Fig. S2. Actigraph-assessed motor activity in intervals wearing glasses (6 p.m.–8 a.m.) and daytime intervals (8 a.m.–6 p.m.) for patients assigned to blue-blocking (BB) glasses (n = 12) or clear glasses (placebo) (n = 10), and the healthy control group wearing BB glasses (n = 35). p gr = p-value for time independent group effect.

Table S1. Means and standard deviations (SDs) for YMRS total score for patients assigned to blue-blocking (BB) glasses or clear glasses (placebo) and corresponding Cohen's *d* effect sizes for all days during the intervention.

Figure legends for Supplementary figures

Fig. S1. Transmittance (%) of light versus wavelength (nm) through blue-blocking (BB) glasses and clear glasses (placebo).

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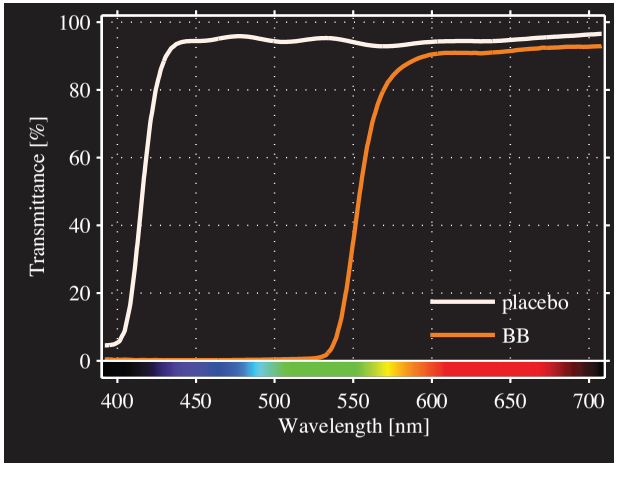
100
80
60
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20
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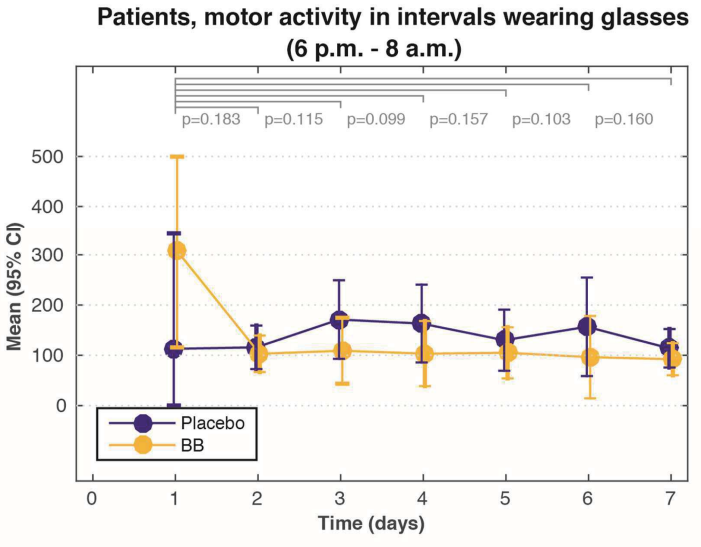
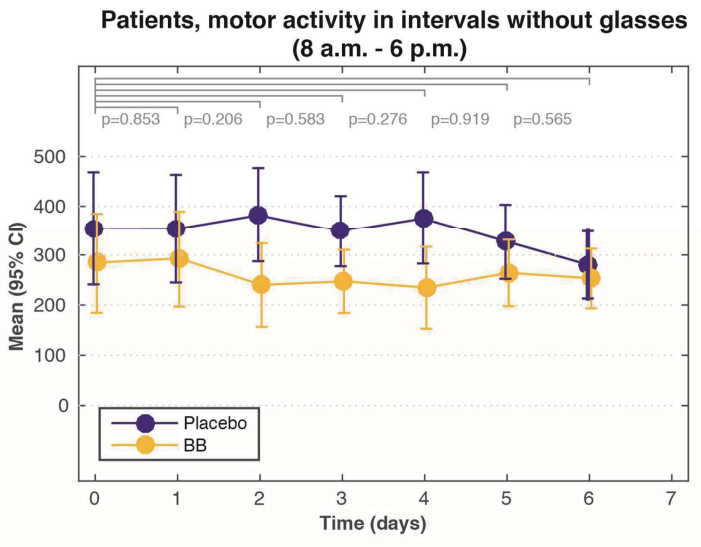
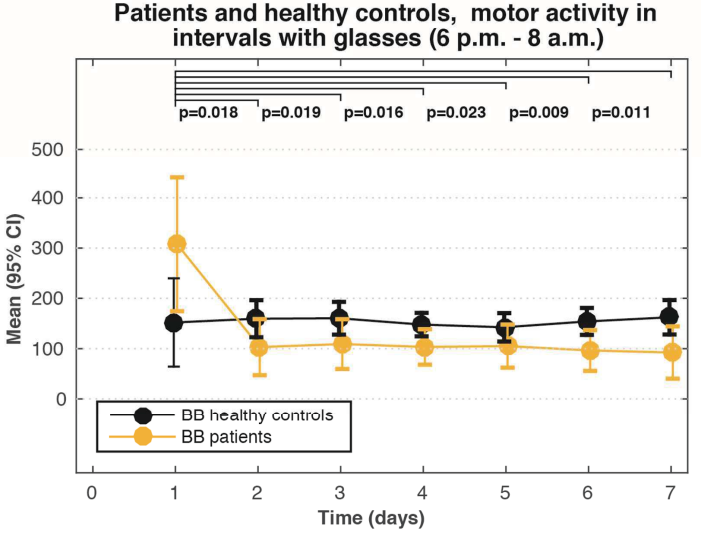
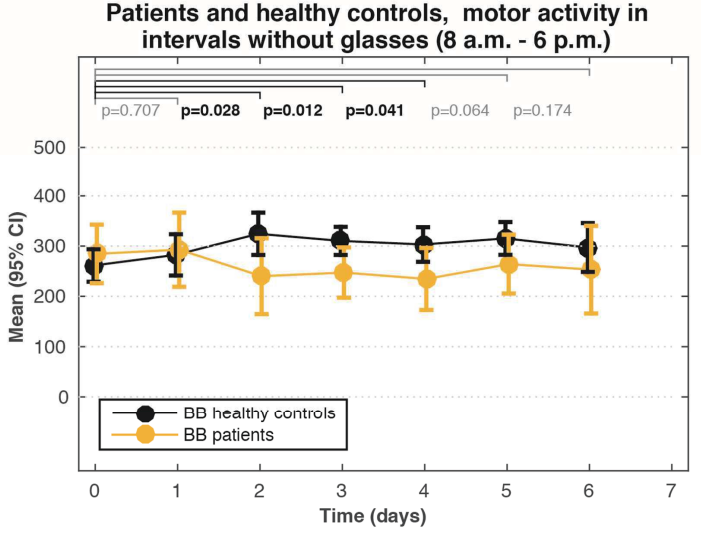
Transmittance [%]
placebo
BB
400
450
500
550
600
650
700
Wavelength [nm]


Patients, motor activity in intervals wearing glasses (6 p.m. - 8 a.m.)
p=0.183
p=0.115
p=0.099
p=0.157
p=0.103
p=0.160
Mean (95% CI)
Time (days)
Placebo
BB


Patients, motor activity in intervals without glasses (8 a.m. - 6 p.m.)
p=0.853
p=0.206
p=0.583
p=0.276
p=0.919
p=0.565
Mean (95% CI)
Time (days)
Placebo
BB


Patients and healthy controls, motor activity in intervals with glasses (6 p.m. - 8 a.m.)
p=0.018
p=0.019
p=0.016
p=0.023
p=0.009
p=0.011
Mean (95% CI)
Time (days)
BB healthy controls
BB patients


Patients and healthy controls, motor activity in intervals without glasses (8 a.m. - 6 p.m.)
p=0.707
p=0.028
p=0.012
p=0.041
p=0.064
p=0.174
Mean (95% CI)
Time (days)
BB healthy controls
BB patients

Interval	Placebo	n	BB	n	Cohens'*d*
Day 1-0	0(6.622)	11	-5.542(8.236)	12	0.74
Day 2-0	-3.45(4.764)	10	-5.591(5.847)	11	0.40
Day 3-0	-2.1(5.384)	10	-8.409(8.619)	11	0.877
Day 4-0	-1.555(3.762)	9	-8.318(5.293)	11	1.472
Day 5-0	-3.850(9.138)	10	-12.455(7.147)	11	1.048
Day 6-0	-3.944(6.278)	9	-13.318(6.813)	11	1.43
Day 7-0	-1.688(6.819)	8	-14.09(6.419)	11	1.86

Supplementary table 1: Means and standard deviation (SD) for YMRS total score for patients assigned to Blue-Blocking (BB) glasses or clear glasses (Placebo) and corresponding Cohens'*d* effect-sizes for all days during the intervention.

II

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REGULAR RESEARCH PAPER

Journal of Sleep Research

Blue-blocking glasses as additive treatment for mania: Effects on actigraphy-derived sleep parameters

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Abstract

Improvement of sleep is a central treatment goal for patients in a manic state. Blue-blocking (BB) glasses as adjunctive treatment hasten overall recovery from mania. This method is an evolvement from dark therapy and builds on the discovery of the blue-light-sensitive retinal ganglion cell that signals daytime to the brain. We report effects of adjunctive BB glasses on actigraphy-derived sleep parameters for manic inpatients as compared to placebo. Hospitalized patients with bipolar disorder in a manic state aged 18–70 years were recruited from five clinics in Norway from February 2012 to February 2015. The participants were randomly allocated to wearing BB glasses or placebo (clear glasses) as an adjunctive treatment from 18:00 to 08:00 hours for seven consecutive nights. Sleep and wake were monitored by actigraphy. From 32 eligible patients, 10 patients in each group qualified for the group analyses. The BB group's mean sleep efficiency was significantly higher at night 5 as compared to the placebo group (92.6% vs. 83.1%, p = .027). The 95% confidence interval (CI) was 89.4%–95.8% in the BB group and 75.9%–90.3% in the placebo group. There were fewer nights of interrupted sleep in the BB group: 29.6% versus 43.8% in the placebo group. The BB group received less-intensive sleep-promoting pharmacological treatment and showed significantly higher sleep efficiency and more consolidated sleep as compared to the placebo group. Our findings suggest sleep-promoting effects through deactivating mechanisms. Adjunctive BB glasses seem to be useful for improving sleep for manic patients in the hospital setting.

KEYWORDS

amber, bipolar disorder, chronotherapy, darkness, orange, virtual

1 | INTRODUCTION

Bipolar disorders (BDs) have traditionally been regarded as disorders of mood. Several coinciding symptoms, however, cycle in remarkable synchrony with the mood swings, in particular alterations in sleep and activity (Scott et al., 2017; Wehr et al., 1998).

Sleep disturbances are common in all states of BD, but usually exacerbated during episodes (Bauer et al., 2006; Gruber et al., 2011). The most dramatic changes in sleep patterns and subjective need for sleep occur during mania. Many patients report the first sign of an emerging manic episode as a sudden change in sleep, which predicts the onset of a mood episode with a latency of 1 day (Bauer et al., 2006). With hypomania, the subjective need for sleep and motivation for going to bed diminishes. At the transition to frank mania, activation, irritability and grandiosity rise even further. Grandiose psychosis usually interferes with the patients' insight and ability to comply with the treatment. Even with good cooperation from the patient, pharmacological restoring of sleep during mania can be challenging and may require high doses of antipsychotics, sedatives and hypnotics. This unsatisfactory clinical shortcoming may arise from an incomplete understanding of the mania-sustaining processes.

Converging evidence from several lines of research points to light as a major environmental influence in BD (Bauer et al., 2015; Esaki et al., 2019; Lewy et al., 1985). The effectiveness of chronotherapeutic interventions for BD strongly indicates that light plays a key role (Gottlieb et al., 2019). The first report on dark therapy for a severe case of rapid-cycling BD showed an almost instant transition from irregular to regular sleep concomitant with stabilization of mood (Wehr et al., 1998). The findings were replicated in another case report the following year, and the method was extended to manic inpatients in a very promising pilot study (Barbini et al., 2005; Wirz-Justice, Quinto, Cajochen, Werth, & Hock, 1999). The discovery of the daylight receptor (the intrinsically photo-responsive retinal ganglion cell; ipRGC), which is mainly blue-light sensitive, paved the way for the use of blue-blocking (BB) glasses as a means of creating a virtual darkness for the brain (Kayumov et al., 2005; Phelps, 2008).

Light at night may disrupt circadian rhythms and inhibit sleep Esaki et al., 2019; Green, Cohen-Zion, Haim, & Dagan, 2017). The retinal daylight receptors project directly to the circadian master clock, the suprachiasmatic nucleus (SCN) (LeGates, Fernandez, & Hattar, 2014). Additionally, the ipRGCs have projections to several other brain areas central to regulation of mood, cognition, emotion and arousal (Fernandez et al., 2018; LeGates et al., 2014; Vandewalle et al., 2010). Light in the blue and blue-green spectrum comprises a daylight signal and suppresses melatonin production via the ipRGC-SCN projections. Conversely, light depleted of wavelengths shorter than approximately 530 nm has a low capacity for stimulating the ipRGCs and hence allows melatonin production (Kayumov et al., 2005). Blue-blocking devices also protect from alerting effects of light in the evening (van der Lely et al., 2015).

Studies on the effects of blue-blocking (BB) interventions on sleep-related outcomes for BD patients are still few but very promising (Henriksen et al., 2014; Phelps, 2008). In the first case report on BB glasses used during mania, sleep was rapidly regularized. In this respect, the change in sleep was a replication of the preceding dark-therapy case observations. The patient showed fewer limb movements during sleep, which suggested deactivation. In the Virtual darkness as additive treatment in mania (VATMAN) trial (ClinicalTrials.gov, NTC01818622), we found a clear and rapid effect on overall Young Mania Rating Scale (YMRS) outcomes after intervention with adjunctive BB glasses, as compared to placebo (clear-lensed glasses) (Henriksen et al., 2016; Young, Biggs, Ziegler, & Meyer, 1978).

Here we present the sleep outcomes from the same trial, as measured by wrist-worn actigraphs. We chose sleep efficiency as the primary outcome, and motor activity during the main sleep interval as the outcome most directly reflecting nightly activation. As secondary outcomes we analysed group differences in total sleep, wake after sleep onset, number of wake episodes, sleep fragmentation index, sleep onset, sleep offset and mid-time sleep. The sleep pattern characteristic mid-sleep awakening is descriptively presented. Finally, we discuss current theories relevant for possible mechanisms of action.

2 | METHODS

2.1 | Study design

The study was part of a multicenter randomized placebo-controlled single-blinded trial, recruiting patients from five hospitals in the southwest of Norway, latitude 58–59′N, in the time period February 2012 to February 2015 (Henriksen et al., 2016). The trial is registered with ClinicalTrials.gov: NTC01818622.

Eligible participants were patients in hospital with BD in a manic phase, aged 18–70 years. Adherence to the allocated intervention and valid actigraphy recordings for night 1 and night 5 qualified patients for inclusion in the statistical analyses of difference between the groups. For the description of nights with interrupted sleep, all nights of adherence to the protocol and with valid actigraphy recordings were used. Interrupted sleep was defined as one or more periods of active wake (wake and continuous motor activity) lasting 30 min or longer, within the main sleep interval.

2.2 | Ethics

The Regional Ethical Committee in Norway (REK registration 2011/1668) approved the procedures, which were in accordance with the Helsinki Declaration. All patients included in the study provided written informed consent.

2.3 | Randomization and masking

The included patients were randomly assigned to BB glasses or clear (placebo) glasses, by a manual draw performed by secretaries

not otherwise involved in the trial. All participants received identical information about the purpose of the study, which was testing the effectiveness of different glasses in reducing manic symptoms. The included patients had no previous knowledge of effects of BB glasses. No patients observed glasses of different color to their own.

2.4 | Procedures

Experienced psychiatrists trained in the use of the Mini International Neuropsychiatric Interview-Plus verified a diagnosis of 'bipolar disorder type I, current episode manic' (Sheehan et al., 1998). The patient's eyes were physically examined for transparency and vision by inspection of the red reflex and finger-count test.

2.5 | Interventions

The participants wore blue-blocking glasses (LowBlueLights.com, University Heights, OH, USA) or clear-lensed glasses (Uvex, Furth, Germany, and 3M, Austin, TX, USA) from 18:00 to 08:00 hours for 7 days. For transmittance of the intervention glasses, we refer to a previous publication from the trial (Henriksen et al., 2016). All patients received treatment as usual (TAU), individualized according to daily symptom levels, acceptance by patients, best medical judgement and law restrictions. The pharmacological TAU is shown in Table 1. Participants and nursing staff were instructed that neither type of glasses could be taken off unless turning out the light at bedtime. In the case of wake before 08:00 hours, the glasses should be put on. The participants could choose between different models of glasses according to individual comfort and preference of style.

2.6 | Measures

Motor activity, sleep and wakefulness were monitored continuously by actigraphy during the intervention (7 days or until dropout), with supporting data from daily nurse reports on sleep and wakefulness. All participants wore an actigraph device (Actiwatch Spectrum, Philips Respironics Inc.) on the wrist, left or right according to personal preference. Data were recorded in 30-s epochs. Start and end of major rest intervals were manually scored based on inspection of raw data supported by sleep logs, as recommended for actigraphy-derived sleep analyses (Smith et al., 2018). The inspection included both motor activity and light exposure. Wake thresholds and time of inactivity for calculating sleep onset and offset were set to medium sensitivity (40 counts/min) and 10 min, respectively (Actiware version 6.0, Philips Respironics Inc.). A detailed description of the criteria used for defining the major rest intervals is available in Appendix S1.

Habitual morningness or eveningness was assessed by the self-report Horne-Östberg Morningness-Eveningness Questionnaire (MEQ) at the time of discharge (Horne & Ostberg, 1976). The patients were asked to recollect their habitual preferences when in a stable state. The MEQ constitutes 19 items: five items describing actual daily behaviour and 14 items referring to preferred timing in a self-regulated environment (i.e., preferred time of sleep and what time of day the person feels most competent to perform demanding tasks). MEQ scores between 59 and 86 indicate morning types, 42–58 indicates neither type and 16–41 indicates evening types.

The global seasonality score (GSS) derives from sub-scores in the Seasonal Pattern Assessment Questionnaire (SPAQ), which was originally made to assess seasonal affective disorder (SAD) (Melrose, 2015). The GSS measures seasonal variations in the items sleep, mood, weight, energy, social activity and appetite. Each of the six items is scaled 0–4, ranging from no seasonality to extremely marked seasonal variation, yielding a total score range of 0 to 24. We used an authorized Norwegian version of the questionnaire, translated by Dr Lingjaerde (Lingjærde, 1996). The cut-off levels of the GSS are usually set to 9–10 for sub-SAD and ≥11 for SAD (Melrose, 2015).

2.7 | Outcomes

The primary outcomes were sleep efficiency (percentage sleep during the main rest interval) and motor activity during sleep intervals. The secondary outcomes were total sleep (hours) during the main rest interval, wake after sleep onset (minutes), number of wake episodes, sleep fragmentation index (percentage active time in sleep interval + percentage inactive bouts of 1 min duration), sleep onset, sleep offset and mid-time sleep. For the descriptive presentation of nights with interrupted sleep, all valid night recordings from night 1 through to night 5 were included.

2.8 | Statistical analyses

To characterize the sample, descriptive statistical methods were used. The effect of BB glasses at night 5 was assessed using the ANCOVA; that is, the linear regression for the outcome variable at night 5 depending on the group assignment adjusted for the outcome at night 1. We chose to analyse for group differences at night 5 because of two dropouts in the placebo group after this time-point. We considered these events to be not at random but a consequence of the allocation as described in the trial profile in a previous publication (Henriksen et al., 2016). At night 5, the integrity of the RCT design was, however, still sufficiently maintained.

In the graphical presentation, we used the raw data for each patient and the mean (95% confidence interval [CI]) at night 1 and night 5. Sleep efficiency, activity, wake after sleep onset, wake bouts and sleep fragmentation index were log-transformed before

TABLE 1 Individual medications for patients assigned to blue-blocking glasses or clear glasses (placebo)

Patient	Antipsychotics, mean dosage (mg/day)	Anticonvulsants, mean dosage (mg/day)	Lithium, mean dosage (mg/day)	Anxiolytics/hypnotics/sedatives, mean dosage (mg/day)
Clear glasses (placebo)				
1	Olanzapine 5.6 Quetiapine 600.0	Valproate 837.5		Diazepam 21.3 Zopiclone 15
2[a]	Quetiapine 200.0			
3		Valproate 3,300.0	Lithium sulphate 84.0	Zopiclone 7.5, Alimemazine 40.0
4	Haloperidol 6.25 Levomepromazine 50.0	Valproate 1,537.5		Diazepam 10.0, Zopiclone 7.5
5[a]	Haloperidol depot 50.0 (every 14 days) Chlorpromazine 162.5		Lithium sulpate 119.9	Diazepam 16.3
6	Haloperidol 0.75 Olanzapine 22.5	Carbamazepine 325.0		Diazepam 34.4
7	Olanzapine 20.0 Quetiapine 100.0		Lithium carbonate 1,200.0	Oxazepam 17.0 Zopiclone 3.3 Alimemazine 10.0, Cetirizine 10.0
8	Chlorprothixene 123.1 Olanzapine 23.6			Oxazepam 10.0
9	Levomepromazine 6.3, Olanzapine 3.8		Lithium sulphate 166.0	Diazepam 5.0 Melatonin 0.5
10	Aripiprazole 9.0 Quetiapine 30.0 Zuclopenthixol 10.0	Valproate 936.0		Cetirizine 10.0
Blue-blocking glasses				
11	Quetiapine 350.0 Zuclopenthixol 20.0		Lithium sulphate 84.0	
12	Olanzapine 20.0	Valproate 562.6		
13	Olanzapine 15.0			
14	Chlorpromazine 500.0		Lithium sulphate 166.0	Clonazepam 1.25 Cetirizine 10.0, Promethazine 25.0
15	Olanzapine 6.9 Quetiapine 600.0	Valproate 450.0		
16	Olanzapine 25.0	Lamotrigine 200.0	Lithium sulphate 192.6	Clonazepam 0.9
17	Aripiprazole 10.0			
18	Chlorprothixene 100.0, Olanzapine 40.0		Lithium sulphate 249.0	Buspirone 30.0, Clonazepam 2.25
19	Risperidone 0.6	Lamotrigine 162.5	Lithium sulphate 120.8	Alimemazine 3.75, Mirtazapine 24.4[b]
20	Olanzapine 15.0	Valproate 600.0		

[a]Patients 2 and 5 were administered ibuprofen 250 mg/day. Ibuprofen may affect melatonin production.
[b]Sedation is a recognized side-effect of the antidepressant mirtazapine

the regression analysis and computation of mean (95% CI). The significance level was set to 0.05. The computation was carried out in SPSS 25 and R 3.5.0 (R Team, 2018). The graphics were created using Matlab 9.0.

3 | RESULTS

Thirty-two patients were randomized to one of the two intervention groups (Figure 1). Two patients were unable to adhere to the protocol and six patients withdrew consent. One patient was excluded due to withdrawal symptoms and one patient's actigraphy recording failed. In the BB group, one patient dropped out after one night and for another patient the first night recording was invalid. In the placebo group, two patients dropped out after five and six nights, respectively. This yielded 20 patients for the ANCOVA analyses, 10 patients in the BB group and 10 patients in the placebo group.

Clinical characteristics of the current episode, previous medical history and measures of seasonality and morningness/eveningness

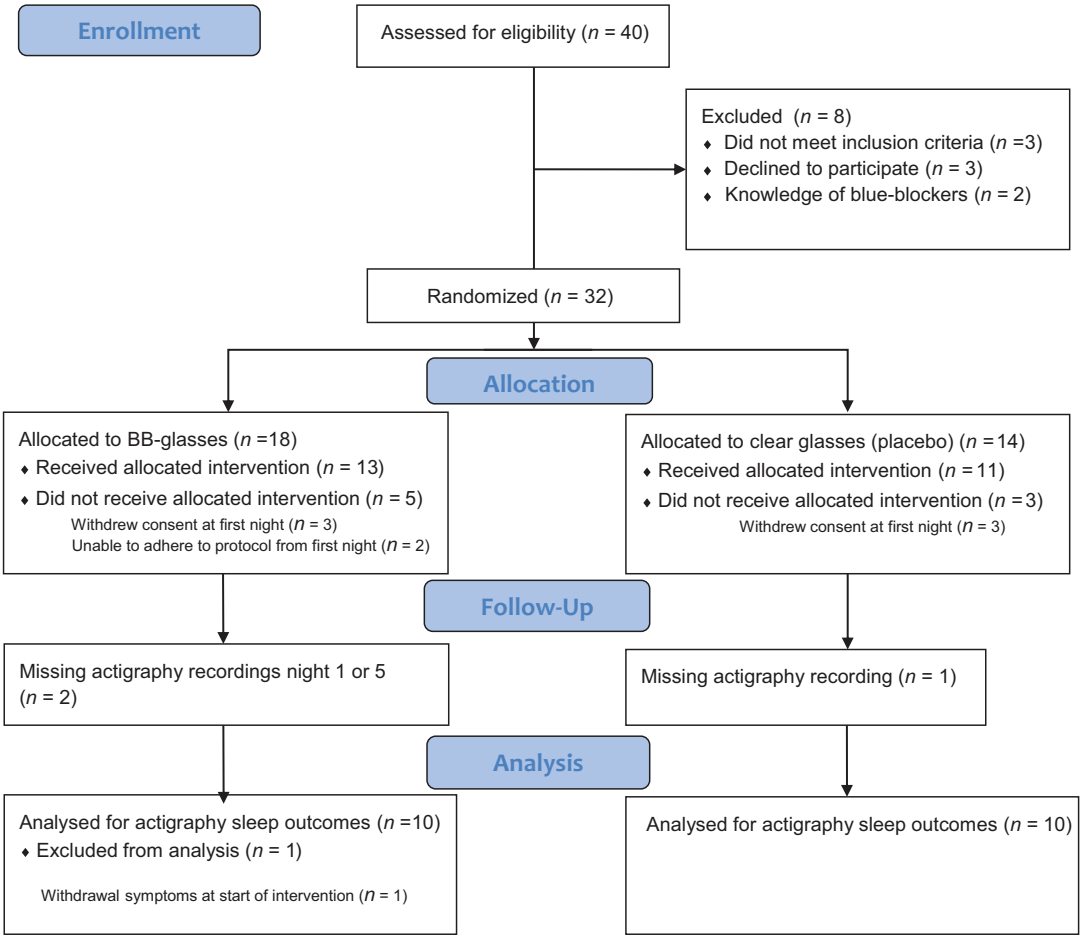


FIGURE 1 Trial profile

are shown in Table 2. The placebo group was somewhat older (mean 48.8 years vs. 43.9 years) and had a modestly higher mean YMRS total score at the start of the intervention (26.8 vs. 23.9). The placebo group scored on average as more morning type than the BB group (MEQ: 60.4 ± 5.8 vs. 52.4 ± 14.8, respectively). The data on seasonality were similar across the groups; mean GSS scores were under the cut-off for sub-SAD for both the placebo and the BB groups (8.1 vs. 7.3, respectively). Approximately the same proportion of patients in the two groups reported a seasonal change in sleep of 1 hour or more.

The BB group received less medication per TAU than the placebo group. Only 3/10 patients in the BB group received two or more different types of antipsychotics, versus 8/10 in the placebo group. For anxiolytics, hypnotics or sedatives, the ratios were 4/10 for the BB group and 9/10 for the placebo group (Table 1).

After five nights of intervention, the BB group's mean sleep efficiency was significantly higher as compared to the placebo group (p = .027). The mean sleep efficiency in the BB group increased from day one (88.1%; 95% CI, 82.4%–93.8%) to night 5 (92.6%; CI, 89.4%–95.8%), whereas the placebo group's mean sleep efficiency showed little change from night 1 (83.4%; CI, 71.2%–95.6%) to night 5 (83.1%; CI, 75.9%–90.3%) (Figure 2, Table S1).

The BB group showed lower activity counts per epoch (one epoch = 30 s) during the main sleep interval at night 5 compared to the placebo group (p = .007). In the BB group, the mean activity during the main sleep interval declined from night 1 (20.0; CI, 9.1–30.9) to night 5 (11.7; CI, 5.6 – 17.8), whereas the placebo group's mean activity during the sleep period increased markedly from night 1 (33.3; CI, −0.1–66.6) to night 5 (47.4; CI, 17.5–77.3).

Wake after sleep onset at night 5 was significantly lower in the BB group (p =.010), for which the wake time nearly halved from night 1 (60.7 min; CI, 23.6–97.7 min) to night 5 (33.5 min; CI, 19.8–47.1 min). The placebo group's wake time increased from night 1 (64.8 min; CI, 14.7–114.9 min) to night 5 (79.2 min; CI, 48.0–110.3 min) (Figure 3, Table S1).

TABLE 2 Characteristics of patients with mania assigned to blue-blocking (BB) glasses or placebo glasses (mean/*SD*)

	Placebo *n* = 10	BB glasses *n* = 10
Age (years)	48.8 (14.1)	43.9 (11.8)
Sex (male)	8/10	6/10
Current episode		
Days from admittance to start of intervention[a]	5 (1–21)[b]	6 (1–20)
YMRS day 0	26.8 (7.5)	23.9 (8.7)
Change in YMRS day 0 to day 1	−1.7 (1.6)	−5.5 (2.9)
Change in YMRS day 0 to day 5	−3.8 (9.1)	−12.9 (7.5)
Data on season, seasonality, morningness/eveningness		
Season for data collection		
Spring (March–May)	3/10	2/10
Summer (June–August)	2/10	1/10
Autumn (September–November)	2/10	5/10
Winter (December–February)	3/10	2/10
Global seasonality score (GSS)	8.1 (5.5)	7.3 (4.6)
Seasonal sleep variability 1 hr or more	5/9	7/10
Morningness–Eveningness Questionnaire (MEQ)	60.4 (5.8)	52.4 (14.8)
Clinical characteristics, medical history		
Self-reported age at first affective episode	22.3 (9.5)	23.4 (12.0)
Duration of illness (years)	24.0 (12.5)	18.1 (11.7)
Lifetime medication use		
Antidepressants	2/10	7/10
Antipsychotics	8/10	09/10
Anticonvulsants	7/10	8/10
Lithium	7/10	5/10
Hypnotics/sedatives	7/10	7/10
Anxiolytics	4/10	6/10

[a]Median/range.

[b]Without patient with extreme value of 535 days, *n* = 9.

For the secondary outcome measures total sleep time, sleep maintenance, sleep fragmentation index and wake bouts, the BB group improved and the placebo group worsened, but the differences were not statistically significant in this sample (Figure 3, Table S1).

Descriptively, there were fewer nights of biphasic or polyphasic sleep in the BB group as compared to the placebo group, when counting number of nights with one or more periods of active wake for 30 min or longer. During the first five nights of actigraphy monitoring, 29.6% (16/54) of valid night recordings for the BB group showed interrupted sleep, compared to 43.8% (21/48) in the placebo group (Table S2). Because the observation of less biphasic or polyphasic sleep in the BB group was made during the course of the study, without an *a priori* hypothesis, we chose to merely describe this without pursuing statistical testing.

We also observed that several patients in both groups showed irregular sleep timing during the intervention. High day-to-day variability of the length of the sleep interval, centred on a relatively stable mid-sleep time, was a characteristic sleep–wake pattern in several patients, as shown in data on sleep outcomes for the full 7 days of observation (Figure S1). For several patients, every other night's sleep interval was either short or contained one or more long active wake periods. This pattern could be seen in both groups, but seemed to be most prominent in the placebo group (Figure 4). The 48-hr-like rhythm is also recognizable in the overview of data for the 7 days shown in Figure S1.

4 | DISCUSSION

In this paper, we present data from the first study on change in actigraphy-derived sleep outcomes and sleep patterns during intervention with BB glasses for BD patients in a manic episode as compared to clear-lensed placebo glasses. Data on the effect on overall manic symptoms have been published previously (Henriksen et al., 2016).

Sleep efficiency increased and mean motor activity in the sleep interval decreased in the BB group. For both primary outcomes, the BB group significantly improved as compared to the placebo group by night 5. Time in wakefulness after sleep onset was also significantly lower in the BB group. For the remaining measures of sleep fragmentation, there were no significant group differences.

Several patients showed a 48-hr-like rhythm of a night of longer sleep alternating with a night of shorter sleep with mid-sleep–wake periods. This pattern could be seen in both groups, but seemed to be more pronounced in the placebo group (Figure 4). Many authors have previously described a distinct 48-hr pattern of activity in bipolar patients, but after a burst of papers in the 1970s the interest faded (Wehr, Goodwin, Wirz-Justice, Breitmaier, & Craig, 1982). It has recently been suggested that the 48-hr-like rhythm of interrupted sleep in bipolar disorder might reflect an amplified dopamine tone, as a footprint of a pathologically prolonged dopamine ultradian oscillator (DUO) rhythm (Blum et al., 2014). In mice, a similar 48-hr activity rhythm is provoked by pharmacologically increasing the availability of dopamine (Blum et al., 2014). Based on the observed decline in Young Mania Rating Scale items reflecting dopamine function in the BB group of the VATMAN trial, we have previously hypothesized that the BB intervention may decrease dopamine tone (Henriksen et al., 2016). The multiple examples of 48-hr-like activity patterns in this sample are interesting in relation to the theory of DUO-influenced sleep disturbance in mania (Blum et al., 2014). More research is needed to establish whether the rhythm of motor activity bursts can serve as a proxy for dopamine tone in humans.

It is also of note that during the first five nights the placebo group's sleep worsened on all outcomes related to activated sleep. Our findings add to the growing literature on poor sleep quality for

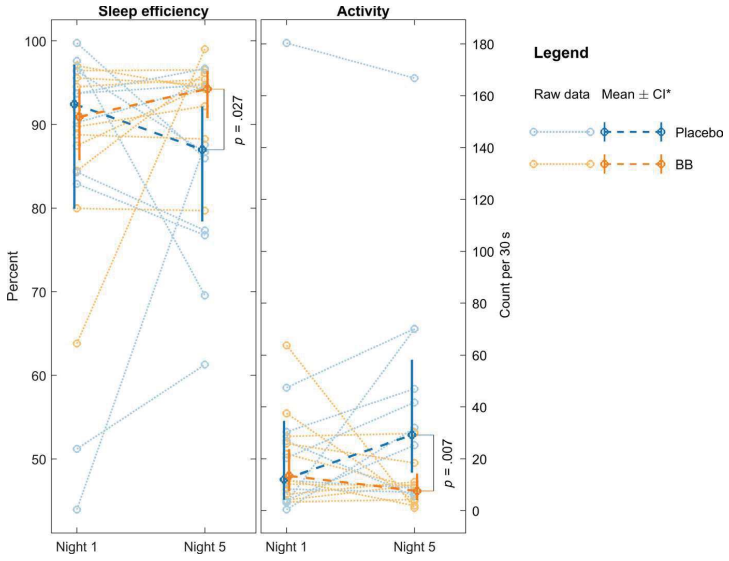


FIGURE 2 Sleep efficiency and motor activity during the sleep interval (counts per 30 s) for the patients included in the ANCOVA analysis at night 5. Raw data and the retransformed means for the blue-blocking glasses (BB) group (n = 10) and the placebo group (n = 10) are shown, and 95% confidence interval (CI), for which the 1-log transformation still applies

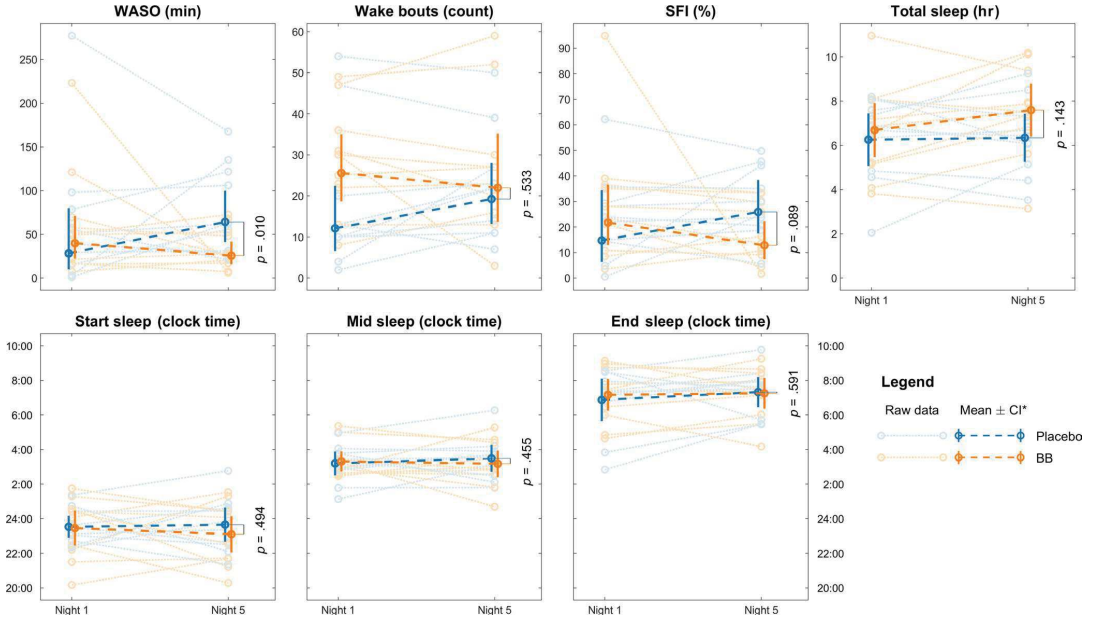
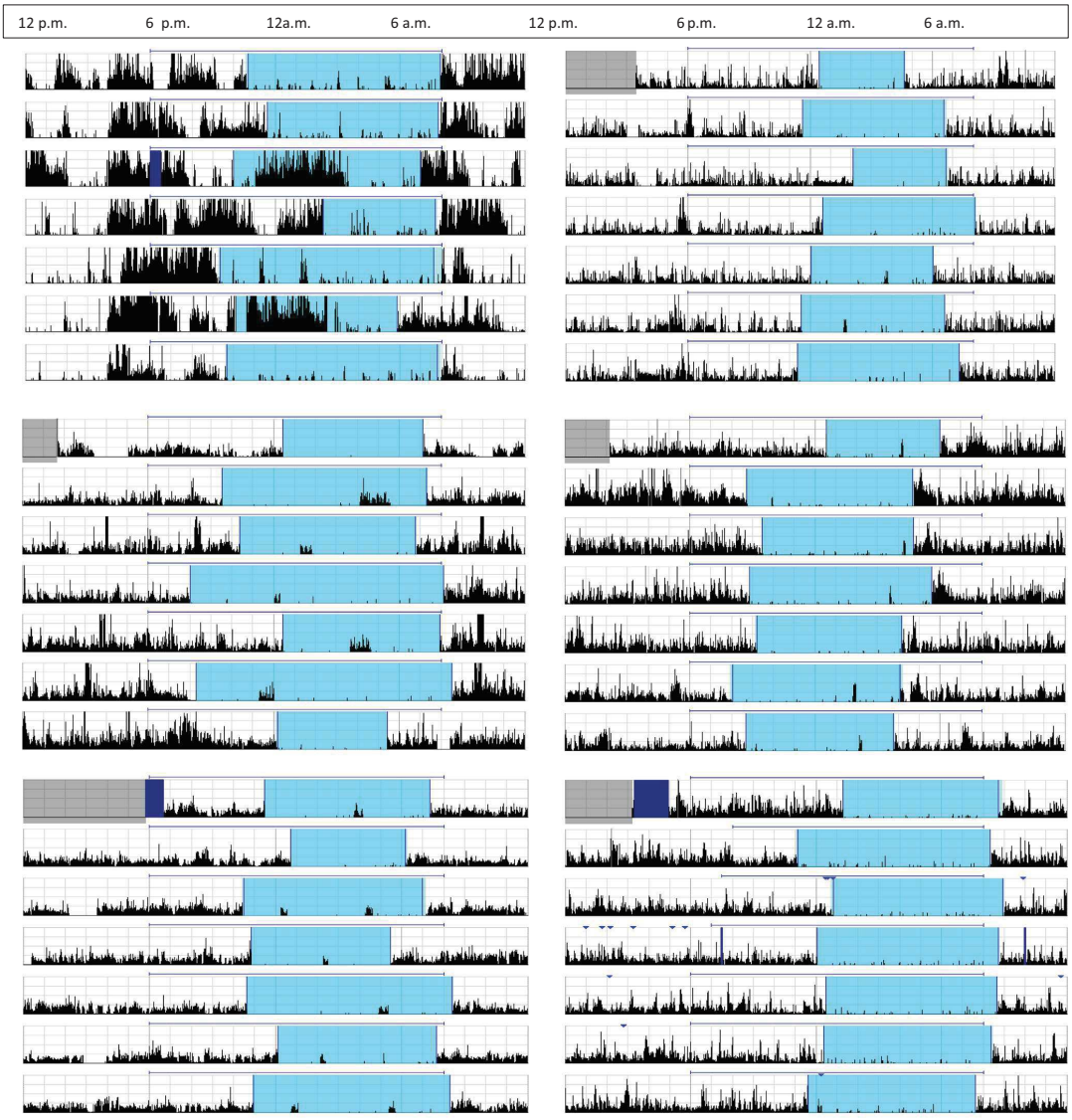


FIGURE 3 Secondary sleep outcomes for the patients included in the ANCOVA analysis. For the outcomes wake after sleep onset (WASO), wake bouts, sleep fragmentation index (SFI) and total sleep, the means were 1-log transformed for the analysis and retransformed for the figure, whereas the 95% confidence intervals (Cis) are still 1-log transformed

hospitalized patients, and how the hospital environment may even worsen sleep (Horne, Hay, Watson, & Anderson, 2018; Lei et al., 2009; Muller, Olschinski, Kundermann, & Cabanel, 2016; Veale, 2019). Several factors in the hospital setting could have an impact on sleep; for example, noise, regular nightly inspection rounds and light flashes. Because the sole intervention in this study was to alter light exposure in the evening and night, it is plausible that the BB group was protected from the activating effects of light at night, whereas the placebo group was not.

The placebo group received more intensive pharmacological treatment than the BB group, as reported in a previous paper from the trial and shown in Table 1 (Henriksen et al., 2016). The design was strictly



(a) Three actograms from placebo group **(b)** Three actograms from BB group

FIGURE 4 Seven-day actograms (one column, 24 hr) of three patients in the placebo group column (a, left) and three patients in the blue-blocking glasses (BB) group column (b, right). Black bars show activity counts; epoch 30 s, scale 1,000 counts maximum. Background colour: dark blue, excluded interval; light blue, main rest interval. Blue lines indicate verified use of glasses or indoor lights off. Note the more pronounced wake periods and irregular sleep–wake cycles of the three patients in the placebo group (column a, left)

naturalistic, except for the interventions, which indicates that the treating doctors regarded sleep as less of a problem for the BB group. We regard the less intensive pharmacological treatment for the BB group as a very important and clinically relevant observation.

Light at night may interfere with sleep through several mechanisms. The original two-process model of sleep regulation describes two independent synergistic processes regulating sleep propensity (Borbely, 1982). Process S describes the homeostatic build-up of sleep debt during wake. Process C refers to the circadian rhythm component (Borbely, 1982). This model still holds ground, but the original model of two independent factors has recently been revised (Xu & Lang, 2018). New research has revealed multiple

reciprocal interactions between these two processes; examples are reduced circadian amplitude and altered clock functioning by increased sleep homeostatic pressure (Borbely, Daan, Wirz-Justice, & Deboer, 2016). Hubbard et al. go further and suggest an expansion of the two-process model to also include the influence of ambient light as a third separate process (Hubbard, Ruppert, Gropp, & Bourgin, 2013).

In modern society, light exposure is a concomitant of wakefulness. Picture a manic patient waking up at 03:00 hours feeling rested. This patient will surely not stay in bed in a dark room but rather reach for the light switch and suddenly feel even more awake and energetic. In this example, wake and light form a reinforcing feedback loop, directly and rapidly affecting the sleep-regulation processes. Short-wavelength light through the ipRGC system counteracts and withholds the effects of the sleep-promoting factor S (sleep depth), through activating wake-promoting projections to the hypothalamus, and via SCN-hypothalamic and brainstem-hypothalamic projections (Hattar et al., 2006; LeGates et al., 2014; Saper & Fuller, 2017). Light also exerts effects on factor C, the circadian rhythm, through change in timing and amplitude of the incoming daylight signal to the SCN and suppression of melatonin secretion (LeGates et al., 2014).

Conversely, BB glasses should have the potential to reduce the nightly sleep-inhibiting effects of the third factor, light, on both process S and process C. Elimination or reduction of the daylight signal in the evening and at night allows for less light-mediated activation and thereby stronger sleep-promoting influence from the homeostatic factor S. Several patients spontaneously reported a sudden awareness of feeling calm, tired or sleepy after putting on the BB glasses. Patients in a manic state are relatively sleep deprived and in this state may be particularly sensitive to the activating effects of light (Gold & Sylvia, 2016; Henriksen et al., 2016).

The previously reported YMRS and activity data from the RCT suggested that deactivation was the first and foremost effect of the BB intervention (Henriksen et al., 2016). The findings on sleep outcomes supported the interpretation of reduced activation in the BB group, seen as effects on sleep efficiency and reduced nightly limb movements.

In the analyses of the sleep outcomes related to circadian factors (process C), such as phase shift of rest and activity rhythm, no effect was found. Synergistic contributions to improved sleep efficiency through effects on melatonin, circadian phase, amplitude and rhythmicity are likely, but need to be tested in larger samples with longer observation.

As described in a previous publication, the interventions were visible to the participants and the nursing staff (Henriksen et al., 2016). No patients observed any intervention other than their own. We instructed the nursing staff to present a uniform approach towards the two groups; that is, encourage equally the use of the glasses according to the protocol. The study was undertaken before there was any knowledge in the patient population on the effects of BB glasses, so we regard clear glasses as a valid placebo at the time of the data collection. The patients could choose the position of the Actiwatch (left or right wrist). We did not note the individual choices, but previous studies have shown no significance of position of the actigraph regarding sleep outcomes (Littner, Kushida, Anderson, Bailey, & Berry, 2003).

The sample was small for analysing actigraphy data, making the study susceptible to type II errors. Two patients dropped out towards the end of the intervention because they were allocated to the placebo condition and not to the BB intervention (worsening of symptoms and no subjective effect). This limited the interpretation of the outcomes in the placebo group after night 5. The lack of baseline data is, however, the most serious limitation, preventing precise effect-size calculations. Based on previous observations, it is likely that some effects were present already on the first night (Henriksen et al., 2014).

From this actigraphy study on the effects of BB glasses on sleep as an adjunctive treatment for mania, we found that the BB group had significantly higher sleep efficiency and lower motor activity in sleep intervals during the course of treatment, as compared to the placebo group. The BB group received substantially less sleep-promoting medication than the placebo group. The outcomes suggest a primary sleep-promoting effect through deactivating mechanisms. Our findings support the suggestion that BB glasses are useful for improving sleep in hospitalized patients in a manic state.

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CONFLICT OF INTEREST

Tone E. G. Henriksen is a shareholder in Chrono Chrome AS. The disclosure does not apply to the planning and data collection for the VATMAN trial.

AUTHOR CONTRIBUTION

TEGH has contributed substantially to the conception and design, literature search, the acquisition of data, processing, analysis and interpretation of data, and drafting and revision of the manuscript. OBF and AL have contributed substantially to the design, interpretation of data and revision of the manuscript. HS, IL and JBB have contributed substantially to the acquisition of data and revision of the manuscript. JG has contributed substantially to the processing, analysis and interpretation of data, and drafting and revision of the manuscript. JA has contributed substantially to the analysis and interpretation of data, and drafting and revision of the manuscript. KY has contributed substantially to the interpretation of data, and drafting and revision of the manuscript.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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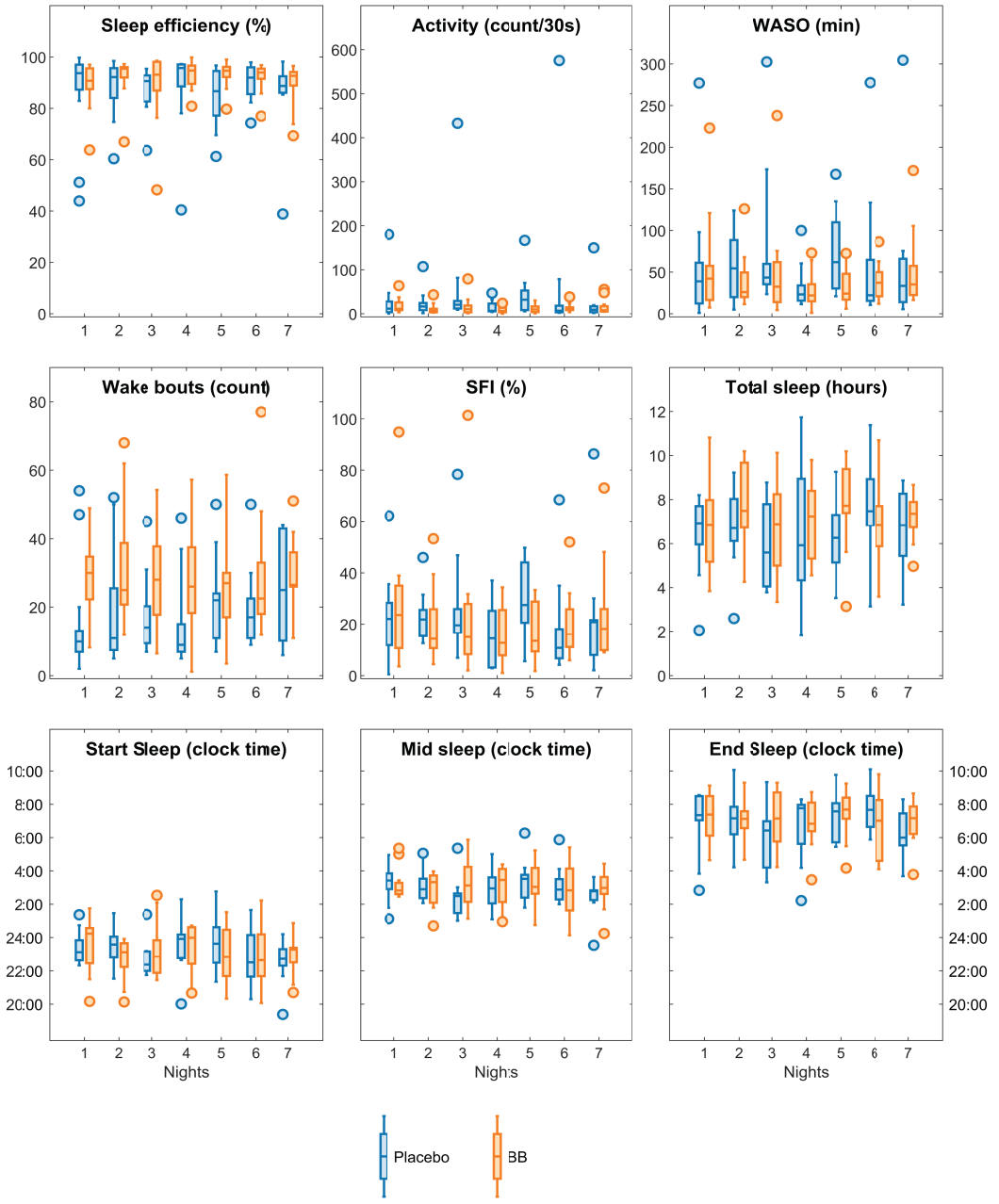
Figure legend for Supplemental figure 1

Boxplot of the distribution of the actigraphy-derived sleep outcomes for all seven days of intervention for the BB-group (orange) and the placebo-group (blue). The horizontal line of the boxes represent the median = 50% quartile (Q1) . The boxes is the the interquartile range (IQR) from the 25 % (Q1) -75% (Q3) quartiles. The whiskers extends from Q1 -1.5*IQR to Q3 + 1.5*IQR Circles represent outliers.


Sleep efficiency (%)
Activity (count/30s)
WASO (min)
Wake bouts (count)
SFI (%)
Total sleep (hours)
Start Sleep (clock time)
Mid sleep (clock time)
End Sleep (clock time)
Nights
Placebo
BB

Supplemental table 1. Means and 95% confidence intervals (CI) for motor activity, sleep and wake outcomes for patients assigned to blue-blocking glasses (BB) or clear glasses (placebo)

	Night 1		Night 5	
	N	Mean (95%CI)	N	Mean (95%CI)
Sleep eficiency (%)				
Placebo	10	83.4 (71.2 , 95.6)	10	83.1 (75.9 , 90.3)
BB	11	88.1 (82.4 , 93.8)	11	92.6 (89.4 , 95.8)
Activity (counts/30 seconds)				
Placebo	10	33.3 (-0.1 , 66.6)	10	47.4 (17.5 , 77.3)
BB	11	20 (9.1 , 30.9)	11	11.7 (5.6 , 17.8)
WASO (minutes)				
Placebo	10	64.8 (14.7 , 114.9)	10	79.2 (48 , 110.3)
BB	11	60.7 (23.6 , 97.7)	11	33.5 (19.8 , 47.1)
Wakebouts (number)				
Placebo	10	18.3 (7.3 , 29.3)	10	22.6 (14.3 , 30.9)
BB	11	28.5 (21.1 , 36)	11	27.3 (17.7 , 36.8)
Sleep fregmentation index				
Placebo	10	23.5 (12.7 , 34.3)	10	29.8 (21.2 , 38.4)
BB	11	29.5 (15 , 44.1)	11	17.3 (10.5 , 24)
Total sleep time (hours)				
Placebo	10	6.3 (5.1 , 7.4)	10	6.3 (5.3 , 7.4)
BB	11	6.7 (5.5 , 7.9)	11	7.6 (6.4 , 8.8)

Supplemental table 2. Number of patients showing interrupted sleep by active wake period(s) in main sleep interval (wake and continuous motor activity for 30 minutes or longer) and valid actigraphy recordings (N) in the blue-blocking (BB)-group and placebo-group (clear glasses).

Night#	BB	(N)	Patients with interrupted sleep BB-group	Placebo	(N)	Patients with interrupted sleep placebo-group
Night 1		11	5		10	3
Night 2		10	2		10	5
Night 3		11	3		10	6
Night 4		11	3		8	1
Night 5		11	3		10	6

Supplemental information 1

Criteria for manually setting of major rest-intervals:

Start of major rest-interval was defined a significant drop in activity after 6 p.m. Sudden reduction in white light levels (lux) was interpreted as time for intent to fall asleep and guided the placement of start-time of rest intervals if accompanied by significant and drop in activity. Nurse-reports used as additional information.

In cases where a sustained decrease of activity was present but light intensity did not change, this was interpreted as the patient rested without turning off the light. In these cases the light exposure was not used as a help criterion. In cases where the nurse-reports differed from decrease of activity, the nurse-reports were not used as help criterion.

A short period of increased activity and/or light exposure was interpreted as shorter time out of bed to go to the bathroom etc. A longer period of time of increased activity and/or light exposure was kept within the major rest interval if it was followed by a period of inactivity indicating sleep (starting with minimum 10 minutes of inactivity followed by significant and sustained decrease in activity) for minimum 60 minutes starting before 8 a.m.

End of the rest interval was defined as significant and sustained increase in activity level. Significant and sustained increase in light exposure was used as help criterion. The first (30 second) epoc of 0 (movements) preceding the epoch of abrupt increase in lux was set as end time of rest interval, if the criterion of significant and sustained increase in activity was also fulfilled from that same time-point. In cases where the activity level was low and stable but light intensity increased, this was interpreted as sunrise or another person controlling the light. In these cases the light exposure was disregarded as help criterion. Nurse-reports on the patients getting out of bed were used as help criterion. In cases where the nurse report differed from abrupt increase in activity, the nurse-report was overruled by the activity-data.

III

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Motor activity patterns in acute schizophrenia and other psychotic disorders can be differentiated from bipolar mania and unipolar depression

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ABSTRACT

The purpose of this study was to compare 24-h motor activity patterns between and within three groups of acutely admitted inpatients with schizophrenia and psychotic disorders (n = 28), bipolar mania (n = 18) and motor-retarded unipolar depression (n = 25) and one group of non-hospitalized healthy individuals (n = 28). Motor activity was measured by wrist actigraphy, and analytical approaches using linear and non-linear variability and irregularity measures were undertaken. In between-group comparisons, the schizophrenia group showed more irregular activity patterns than depression cases and healthy individuals. The schizophrenia and mania cases were clinically similar with respect to high prevalence of psychotic symptoms. Although they could not be separated by a formal statistical test, the schizophrenia cases showed more normal amplitudes in morning to evening mean activity and activity variability. Schizophrenia constituted an independent entity in terms of motor activation that could be distinguished from the other diagnostic groups of psychotic and non-psychotic affective disorders. Despite limitations such as small subgroups, short recordings and confounding effects of medication/hospitalization, these results suggest that detailed temporal analysis of motor activity patterns can identify similarities and differences between prevalent functional psychiatric disorders. For this purpose, irregularity measures seem particularly useful to characterize psychotic symptoms and should be explored in larger samples with longer-term recordings, while searching for underlying mechanisms of motor activity disturbances.

1. Introduction

Disturbed motor activity is a frequently occurring symptom in psychotic disorders (APA, 2000; WHO, 1993). Motor behavior in schizophrenia is traditionally detected clinically through observation and rating scales, even though clinical evaluation in general and individual rating scale items in particular appear to correlate poorly with objective quantifications of movement (Walther et al., 2009c). If assessment of motor symptoms was made more comprehensive and reliable, specific motor characteristics related to psychosis could help distinguish subtypes within the schizophrenia spectrum and delineate the boundaries to other psychiatric illness categories (Hauge et al., 2011; Walther et al., 2009b).

Actigraphy is a validated approach to record movement as longitudinal rest-activity patterns (Ancoli-Israel et al., 2003). Most devices are wrist-worn and well-tolerated by patients in psychiatry. Relatively few studies have applied actigraphy to samples with schizophrenia and psychotic disorders, usually to assess sleep estimates or mean activity levels (Docx et al., 2013; Tahmasian et al., 2013; Wichniak et al., 2011). Actigraphy studies that consider motor activity patterns in more complex time series analyses do, however, seem to be more promising regarding correlation with specific symptom characteristics. These studies have predominantly come from one group in Switzerland (Walther et al., 2009a; Walther et al., 2009b; Walther et al., 2014; Walther et al., 2015), and our collaborators in Bergen, Norway (Berle et al., 2010; Fasmer et al., 2016; Hauge et al., 2011). This research shows that negative symptoms correlate with reduced activity and inversely, that less rest is common during marked positive

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syndromes (Walther et al., 2009b). In a group of patients with chronic psychosis, activity patterns were more variable and more irregular compared to healthy individuals, but in contrast, contained longer periods of inactivity and lower variability compared to depressed patients (Fasmer et al., 2016; Hauge et al., 2011).

In several publications on acutely ill inpatients with affective disorders, we have applied linear and nonlinear analytical methods to 24-h actigraphy recordings (Krane-Gartiser et al., 2015; Krane-Gartiser et al., 2014; Krane-Gartiser et al., 2016). For mania, we found irregular activity patterns that are stable within 24 h, whereas depressed subgroups demonstrated low total activity, higher variability between active and inactive periods and several changes in activity parameters within 24 h (Krane-Gartiser et al., 2014; Krane-Gartiser et al., 2017). As schizophrenia cases in other studies have shown motor features that resemble our findings for both mania and depression, the aim of the current study was two-fold: first, to characterize 24-h motor activity patterns in a new group of inpatients with schizophrenia and psychotic disorders, and second, to compare them to inpatients from the same setting with bipolar mania and motor-retarded unipolar depression and to a non-hospitalized group of healthy individuals. We hypothesized that cases with depression would have lower activity levels and more regular patterns compared to the other groups, and that cases with mania and schizophrenia would show similar features of irregularity in activity patterns. Because our application of linear and nonlinear dynamics in between-group comparisons as well as in within-group analyses from morning to evening has proven valuable, we wanted to undertake the same procedure for the group with schizophrenia and psychotic disorders.

2. Materials and methods

2.1. Sample

Inpatients were asked to participate in the study as they were consecutively admitted to Østmarka Department of Psychiatry, Trondheim University Hospital, Norway. This is the only department for acute psychiatric admissions in the catchment area, and all psychiatric emergency services in Norway are public. The only exclusion criterion was inability to grant informed consent. Patients were asked to wear an actigraph for 24 h on one of the first days after admission, and a total of 280 actigraphy recordings were undertaken between September 1st, 2011 and March 31st, 2012. Diagnoses were set in an expert consensus meeting according to ICD-10 research diagnostic criteria (WHO, 1993), by at least three specialists in psychiatry of whom one had been the patient's therapist and another personally knew the patient. The experts reviewed all available information when setting the diagnosis. Twenty-eight patients with a 24-h actigraphy recording had a primary diagnosis of schizophrenia and other psychotic disorders. Eighteen of them fulfilled the criteria for schizophrenia (13 paranoid schizophrenia (F20.0), 3 hebephrenic schizophrenia (F20.1), 1 simple schizophrenia (F20.6) and 1 schizophrenia unspecified (F20.9)), 2 patients had persistent delusional disorders (F22.0), 3 had acute and transient psychotic disorders (F23), 4 had schizoaffective disorders (F25) and 1 had an unspecified nonorganic psychosis (F29). Thus, 28 cases with schizophrenia spectrum disorders were compared to 18 inpatients with a primary diagnosis of bipolar disorder, current episode manic (7 patients without psychotic symptoms (F31.1) and 11 with psychotic symptoms (F31.2)) and 25 inpatients with unipolar depression (UP) and psychomotor retardation. UP cases with any observable motor retardation were classified as motor-retarded, as defined by the Symptomatic Organic Mental Disorder Assessment Scale, item B: “Degree of motor retardation, rated during the period or periods of the previous 24 h in which the patient was most depressed.” (Krane-Gartiser et al., 2015). Three of the patients with unipolar depression were in a mild depressive episode (F32.0 or F33.0), 15 in a moderate episode (F32.1 or F33.1) and 7 in a severe episode without psychotic symptoms (F32.2 or F33.2).

2.2. Recordings of motor activity

Motor activity was recorded by wrist-worn actigraphy (Actiwatch Spectrum, Philips Respironics Inc., Murrysville PA, USA). The actigraph integrates the intensity, amount and duration of wrist movement in all directions into an activity count per time unit. Patients and healthy controls were instructed to wear the actigraph continuously during 24 h, constituting 1440 min for analysis for complete recordings. Three cases from each patient-group had recordings with a duration < 22 h; the median recording was 1429 min (schizophrenia group), 1436 min (mania group) and 1439 min (UP group).

Activity counts were recorded for one-minute intervals (epochs). Data were analyzed for the total time of recording (24 h). For each case, we also selected morning and evening epochs by inspecting each recording for the first 64-min period of continuous activity in the morning after 6 AM and for the last 64-min period of continuous activity in the evening before midnight. 64 min were chosen because the Fourier analysis requires sequence lengths to be potencies of 2 (32, 64, 128…) and from previous experience, it can be difficult to find periods of continuous activity that are longer than one hour.

One patient from the schizophrenia/psychotic disorders group lacked a 64-min active sequence in the morning, as well as two patients with mania and two UP patients. These patients were omitted from morning series analyses, reducing the group with psychotic disorders to 27, the group with mania to 16 and the group with UP to 23 patients. One patient with a psychotic disorder, two UP patients and one healthy control lacked a 64-min active sequence in the evening. Thus, in the evening series analyses, 27 patients with psychotic disorders were compared to 18 patients with mania, 23 patients with depression and 27 healthy individuals.

2.3. Mathematical analyses

We calculated means for the whole recording period and for the 64-min periods of continuous motor activity. As measures of variability in activity counts, for each time series we also calculated:

a) the standard deviation (SD) as an intra-individual measure of fluctuations from the mean
b) the root mean squared successive difference (RMSSD), which describes the difference in successive counts from minute to minute
c) the RMSSD/SD ratio

For the 64-min periods we further assessed:

a) sample entropy as a measure of complexity or irregularity
b) autocorrelation (lag 1)
c) ratios between high-frequency and low-frequency variance in a Fourier analysis

All these mathematical approaches characterize different phenomena of a time series: mean levels, variability and complexity features. For the calculation of sample entropy and the Fourier analysis, free software is available from the Physio Toolkit Research Resource for Complex Physiologic signals (Goldberger et al., 2000), see http://www.physionet.org.

2.3.1. Sample entropy

Sample entropy is a nonlinear measure that indicates the degree of regularity (complexity) of a time series. A low sample entropy value corresponds to a more regular series. It is the negative natural logarithm of an estimate of the conditional probability that subseries of a certain length (m) that match point-wise, within a tolerance (r), also match at the next point. We chose the following values, $m = 2$ and

$r = 0.2$. Data were normalized by transforming the time series to have sample mean 0 and sample variance 1 (Richman and Moorman, 2000).

2.3.2. Autocorrelation at lag 1

The autocorrelation at lag 1 is the correlation of a time series with itself lagged one step, in this case from minute to minute. Values closer to one indicate a stronger correlation. Autocorrelation analyses were performed using SPSS version 24.0.

2.3.3. Fourier analysis

Results are presented as the relation between variance in the high frequency part of the spectrum (0.0021–0.0083 Hz, corresponding to the period from 2–8 min) and the low frequency part (0.00026–0.0021 Hz, corresponding to 8–64 min). Data were normalized before analysis, and no windows were applied.

2.4. Statistics

Statistical analyses were planned in advance, based on previous studies (Krane-Gartiser et al., 2017) and carried out using SPSS version 24.0. For comparison of counts of categorical data we used chi-square tests, and for comparison of means, we used one-way analyses of variance (ANOVAs) with Least Significant Difference (LSD) post-hoc tests to obtain differences between groups. In covariance analyses (ANCOVAs), we controlled for antipsychotic medication treatment. To obtain within-group differences between variables in the morning and evening, we used paired samples T-tests. Finally, we tested group differences in changes from morning to evening using linear mixed models for patient groups only. A p-value $\leq .05$ was considered significant.

2.5. Ethics statement

The patient study and healthy control study were approved by the Regional Committee for Medical and Health Research Ethics of Central Norway and Western Norway, respectively. All participants gave written informed consent to participation before inclusion. The patients' capacity to consent was established by a senior psychiatrist or a specialist in clinical psychology.

3. Results

Subject characteristics are shown in Table 1. There were no significant between-group differences in age or gender distribution. Body mass index (BMI) data were not available for the healthy controls, but the patient-groups did not differ in BMI. Psychotropic drug treatment for the three patient-groups is summarized in Table 2. We were unable to compare medication statistically between groups due to a variety of medications used and uneven and/or small numbers per category. As can be expected, a larger proportion of cases with schizophrenia and mania were prescribed antipsychotics and cases with depression antidepressants; cases with mania received mood stabilizers most often.

24-h actigraphy recordings for one representative subject from each group are presented in Fig. 1. All patient-groups showed a significantly reduced mean level of activity over 24 h compared to healthy individuals, the depressed cases demonstrated the lowest mean level among all groups (Table 3). In addition to lower mean activity, the depression cases further displayed increased fluctuations from the mean and more shifts between inactivity and activity, as given by an increased SD/min. In terms of successive count variability (RMSSD/min), both the schizophrenia/psychotic disorders group and the UP group showed increased levels compared to healthy controls, and all patient-groups had higher RMSSD/SD ratios than healthy individuals.

In the 64-min periods of continuous motor activity, there were more between-group differences in the morning than in the evening period (Table 4). Patients were significantly less active in the morning compared to healthy individuals. Again, the UP cases showed an increased SD/min compared to other groups in both the morning and evening periods. The schizophrenia and UP groups had higher RMSSD values than healthy individuals in the morning, indicating more minute-to-minute differences in activity counts. With regards to the relationship

Table 2
Medical treatment.

Treatment	Schizophrenia (n = 28)	Mania (n = 18)	Unipolar depression (n = 25)
Antipsychotics	20 (71%)	15 (83%)	6 (24%)
Hypnotics/anxiolytics	10 (36%)	9 (50%)	12 (48%)
Anticonvulsants	4 (14%)	7 (39%)	3 (12%)
Lithium	0	2 (10%)	0
Antidepressants	3 (11%)	1 (5%)	9 (36%)
Antihistamines	2 (7%)	0	2 (8%)
ECT	0	0	1 (4%)
No psychotropic drug treatment	5 (18%)	1 (5%)	5 (20%)

All values are shown as n (%).

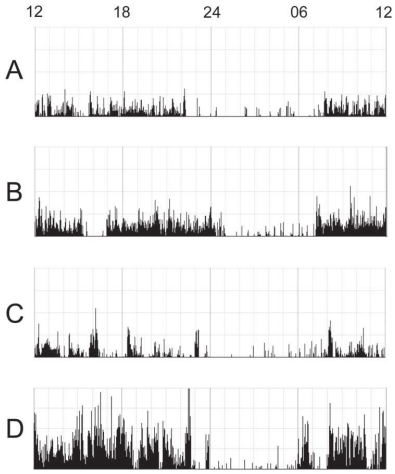

Fig. 1. 24-h actograms from a representative subject in each group. Actogram A is from a patient with schizophrenia, Actogram B from a patient with mania, Actogram C from a patient with motor-retarded unipolar depression and Actogram D from a healthy control subject. Time of day is shown at the top from 12 h to 12 h the next day (24-h clock). Activity counts are shown as black, vertical lines on a scale from 0–1000 counts. One square in the grid thus represents one hour on a horizontal axis and 250 activity counts on a vertical axis.

Table 1
Demographic data.

Variable	Schizophrenia (n = 28)	Mania (n = 18)	Unipolar depression (n = 25)	Healthy controls (n = 28)
Age (years) (mean ± SD)	41.5 ± 11.5	51.2 ± 15.4	43.8 ± 15.9	41.7 ± 11.6
Gender (female, n (%))	15 (54%)	11 (61%)	15 (60%)	13 (46%)
Body Mass Index (mean kg/m^2 ± SD)	27.9 ± 6.6	27.0 ± 5.8	25.1 ± 5.6	–

Table 3
24-h actigraphy recordings of motor activity.

Variable	Schizophrenia (SCZ)	Mania	Unipolar depression (UP)	Healthy controls (HC)	*p*-value[a]	Post hoc test[b]
Duration of recording in minutes	1381 ± 129	1344 ± 244	1363 ± 207	1440 ± 0	.188	
Mean activity count/minute	139 ± 81	157 ± 84	91 ± 47	203 ± 71	**< .001**	SCZ vs. UP: 0.015; SCZ vs. HC: 0.001; Mania vs. HC: 0.036; Mania vs. UP: 0.004; UP vs. HC: < 0.001
SD/minute in % of mean	169.7 ± 49.7	145.1 ± 39.1	206.1 ± 49.0	147.3 ± 29.8	**< .001**	SCZ vs. UP: 0.003; Mania vs. UP: < 0.001; UP vs. HC: < 0.001
RMSSD/minute in % of mean	137.5 ± 55.5	113.7 ± 41.8	160.7 ± 54.8	99.1 ± 21.5	**< .001**	SCZ vs. HC: 0.002; Mania vs. UP: 0.001; UP vs. HC: < 0.001
RMSSD/SD	0.794 ± 0.121	0.774 ± 0.094	0.772 ± 0.133	0.675 ± 0.077	**< .001**	SCZ vs. HC: < 0.001; Mania vs. HC: 0.003; UP vs. HC: 0.002

All data are given as mean ± SD.
[a] *p*-values obtained in a one-way ANOVA.
[b] LSD post hoc test.
SCZ: schizophrenia and psychotic disorders; UP: unipolar depression; HC: healthy controls.
SD/minute in % of mean: Standard deviation per minute in percent of mean activity count.
RMSSD/minute in % of mean: Root mean square successive difference per minute in percent of mean activity count.

between RMSSD and SD, cases with mania or schizophrenia had increased RMSSD/SD ratios compared to UP cases and healthy individuals in the morning and compared to healthy individuals only in the evening. Variation in the high-frequency part of the spectrum relative to the low-frequency part in the Fourier analysis in the morning was higher for the schizophrenia group compared to UP cases and healthy controls. The mania group also had a significantly increased Fourier finding compared to healthy controls. The cases with schizophrenia and mania further showed more irregular patterns in the morning period, as given by increased sample entropy levels and lower autocorrelation compared to the two other groups.

After adjustment for antipsychotic medication treatment, there were fewer or less significant differences between UP cases versus schizophrenia or mania cases (mean activity over 24 h, SD in % in morning and evening periods), whereas other differences remained highly significant (RMSSD/SD, sample entropy, Fourier analysis and autocorrelation in the morning). The differences in sample entropy in the morning between schizophrenia or mania cases compared to healthy controls were no longer significant. On the other hand, other differences between schizophrenia or mania cases versus healthy controls became more significant after adjustment for antipsychotics (24-h mean activity, RMSSD/SD morning and evening, Fourier analysis and autocorrelation morning). (See Supplementary Tables S1 and S2.)

There was a greater morning to evening reduction in mean activity for healthy controls (38%) than in the schizophrenia group (20%), the UP group (20%) and the mania group (increase of 4%) (Table 5). In the evening, the schizophrenia group had increased fluctuations in activity (increased SD/min) and reduced sample entropy. The UP group showed significant changes in several variables from morning to evening: increased RMSSD and thus an increased RMSSD/SD ratio and a higher Fourier value. The healthy individuals also displayed more variability in the evening, as given by both increased SD and RMSSD levels, while there were no significant changes from morning to evening in the mania group.

In group-by-time analyses for the three patient groups only, there were no significant differences in any of the activity variables, but trend findings ($p < .1$) for Fourier analysis ($p = .065$) and autocorrelation ($p = .095$). (Supplementary Table S3.) Adjusting for antipsychotic medication treatment did not alter the results of morning to evening activity differences for any of the patient groups (data not shown).

4. Discussion

In this study, we wanted to explore whether activity patterns in schizophrenia and psychotic disorders are more similar to bipolar mania or motor-retarded unipolar depression, and if and how they differ from healthy individuals. In between-group analyses, the schizophrenia cases separated themselves from inpatients with depression and non-hospitalized healthy controls. Neither variable could distinguish schizophrenia from mania during 24 h, or in active periods. These groups characteristically showed higher activity complexity in the morning periods than depressed and healthy individuals. However, in the within-group analyses of morning to evening differences in activity, schizophrenia cases showed larger differences in several variables compared to patients in a manic episode, who were strikingly stable in activity measures from morning to evening. These within-group differences were however not statistically significant in group comparison analyses. We found that the schizophrenia and psychotic disorders group constituted an independent entity in terms of motor activity patterns, relative to inpatients with affective disorders as well as to healthy individuals.

Activation has gained renewed attention as a central phenomenon of bipolar disorder in particular, but remains understudied in psychiatric research as a whole (Scott et al., 2017a). Activation seems to represent a distinct dimension according to a recent meta-analysis of factor analytic studies, and actigraphy as an objective measure may

Table 4
Actigraphy variables from 64-min periods of continuous motor activity in the morning and evening.

Activity variable	Sequence	Schizo-phrenia (SCZ)	Mania	Unipolar depression (UP)	Healthy controls (HC)	Between- group *p*-value[a]	Post hoc test[b]
Mean activity count/ minute	Morning	232 ± 112	215 ± 144	200 ± 103	391 ± 139	**<.001**	SCZ vs. HC: < 0.001; Mania vs. HC: < 0.001; UP vs. HC: < 0.001
	Evening	195 ± 93	213 ± 122	162 ± 109	247 ± 137	.080	
SD/minute in % of mean	Morning	96.8 ± 34.7	87.3 ± 21.7	113.7 ± 26.4	89.4 ± 24.3	**.009**	SCZ vs. UP: 0.035; Mania vs. UP: 0.005; UP vs. HC: 0.003
	Evening	112.8 ± 32.5	97.4 ± 37.8	136.1 ± 48.9	112.5 ± 41.7	**.025**	SCZ vs. UP: 0.046; Mania vs. UP: 0.003; UP vs. HC: 0.043
RMSSD/minute in % of mean	Morning	96.4 ± 43.4	86.1 ± 28.6	97.5 ± 29.7	74.7 ± 23.1	**.043**	SCZ vs. HC: 0.015; UP vs. HC: 0.015
	Evening	109.7 ± 40.6	99.1 ± 46.9	128.2 ± 51.0	96.4 ± 39.0	.066	
RMSSD/SD	Morning	0.988 ± 0.165	0.980 ± 0.178	0.857 ± 0.174	0.844 ± 0.140	**.002**	SCZ vs. UP: 0.006; SCZ vs. HC: 0.001; Mania vs. HC: 0.009; Mania vs. UP: 0.023
	Evening	0.970 ± 0.156	1.011 ± 0.171	0.953 ± 0.191	0.866 ± 0.166	**.033**	SCZ vs. HC: 0.028; Mania vs. HC: 0.006
Sample entropy (m = 2, r = 0.2)	Morning	1.471 ± 0.681	1.474 ± 0.624	0.911 ± 0.432	1.114 ± 0.407	**.001**	SCZ vs. UP: < 0.001; SCZ vs. HC: 0.016; Mania vs. HC: 0.037; Mania vs. UP: 0.002
	Evening	1.038 ± 0.507	1.309 ± 0.703	0.919 ± 0.627	0.976 ± 0.516	.166	
Fourier analysis	Morning	0.98 ± 0.59	0.87 ± 0.48	0.60 ± 0.32	0.55 ± 0.27	**.001**	SCZ vs. UP: 0.003; SCZ vs. HC: < 0.001; Mania vs. HC: 0.024
	Evening	0.81 ± 0.40	1.08 ± 0.71	0.88 ± 0.58	0.72 ± 0.59	.203	
Autocorrelation	Morning	0.475 ± 0.164	0.494 ± 0.163	0.618 ± 0.148	0.628 ± 0.116	**<.001**	SCZ vs. UP: 0.001; SCZ vs. HC: < 0.001; Mania vs. HC: 0.005; Mania vs. UP: 0.011
	Evening	0.508 ± 0.147	0.470 ± 0.171	0.519 ± 0.170	0.538 ± 0.167	.131	

All data are given as mean ± SD.
[a] *p*-values obtained in a one-way ANOVA.
[b] LSD post hoc test.
SCZ: schizophrenia and psychotic disorders; UP: unipolar depression; HC: healthy controls.
SD/minute in % of mean: Standard deviation per minute in percent of mean activity count.
RMSSD/minute in % of mean: Root mean square successive difference per minute in percent of mean activity count.

Table 5
Within-group analysis of activity variables from morning to evening.

Activity variable	Within-group analysis[a]	Schizophrenia (n = 26)	Mania (n = 16)	Unipolar depression (n = 21)	Healthy controls (n = 27)
Mean activity count/ minute	Paired difference	−47	9	−41	−152
	p-value	**0.038**	0.750	0.192	**<0.001**
SD/minute in % of mean	Paired difference	16.1	7.7	21.8	24.0
	p-value	**0.023**	0.329	0.097	**0.008**
RMSSD/minute in % of mean	Paired difference	14.0	9.1	30.1	22.7
	p-value	0.067	0.405	**0.011**	**0.004**
RMSSD/SD	Paired difference	−0.010	0.018	0.102	0.024
	p-value	0.771	0.809	**0.042**	0.586
Sample entropy (m = 2, r = 0.2)	Paired difference	−0.377	−0.133	0.006	−0.133
	p-value	**0.017**	0.593	0.969	0.272
Fourier analysis	Paired difference	−0.16	0.22	0.29	0.16
	p-value	0.243	0.401	**0.016**	0.242
Autocorrelation	Paired difference	0.019	−0.012	−0.103	−0.046
	p-value	0.552	0.862	**0.023**	0.249

[a] Paired Samples T-test (morning vs. evening).

provide more knowledge about the dynamics of motor activation (Scott et al., 2017a). Along these lines, actigraphy analyses may help identify similarities and differences between functional psychiatric disorders. Ultimately, classification according to activity characteristics may complement current diagnostics of psychiatric disorder subcategories (Scott et al., 2017b). The current study is yet another contribution to decipher the linear and non-linear dynamics of motor activity between prevalent psychiatric conditions, this time with a particular emphasis on schizophrenia.

All patient groups were less active than healthy individuals, even the mania cases, which is a consistent finding in comparisons of hospitalized to non-hospitalized individuals (Burton et al., 2013) and can be due to the state of illness, medical treatment or a restricted living space. The depressed cases had significantly lower mean activity than other patient groups, but this was to be expected, as they were specifically selected for displaying motor retardation. A reduction in mean activity from morning to evening seems to be a normal feature, as found in healthy individuals. All patient groups displayed less variation/amplitude in activity from morning to evening and in particular, the mania group lacked a morning to evening variation. One can speculate whether this reduced amplitude of mean activity during active wake periods is caused by the hospital setting or influenced by medication. However, with respect to the latter, adjusting for antipsychotic medical treatment did not change the significance of within-group activity changes from morning to evening.

All patients showed increased RMSSD/SD ratios compared to healthy individuals during 24 h, which suggests that it is not a trait of any specific diagnostic group, although the ratios were significantly more elevated for psychotic disorders. A particular characteristic of the schizophrenia and depression cases was increased minute-to-minute-variability or a more fragmented pattern in the overall 24-h analysis and in the active morning period compared to other groups. While there were no significant differences to mania, schizophrenia cases showed more variable patterns as given by an increased SD/min. Osipov et al found that the standard deviation of activity was one of the most predictive motor activity features of schizophrenia (Osipov et al., 2015), which was only a trend in the current study, but the former recorded activity in 5-min intervals, as opposed to our use of 1-min intervals.

The schizophrenia and manic groups presented more complex patterns compared to both depressed patients and healthy individuals in active periods, particularly in the morning: increased short-term variability as given by findings for RMSSD/SD ratios and the Fourier analysis, and more irregularity as given by the increase in sample entropy and lower autocorrelation from minute to minute. This complexity in activity is a repeated finding for several activated states: chronic and acute psychotic disorders, acute mania, and depression with increased motor activity (Hauge et al., 2011; Krane-Gartiser et al., 2015; Krane-Gartiser et al., 2014). It is thus possible that psychotic symptoms are reflected as a higher degree of disorder in activity patterns, particularly considering that nearly 70% of manic cases presented with psychotic symptoms. This corroborates indications from the Bern group that positive syndromes and general psychopathology severity may be predicted by less structured movement patterns irrespective of the overall level of motor activity (Walther et al., 2014). Walther et al hypothesized that such disorganized motor behavior results from a conceptual disorganization that prevents proper action planning, and future studies that combine imaging and actigraphy can provide more insight into the correlation between brain activity and motor behavior (Farrow et al., 2005).

It is thinkable that more negative symptoms correspond to more prominent reductions in activity, whereas more positive symptoms rather affect other activity parameters. Consequently, with access to concurrent symptom ratings, we could have attempted to consolidate the findings of the Bern group by complementary measures (Walther et al., 2009b). Other approaches to describe variability in activity should also be pursued more definitely for schizophrenia, e.g. Van Someren's measures of intradaily variability and interdaily stability (Berle et al., 2010; Castro et al., 2015; Gonçalves et al., 2014) and the distribution of active and inactive periods (Fasmer et al., 2016; Sano et al., 2012). However, added together, these studies using slightly different methods of temporal analysis suggest that changes in psychiatric symptoms may be objectively validated by activity monitoring in future clinics. For now, actigraphy and its analytical approaches remain to be properly explored on a systematic research level to obtain a consensus on the most appropriate methodology.

In this regard, we have replicated findings for schizophrenia in the Bergen study by applying similar nonlinear measures of analysis (Hauge et al., 2011), namely increased irregularity in activity patterns. Differences, e.g. in the level of fragmentation, may be due to a more general psychotic disorders group in the current study and not simply schizophrenia, different time frames and/or the emergency inpatient setting. Furthermore, we included a within-group comparison that showed differences in the way activity profiles change from morning to evening between schizophrenia and depression, and in fact, none of these changes applied to the same variables between the two disorders. In a study of the distribution and characteristics of active and inactive periods, longer periods of inactivity were found for schizophrenia compared to depression and controls (Fasmer et al., 2016; Sano et al., 2012). It is clear that while both disorders are clinically characterized by low or disrupted movement, the microstructure of activity patterns reveals distinct differences.

A possible mechanism for the normal fluctuation in motor activity in healthy people and the pathological activity patterns seen in the patients, could be found in the interplay between the circadian (near 24

h) and ultradian (near 4 h) rhythms of arousal and motor activity (Blum et al., 2014). In nearly all species, there are regular fluctuations in arousal and motor activity influenced by endogenous chronobiologic rhythms. The most striking of these rhythms is the sleep/wake cycle, the rhythmicity of which is partly regulated by the circadian rhythm of cellular function, orchestrated by the suprachiasmatic nucleus (SCN). Less known is the existence of a faster (near 4 h) so-called ultradian rhythm of arousal and motor activity superimposed on the 24-h circadian rhythm. The ultradian rhythm is proposed to be generated by a striatal dopamine oscillator that is not controlled by the SCN (Blum et al., 2014). An intriguing recent theory is that the desynchronization of the circadian and ultradian rhythms is the cause of the pathological rhythms of motor activity and sleep/wake cycles in serious mental disorders (Blum et al., 2014). In animal studies, increased striatal dopaminergic tone causes lengthening and increased amplitude of the ultradian rhythms, producing strikingly similar activity patterns as seen in patients with rapid cycling bipolar disorder (Blum et al., 2014; Wehr et al., 1998). A complex dysregulation of dopamine in the striatum and prefrontal cortex is implied in schizophrenia, and elevated dopaminergic tone is believed to be central for the manifestation of manic symptoms (Abi-Dargham et al., 2000; Berk et al., 2007; Stahl, 2007). Conversely, symptoms correlated with low dopaminergic tone are central symptoms of depression; lack of initiative and anhedonia. As such, the different characteristics of activity patterns seen for the different categories of disorders in the present study may reflect differences in dopaminergic tone, thus causing a different amplitude and length of the ultradian motor activity rhythm and different patterns of asynchrony in relation to the more stable circadian rhythm governed by the SCN.

A potentially contrasting theory on the development of manic episodes is the theory of bifurcation of the circadian rhythm from a 24-h cycle to a 12-h SCN-generated cycle, in other words, two days and two nights per 24 h (Kripke et al., 2015). During exposure to 12-h light/dark cycles, this bifurcation can be provoked in Siberian hamsters and astonishingly, in a human study of 24-h melatonin samples from patients in a manic episode, two peaks of melatonin were found, supporting this compelling theory (Novakova et al., 2015; Raiewski et al., 2012). The abnormally stable activity patterns from morning to evening for the patients with mania in the present study may this way reflect the presence of two consecutive endogenous days with similar activity structures.

Obviously, we need to take into account that medications could confound the results through effects on motor activation. In an effort to meet this problem, analyses where repeated with adjustment for antipsychotic medication. Most antipsychotics are antidopaminergic compounds with potential to influence motor activity. The main findings in the study remained unaltered after controlling for effect of antipsychotics. In our view, this strengthens the validity of results, having in mind the relatively small sample and the likelihood of correlation between use of antipsychotics and severity of illness. The patient groups in our study differed somewhat with regard to medication, most importantly the unipolar depression cases compared to cases with mania or schizophrenia. The unipolar depressed group received more antidepressants, less antipsychotics and less anticonvulsants. It is however less likely that the lower activity for the unipolar depressed group is caused by these differences in medication alone for the following reasons: Antidepressants can be activating (e.g. venlafaxine) or sedative (e.g. mianserin). The sedative antidepressants are usually prescribed for the nighttime in the subjects' resting phase, so the impact on mean activity would be small. If any effect of the higher percentage of antidepressant users in the unipolar depressed group, one would expect a moderating effect toward normalized activity with higher mean activity and normalized activity patterns. Also, any confounding effects from less antipsychotics and less anticonvulsants in the unipolar depressed group would make group differences of mean activity smaller since these substances are usually sedative and not activating (except for aripiprazole). With regards to potential effects of medication on mean activity in the patients with mania, a previous study of recovered bipolar I patients still using medication found no relation between type or dose of psychotropic medication and actigraphic measures (mean activity and measures of circadian rhythm) compared to during the illness episode (Salvatore et al., 2008). Also, among the few investigations of the relative contribution of psychiatric symptoms and psychotropic medications on the sleep-wake cycle, one study found that mania symptoms were predictive of lower circadian amplitude and rhythmicity, independently of medications (Robillard et al., 2016). Antipsychotics and certain antidepressant agents had an effect on several sleep parameters, but not on activity rhythms. Moreover, lower activity in mania is in line with other studies (De Crescenzo et al., 2017). In the patients with schizophrenia, the percentage of potentially sedative medications (antipsychotics, hypnotics/anxiolytics and antihistamines) was the same or lower than in the mania group and higher than in the unipolar depressed group (except for slightly fewer patients receiving hypnotics/anxiolytics than in the UP group). Therefore, this cannot explain the second lowest mean level compared to the other patient groups. Effects of medication on other aspects of activity patterns cannot be ruled out. Given that certain antidepressants and antipsychotics alter dopaminergic tone, they could influence on ultradian rhythms that are potentially generated by the dopamine oscillator (Blum et al., 2014). Our findings are in line with previous studies on motor activity patterns in psychotic and affective disorders (Walther et al., 2014; Hauge et al., 2011). Also, there is extensive overlap of medication used for psychotic and affective disorders and much heterogeneity of psychotropic medication as well. All in all, we consider that the medication profile of the subgroups suggests that there are disorder-specific motor activity markers that cannot be fully explained by psychotropic medication. However, we also acknowledge that there is a general lack of large studies that could provide valid answers on the moderating effects of different psychotropic drug classes on motor activity patterns. Our study was too small to allow for further stratification of the sample and cannot resolve to which extent medication influenced on different patterns between separate acute psychiatric states.

There are other limitations than psychotropic drug treatment and differential medication per subgroup that should be considered, the most important being: short recordings (24 h) and relatively small subgroups. Future studies should have larger sample sizes and longer recordings that enable multilevel modeling or mixed analyses, in order to formally test diagnosis *x* time interaction effects on activity rhythm differences. In this study, which was probably underpowered to detect such interaction effects, there were some trend differences in mixed analyses. Also, there is no consensus on the ideal monitoring methodology or epoch length. While our use of 1-min epochs seems interesting given the findings and in comparison to studies that have usually looked at activity per hour, it is possible that shorter intervals would yield other results. No symptom ratings or information on illness duration were available, which prevents further exploration of effects on activity due to symptoms or course of illness, as well as comparison of more homogenous groups. Analyzing wake periods separately from sleep periods could have given a better signal-to-noise ratio, but this was not possible in the current study. However, hospital routines were the same for all patients (including social rhythms, meals and bedtimes), and sleep is more likely to affect mean activity than other parameters. Abnormal circadian rhythms between patient-groups are therefore believed to be of less importance than in a naturalistic setting outside hospitals. Similarly, weekdays and weekends differ less during hospitalization. Being hospitalized and/or medication could, however, explain the observed differences between patients and healthy individuals, but considering that patients differed from controls in different variables, it is unlikely to be the only explanation. For instance, the stability in activity profiles from morning to evening in the mania group is uniquely different to other inpatients and to healthy

individuals.

The main finding of this study is that schizophrenia and psychotic disorders can be separated from motor-retarded unipolar depression and healthy individuals by detailed analysis of motor activity patterns. Using linear and nonlinear analytics, the activity patterns for a group of inpatients with schizophrenia spectrum disorders are more complex or irregular compared to depression and healthy individuals in several measures, such as Fourier analysis, sample entropy and autocorrelation. While schizophrenia could not be distinguished from mania in between-group or mixed analyses, the schizophrenia cases showed more normal amplitudes of motor activity variables from morning to evening, contrasting manic cases who remained strikingly stable during the course of day. In summary, these findings encourage the continued exploration of actigraphy to characterize diagnostic entities in clinical psychiatry. Measures of motor activity complexity may be particularly useful to assess psychotic symptoms in affective and non-affective psychosis.

Conflicts of interest

All authors declare that they have no conflict of interest.

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Supplementary materials

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Errata

Page 3 Missing word: “Mental Health” – corrected to “ Mental health Care”

Page 21 Grammatical error “The circadian phases of patients with mixed symptoms was…” – corrected to “ The circadian phases of patients with mixed symptoms were…”

Page 22 Full stop missing: “ … independent of SCN involvement [77, 78].”

Page 23 Grammatical error: “Furthermore, solar insulation at the latitude of residence and season of birth seem to modulate the course of illness [92-94].” – corrected to “ Furthermore, solar insulation at the latitude of residence and season of birth seems to modulate the course of illness [92-94].”

Page 25 Excessive word: “These interventions have modest effects as compared with those light and wake therapies,…” – corrected to “ These interventions have modest effects as compared with light and wake therapies,…”

Page 26 Missing word and reference error: “In spite of relatively small sample sizes, all published studies have described improvement in psychiatric outcome measures, sleep outcomes, melatonin profile or cognitive performance [130, 133-143].” – corrected to “In spite of relatively small sample sizes, all published studies have described improvement in either psychiatric outcome measures, sleep outcomes, melatonin profile or cognitive performance [130-143].”

Page 45 Wrong word: “Both groups recorded less than the global seasonality score (GSS) cut-off value of 9 points for sub-SAD,…” – corrected to “Both groups reported less than the global seasonality score (GSS) cut-off value of 9 points for sub-SAD,…”

Page 53 Wrong word: “No difference between the groups was demonstrated for this item; however, when we analyzed the autography data,…” – corrected to “No difference between the groups was demonstrated for this item; however, when we analyzed the actigraphy data,…”

Page 56 Excessive words: “This should speak for high generalizability to sample to the BD-I patient group overall.” – corrected to “This should speak for high generalizability to the BD-I patient group overall.”

Page 62 Missing word: “This means activating motor retarded depressed patients…”– corrected to “This means activating the motor retarded depressed patients…”

Page 69 Wrong word/misspelling: “It was not and aim of the VATMAN trial to study mechanisms;…”– corrected to “It was not an aim of the VATMAN trial to study mechanisms;…”

Page 71 Missing words and suboptimal synonym: “YMRS items most related to activation decreased first,..” – corrected to “Scores in YMRS items most related to activation declined first,..”

Page 73 Wrong word: “There is a lack of other data in the occurrence of a bifurcated circadian rhythm in humans.” – corrected to “There is a lack of other data on the occurrence of a bifurcated circadian rhythm in humans.”

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