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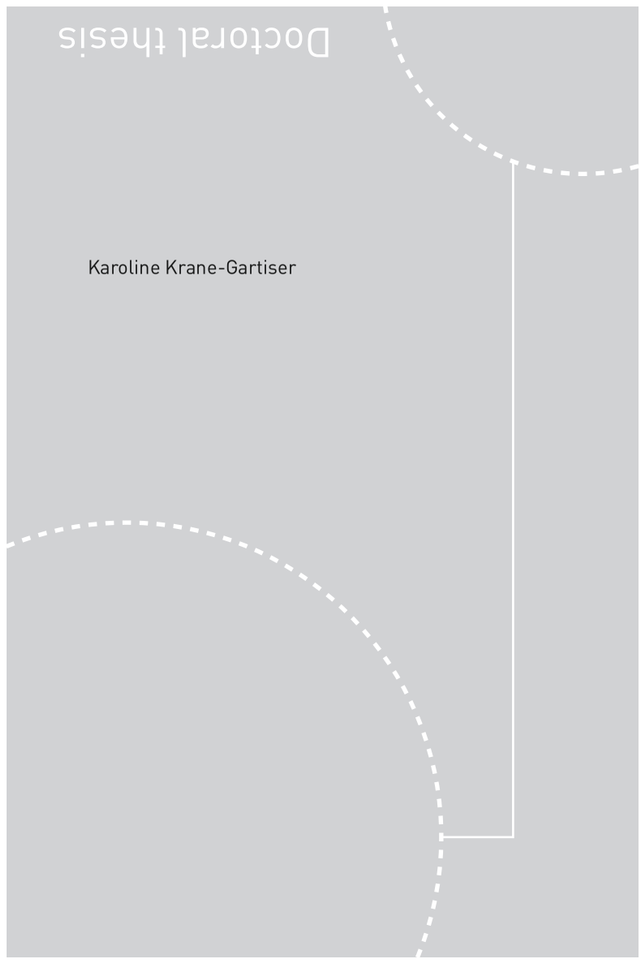
Karoline Krane-Gartiser

ACTIGRAPHY IN AFFECTIVE DISORDERS



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Trondheim, June 2016

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Norsk sammendrag

Norsk tittel: Aktigrafi ved stemningslidelser

Det er i dag ingen objektive mål på symptomene ved psykiske lidelser. I dette doktorgradsarbeidet er det vist at mennesker med ulike former for depresjoner og manier har bevegelsesmønstre som skiller seg fra hverandre. Akuttinnlagte pasienter med stemningslidelser (bipolar lidelse og depresjon) har gått med en bevegelsesmåler (aktigraf) i 24 timer under innleggelse ved avdeling Østmarka, St Olavs Hospital. Ved bruk av avanserte matematiske metoder ble mengde bevegelse, grad av variasjon og stabilitet av aktivitet beregnet. Ved alle depresjonstyper var det lav gjennomsnittsaktivitet og høy variasjon av aktivitet sammenlignet med hos friske personer. Det var også objektive forskjeller i aktivitetsmønstre mellom de pasientene med depresjon som etter legenes vurdering hadde langsomme kroppsbevegelser (såkalt psykomotorisk retardasjon) og deprimerte som var motorisk urolige. De deprimerte pasientene som var mer urolige, hadde et uorganisert bevegelsesmønster som lignet mønsteret for pasienter med mani. I en annen studie av pasienter som var i stabil fase av bipolar lidelse og som samtidig hadde søvnvansker, fant vi at de som ikke hadde stabil døgnrytme, var yngre, og en større andel hadde forsinket søvnfase og hyppige dag-til-dag-forandringer i stemningsleie. Det var også forskjeller i bevegelsesmønstrene mellom gruppene.

Analyser av bevegelsesmønstre målt ved hjelp av instrumenter på størrelse med et armbåndsur, kan trolig utvikles til å skille undergrupper med stemningslidelser fra hverandre og få betydning for klassifisering og behandling av depresjoner og manier både ved tilbakevendende depresjoner og ved bipolar lidelse.

Navn kandidat: *Karoline Krane-Gartiser*
Institutt: *Institutt for nevromedisin (INM)*
Veiledere: *Professor Gunnar Morken, MD, PhD (hovedveileder), professor Trond Sand, MD, PhD, og professor Ole Bernt Fasmer, MD, PhD*
Finansieringskilde: *Institutt for nevromedisin*

Ovennevnte avhandling er funnet verdig til å forsvares offentlig
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Table of Contents

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- My father: For passing on the spirit of research and academic thinking. And for exemplary babysitting skills at crucial times.

- Finally, although she could never take part in it, I owe a lot of this thesis to my mother.

List of Papers

Paper I (Study I):

Actigraphically Assessed Activity in Unipolar Depression – A Comparison of Inpatients with and without Motor Retardation

Krane-Gartiser K, Henriksen TE, Vaaler AE, Fasmer OB, Morken G

Journal of Clinical Psychiatry 2015 Sep; 76(9):118-7

Paper II (Study I):

The Distribution and Characteristics of Active and Inactive Periods Distinguish Unipolar Depression with and without Motor Retardation

Krane-Gartiser K, Vaaler AE, Fasmer OB, Morken G

Journal of Clinical Psychiatry (Letter of original research, accepted in November, 2015)

Paper III (Study II):

Actigraphic Assessment of Motor Activity in Acutely Admitted Inpatients with Bipolar Disorder

Krane-Gartiser K, Henriksen TE, Morken G, Vaaler AE, Fasmer OB

PLoS One 2014 Feb 20;9(2):e89574

Paper IV (Study III):

Unstable Rest-Activity Cycles in Euthymic Bipolar Disorder and Clinical Implications for Sleep, Mood and Activity

Krane-Gartiser K, Steinan MK, Langsrud K, Vestvik V, Sand T, Fasmer OB, Kallestad H, Morken G

(Submitted in December, 2015)

Acronyms and Abbreviations

ADHD	Attention deficit hyperactivity disorder
AHI	Apnea hypopnea index
ANOVA	Analysis of variance
BD	Bipolar disorder
BMI	Body mass index
BRAIN	Bipolar Research and Innovation Network, Norway
CBT-I	Cognitive behavioral therapy for insomnia
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, 4th edition
DSM-V	Diagnostic and Statistical Manual of Mental Disorders, 5th edition
DSPD	Delayed sleep phase disorder
ICD-10	International Classification of Diseases, 10th revision
IQR	Interquartile range
ISI	Insomnia Severity Index
LSD	Least significant difference test
MADRS	Montgomery Åsberg Depression Rating Scale
MEQ	Horne-Östberg Morningness-Eveningness Questionnaire
NEQ	Network Entry Questionnaire
NMDA	N-methyl-D-aspartate
PA	Pennsylvania, USA
PANSS	Positive and Negative Syndrome Scale
PICU	Psychiatric intensive care unit
RCT	Randomized controlled trial
RMSSD	Root mean square successive difference
SOMAS	Symptomatic Organic Mental Disorder Assessment Scale

SCID-I	Structured Clinical Interview for DSM-IV Axis I Disorders
SD	Standard deviation
SE	Sleep efficiency
SPSS	Software package (Statistical Package for the Social Sciences)
SQ	Sleep quality
STEP-BD	Systematic Treatment Enhancement Program for Bipolar Disorder
TST	Total sleep time
UD	Unipolar depression
WHO	World Health Organization
YMRS	Young Mania Rating Scale

Summary

Introduction and aims:

Affective disorders, characterized by recurrent episodes of low and/or elevated mood, are among the most costly and burdensome chronic diseases. Diagnostic categories and episode-specific symptoms overlap, and prevention of illness progression is hampered by an inability to detect early signs of new episodes in due time. Psychiatry as a medical discipline is uniquely dependent on clinical observation of signs and symptoms with few objective markers of disease.

In all states of affective disorders, there are variations in mood symptoms, sleep, circadian rhythms and motor activity. While mood is an ambiguous and subjective symptom, circadian rhythms and motor activity patterns are objectively assessable via the use of actigraphy. Actigraphs are convenient and non-invasive devices for monitoring wrist movement, and they are increasingly employed in psychiatric settings to record sleep-wake and motor activity rhythms. To date, analytical methods have focused on mean levels and simple variability measures. This thesis aimed to analyze motor activity patterns in inpatients and outpatients with affective disorders, using linear and non-linear mathematical methods, in order to compare groups of patients defined by phenotypes.

Methods:

In two studies, 24-hour actigraphically recorded motor activity patterns in acutely admitted inpatients with affective disorders and recordings from healthy controls were included. In the first study, 52 patients with unipolar depression were divided into groups with and without clinically assessed motor retardation. The second study included 30 patients with mania or bipolar depression. In a third study, 1-week actigraphy recordings in 43 outpatients with euthymic bipolar disorder and subjective sleep disturbance were compared between groups with actigraphically determined stable and unstable rest-activity cycles. Actigraphy recordings were compared to concurrent reports of mood and sleep. In all studies, motor activity patterns were analyzed by measures of variability (standard deviation (SD), root mean square successive difference (RMSSD), RMSSD/SD ratio). Studies I and II additionally employed other measures of variability (autocorrelation lag 1, Fourier analysis) and complexity (sample entropy, symbolic dynamics) and other non-linear methods for studying the distribution of active and inactive periods.

Results:

Within the unipolar depression sample, patients with motor retardation had reduced activity levels and higher intra-individual variability in activity compared to patients without motor retardation. Motor retardation implied being active in shorter bursts with fewer long bursts of activity. Patients without motor retardation displayed increased complexity in activity during an active morning sequence of approximately one hour. Bipolar depression was characterized by significantly lower mean activity and higher variability compared to healthy controls, similar to all depression groups relative to controls. Patients with mania showed higher minute-to-minute variability (higher RMSSD values) during 24 hours compared to healthy controls, and increased complexity (higher sample entropy) during the active morning sequence compared to patients with bipolar depression.

In euthymic bipolar disorder and sleep disturbance, a subgroup of patients demonstrated unstable rest-activity cycles in combination with variability in mood and motor activity patterns. The unstable subgroup was younger and showed delayed sleep phases compared to the group with stable rest-activity cycles.

Discussion:

Patients with unipolar depression with and without motor retardation differed in 24-hour activity patterns, and the two phenotypes could be distinguished by complementary methods. Findings in unipolar depression without motor retardation resembled findings in the manic state, which further resembled findings from previous studies of schizophrenia and glutamate antagonism. Results from the euthymic bipolar group with unstable rest-activity cycles resembled variability findings in activity during affective episodes. Here, the activity findings could be associated to mood variability and/or circadian instability.

In conclusion, activity characteristics are potentially important clinical signatures of affective disorders, and it may be possible to distinguish phenotypically different subgroups based on activity levels and patterns. Actigraphy recordings combined with a set of advanced analytical methods from linear and non-linear dynamics could provide a future diagnostic and prognostic tool in affective disorders, of importance to the accuracy of diagnostics, treatment response, prevention and classification of disease.

1 INTRODUCTION

1.1 AFFECTIVE DISORDERS

Affective disorders are characterized by recurrent depressive episodes, episodes with elevations in mood, states with a mixture of depression and elevated mood or normal mood called euthymia.[1] The severe episodes of elevated mood are defined as mania and the less severe episodes with little loss of function as hypomania. Both the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) or the recently revised 5th edition (DSM-V), and the International Classification of Diseases, 10th edition (ICD-10), classify illness courses of depressions only as recurrent depressions or unipolar disorder (UD) while courses with both depressions and elevated mood or mixed episodes are classified as bipolar disorder (BD). Patients who have experienced two episodes or more and at least one mania are classified as having BD type I, and patients with hypomania as the most severe episode of elevated mood as BD type II. The time interval between episodes with normal or close to normal mood is called euthymia (Greek, *eu* – well/neutral, *thymos* – mind). Course of illness and frequency of episodes vary between patients; some have several episodes during a year, others spend years between episodes. Discovering early signs of new episodes and activating medical or psychosocial therapeutic changes is an important tool in treatment.[2]

1.1.1 Rationale for Accuracy of Clinical Assessments

The World Bank and WHO studies of the global burden of disease in working age adults identify that unipolar disorder (UD) and bipolar disorders (BD) are ranked among the leading causes of disability due to chronic disease.[3] Total yearly costs of affective disorders were in 2010 estimated to approximately 1.5 billion euros in Norway and 113 billion euros in Europe alone,[4] making prevention and treatment of affective disorders a global target to reduce the costs of chronic disorders. However, progress has been slow towards improved prediction of the affective course of illness,[5] which is imperative in disorders characterized by recurrences and highly individual trajectories. Also, the failure to distinguish disease boundaries between those who will only have a UD course and those who will develop BD has clinical consequences. Some medications used to treat UD depression (such as antidepressants) may worsen the course of an underlying BD, as they may precipitate manic episodes or episodes of mixed symptoms of concurrent depression and mania.[6] In activated depressive episodes, the patients experience depressive symptoms psychologically, but may have activity and energy

as in hypomania or mania. It is important to recognize activated depressive episodes and differentiate them from other subtypes of depressive episodes, as there is an increased risk of potentially harmful behavior, including suicidality.[6, 7] As such, better predictive validity of clinical assessments is a major goal to improve the health and well-being of individuals with these prevalent clinical conditions.

1.1.2 Clinical Diagnostics and Monitoring of Affective Disorders

Diagnostics and monitoring changes of clinical status in psychiatry is uniquely dependent on observation and interpretation of signs and symptoms, with a lack of more objective diagnostic tools. In general, episodes of unipolar depression are clinically indistinguishable from episodes of bipolar depression, and most individuals who develop BD usually experience several depressive episodes before the first onset of mania/hypomania.[1] Also, episodes in affective disorders may include mixed features with symptoms of both depression and mania/hypomania, and mood states may overlap: contrary to popular assumptions, mood states in mania are not necessarily elated, and it is frequent for individuals in a manic episode to be dysphoric (feeling depressed or tense/uncomfortable) and paranoid.[8] Furthermore, despite the definition of euthymia as mood stability, patients in the euthymic state frequently experience subsyndromal mood symptoms and minor mood shifts, which have been shown to reduce functioning and worsen the long-term outcome.[9, 10] In short, mood alone seems to be an unstable marker of episodes and disease progression.

Psychiatric practice has not benefited in the same way from advances in technology that have been at the forefront of developments in personalized medicine for chronic physical disorders. There have been only few attempts to develop personalized models in psychiatry,[5] mainly due to lack of biomarkers of mental illness or biological predictors of disease courses. Given that clinical observations are imprecise, finding objective tools for diagnostics and follow-up of psychiatric disorders is an area of major interest in clinical psychiatry and research.[11-13]

1.2 Motor Activity in Affective Disorders

UD and BD are both characterized by changes in mood and emotions, but also by somatic symptoms such as motor retardation (slowing of fine and gross motor movements) or agitation (restlessness associated with tension).[1] Alterations in motor activity are important clinical features of affective disorders, but it is challenging to assess them accurately and

consistently.[14] In acute bipolar disorder, motor behavior patterns are mostly considered as opposite manifestations; mania is traditionally associated with overactivity, whereas depression usually is characterized by reduction in activity.[1] Motor retardation is common in melancholic depression,[15] while activated or agitated depressions include mixed symptoms of depression and hypomania/mania.[16, 17] Motor-retarded and activated depressive episodes may both relate to either unipolar or bipolar depression,[7, 18] and motor agitation can thus occur in both depression and mania.[19, 20] In some subtypes of depression, motor retardation and low mood are often more pronounced in the morning than in the evening,[21, 22] implying a phase-delayed peak of activity.[23] Motor activity during euthymia in BD is understudied, but there are reports of overall reduced activity levels, as well as variable activity levels and both a phase advance and phase delay of the daily activity peak.[23-26]

In other words, changed motor activity levels are observed in all states of affective disorders, and activity is gaining increased focus as a symptom of importance.[8, 17] Recent family studies with diagnostic interviews capturing both diagnostic constructs and symptoms in affective disorders, indicated that depression and mania seem to be transmitted independently of each other.[27, 28] The heritability of mania was greater than that of depression, and increased motor activity was the most frequent symptom of mania, not mood change.[29] This raises new questions regarding the conceptualization of affective disorders, and the role of activation as a core dimension.[30] With the ongoing debate on the classification of bipolar disorders including bipolar spectrum disorders,[31] motor activation may become a key factor in categorizing affective disorders. It is assumed that motor symptoms may characterize subtypes of depressive episodes,[32] and one study has also suggested that level of activation could be predictive of treatment response.[33] Previously, monitoring the course of illness and disease progression has relied heavily on mood ratings. Since mood is such an ambiguous symptom, many researchers and the DSM-V committee have been led to review the diagnostic criteria for BD to include activation (daytime activity) as an additional criterion to try to improve the reliability of the diagnosis. Compared to internal symptoms (e.g. cognitive-emotional styles), the physical signs of any mental or mood disorder are observable, yet they are traditionally not assessed systematically or via the use of objective technological measures.

1.3 Circadian Instability in Affective Disorders

Many human behaviors and physiological variables have near-24-hour periods or circadian rhythms (*circa diem* – about a day).[34] These rhythms include cellular, neural, biochemical and behavioral processes, with examples ranging from body temperature and hormonal secretion of e.g. melatonin and cortisol, to rest-activity and sleep-wake cycles.[35, 36] Most human rhythms are believed to be endogenously generated, but environmentally entrained to a 24-hour period, under stringent control by the central clock located in the suprachiasmatic nuclei of the brain's hypothalamus.[37] The circadian balance can therefore be disturbed on many levels. Accordingly, several parameters or proxies of circadian rhythmicity or lack of rhythmicity can be assessed, but no single measure is accepted for standard evaluation of circadian cycles.[25, 35] Equally, there are various terms that describe circadian instability. In this thesis "diurnal" and "circadian" are used interchangeably to characterize variation related to 24-hour periods.

1.3.1 Changes in Sleep and the Sleep-Wake Cycle

In addition to cyclic changes in mood and activity levels, affective disorders are often associated to changes in the sleep-wake cycle and in sleep patterns.[35] Sleep disturbance is one of the diagnostic criteria for mood episodes in affective disorders,[38] and one of the most recognized prodromal symptoms of mania.[39] During depression, up to 70-90 % of patients report sleep problems.[40, 41] The most common comorbid sleep disorder is insomnia, but hypersomnia and delayed sleep phase disorder (DSPD) also occur frequently.[42-44] DSPD may be more prevalent in affective disorders, particularly in bipolar disorder, than in the general population.[44] In relation to this, it has been suggested that patients with bipolar disorder may have an evening preference for daily activities.[45] Although the euthymic phase is often considered to be a period of stability, sleep problems and disturbances of the 24-hour rhythm are common also between BD episodes and have been found to increase the risk of relapse.[46-48] Consequently, stabilizing social schedules and timing of sleep is a central aspect of non-pharmacological treatment options available for bipolar disorder.[5, 49, 50]

To date, differences in changes in the sleep-wake cycle and circadian instability in bipolar disorder compared to controls[35, 46, 51] have led to proposals that a number of clinical phenotypes can be related to, for instance, different clock genes.[52-54] Many of these observations are inconsistent and may be undermined by a focus purely on sleep, rather than

considering daytime activity as well, and by relying too much on 'mean scores' rather than exploring other features such as inter- and intra-individual variability in sleep-wake patterns.[55] Also, addressing inter-episodic symptoms of circadian instability is difficult due to lack of definitions and lack of comprehensive assessments.[48]

Sleep is thought to occur from a complex interaction between a wake-dependent homeostatic process (process S) and a 24-hour circadian process (process C) that synchronizes activity to the light phase of the 24-hour day and sleep to the dark phase.[56] The circadian rhythm is thus entrained to the 24-hour cycle by cues (zeitgebers), of which the light-dark cycle is the most potent. Habits and environmental factors, such as social stimuli, also play their part in the alignment of the organism to its environment. Interruptions both to the external rhythm and weaknesses in the internal regulation of the circadian rhythm may result in insomnia and circadian rhythm sleep disorders.[36, 57, 58] A shift in the relationship between process S and process C could lead to lower mood as well.[59] Two hypotheses for circadian abnormalities resulting in DSPD have been proposed: either the circadian rhythm is biologically delayed, or the circadian period is longer than 24 hours, which would make it difficult to advance sleep timing to match the 24-hour cycle.[60] Artificial lighting at the wrong time of this cycle could further disturb sleep-wake regulation, and lack of structured routine is another cause of circadian instability, which is common in affective disorders.[23]

1.3.2 Possible Explanations of Circadian Instability in Bipolar Disorder

Multiple lines of evidence point to a disruption of the general circadian system in bipolar disorder on genetic, behavioral and environmental levels. Support for genetic causality is the participation of molecular clocks, which are found throughout the brain and take part in the regulation of mood.[54] It has been suggested that patients with bipolar disorder could have less robust molecular clocks,[61] and variations in circadian genes may be associated to clinical aspects of the illness.[35] Also, the effect of lithium, a traditional drug used in treatment of bipolar disorder, may be exerted through an influence on molecular clocks.[62] Lithium is likely to act as a stabilizer of circadian rhythms.[63] Circadian instability may also be secondary to factors, such as unemployment or lack of social schedules,[64] which negatively affect the synchronization of the organism with its environment. An interaction of genetic and environmental factors is a possibility: a biologically weak circadian rhythm in patients with bipolar disorder could make them more susceptible to further desynchronization by external

factors.[36] In line with this theory, one study demonstrated a hypersensitive melatonin secretion response to light exposure in euthymic patients with bipolar disorder.[65] Melatonin is a fundamental hormone of the circadian timing system, produced and secreted in a diurnal fashion by stimulation of darkness, which may also be disturbed in bipolar disorder.[35, 66, 67] In addition to a phase-shifting effect, melatonin has been found to affect the amplitude of fluctuations in activity.[68]

1.3.3 Clinical Aspects of Rhythm Disruption

While the biological theories for circadian instability in affective disorders are extensively discussed in recent literature,[52, 54, 69] clinical presentations of rhythm disturbances during euthymia are fewer. Circadian instability and associations to sleep, mood and activity are likely to be bidirectional and interconnected.[24, 36, 70] Self-reported variability in sleep duration has been related to self-reported changes in mood,[71] and sleep loss has resulted in increased emotional reactivity, evaluated on both a brain and behavioral level.[72] Disturbed sleep parameters and mood symptoms, and reduced physical activity and sleep difficulties may respectively be mutually maintaining processes.[70, 73] Such bidirectional coupling could be stronger in BD, and individuals with BD may thus be more reactive to stressors like sleep difficulties or circadian instability than persons without affective disorders.[74] Several clinical investigations find correlations between mood states or symptom scores and rhythm disruptions, particularly in BD.[23, 59, 75, 76] The manic state has been associated to low diurnal rhythmicity, meaning reduced difference between daytime and nighttime activity levels.[26]

Further evidence of an association between mood symptoms and circadian instability comes from recent treatment trials studying the effect of chronotherapeutic interventions aimed at stabilizing the circadian rhythm. Wake therapy and bright light therapy have been found to improve remission from depression,[77] and oppositely, a Norwegian case report adds promise to dark therapy in the reduction of manic symptoms and sleep regulation.[78] Originally, dark therapy implied placing the patient in a dark room for the majority of the day, but modern development of orange-tinted glasses that create a virtual darkness situation are easier to implement in practice.[78, 79] Orange glasses prevent blue light from reaching the retina and thus preserve nocturnal melatonin levels even in highly lit surroundings. Blue light at the wrong time of the circadian rhythm is thought to be particularly deleterious.[80] In the study by Henriksen et al,[78] the main effect of blue-blocking glasses was a rapid decline in manic

symptoms. In addition to mood amelioration, one common mechanism in these chronotherapeutic trials is a stabilization of the sleep-wake cycle.[81] This is also a central part of cognitive behavioral therapy for insomnia (CBT-I), where the patient should rise at the same time every morning, throughout the 6-8 week intervention.[82] Harvey et al[83] conducted a study on CBT-I for patients with BD type I in the euthymic state. They found that CBT-I led to improved sleep quality and also reduced the time in affective episodes the following six months after treatment.[83] Furthermore, in a study of patients with unipolar depression and insomnia, Manber et al[84] found that patients who were treated with CBT-I in addition to antidepressant medication had twice as large remission rates from depression compared to those who were treated with antidepressant medication alone. Thus, interventions that target circadian stability, from chronotherapy to cognitive behavioral therapy, seem to have several beneficial effects in affective disorders.

1.4 ACTIGRAPHY

Figure 1.
An actigraphy device by Philips Respironics

An actigraph is a device for activity monitoring and sleep-wake estimation, which is a cheap and handy objective tool with possible utility in both daily clinical practice and in research. It contains an accelerometer and is often placed around the wrist, although truncal and hip-worn models exist, and some smartphones have similar technology. Wrist-worn devices have proved to be most accurate in recording motor activity in depression compared to healthy controls.[85] In research, it is not always indicated if the actigraph is worn around the dominant or non-dominant wrist, but when indicated, the non-dominant hand is most often used. However, for long-term studies the right hand may be more convenient since it is less practical to have both the actigraph and the wrist-watch on the same hand. In studies specifically focused on laterality, no differences between the left and right wrist have been found.[86, 87] Periods of sleep and wakefulness may be inferred from the recordings of activity.

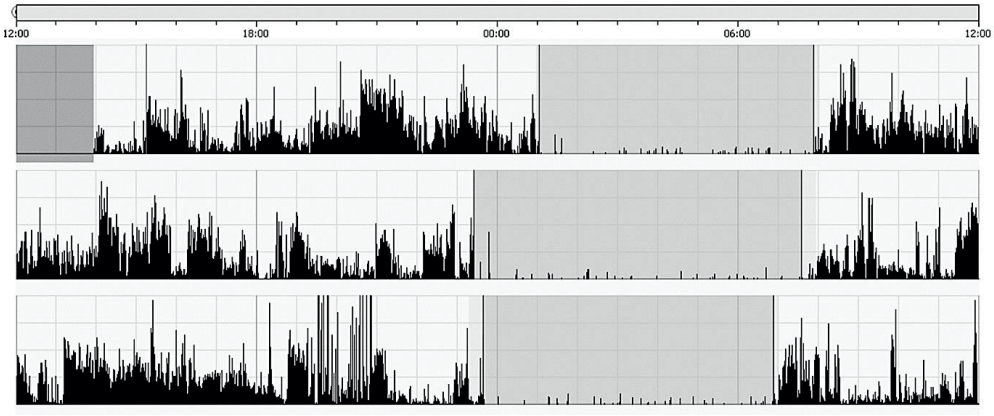

Figure 2. 3-day actigraphy recording from 12h to 12h, where activity counts are shown in black on a scale from 0 – 1000. The actigraph was worn from 14h on day 1. Gray-colored time periods are sleep intervals calculated by the actigraphy software program.

1.4.1 Application of Actigraphy to Clinical Practice and Research

Wrist-worn activity monitors were first described in 1959,[88] and the piezoelectric accelerometers (called actigraphs) we use today were developed in the 1970s.[89] In recent time, actigraphs have been mostly applied to study sleep disorders and circadian sleep-wake cycles.[12, 90, 91] The temporal resolution, storage and battery capacity have improved in the past years,[92, 93] and actigraphy is increasingly employed in assessment of motor activity in addition to sleep.[32, 94-97] With the use of actigraphy in psychiatric disorders and more specifically affective disorders, the role of motor activity as an indicator of mood state has been explored. Promising research findings suggest that actigraphs may become a valuable supplement to clinical diagnostics of affective disorders.[33, 75, 98-103] Although motor activity has been an understudied factor, it may be a more useful marker of illness course and treatment than current standards, and activity can easily be measured objectively by an actigraph that causes minimal disruption to the individual wearer. Still limited by variable data compression and storage methods, the full potential of actigraphy data can be achieved by employing carefully selected appropriate analytical methods.

A plethora of activity monitoring equipment is under development and will become available to practically everyone as wearable appliances: activity tracking bracelets and belts, smart phone apps and smart watches. Traditional actigraphs are best validated for research at the present time, but it seems that we are at the beginning of an era of objective monitoring in

psychiatric disorders. Knowledge of activity patterns in health and disease states will be important to clinicians and individual patients for future application of such technology to clinical practice.

1.4.2 Actigraphy Findings in Affective Disorders

Actigraphy recordings in a small, but increasing, number of studies in affective disorders the past decades have confirmed what centuries of clinical observations have identified: Motor activity levels in the depressed state seems to be lower than in the euthymic state.[100, 104, 105] According to one review, activity levels increase with treatment.[94] Furthermore, unipolar depression may be related to a delayed peak of activity, contrary to an early peak of activity in bipolar disorder.[68] Studies looking at more than mean levels have found that activity patterns in patients with unipolar depression seem to be different from those of control groups.[102, 106] Yet, little is known about actigraphically recorded activity characteristics across different phases of bipolar disorder. In euthymic BD, there are reports of lower activity levels, greater fragmentation of rest-activity patterns and greater variability in the 24-hour rhythm compared to healthy controls.[23, 24, 46, 51, 107, 108] These variability measures are quite crude, and it remains unclear how motor activity as a biological rhythm oscillates during the euthymic state of bipolar disorder.

Although the lower levels of activity in actigraphy studies of depression have been interpreted as an expression of motor retardation, previous studies have failed to find correlations between total scores in depression rating scales and actigraphic daytime activity.[92, 101, 109, 110] It has been suggested that motor retardation may be better assessed by specific retardation scales,[92] at least until there exists an objective alternative.

Actigraphy studies of sleep in euthymic bipolar disorder find disturbances in several sleep parameters.[12] However, the main interest in this thesis was use of actigraphy in the study of motor activity and rest-activity rhythms rather than sleep.

1.5 Mathematical Analysis of Actigraphy Data

Few actigraphy studies have used advanced analytical methods to extract all relevant features from actigraphy data, irrelevant of study population.[94] To date, analyses have focused mainly on mean levels and parametric variability measures. Among the sparse number of studies that include non-parametric analysis, cosine functions and Van Someren's measures of intra-daily

variability, inter-daily stability and the ratio between most and least active hours within 24 hours, are most common.[75, 111] However, the rest-activity rhythm does not behave exactly as a cosine function, and an hourly sampling rate reduces the sensitivity of these analyses.[112] New methodological approaches are required to assess patterns of motor activity in psychiatric illness.

1.5.1 Non-Linear Dynamics

In recent years it has been found that mathematical techniques with a theoretical basis in non-linear dynamics and chaos theory may be used to describe the complexity seen in behavioral patterns.[68, 113-117] The complexity of a biological system reflects its ability to adapt and function in a changing environment.[118] Complex systems appear to be randomly variable and imply a higher degree of unpredictability compared to structured systems, which can often be characterized by linear dynamics. Goldberger described it this way: "Linear systems are well-behaved. The magnitude of their responses is proportional to the strength of the stimuli. (…) The subunits of the system add up – there are no surprises or anomalous behavior."[119] An example of a linear system is a sine wave. In contrast, non-linear systems cannot be understood by examining the components individually, because the components are coupled or interact with each other. An example of a non-linear system is the neuronal network, where one neuron is coupled to multiple other neurons. A signal from a single neuron results in complex changes in the network as a whole. This coupling thus generates behaviors, such as sudden changes and disorder that cannot be explained by traditional, linear measures.

Another feature of complex processes, which can be used in analysis, is their short and long-range correlations, a mechanism underlying the "memory effect", meaning that a variable at a certain point in time is related to the immediately preceding value, but also to those further in the past.[119] Furthermore, complex behavioral patterns assessed by actigraphic recording of motor activity, may be analyzed by studying the distribution of active and inactive periods, which has shown differences between depressed patients and healthy controls.[120]

1.5.2 Application of Non-Linear Dynamics to Assessment of Human Behavior

Complex behavior is thought to be organized on several scales or frequencies, and its opposite is a system dominated by one scale or frequency, which would be easily recognizable and

predictable. A theory of disease physiology is such loss of complexity.[121] Physiological systems that lose complexity may be less adaptable and less able to cope with changing environments. Random-type variability and complexity in disease processes have thus been of interest.[115] Non-linear variability measures have mostly been used in cardiology and studies of heart-rate variability,[122] but is also increasingly considered in psychiatric research.[103, 113, 116, 123, 124] Indic et al applied methods of non-linear dynamics to actigraphic motility data and developed a parameter called the Vulnerability Index, which has interesting potential implications for affective disorders.[103, 125] In addition to activity analysis, mood fluctuations have been assessed by non-linear measures: These studies found that mood swings in individuals with unipolar depression were more regular than in healthy individuals, accordant with the theory of reduced complexity in disease.[124, 126]

Recently, a group in Bergen studied activity patterns in groups with depression, schizophrenia, Attention Deficit Hyperactivity Disorder (ADHD) and healthy individuals treated with a glutamatergic N-methyl-D-aspartate (NMDA) antagonist and found differences in variability and complexity measures.[102, 114, 127, 128] On this basis, variability in motor activity seemed to be a promising, but unexamined marker of psychiatric disease, which had not been applied to other groups of affective disorders than unipolar depression.

1.6 Study Aims

The overall aim of this thesis was to analyze actigraphically recorded motor activity patterns in inpatient and outpatient populations with affective disorders, using linear and non-linear mathematical methods, in order to compare groups of patients defined by phenotypes. Specifically, we wanted to compare 24-hour recordings from diagnostic subgroups in an acute state and those of healthy controls and to compare 1-week recordings in euthymic bipolar disorder to concurrent reports of mood and sleep between groups with stable and unstable diurnal rest-activity cycles.

Study I: The aim in **Paper I** was to assess the mean activity level, variability and complexity of motor activity in 24-hour actigraphy recordings from acutely admitted inpatients with unipolar depression, who had been divided in motor retarded and non-motor-retarded patients prior to actigraphy analysis. 9-hour periods and 64-minute active periods in the morning and evening would be selected, and both patient groups would be compared to healthy controls. The aim in **Paper II** was to reanalyze actigraphy data from the same patient sample using

new advanced methods to study the distribution of active and inactive periods and distinguish the groups with and without motor retardation.

Study II, Paper III: The aims were to compare 24-hour motor activity patterns in acutely admitted inpatients with mania or depression in bipolar disorder to healthy controls and also to compare active periods in the morning and evening.

Study III, Paper IV: In patients with euthymic bipolar disorder and sleep disturbance the aims were to 1) compare characteristics related to mood and sleep between two groups with stable and unstable rest-activity cycles and 2) detect between-group differences in motor activity patterns.

2 MATERIALS AND METHODS

2.1 SAMPLES AND SETTINGS

All four papers in this thesis are actigraphy studies in patients with affective disorders. The first three papers (Studies I and II, Papers I, II and III) include acutely admitted inpatients with unipolar depression (UD) and bipolar disorder (BD), divided into four clinical groups: mania, bipolar depression, motor-retarded UD and non-motor-retarded UD. All four groups were compared to a group of healthy controls from the Western region of Norway. Study III, Paper IV, includes outpatients with euthymic BD and subjective sleep difficulties. All patient studies were conducted at Østmarka Department of Psychiatry, St. Olav's University Hospital, Trondheim, Norway; at the acute wards (Studies I and II) and at the Bipolar Outpatient Clinic in collaboration with the Sleep Clinic (Study III), respectively.

2.1.1 Patient Samples in Studies I and II

All Norwegian acute psychiatric services are public. All patients above 18 years in the catchment area of Sør-Trøndelag county, corresponding to 228.000 people in 2011,[129] who suffer from any acute psychiatric condition and are in need of acute inpatient admittance are admitted to Østmarka Department of Psychiatry.

Studies I and II include consecutively, acutely admitted inpatients, who were asked to participate in a study assessing symptoms of agitation during admission. A total of 380 unique patients, accounting for 424 admissions, were included in this study of agitation. If patients were admitted more than once, up to three admissions could be included. The only exclusion criterion was inability to give an informed consent in the primary examination by a senior psychiatrist or specialist in clinical psychology the first day after admittance. The patients with an inpatient stay of more than one day after inclusion were asked to wear an actigraph for 24 hours. 280 actigraphy recordings were effectuated during hospitalizations between September 1st, 2011 and March 31st, 2012. Diagnoses according to ICD-10 "Criteria for research"[130] were set at discharge in a department's staff consensus meeting, including the patient's therapist and at least two psychiatrists of whom at least one personally knew the patient. The largest diagnostic group was affective disorders, which included 110 admissions (39.3 % of the 280 admissions). Of these, 62 admissions were due to a primary ICD-10 diagnosis of a depressive episode or recurrent depressive disorder (F32 and F33), which were

evaluated for inclusion in Study I. 43 admissions were due to a primary ICD-10 diagnosis of bipolar disorder (F31). Admissions due to a current manic episode (F31.1-2) or bipolar depression (F31.3-5) were evaluated for inclusion in Study II of this thesis.

Grouping of Patients in Study I

The final sample in Paper I consisted of 52 inpatients in a unipolar depressive episode, who were divided into 25 with clinically assessed motor retardation and 27 without motor retardation, based on the degree of motor retardation assessed by the Symptomatic Organic Mental Disorder Assessment Scale (SOMAS), item B (see Instruments below). Of the 62 admissions in a depressive episode with a valid actigraphy recording, three patients were not rated for motor activation and were excluded, as well as 5 patients who had mixed ratings of both retardation and increased motor activity. Two of the patients in the non-motor-retardation group were admitted twice; only their first admissions were included in the analyses. 10 admissions were thus excluded from the original sample of 62 admissions. Both groups of 25 and 27 inpatients were compared to 28 healthy controls.

Paper II was a reanalysis of the previous patient sample in Paper I. The new analysis required recordings to be complete without excluded intervals and of a certain length. We had 47 satisfactory recordings, but because the duration of the recordings in the non-motor-retarded group was significantly shorter, we excluded the 4 shortest recordings in this group to have comparable recording time between groups. 43 of the patients in Paper I were thus included in the reanalysis; 22 in the motor retardation group were compared to 21 in the non-motor retardation group. The group of healthy controls was not included.

Grouping of Patients in Study II

Of the 43 admissions with bipolar disorder as the primary diagnosis, patients who got diagnoses from F31.6 to F31.9 (mixed episodes, other bipolar and unspecified bipolar disorder) were excluded. 20 admissions were due to a current manic episode (F31.1, current episode manic without psychotic symptoms, and F31.2, current episode manic with psychotic symptoms), and 13 admissions were due to a current episode of depression (F31.3, current episode mild or moderate depression, F31.4, current episode severe depression without psychotic symptoms, and F31.5, current episode severe depression with psychotic symptoms). Two patients were admitted twice; one patient was first admitted in an episode of depression,

then in an episode of mania, and one patient was admitted twice with mania. Second admissions were excluded from analysis, so that all patients were represented with only one admission. One recording was incomplete and therefore excluded. Finally, a total of 18 recordings from patients in a manic episode were compared to 12 recordings from patients in an episode of depression. Both patient groups were compared to the same sample of 28 healthy controls as in Paper I.

2.1.2 Healthy Controls in Studies I and II

The comparison group of 28 healthy controls in Paper I (Study I) and Paper III (Study II) primarily consisted of employees at the Department of Psychiatry, Fonna Regional Health Authority in Western Norway, who were recruited through oral and written presentations. None of the controls reported to be diagnosed with an affective disorder or prescribed psychopharmacological drugs. They wore an actigraph for at least 24 hours during the period March 13th, 2012 - June 6th, 2013. 18 of them wore the actigraph in spring or summer months (April – August). 15 healthy controls wore the actigraph on a weekday, 11 healthy controls during the weekend, and 2 were retired. They were not age- nor gender-matched to the patients. No information about the weight of the healthy controls was available, and the samples could therefore not be matched by BMI.

2.1.3 Patient Sample in Study III

The Bipolar Outpatient Clinic is uniquely specialized on diagnostics and treatment of bipolar disorder as one of few affective disorder clinics in Norway. In addition to patient assessments and treatment, the clinic provides psychoeducation courses and several clinical research projects as part of their main services. Clinical work and research projects are highly integrated. Patients are referred by general practitioners and hospital units, which primarily reside in the Sør-Trøndelag County. One of the current research projects at the clinic is a randomized controlled trial (RCT) examining the effects of CBT-I.[131] Patients who were included in Study III were considered for participation in this RCT.

In Study III, participants were recruited by referrals from psychiatric outpatient units, general practitioners or through advertisements in the local newspaper, in the period between January 2013 and October 2015. Inclusion criteria were 1) having a bipolar disorder, 2) currently being euthymic and 3) having subjective sleep difficulties in the euthymic phase. Recruitment

methods consisted of advertisements and articles in the local newspapers, websites, social media, patient organizations and general practitioners' offices, oral and written information given at hospital units and psychoeducation classes for patients with bipolar disorder in the euthymic phase. For approximately 200 patients, who claimed to have a bipolar disorder diagnosis and sleep disturbance, eligibility was further explored by telephone or meeting with a specialist in clinical psychology. Of these individuals, more than ¾ were not eligible for Study III, due to 1) currently not euthymic, 2) sleep disturbance associated to affective episodes 3) improvement of sleep disturbance prior to inclusion, either due to medical treatment or unstable sleep difficulties, 4) not interested in research participation after information about procedure or 5) non-residents within the Trondheim area. The bipolar disorder diagnosis was not verified in all cases, and a substantially larger number of individuals made contact without fulfilling eligibility criteria. Criteria for SCID-I (Structured Clinical Interview for DSM Axis I Disorders)[132] verified bipolar I or II disorder were confirmed for all eligible participants after preliminary assessments. Euthymia was defined as a score on the Montgomery Åsberg Depression Rating Scale (MADRS)[133] not higher than 14 and by a score on the Young Mania Rating Scale (YMRS)[134] not higher than seven. Euthymia was in addition clinically assessed by an experienced specialist in clinical psychology. All patients fulfilled a sleep disorder diagnosis of either insomnia or a circadian rhythm disorder, according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV). Diagnoses were set in a consensus meeting with at least two psychiatrists or specialists in clinical psychology of whom at least one had interviewed the participant. Exclusion criteria: 1) having an ongoing alcohol or substance abuse, 2) working night shifts, 3) less than one month since last defined episode, 4) less than two months since last hospitalization, 5) having medical conditions that may account for sleep disturbance, 6) changes in medical treatment regime during the past month and 7) inability to complete the 1-week study procedure. 47 patients met criteria for inclusion. Three patients were excluded due to incomplete actigraphy recordings and one due to infectious disease during the week of monitoring. Finally, a total of 43 participants were included in the analysis.

Grouping of Patients in Study III

The 43 patients' actigraphy recordings during 6-8 consecutive 24-hour periods were separated into alternating rest-activity intervals, defined by all available subjective and objective indications of bedtime and get-up-time. The duration of each active interval was calculated

and averaged across the total number of active intervals for each participant. The median standard deviation (SD) of the daily active interval durations in each participant of 119.5 minutes was used to divide patients into two groups: one group of 22 individuals with stable rest-activity cycles defined by SD < 2 hours, and one group of 21 individuals with unstable rest-activity cycles defined by SD > 2 hours.

2.2 Ethical considerations

The patient studies in Papers I-III had been approved by the Regional Committee for Medical and Health Research Ethics of Central Norway, and the healthy control study in Papers I and III by the Regional Committee for Medical and Health Research Ethics of Western Norway. The patients' capacity to consent was established by a senior psychiatrist or specialist in clinical psychology, and patients who were unable to consent were not included in the study. Study III, Paper IV, had a separate approval from the Regional Committee for Medical and Health Research Ethics of Central Norway, for both the current study and the following RCT. All included participants in this thesis had signed a written informed consent form prior to inclusion. The funding organizations had no role in the design or conduct of either study.

2.3 Study Procedures

All three studies involve group comparisons of socio-demographic, clinical and actigraphy data. Demographic and clinical data were collected as part of the study procedure during hospitalization in Studies I and II. In Study III, one or more clinical interviews with an experienced psychologist provided a description of the bipolar disorder, medication and socio-demographics, and patients completed self-report forms and daily symptom ratings during the study period. In all studies, patients were categorized in groups prior to data analysis.

2.3.1 Actigraphy Procedure

A common part of the three studies is the use of actigraphy. Motor activity was recorded using an actigraph of the same model (Actiwatch Spectrum, Philips Respironics Inc., Murrysville PA, USA), which contains a piezoelectric accelerometer programmed to record the integration of intensity, amount and duration of movement in all directions. A corresponding voltage is produced and stored as an activity count in the memory unit of the

actigraph. All subjects wore the actigraph around the wrist of their choice and were instructed not to take it off during the time of monitoring, which was 24 hours in Studies I and II and 6-8 consecutive days in Study III. Which wrist was not noted in either study, but previous studies have not found significant differences between the left and right wrist.[86, 87] Activity counts were recorded for one minute epochs.

2.3.2 Specific Procedures in Studies I and II

In addition to 24-hour actigraphy, collected data included age, gender, employment status, higher education, days admitted, primary diagnosis and medical treatment. In Study II, body mass index (BMI) was also given.

2.3.3 Specific Procedures in Study III

In addition to assessments for diagnostics and level of affective symptoms prior to inclusion (SCID-I,[132] MADRS,[133] YMRS[134]), demographics and clinical background information were provided through clinical interviews and the Network Entry Questionnaire for Bipolar Disorder (NEQ).[135] The NEQ is used in the Norwegian Bipolar Research and Innovation Network (BRAIN), which is a large ongoing Norwegian multicenter study including inpatients and outpatients with bipolar disorder (DSM-IV) from several hospitals in Norway. All included patients are ≥ 18 years old, and there are no exclusion criteria except lacking Norwegian or English language skills. The majority of patients in Study III were asked to participate in the BRAIN study, and nearly all of them accepted.

After inclusion, the self-rated Insomnia Severity Index (ISI)[136] estimated the severity of sleep disturbance. The Horne-Östberg Morningness-Eveningness Questionnaire (MEQ)[137] assessed patients' diurnal preference. All participants wore an actigraph for 6-8 consecutive days while completing a daily mood and sleep diary and 2 nights of polysomnography.

2.3.4 Instruments

Measures of Affective Symptoms and Affective Illness History

- The Symptomatic Organic Mental Disorder Assessment Scale (SOMAS) is a 5-item scale, developed to measure the prevalence and degree of atypical depressive mood symptoms. Item B is modified from the Positive and Negative Syndrome Scale (PANSS) item "Motor

retardation" (General Psychopathology scale) and is defined as: "Degree of motor retardation, rated during the period or periods of the previous 24 hours when the patient was most depressed",[138] and item C, which rates the degree of increased motor activity during the period or periods the previous 24 hours when the patient was most depressed, is modified from the PANSS item "Hyperactivity" (Positive scale).[139] In Study I, patients with any observable motor retardation according to SOMAS item B were classified as motor-retarded, whereas patients rated to have increased motor activity (SOMAS item C) or neither retardation nor increased motor activity, were classified as non-motor-retarded. In a pre-study of patients consecutively admitted to the psychiatric emergency unit (n = 22), the full-scale SOMAS showed good inter-rater reliability and internal consistency (non-published data).[138] (Study I).

- Structured Clinical Interview for DSM Disorders (SCID-I) is a structured diagnostic interview assessing the patients' symptoms and behaviors as criteria for Axis I diagnoses in the DSM-IV.[132] The instrument is considered as a gold standard in psychiatric research. (Study III)

- The Network Entry Questionnaire for Bipolar Disorder (NEQ): This is a Norwegian adaptation of the NEQ used in the Bipolar Collaborative Network[140] and in the Bipolar Research and Innovation Network, Norway (BRAIN). It contains 48 main items covering a range of demographic and clinical factors that describe the course of illness, family history and past and current treatment.[135] (Study III)

- Montgomery Åsberg Depression Rating Scale (MADRS): This is an interview-based questionnaire used to assess the level of depression. It includes ten questions, each rated from 0 to 6.[133] Setting the cut-off value to 14 in Study III took into account that most participants in this study would probably score up to four points on the question regarding sleep. Lower cut-off scores are common in studies of euthymia. (Study III)

- Young Mania Rating Scale (YMRS): This is an interview-based questionnaire used to assess level of mania or hypomania with 11 questions, each rated from 0 to 4.[134] Setting the cut-off value to 7, instead of 6, which is frequently used, took into account that most participants in this study would probably score two points on the question regarding sleep. (Study III)

- Mood diary: Participants were instructed to rate their mood for the previous day when completing the sleep diary the following morning. The mood diary was adopted from the

Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) study,[141] a 7-item rating scale with three levels of depression (mild, moderate, severe), one neutral level and three levels of elevated mood (mild, moderate, severe). Participants were instructed to rate daily symptoms of both elevated and depressed mood. We defined mood variability as at least one day of moderate mood symptoms and a shift in mood across two levels during one week. (Study III)

Measures of sleep disturbance:

- Actigraphy: For information about equipment see paragraph above (*2.3.1 Actigraphy Procedure*), and for details about analysis of sleep variables, see paragraph below (*2.4.1. Analysis of Actigraphy Data*). (Study III)

- Polysomnography: Sleep was recorded with standard Somnoscreen equipment analyzed with Domino software. Polysomnography was performed for two non-consecutive nights; sleep apnea and periodic leg movements were assessed only the first night. Sleep apnea was defined as an apnea-hypopnea index (AHI) > 15 per hour, corresponding to moderate sleep apnea.[142] Polysomnographic sleep variables were not analyzed. (Study III)

- Sleep diary: The sleep diary was kept in accordance with the consensus recommendation for sleep diaries.[143] Information from the sleep diary was used to set bedtimes and get-up-times and also to calculate the use of alcohol during the period of actigraphy monitoring. Sleep quality was rated from 0 - 4, 0 corresponding to "very poor" and 4 to "very good". Other self-reported sleep data were not analyzed. (Study III)

- The Insomnia Severity Index (ISI) is a self-rated assessment of the severity of insomnia symptoms. The ISI has 7 items, scored on a 1 to 4 Likert scale. A sum score of 15 points or more is indicative of clinical insomnia problems. The ISI has good psychometric properties.[136] (Study III)

- The Morningness-Eveningness Questionnaire (MEQ): This is a self-report questionnaire used to assess the patients' diurnal preference.[137] The MEQ consists of 19 items, and cut-off norms based on sum scores have been developed: a sum score of 70 or above is definitely morning type, 59-69 moderately morning type, 42-58 neither type, 31-41 moderately evening type, and 16-30 definitely evening type.[144] (Study III)

2.4 DATA ANALYSIS

2.4.1 Analysis of Actigraphy Data

In Studies I and II (Papers I, II and III), actigraphy data were analyzed for the total time of recording (24 hours). Furthermore, in Papers I and III, the time period from 6 AM to midnight was separated in morning epochs from 6 AM to 3 PM and evening epochs from 3 PM to midnight. These 9-hour epochs were only analyzed in Paper I, but in both Papers I and III we selected the first period of 64 minutes of continuous activity (no more than 2 – 4 consecutive activity counts of zero activity) during the 9-hour morning and evening epochs from each participant. The active morning period was searched from the start of the series (6 AM), and the active evening period from the end of the series (midnight). We used the 64-minute periods to see if the regulation of continuous motor behavior was different for the three groups. Continuous periods of activity were important for some of the mathematical analyses of complexity, where inactivity would indicate regularity in the activity pattern. 64 minutes were chosen due to the Fourier analysis, which requires sequence lengths to be potencies of 2 (32, 64, 128…). Recordings in Studies I and II had somewhat unequal lengths: Five patients in Paper I were excluded in Paper II due to several excluded periods. In Paper III, three patients with mania and one patient with depression had 24-hour recordings with valid monitoring time below 1300 minutes. In Paper III, a separate analysis without the short recordings was conducted.

In Study III, Paper IV, the rest intervals were analyzed for sleep variables by the actigraph software program (Actiware, version 5.70.1). Sleep estimates were automatically calculated using the Immobile Minutes algorithm of 10 minutes, and a wake threshold after sleep onset of 40 activity counts (medium sensitivity), which has commonly been used in actigraphy validation studies.[91, 145] Estimated sleep variables included total sleep time (TST) and sleep efficiency (SE), which is defined as “total sleep time” divided by “time in bed”, in this case rest interval duration. The active intervals in Study III were each analyzed separately using some of the variables from the 24-hour recordings in Papers I and III. Means and standard deviation values for all variables across the total number of active intervals or days were then calculated.

2.4.2 Mathematical Methods for Calculation of Activity Variables

In Papers I, III and IV, we calculated the mean activity count per minute for each time interval. We further calculated three measures of variability: the intra-individual standard deviation (SD), which is a measure of fluctuations in activity, the root mean square successive difference (RMSSD), which describes the difference in successive counts from minute to minute, and the RMSSD/SD ratio. SD is a parametric measure of variability from the mean, whereas RMSSD calculates the point-to-point variability.[146] Many of the values in Papers I and III from 24-hour recordings are not directly comparable to the values in Paper IV, which were calculated from the patients' active periods, i.e. time spent awake, whereas recordings in Papers I and III also include time spent in bed (rest or sleep).

For the 64-minute time periods in Papers I and III, we additionally performed a Fourier analysis and used sample entropy, and in Paper III autocorrelation at lag 1 and symbolic dynamics. Sample entropy and symbolic dynamics provide measures of complexity in time series. Complexity analyses are methods to describe the disorganization of a pattern. All techniques represent distinct means of characterizing a series of data in time. The software used for the estimation of sample entropy and for the Fourier analysis was obtained from the Physio Toolkit Research Resource for Complex Physiologic signals,[147] see http://www.physionet.org.

- Sample entropy is a nonlinear measure, which indicates the degree of regularity (complexity) of a time series, and 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. Data were normalized by transforming the time series to have sample mean 0 and sample variance 1. We chose the following values, m = 2 and r = 0.2. Sample entropy was used since it can be employed with comparatively short time series (> 50 points) and is robust with regard to outliers.[148] (Studies I and II, Papers I and III)

- Fourier analysis: Data were normalized before analysis. No windows were applied. Results were 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 minutes) and the low frequency part (0.00026 - 0.0021 Hz, corresponding to 8 – 64 minutes). The choice of defining the high and low frequency part of the spectrum corresponding to the periods 2-8 min and 8-64 min in the Fourier analysis was based on a previous paper.[114] (Studies I and II, Papers I and III)

- Autocorrelation at lag 1: An autocorrelation function is a mathematical tool to measure the degree of relationship between observations that are *k* lags apart. The autocorrelation at lag 1 is the correlation of a time series with itself lagged one step, in this case from minute to minute. As such, values closer to one indicate a stronger correlation. Autocorrelation analyses were performed using SPSS version 20.0. (Study II, Paper III)

- Symbolic dynamics: The time series were transformed into series of symbols according to the method described by Guzzetti et al.[122] and Porta et al.[149] For the analyzed active morning and evening sequences, the difference between the maximum and minimum value was divided into 6 equal portions (1 – 6) and each value of the series was assigned a number from 1 – 6, such that the transformed time series consisted of a string of numbers from 1 – 6. To avoid the problem with outliers the maximum value was set at no more than the mean + 3 times the SD, and the minimum value was set at no less than the mean – 3 times the SD. The series were then divided into overlapping sequences of three consecutive numbers. The series thus contained 62 such sequences, and the number of different sequences was counted, giving an indication of the complexity of the time series.[150]

For the symbolic dynamics analyses we also used an alternative method to analyze the data, described by the same authors.[122, 149] Each sequence of three consecutive numbers was assigned one of four symbols, according to the following rule: 1) a pattern with no variation (e.g. 333), 2) a pattern with only one variation: two consecutive symbols are equal and the remaining symbol is different (e.g. 331), 3) a pattern with two like variations, such that the 3 symbols either ascend or descend (e.g. 641 or 235) and 4) a pattern with two unlike variations, both ascending and descending values (e.g. 312 or 451). The rates of occurrence of these four patterns were counted and the results given as the percentage of the total number of sequences analyzed (n = 62). (Study II, Paper III)

In Study I, Paper II, the characteristics and distribution of active and inactive periods [120, 151-153] during 24 hours were examined. First, each minute was defined as active or inactive, according to whether the activity count was above or below 10% of the mean for the whole 24-hour period. An active or inactive period was defined as a continuous sequence of active or inactive intervals with a length (A) of one minute and upwards. The cumulative probability (P) that an active or inactive period had a length of ≥ A minutes was then determined. In accordance with a previous study by Fasmer et al,[153] we plotted P vs. A on a log-log graph

using lengths from 1 to 35 min for active periods and 1 to 20 min for inactive periods. We further calculated the slope of the line (scaling exponent, absolute value) that best fitted the data, using the least squares method. For each patient we also calculated the mean duration of active and inactive periods, the longest active and inactive periods, the number of active periods with a length of ≥ 36 min (expressed as % of all active periods), and the number of inactive periods with a length of ≥ 21 min (expressed as % of all inactive periods). The thresholds of 36 min and 21 min were defined on the basis of a previous study,[153] where these specific numbers were found by visual inspection of log-log graphs.

2.5 STATISTICS

Statistical analyses were carried out using SPSS version 20.0. Numbers and percentages were reported for categorical variables, and means and standard deviations (SD) for continuous variables showing normal distributions; variables were given as medians and interquartile ranges (IQR) when appropriate. For comparison of counts of categorical data chi-square tests were used, and percentages were expressed for most numbers. For comparison of normally distributed variables we used Student's independent samples t-tests between two groups and one-way ANOVAs between three groups with post-hoc tests to obtain differences between groups. In Paper I, the post-hoc tests were Least Significant Difference (LSD) tests, and in Paper III, Bonferroni tests. If unequal variances were assumed, Tamhane's T2 post-hoc test was used. In Paper IV, some variables showed non-normal distributions. For simplicity in presentation, all variables apart from activity variables were given as medians and IQR and compared using Mann-Whitney tests. A p-value ≤ 0.05 (two-tailed tests) was considered significant.

3 RESULTS

3.1 PAPER I, STUDY I

Actigraphically Assessed Activity in Unipolar Depression – A Comparison of Inpatients with and without Motor Retardation

(Krane-Gartiser K, Henriksen TE, Vaaler AE, Fasmer OB, Morken G. Journal of Clinical Psychiatry 2015 Sep; 76(9):118-7)

Objective: To compare the activity patterns of inpatients with unipolar depression, who had been divided in motor-retarded and non-motor-retarded patients prior to actigraphy monitoring.

Method: 24-hour actigraphy recordings from 52 consecutively, acutely admitted inpatients with unipolar depression (ICD-10) were compared to 28 recordings from healthy controls. The patients, admitted between 09/2011 – 04/2012, were separated in 25 with motor retardation and 27 without motor retardation. 24-hour recordings, 9-hour daytime sequences and 64-minute periods of continuous motor activity in the morning and evening were analyzed for mean activity, variability and complexity.

Results: Patients with motor retardation had a reduced mean activity level ($p = 0.04$) and higher intra-individual variability in activity, as shown by increased standard deviation (SD) ($p = 0.003$) and root mean square successive difference (RMSSD) ($p = 0.025$), during 24 hours compared to the patients without motor retardation. In the 24-hour recording, both patient groups demonstrated significantly lower mean activity compared to healthy controls ($p < 0.001$), as well as higher SD ($p < 0.02$) and RMSSD ($p < 0.001$), and a higher RMSSD/SD ratio ($p = 0.04$). In the active morning period, the patients without motor retardation displayed significantly increased complexity compared to motor-retarded patients ($p= 0.006$).

Conclusion: The patients with and without motor retardation differed in activity patterns. Findings in depressed inpatients without motor retardation closely resembled those of inpatients with mania.

3.2 PAPER II, STUDY I

The Distribution and Characteristics of Active and Inactive Periods Distinguish Unipolar Depression with and without Motor Retardation

(Krane-Gartiser K, Vaaler AE, Fasmer OB, Morken G. Journal of Clinical Psychiatry. Accepted in November, 2015)

Introduction: Studying bursts of activity followed by periods of inactivity could be a complementary way of describing variability in activity. In the present study, we aimed to reanalyze previously published actigraphy data in unipolar depression to quantify the regulation of motor behavior and distinguish groups with and without motor retardation.

Methods: Consecutively, acutely admitted inpatients with unipolar depression (ICD-10 F32 and F33) were divided into two groups based on a clinical assessment of motor activity level: 22 with motor retardation and 21 without motor retardation. 24-hour actigraphy recordings were analyzed using a method for characterizing active and inactive periods and their distribution.

Results: Patients with motor retardation demonstrated significantly shorter mean active period durations, and their longest active sequence was shorter compared to non-motor-retarded patients. Furthermore, the percentage of active sequences with duration of more than 36 min was significantly lower for the motor-retarded patients and the scaling exponent for the active periods higher. None of the variables pertaining to inactive periods differentiated the groups.

Conclusions: Patients with unipolar depression with and without motor retardation differ in characterization and distribution of active periods, which constitutes a complementary way of differentiating depressive subgroups. This study also shows that it is feasible to characterize group differences with only 24-hour observational periods compared to 5-12 days in previous studies, increasing the value in analysis of motor activity patterns in psychiatric disorders.

3.3 PAPER III, STUDY II

Actigraphic Assessment of Motor Activity in Acutely Admitted Inpatients with Bipolar Disorder

(Krane-Gartiser K, Henriksen TE, Morken G, Vaaler AE, Fasmer OB. PLoS One. 2014 Feb 20;9(2):e89574)

Introduction: Mania is reported to be associated with increased activity, whereas motor retardation is often found in bipolar depression. Actigraphy is a promising tool for monitoring phase shifts and changes following treatment in bipolar disorder. The aim of this study was to compare recordings of motor activity in mania, bipolar depression and healthy controls, using linear and nonlinear analytical methods.

Material and methods: Recordings from 18 acutely hospitalized inpatients with mania were compared to 12 recordings from bipolar depression inpatients and 28 healthy controls. 24-hour actigraphy recordings and 64-minute periods of continuous motor activity in the morning and evening were analyzed. Mean activity and several measures of variability and complexity were calculated.

Results: Patients with depression had a lower mean activity level compared to controls, but higher variability as shown by increased standard deviation (SD) and root mean square successive difference (RMSSD) over 24 hours and in the active morning period. The patients with mania had lower first lag autocorrelation compared to controls, and Fourier analysis showed higher variance in the high-frequency part of the spectrum corresponding to the period from 2-8 minutes. Both patient groups had a higher RMSSD/SD ratio compared to controls. In patients with mania we found an increased complexity of time series in the active morning period compared to patients with depression. The findings in the patients with mania are similar to previous findings in patients with schizophrenia and healthy individuals treated with a glutamatergic antagonist.

Conclusion: We have found distinctly different activity patterns in hospitalized patients with bipolar disorder in episodes of mania and depression, assessed by actigraphy and analyzed with linear and nonlinear mathematical methods, as well as clear differences between the patients and healthy comparison subjects.

3.4 PAPER IV, STUDY III

Unstable Rest-Activity Cycles in Euthymic Bipolar Disorder and Clinical Implications for Sleep, Mood and Activity

(Krane-Gartiser K, Steinan MK, Langsrud K, Vestvik V, Sand T, Fasmer OB, Kallestad H, Morken G. Submitted in December, 2015)

Objective: The aims of this observational study of patients with euthymic bipolar disorder and sleep disturbance were to 1) compare characteristics related to mood and sleep between two groups with stable and unstable rest-activity cycles and 2) detect between-group differences in motor activity patterns.

Method: 43 patients wore an actigraph for 6-8 days while reporting daily mood and sleep. Patients were defined as having an unstable rest-activity cycle if their diurnal active period duration presented variation above 2 hours from the mean (standard deviation) during one week: 22 patients had a stable and 21 an unstable rest-activity pattern.

Results: Patients with unstable rest-activity cycles were younger (37 vs. 48 years, $p = 0.01$) and displayed more mood variability ($p = 0.02$). Ten of 11 patients diagnosed with delayed sleep phase syndrome were in the unstable group ($p < 0.01$), and the unstable group had later and more variable get-up-times and bedtimes. In actigraphy recordings, the mean activity counts per minute did not differ between groups, but the minute-to-minute variability was elevated ($p = 0.04$) in the unstable compared to the stable group and increased relative to the overall variability ($p = 0.03$). A higher degree of variation in daily intra-individual variability of activity across the week was also found in the unstable rest-activity cycles group ($p = 0.04$).

Conclusion: A subgroup of euthymic patients with bipolar disorder displayed unstable rest-activity cycles combined with mood variability and motor activity patterns that resemble findings in affective episodes.

4 DISCUSSION

4.1 DISCUSSION OF THE FINDINGS

In three actigraphy studies in mood episodes and the euthymic state of affective disorders, the results can be summarized as follows: In Study I, actigraphy recordings were found to support clinical assessments of motor activation in acutely admitted patients with unipolar depression, who were clinically divided in motor-retarded and non-motor-retarded patients. By employing complementary and non-linear analytical methods, distinct differences in activity between motor-retarded and non-motor-retarded patients were demonstrated in Papers I and II. In acute states of bipolar disorder (Study II), the patterns of motor activity were characterized by variability in bipolar depression, resembling motor-retarded unipolar depression, and more disorganization in mania, resembling findings from non-motor-retarded unipolar depression in Paper I. In the euthymic state of bipolar disorder (Study III), a subgroup of patients with unstable rest-activity cycles displayed variability in motor activity patterns that resembled findings in affective episodes.

4.1.1 Activity Findings

Mean activity levels

Mean activity was calculated as mean activity count per minute for each time sequence. For all three groups with depression in Papers I and III, the mean activity level was lower compared to healthy controls. (See Figure 3 in the appendix.) Among the patients with unipolar depression in Paper I, patients with motor retardation had significantly lower activity counts compared to patients without motor retardation. In Paper III, the group with bipolar depression was less active than healthy controls during 24 hours. Lower activity levels compared to controls were found for both patients with bipolar depression and patients with mania in the 64-minute active morning sequence, but otherwise, the patients with mania did not distinguish themselves from patients with depression or from healthy controls in mean activity level. The mania group included few participants, and differences may be revealed in larger studies. There was no difference in mean activity between patients with euthymic bipolar disorder and sleep disturbance with stable and unstable rest-activity cycles (Paper IV).

Lower activity levels in patients with depression have been found in a number of actigraphy studies.[94] While investigations of mean activity have been done in unipolar and bipolar

depression,[98, 154] the author of this thesis is not aware of other studies that have compared activity levels in motor retardation vs. non-motor-retardation. Differences in mean activity between institutionalized patients and healthy individuals living in the community could be explained by living environment and hospital routines rather than by affective level. For instance, the lower activity found in the patients with mania in the morning may reflect a natural consequence of staying on a hospital ward within a limited area, an effect of psychotropic drug treatment, and/or disturbances in patients' current circadian rhythm influenced by their bipolar disorder. Without constraints associated with hospitalization, one could expect the patients with mania to be more active than the healthy controls, although a small report comparing non-hospitalized patients with mania and healthy controls showed lower activity levels among the patients with mania.[23] It is also possible that increased activity is not the cardinal motor symptom during mania, but rather other features of motor regulation than high or low levels.

Periods of immobility and minimum activity levels could be an important indicator of motor retardation.[100] In Paper I and Paper III, immobility was only reflected in the mean activity count per minute, as well as in periods with more than 4 consecutive activity counts of zero activity, which were excluded from analysis of the 64-minute active sequences in the morning and evening. Excluding immobility was important for the complexity analyses, in which inactive periods would have given a misleading impression of regularity. In Paper II, none of the variables pertaining to inactive periods differentiated the groups with unipolar depression. As such, this supports Royant-Parola's observation that lack of initiation of spontaneous movements in depression also occurs in non-motor-retardation.[100] She further suggested that immobility could be a more fundamental deficiency in depression than low activity levels, but it was not possible to distinguish immobility from low activity in this thesis.

Intra-individual Variability in Activity

Variability measures included SD in % of activity (variability from the mean) and RMSSD in % of activity (minute-to-minute-variability). For all three groups with depression in Papers I and III, intra-individual variability measures were higher compared to healthy controls. Patients with unipolar depression and motor retardation displayed increased SD in % of activity and RMSSD in % of mean activity throughout the 24 hours and during sequences in the morning and evening, compared to patients without motor retardation and to healthy

controls. In the bipolar depression sample in Paper III, increased RMSSD in % of mean activity was found compared to controls over 24 hours and in the active morning sequence, and SD in % of mean activity was higher in the active morning sequence compared to both healthy controls and patients with mania. (See Figure 4 and Figure 5 in the appendix.)

In Paper IV, mean values of RMSSD in % of mean activity over approximately one week were significantly higher in the group with unstable rest-activity cycles. (See Figure 6 in the appendix.) Due to the longer recording in Study III than Studies I and II, it was possible to compare the variation of activity variables from day to day, given by standard deviation values of the daily means. The variability in activity levels within a day changed significantly more from day to day in the unstable group, as evaluated by the greater variation of SD/min in % of mean activity count. Activity patterns in the unstable group thus displayed increased short-term fragmentation within days and greater longer-term variability between days.

These findings of increased variability in acutely admitted patients with depression are in agreement with previous findings from actigraphy studies using the same motor activity variables in unipolar depression[114] and ADHD.[155] In Paper IV, mood variability occurred more frequently in the unstable rest-activity cycles group. It was not possible to conclude if the RMSSD-finding was related to mood or to unstable circadian rhythms. Another actigraphy study in which standard deviation was used as a measure of the within-subject variability in sleep parameters in patients with euthymic BD found increased variability of sleep duration and night wake time across 5 nights compared to healthy controls.[156] Other procedures have been used to describe variability across days in previous studies, and our results in Paper IV correspond to more variable levels of physical activity within and between days in euthymic bipolar disorder.[24, 76, 157] Altogether, these results suggest that short-term and long-term variability may be trait markers in affective disorders.

The Characterization and Distribution of Active Periods

Studying active and inactive periods according to Nakamura's methods[120] is another way to describe non-linearity in activity patterns. In Study I, Paper II, motor retardation seemed to imply being active in shorter bursts compared to non-motor retardation. There were also fewer long bursts in motor retardation, which accords with a higher scaling exponent for active periods. (See Figure 7 in the appendix.) In a previous study using the same method in groups with depression, schizophrenia and healthy controls, the depressed patients displayed

significantly shorter bursts of activity, fewer long active periods and higher scaling exponents for both active and inactive periods.[153] These findings, in concordance with our results in motor-retarded depression, gave the impression that the distribution of active and inactive periods was more disturbed in depression compared to schizophrenia, although both psychiatric disorders commonly include alterations of motor activity and often sedentary behavior.[108, 158] In other words, the methodology seems applicable to distinction of psychiatric subgroups.

RMSSD/SD Ratio, Autocorrelation Lag 1 and Fourier Analysis

SD assesses variability independently of the order of observations, and RMSSD assesses variability from one observation to the next. An increased RMSSD/SD ratio thus signifies that the alteration between minute-to-minute counts in activity increases relative to overall variability. Increased RMSSD/SD ratios were found for several patient groups: the motor-retarded UD group in Paper I, bipolar depression and mania in Paper II and the unstable rest-activity cycles group in Paper IV. As such, an increased RMSSD/SD ratio is not likely to represent a disease-specific motor trait.

In Paper III, patients with mania had the highest RMSSD/SD ratio in the active morning and evening sequences. They also had significantly lower autocorrelation in the first lag compared to healthy controls in the morning sequence. Lower autocorrelation in the first lag indicates less correlation from minute to minute and comply with increased RMSSD/SD ratios. (See Figure 8 and Figure 9 in the appendix.) Higher RMSSD/SD ratios could also be interpreted as greater variability in the high-frequency spectrum relative to overall variability. Consequently, in the manic group, increased RMSSD/SD ratios are in agreement with findings from the Fourier analysis of a higher variance in the high-frequency part of the spectrum, corresponding to the period from 2 to 8 minutes. The UD group without motor retardation in Paper I resembled the patients with mania by the Fourier analysis findings, although it was not a significant difference compared to the motor-retarded patients. (See Figure 10 in the appendix.) An increased ratio between variance in the spectrum's high and low frequency in the Fourier analysis and increased RMSSD/SD ratios were also found in a sample of patients with schizophrenia[114] and in healthy individuals treated with a glutamatergic antagonist.[127] Altogether, these findings demonstrate other changes in motor function than reduced mean activity in affective episodes and in subgroups during euthymia.

There could be cross-diagnostic similarities in certain variables which warrant further exploration.

Sample Entropy and Symbolic Dynamics

These measures estimate complexity of activity. The symbolic dynamics analysis, only performed in Paper III, showed the highest number of unique sequences in the mania group, significantly different from the bipolar depression group. In accordance with the symbolic dynamics findings, the activity patterns of the patients with mania also had the highest sample entropy between all three groups in Study II. The non-motor-retarded patients with unipolar depression in Paper I displayed significantly higher sample entropy in the 64-minute active sequence in the morning compared to motor-retarded patients, again resembling findings in the manic group. In summary, mania and non-motor-retarded UD were accompanied by increased complexity in motor activity patterns. (See Figure 11 and Figure 12 in the appendix.)

Increased entropy indicates a higher level of disorder and unpredictability in a time series. This has been found in patients with schizophrenia and has been suggested to represent a partial breakdown in structured normal activities of everyday life.[114] Findings of increased complexity may seem in conflict with Goldberger's postulations of reduced complexity as a characteristic of diseases and aging,[121] but disease processes with intrinsic oscillations may instead be accompanied by increased complexity.[159] Goldberger himself distinguished between entropy as a measure of irregularity and other measures of unpredictability and suggested that several parameters may be required to describe physiologic complexity.[160] The study in individuals treated with an NMDA antagonist that induced movement patterns with similar characteristics as in patients with schizophrenia[127] and our samples of patients with mania in Paper III and non-motor retarded UD in Paper I, suggests that the NMDA receptor could be involved in movement disturbances. Bipolar disorder has been associated with a dysfunctional frontal glutamate system.[161] On these grounds it should be further explored how the NMDA receptor may be involved in activity patterns associated with motor agitation. Furthermore, the role of other neurotransmitters involved in the regulation of motor activity should also be examined, in particular dopamine, since alterations of motor behavior may reflect activity in central dopaminergic neurons.[117, 162]

4.1.2 Implications of Diurnal Variation

Diurnal Variation in Studies I and II, Papers I-III

Because detecting differences in diurnal variation of activity was not the main focus of Studies I and II of this thesis, direct testing for differences in diurnal profiles between the groups was not included in Papers I, II and III. However, in Paper I, patients with unipolar depression displayed higher variability compared to healthy controls only in the active sequence in the morning and not in the active evening sequence. Also, there were differences in how the two patient groups respectively separated themselves from healthy controls. As an example, patients with motor retardation had increased SD in % of mean activity in the morning, evening and active morning sequences, whereas the patients without motor retardation did not distinguish themselves from healthy controls in this way. Interpretation of these results suggests that the two groups of depression both differ in patterns of motor activity and in patterns of disturbances in diurnal rhythms. In Paper III, the most pronounced between-group differences were found in the active morning sequence compared to the lesser between-group differences in the active evening sequence. In conclusion, there are indications of differences in the diurnal rhythms between the groups, although that was not the focus of Studies I and II.

Diurnal Variation in Study III, Paper IV

In Paper IV, among a group of outpatients with verified bipolar disorder, currently euthymic and experiencing sleep disturbance, approximately half of them had unstable diurnal rest-activity cycles, as defined by a standard deviation in length of the active intervals during one week of more than 2 hours from the mean. This group with unstable rest-activity cycles displayed several characteristics that differed from the stable group, among which were significantly younger age and later bedtimes and get-up-times. This corresponds to knowledge about delayed sleep phase.[57, 163] The unstable group included nearly all patients with a diagnosis of delayed sleep phase disorder (DSPD) in the study. DSPD has been found in 60 % of patients with bipolar disorder vs. 14 % in otherwise healthy individuals of the same age,[44] and a number of studies report on co-occurring symptoms of depression and delayed sleep phase.[164] For patients with unstable rest-activity cycles, bedtimes and get-up-times varied significantly more during a week, which may seem related to the grouping, but importantly, both times varied, and not one rather than the other. Instability in sleep timing is not part of

the definition of DSPD, but there could be some overlap between the two clinical entities, or the instability in bedtimes and get-up-times is particularly associated with bipolar disorder combined with DSPD. Several reports have suggested that bipolar disorder is related to an evening preference for daily activities and a phase-delay in activity.[25, 45, 59] In a study of sleep-wake cycle disturbances associated with mood disorders, it was found that younger age and higher symptoms severity were both associated with delayed sleep-wake schedules and delayed daily activity peak.[163] Symptomatic participants had later sleep offset times than asymptomatic participants, and sleep offset was the only variable to be significantly predicted by both age and depression severity. Accordingly, sleep offset could be a specific phase marker especially sensitive to the additive effects of age and depression, which is partly supported by our findings in Study III, Paper IV. (See Figure 13 in the appendix.)

Factors thought to stabilize daily routines, such as social structure exemplified by employment, living with a partner or taking care of younger children, did not differ between the two groups in Paper IV. These findings indicate that diurnal variations in bipolar disorder may be an endogenous rhythm disruption rather than a primary environmental influence, which is further consolidated by the findings of variability in mood and motor activity in the patients with unstable rest-activity cycles.

Clinical Implications of Unstable Rest-Activity Cycles in Study III, Paper IV

Interestingly, a significantly larger proportion of participants in the unstable rest-activity cycles group in Paper IV reported mood variability, defined as at least one day of moderate mood symptoms and a shift in degree of symptoms between two levels on a 7-level scale during the week of actigraphy. (See Figure 14 in the appendix.) Seven of the 11 patients who in total displayed mood variability reported both elevated and depressed symptoms, which may be interpreted as significant symptom distress despite clinically assessed euthymia and similar sum scores on mood rating scales just prior to the daily mood reports. Another study in euthymic BD found that abnormal circadian measures were associated to course of illness and symptoms, so that the more abnormal the circadian measure, the longer the duration of illness or the greater the severity of symptoms.[76] While Study III could not explore a causal relationship between mood instability and unstable rest-activity cycles, it is possible that among patients with bipolar disorder, individuals with greater circadian instability also more frequently experience rapid moderate mood shifts.

The majority of participants (76.7 %) in Study III, Paper IV, had bipolar disorder type II, evenly distributed between groups. Apart from the difference in age between groups, no demographic characteristics or easily distinguishable clinical characteristics, such as bipolar type, BMI, age at illness onset, number of episodes per illness duration, number of medications, clinical mood assessments, severity of sleep disturbance or sleep duration, separated patients with unstable rest-activity cycles from those with stable cycles. Consequently, it is necessary to explore the possible instability in sleep timing either through a detailed history, sleep diaries or actigraphy.

Including MADRS scores up to 14 and YMRS scores up to 7, and the degree of mood symptoms reported by some of the participants, could argue against euthymia and be residual effects of a previous episode or the beginning of a new episode.[25] Regardless, mood variability and subsyndromal mood symptoms are common in euthymic bipolar disorder and have been found to predict worse long-term outcome.[10] Mood variability could therefore be an important target for early therapeutic interventions. As such, patients with unstable rest-activity cycles, particularly the younger ones with delayed sleep phase, should be closely monitored for changes in mood, sleep and activity. Psychoeducation[5], rhythm treatment[50] and cognitive behavioral therapy for insomnia (CBT-I)[49] have all shown stabilizing effects on rest-activity cycles. Chronotherapy, such as light therapy, dark therapy and melatonin, may have adjuvant secondary effects on mood as well.[77, 78, 81]

4.1.3 Similarities Between Patient Groups Across the Studies

All three groups of inpatients with depression displayed similar findings of mean activity levels and higher intra-individual variability in activity, defined by SD in % of mean activity and RMSSD in % of mean activity. Patients with motor retardation more closely resembled patients with bipolar depression, as given by the finding of less complexity (assessed by lower sample entropy) than that of the non-motor-retarded patients, in addition to increased point-to-point variability relative to overall variability (assessed by an increased RMSSD/SD ratio), compared to healthy controls. The seemingly paradoxical findings of increased variability and less complexity in depression are in line with chaos-theoretical principals of disease physiology and results from investigations of affective instability.[124] Goldberger summarized the combination of high variability and low complexity as "organized variability".[121] Concordantly, Hauge et al found that variability measures and complexity measures were

inversely correlated.[114] This strong negative correlation does not have an immediate explanation, but a possible theory is that reduced variability may be found on a brain level, while variability at the behavioral level may be different.[165, 166]

Some of the characteristics in activity patterns in non-motor-retarded depression were similar to those accompanying a manic state. In mania we found increased complexity of motor activity patterns, which resembled findings in previously studied schizophrenia. There are several theories of mechanisms and significance of increased complexity in disease processes; the exact implications are unknown.[159] In euthymic bipolar disorder, a subgroup showed unstable rest-activity cycles. Half of this subgroup had delayed sleep phases, many additionally experienced mood variability and displayed increased variability in activity, similar to results in the groups with depression. Findings of variability in activity in inpatients and outpatients with affective disorders across disease states suggest that motor activity parameters could be trait markers of affective disorders. The resemblance of findings across diagnostic groups such as motor-retarded and non-motor-retarded depression, bipolar disorder, schizophrenia and ADHD raise questions of shared genetic risk that could be further explored.[167] Yet, differences in activity variability between affective disorder subgroups agree with findings of independent familiar heritability of these subgroups,[27] their questioned conceptualization[30] and different biological correlates between depression subtypes.[168]

Even though activity patterns in patients could be distinguished by differences in variability on a group level and separated from those of healthy controls using state-of-the-art technology, there were marked individual patterns within groups. Based on this observation, we hypothesize that every individual has an inherent activity pattern. Exploration of how mood, sleep and circadian instability affect motor activity on an individual level requires longitudinal monitoring and possibly refinement of analytical methods. As such, although a shorter observational period increases the possibility of application of actigraphy to the acute psychiatric setting, 24-hour group differences are not adequate for diagnostic purposes. Development of a set of complementary methods that consider mean levels, variability and circadian rhythms could lead to personalized methodology for analysis of motor activity.

4.2 Discussion of Materials and Methods

4.2.1 Samples

Strengths of the Norwegian health care system, such as being catchment-area based and primarily publicly funded, implicate providing health services to patients from all social classes and demographic layers. Because the public system is the only provider of psychiatric emergency services, the inpatients included in Studies I and II are likely to represent patients in need of acute hospitalization, although those who did not want to participate might differ from the included patients. Broad inclusion criteria and few exclusion criteria in all three studies further augment representability. By definition, the clinical study III is not representative of the total population of patients with bipolar disorder, because we specifically selected patients with sleep disturbance in the euthymic phase; the patients were either referred to the clinic or contacted the clinic directly.

Diagnostic procedures

In Studies I and II (Papers I-III), the patients were diagnosed at a consensus meeting before discharge from the hospital. At least two experienced psychiatrists of whom at least one had met the patient participated, and diagnoses were set according to ICD-10 research criteria. Even if SCID-I is considered to be the gold standard in diagnostics, the department has published several papers based on such a consensus diagnostic process.[169-172] Co-morbid psychiatric disorders were seldom diagnosed in the two studies. Many consider it difficult to diagnose co-morbid personality disorders during an acute inpatient stay due to the burden of symptoms connected to the acute illness.

In Study III, Paper IV, a SCID-I interview was used and the diagnosis discussed or confirmed in a meeting of at least one clinical specialist in psychology and at least one psychiatrist.

Potential Selection Bias in Studies I and II

654 patients were admitted to the acute wards at Østmarka psychiatric hospital during the study period from September, 2011 to April, 2012. 274 patients declined or were excluded from the study of agitation in acutely admitted patients, from which data for Studies I and II originate. 380 unique patients, accounting for 424 admissions, accepted participation. 280 admissions included patients who wore an actigraph for 24 hours (67 % of participating

admissions). Patients who did not participate could represent a selection bias, and further exploration is difficult due to limited information.

Potential Selection Bias in Study III

In Study III, patients were recruited on the basis of subjective sleep disturbances in the euthymic phase of bipolar disorder, by self-referral or referral by qualified health personnel. Such recruitment through multiple channels is considered to be as wide and general as possible, but could be associated to selection bias. A recent cross-sectional study investigating sleep profiles in Norwegian patients with bipolar disorder (the BRAIN study) found that 55 % of 226 patients in the euthymic state experienced insomnia or hypersomnia.[42] The size of the eligible population for Study III can thus be considered high, but is of course impossible to estimate. The study procedure is also associated to selection bias in being particularly thorough and time consuming. While some patients appreciate professional assessments of symptoms and disorders, others may be intimidated. The study procedure further required a certain level of cognitive functioning, which may have selected particularly well-functioning patients.

Appropriateness of Healthy Controls as a Comparison Group in Studies I and II

The most relevant reason for comparing healthy controls to patient groups is the lack of disease in the control group. Information about current or previous psychiatric diagnoses in healthy controls was given by self-report, which implies a certain information bias. The potential bias in comparing institutionalized and free-living individuals has already been mentioned, and the quality of studies would have been improved if the healthy controls wore an actigraph during inpatient stays. Such bias is thought to primarily concern mean activity levels, and less likely other findings. Including other inpatient control groups could have had advantages, with reference to similarities and differences in the same variables used in previous actigraphy studies in other diagnostic groups.[102, 114, 127, 153]

Activity may further vary between controls and patients due to work schedules, as a difference between workdays and weekends is expected in working adults. Dividing the healthy controls into 15 who wore the actigraph on a weekday and 13 who were monitored in the weekend or were retired, produced only one significant difference in all analyses:

RMSSD/SD for the 24-hour period. This could indicate that the day the actigraph was worn might have affected the findings. The season of monitoring could also have biased results, since 18 of the 28 controls were monitored in spring or summer months, as opposed to the patients who were all monitored in fall or winter months. Seasonal changes in energy levels are possible, but activity may be less influenced by light exposure than mood.[173]

Although healthy controls were not matched to patients by age or gender, there were no major differences between groups in these variables.

Appropriateness of Comparing Inpatient Groups

In Studies I and II, hospital routines were the same for all inpatients. No specific activity should have had a differential impact on findings between patient subgroups. Again, it was not essentially mean levels that separated the patient groups in the respective studies, indicating that grouping of patients in similar settings and in patient groups with the same diagnosis was meaningful. Although a difference in mean activity between mania and bipolar depression could have been expected, the findings in variability and complexity seem all the more important.

In Study II, the patients with mania were older than healthy controls and patients with bipolar depression, and in Study III, the group with unstable rest-activity cycles were significantly younger than those with stable rest-activity cycles. Differences in age may have had an impact on results.

In Study II, a significantly greater proportion of the patients with mania than with bipolar depression were admitted to a psychiatric intensive care unit (PICU). A PICU implies a more restricted area under regular surveillance, and depending on the behavior of the patients, they may be allowed to move about freely, but within a more limited space than on an open ward. Admission to a PICU is a marker of more severe illness than being treated in the ordinary ward. When separating the patients with mania into two groups, one with the patients admitted to a PICU (n = 10) and one with patients admitted to an ordinary ward (n = 8), the patients in the PICU had a significantly increased RMSSD//SD ratio, lower autocorrelation in the first lag and higher variance in the high-frequency part of the spectrum in the Fourier analysis, in the active morning period only. Also, in the 24-hour recording, the patients in a PICU had an increased SD in % of mean activity compared to patients on an open ward. It is

not possible to conclude on whether circumstances related to hospitalization or illness severity primarily account for activity findings in mania.

4.2.2 Design and Procedures

Due to the short-term observational design of all studies, interpretations of causality are impossible. The actigraphy study periods of 24 hours and 6-8 days, respectively, prevent conclusions on long-term characteristics and effects. The cross-sectional approach with respect to collection of other data in Studies I and II relies on accurate clinical assessments. The degree of self-report in Studies I and II was very restricted, and risk of recall bias is therefore considered to be low. However, in Study III, memory impairment for variables related to past course of illness is probable, and current ratings of mood and sleep are subject to individual interpretation and varying accuracy in reporting. Still, such information bias is most likely to mask differential effects between groups and thus increase the risk of failing to detect differences that are present.[174] For all studies in this thesis, the relatively small sample sizes restrict generalizability of results. The impact of psychotropic medication and comorbid disorders, which may have biased the differences in activity found between patients, were not assessed in the studies.

Specific limitations of study procedures in Studies I and II also include lack of mood or sleep logs. Since no self-reported or clinical ratings of affective symptom score were available, a possible influence of severity of depression or mania on motor activity was not evaluated, and it was not possible to correlate activity findings to mood symptoms. The degree of sleep disturbance in inpatients was not known, and there were no indications of when the patients went to bed or how much they slept. An exploration of sleep dysfunction on activity parameters was thus not feasible. Inpatients are expected to have quite similar rest-activity cycles during hospitalization, due to fixed points in time for eating, activities and bedrest. Once more, spending time in bed or sleeping would most likely mainly affect mean activity during 24 hours and have less influence on the differences found in other variables between patient groups in the morning and evening. All patients in Studies I and II were hospitalized in an acute state of an affective disorder and the results should not automatically be extrapolated to outpatients with a less severe course of illness.

Specific limitations of the procedure in Study III: Even though 6-8 days have been found sufficient to study circadian instability,[111] long-term clinical implications of unstable rest-

activity cycles could not be determined. The study procedure may have accounted for some of the observed variation in rest-activity cycles (two nights of polysomnography), but the procedure was the same for all patients. Studying covariation between mood swings and activity would require longer observational periods. Extending studies to include groups of patients with other psychiatric disorders and otherwise healthy individuals with and without sleep disorders could provide more answers on the relationship between mood, circadian instability and activity characteristics.

4.2.3 Instruments

Validity and Reliability of Instruments and Variables Used

Although the SOMAS[138] has been used in few other studies, the two items of motor retardation and agitation extracted for Study I are based on the widely used PANSS.[175] Judging by the objective findings in Papers I and II, the SOMAS was successful in identifying clinically observable motor retardation and agitation by different assessors.

In Study III, the structured clinical interviews SCID-I and NEQ, rating scales MADRS and YMRS and the self-report ratings ISI and MEQ are among the most commonly used for their respective purposes. SCID-I is the diagnostic interview for Axis I disorders in the DSM-IV, and the NEQ was originally developed for the Stanley Foundation Bipolar Outcome Network.[176] MADRS and YMRS cut-off scores for euthymia are usually set lower in other trials,[177] but the participants in Study III were expected to score points on items assessing sleep due to their sleep disturbance, and euthymia was thus defined by a higher cut-off. The ISI is a brief, valid and reliable instrument for detection of insomnia, and the MEQ a standard questionnaire for assessment of diurnal preference.

The mood diary in Study III was based on the one used in the STEP-BD, which was a large descriptive and treatment study in the US.[141] The definition of mood variability was constructed for the scope of Paper IV, but is closely related to the term “rapid shifts in mood of intense effect” proposed in a review of studies on mood instability.[178]

Sleep diaries, actigraphy and polysomnography are subjective, semi-objective and objective assessment methods of sleep. Of the three, sleep diaries are the only provider of data on subjective sleep quality, and polysomnography the only method for assessment of organic sleep disorders, such as sleep apnea. Polysomnography is considered to be the “gold

standard" for evaluating sleep objectively, but actigraphs have the advantages of being minimally disruptive to sleep and can be worn for longer periods of time in naturalistic settings. Also, they are not subject to the recall bias associated with subjective sleep diaries. Comparison of these three tools in a previous study of sleep in a small group of euthymic BD patients showed highly correlating sleep parameters between actigraphy and polysomnography, using the same actigraphy algorithm for sleep estimation as in Study III.[91] Sleep was not compared between these three tools in Study III, Paper IV; only actigraphy was used for evaluation of sleep parameters.

Actigraphy Procedure for Activity Monitoring

During the design of the study of agitation, from which data for Studies I and II are taken, it was a question of including fewer participants who could be monitored for a longer period of time or including a larger number of participants and 24-hour monitoring. The latter solution was chosen for the benefit of evaluating multiple patients with different psychiatric symptoms. In addition, there are great variations in length of stay at the acute department, making longer study periods difficult. Actigraphs are usually appreciated as monitoring devices across multiple days, and one 24-hour period can unlikely provide reliable information about circadian instability. At least five days has been recommended in monitoring of children and adolescents.[179] Furthermore, we did not look at maximum/minimum activity, only the first and last period of continuous motor activity between 6 AM and midnight. Also, we did not perform analyses contrasting morning and evening findings in Studies I or II, thus we cannot draw conclusions about diurnal variation. In this sense, the short monitoring time could be seen as a limitation. However, the results produced in the studies of only 24-hour activity patterns rather strengthen the probability of using actigraphy in the acute psychiatric setting with short inpatient stays, where short assessment periods are an advantage. Even in Study III, Paper IV, where 6-8 consecutive monitoring days should be enough to evaluate diurnal variation, longer time series would be more reliable. Which wrist for actigraphy monitoring was not noted in either study, but previous analyses of placement have not found differences between the dominant or non-dominant hand.[86, 87] In Study II, Paper III, excluding patients with short recordings from the analyses did not change the results.

4.2.4 Data Analysis

Mathematical analyses of time series data

The use of non-linear measures is relatively novel in analyzing actigraphic data in patients with psychiatric disorders. Increased RMSSD values were the most consistent finding across studies. The benefit of RMSSD compared to traditional forms of actigraphy analyses is a description of minute variability as opposed to more long-term variability. It has a long history as a measure of point-to-point variability in time series[124, 180] and is often employed in studies on heart rate variability, since RMSSD is sensitive to vagal activity from second to second.[181] In previous studies of schizophrenia, depression, ADHD and healthy individuals treated with a glutamate antagonist, RMSSD and the corresponding autocorrelation lag 1 have been found useful.[114, 127, 128] We were therefore particularly interested in the ratio RMSSD/SD, which was increased in patients with schizophrenia, and the relationship between RMSSD and RMSSD/SD ratios and measures of complexity, such as sample entropy.

Studying active and inactive periods is another non-linear way to look at variability or fragmentation of activity patterns. Activity patterns are highly individual; some may be best described by increased variability from minute to minute (high RMSSD values), whereas others have more stable minute-to-minute differences and longer bursts of activity (longer active periods). The significant results in several variables measuring the same phenomenon by different methods consolidate results.

To show the robustness of the results, we evaluated the effects of other parameter values for the analyses of symbolic dynamics in Study II, Paper III. Using the alternative method of symbolic dynamics analysis also demonstrated high complexity in patients with mania, but the differences to bipolar depression and healthy controls were not significant. Corresponding findings of complexity, as given by increased entropy values for several groups, suggest that sample entropy may be a better applicable measure than symbolic dynamics. From a mathematical perspective, there may be more appropriate methods for calculation of complexity, but they often require substantially longer time series of thousands of data points without noise. The advantage of sample entropy is that it tolerates outliers and shorter time series of approximately 50 data points.

A limitation of the employed data analysis is that we have used time series with considerable noise, grossly indicated by the similar range of standard deviation and mean values for group

variables. Noise is a general problem with many data sources in biology and medicine.[182] Also, test-retest reliability must be investigated in future research, and actigraphy should be compared to other methods for monitoring activity, although there does not exist a "gold standard". Even if wrist-recordings are considered reliable and may potentially be better for detecting tension-associated movement such as fidgeting, wrist actigraphy does not distinguish between different types of activity. Exploring concurrent electronic reports of daily activities and several body placements for monitoring devices would be beneficial.

We extracted periods of continuous motor activity, because some of the methods are sensitive to inactive periods. Many counts of zero activity would give a misleading impression of a regular pattern and were therefore omitted by extracting active periods. Still, zero-counts are considered important with regard to motor retardation. Therefore, another limitation of the employed methods includes non-detection of immobility. It is also thinkable that some of the outcome variables of activity were influenced by categorization in groups with high and low activity levels. On the other hand, the variability measures (SD and RMSSD) took the mean activity level into account, and once again, measuring the same motor trait by different variables reduces the risk of such confounding.

The exact number of 64 minutes for the active periods is due to the Fourier analysis, which required sequence lengths to be potencies of 2 (32, 64, 128). Previous experience with actigraphy recordings has shown that it may be difficult to find such active sequences that are longer than approximately one hour, in particular in depressed patients (personal communication by Professor Ole Bernt Fasmer, University of Bergen), which is why we chose 64 instead of 128 minutes.

The Fourier analysis requires periodically stable time series, and human activity rhythms are unlikely to be stationary. As such, RMSSD may be a better alternative among the approaches used in this thesis. Other analytical procedures may be more appropriate to study human behavioral rhythms; wavelet analysis and variants of empirical mode decomposition could for instance be considered.[103, 182] Furthermore, application of especially adapted methodology to evaluate critical transitions is a potential aim for future studies in disorders involving abrupt changes, such as bipolar disorder, panic disorder and migraine. Analyzing activity patterns just before these tipping points may be predictors of disease.[117]

4.2.5 Statistical Considerations

In all three studies in this thesis, simple group comparisons were applied. Student's t-tests and ANOVAs were used when normal distribution of continuous variables were observed. Non-normally distributed variables were compared using non-parametric tests. Categorical variables were compared with chi-square tests.

Different post-hoc group comparisons for variables with equal variance were used in Paper I and Paper III; both studies included three groups and ANOVAs. Paper III was conducted first in chronological order and built on a similar study in Bergen, where Bonferroni post-hoc tests were used.[114] The Bonferroni post-hoc analysis is considered to be one of the more conservative post-hoc tests.[174] Because all tests were planned in advance and several variables measured the same phenomenon, we switched to the less conservative Least Significant Differences (LSD) test in Paper I. Similar arguments were used for disregarding correction for multiple testing, but an increased probability of producing findings due to chance still existed, considering the number of tests performed. In order to reduce this risk, it would have been possible to predefine one or two main variables of interest and include the other variables in additional exploratory analyses.

In Paper IV, we could have considered other statistical methods to capture within-person fluctuations in variables of activity, sleep and mood across days (days nested within persons) and to examine the temporal relationship between activity and mood. A multilevel analysis of the within-person relationship between sleep, physical activity and chronic pain is an example.[183] The chosen group comparison of day-to-day changes in variables during a week had advantages in simplicity and understanding.

4.3 Implications and Future Directions

In three studies using actigraphy to assess mean activity levels, variability in activity levels and complexity of activity patterns in inpatients and outpatients with affective disorders, differences in patterns of motor activity have been found between groups. To the knowledge of the author, Study I is one of few studies that have taken the common symptom of motor retardation in depression and provided quantitative information based on new technology in describing a clinical psychiatric symptom. Actigraphy may be used to distinguish between motor-retarded and non-motor-retarded patients with depression, but before application to clinical practice it needs to be validated. Such validation includes assessment with regard to

test-retest variability and diagnostic test statistics (sensitivity, specificity, and positive and negative predictive values). Ability to identify motor retardation in other diagnostic groups should also be investigated, preferably in larger samples.

The findings of variability and complexity in activity are potentially important clinical signatures of affective disorders. Results suggest that there may be phenotypic differences between subgroups based on activity levels and patterns. Covariations with other clinical characteristics or diagnostic groups, such as anxiety, psychosis and mixed features should be explored. Symptom-based monitoring across diagnoses could provide more answers on diagnostics and treatment of psychiatric disorders with overlapping symptoms, as given by the similar activity findings between bipolar and motor-retarded unipolar depression, and between non-motor-retarded depression and mania.

Actigraphy can be used to identify irregular rest-activity cycles, provide reliable sleep-wake estimations and quantify motor activity patterns. It may thus serve as a support for other diagnostic tools. The relationships between variability in activity, sleep and mood need to be further examined. It is possible that circadian instability is associated with mood variability; both factors represent a risk of poor functioning in the euthymic phase. Young patients with delayed sleep phase could be more at risk. Correlating variations in mood and activity across phase-changes in longitudinal studies has a potential of predicting mood episodes. In the longer term, establishing the central role of activity in mood disorders could lead to innovations in the classification and psychopharmacology of mood disorders.

Other parameters than mean activity distinguished groups in all three studies, underlining the importance of variability measures for adequate characterization of differences in motor regulation. The temporal interval for calculation of variability over time has to be considered; traditional variability measures from day to day may be too crude to capture differences, whereas point-to-point-variability and complexity measures are potentially more appropriate. It is possible that a set of complementary variability measures are needed to describe activity patterns, which are highly individual.

Further research might reveal information to assist in choices of treatment, as advanced analytical measures of activity could be used to study mediators and moderators of treatment response. The possible utility of these measures in clinical treatment trials could be beneficial. In summary, application of the approach for monitoring and analyzing motor activity in

psychiatric disorders in general and affective disorders specifically, may in the future lead to advances in phenotyping, illness characterization, symptom monitoring, treatment response and prediction of episodes.

4.4 CONCLUSIONS

In three studies of inpatient and outpatient populations with affective disorders, actigraphy recordings of motor activity analyzed by linear and non-linear mathematical methods showed distinct differences between groups categorized by phenotypes.

All studied groups with acute depression (unipolar depression with and without motor retardation and bipolar depression) differed from healthy controls by lower activity levels and higher intra-individual variability in activity. Patients with unipolar depression and motor retardation distinguished themselves significantly from depressed patients without motor retardation in these variables. Motor retardation could also be identified by shorter bursts of activity. Groups with mania and with non-motor-retarded unipolar depression showed increased complexity of time series in an active morning period of approximately one hour. As such, they resembled previous findings from studies of schizophrenia and glutamatergic antagonism in healthy individuals.

In outpatients with euthymic bipolar disorder and sleep disturbance, a subgroup displayed unstable diurnal rest-activity cycles assessed by actigraphy. The subgroup was younger and showed more mood variability and more delayed sleep phases compared to patients with stable rest-activity cycles. Patients with unstable rest-activity cycles demonstrated motor activity patterns that resembled variability findings in activity during affective episodes.

Overall, results from this thesis encourage further exploration of actigraphy combined with linear and non-linear data analysis as an objective tool in affective disorders.

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Appendix

Additional figures

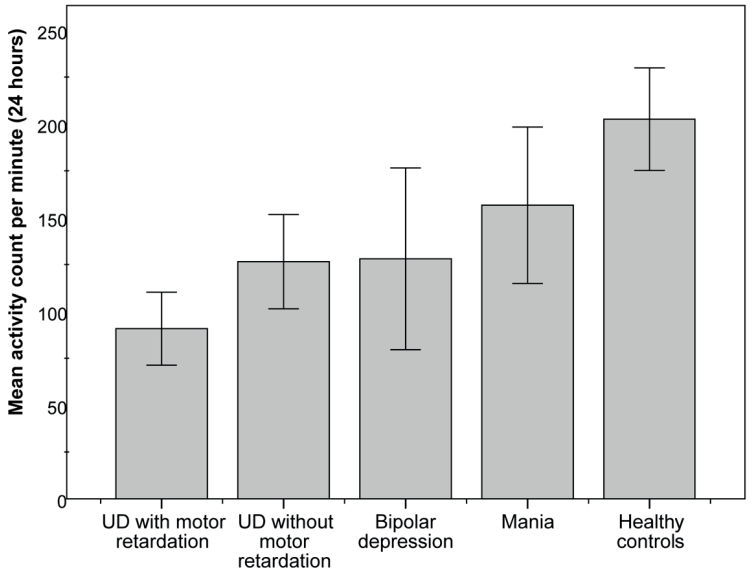

Figure 3. Mean activity levels during 24-hour actigraphy recordings between groups in Studies I and II

(*In all following bar diagrams the error bars show the 95% confidence interval. UD signifies unipolar depression.*)

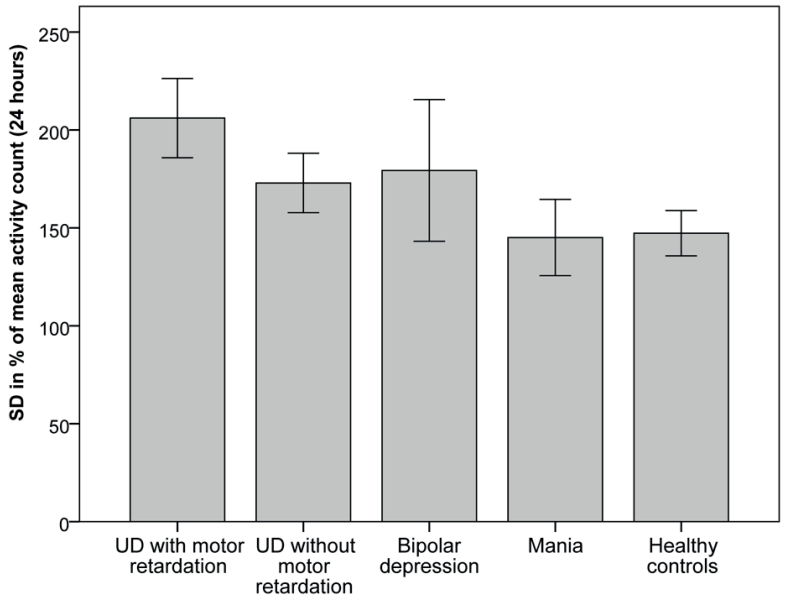

Figure 4. Standard deviation (SD) in percent of mean activity levels during 24-hour actigraphy recordings between groups in Studies I and II

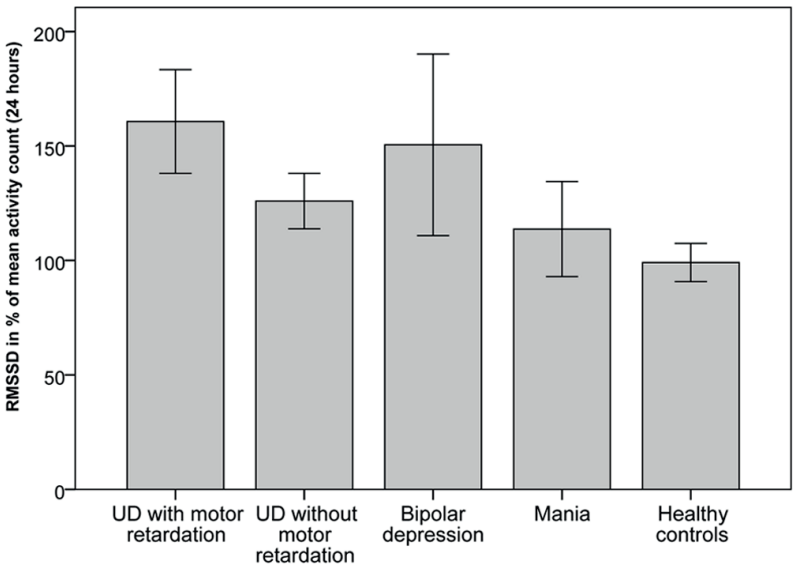

Figure 5. Root mean square successive difference (RMSSD) in percent of mean activity levels during 24-hour actigraphy recordings between groups in Studies I and II

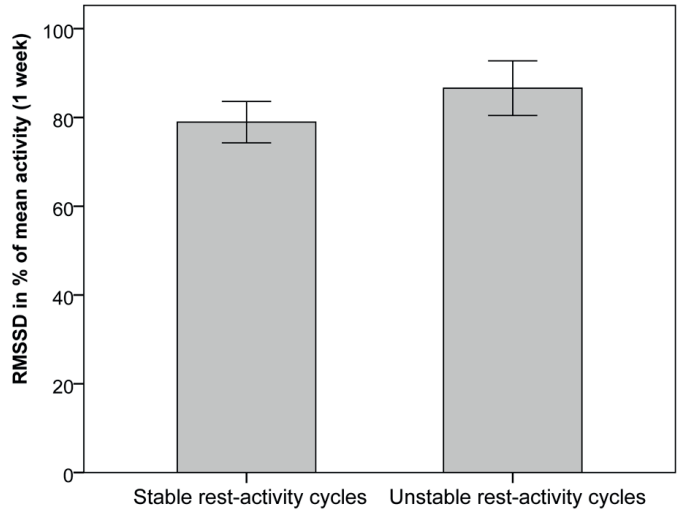

Figure 6. Root mean square successive differences (RMSSD) in percent of mean activity levels during 1-week active intervals in groups with and without stable rest-activity cycles in Study III, Paper IV

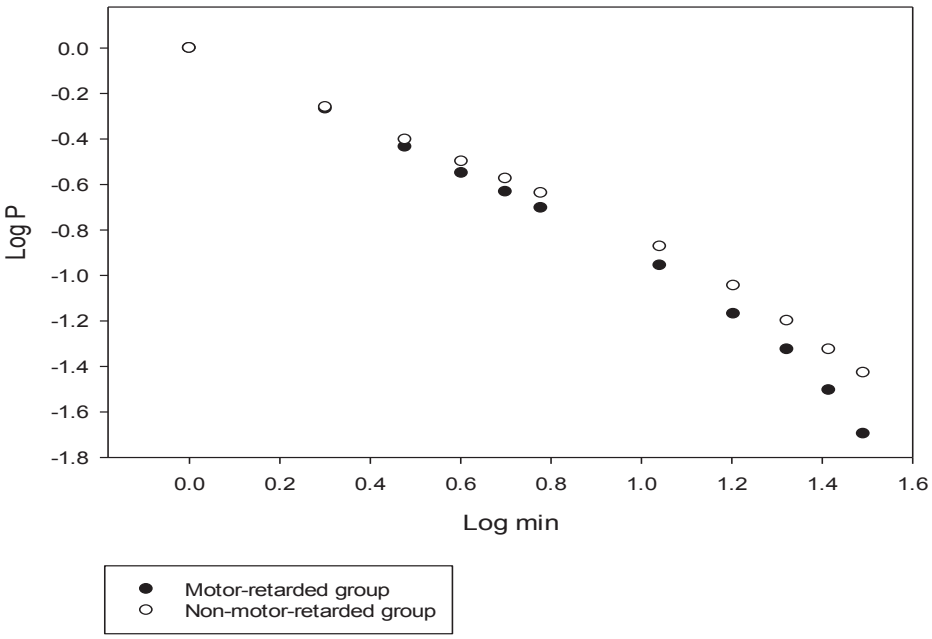

Figure 7. Log-log plot of cumulative probability (P) vs. duration of active periods between groups with and without motor retardation in Study I, Paper II

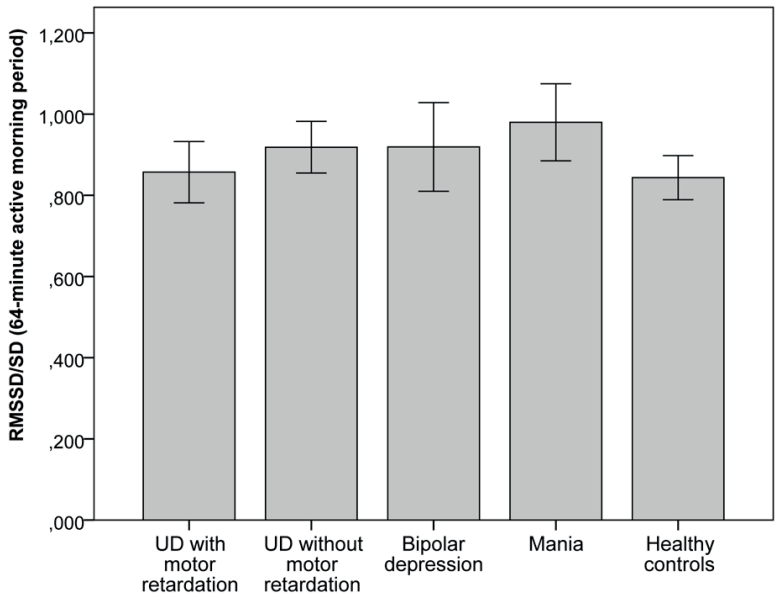

Figure 8. RMSSD/SD ratios from the 64-minute active period in the morning between groups in Studies I and II

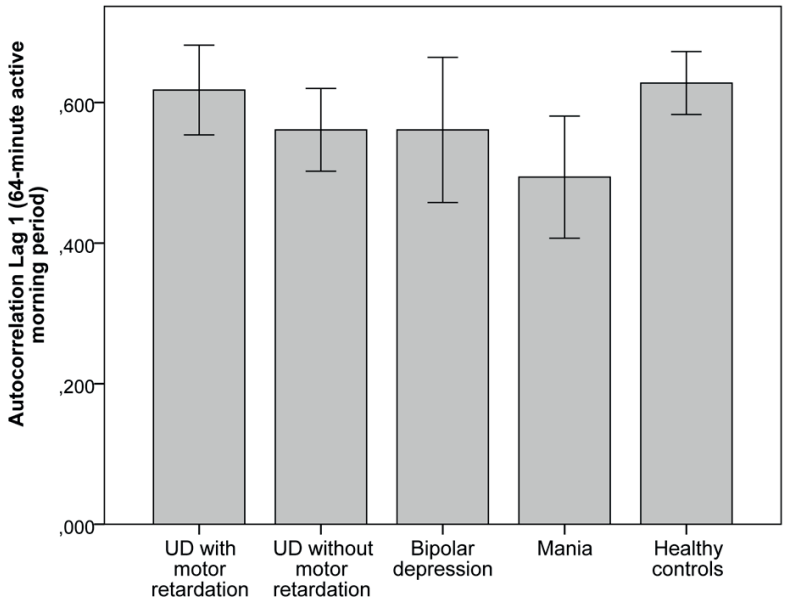

Figure 9. Autocorrelation lag 1 values from the 64-minute active morning period between groups in Studies I and II

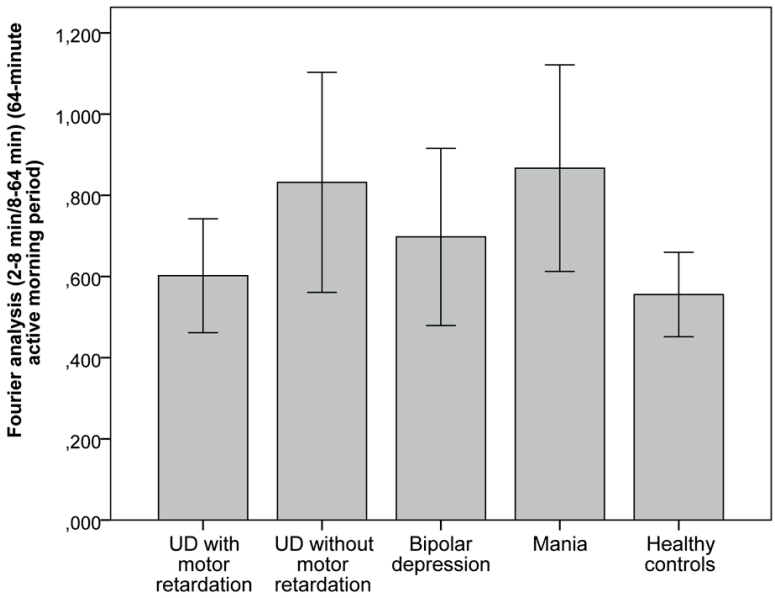

Figure 10. Results from the Fourier analysis during the 64-minute active interval in the morning between groups in Studies I and II

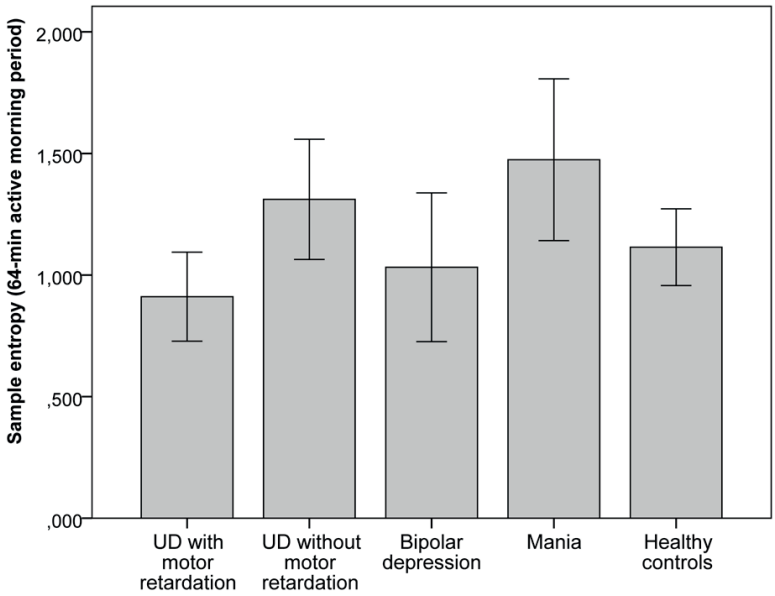

Figure 11. Sample entropy values from the 64-minute active period in the morning between groups in Studies I and II

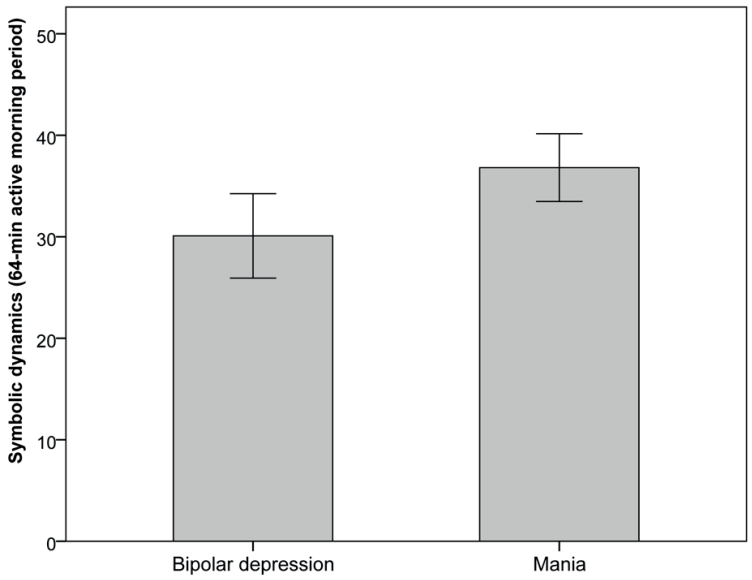

Figure 12. Symbolic dynamic values from the 64-minute active period in the morning between groups with bipolar depression and mania in Study II, Paper III

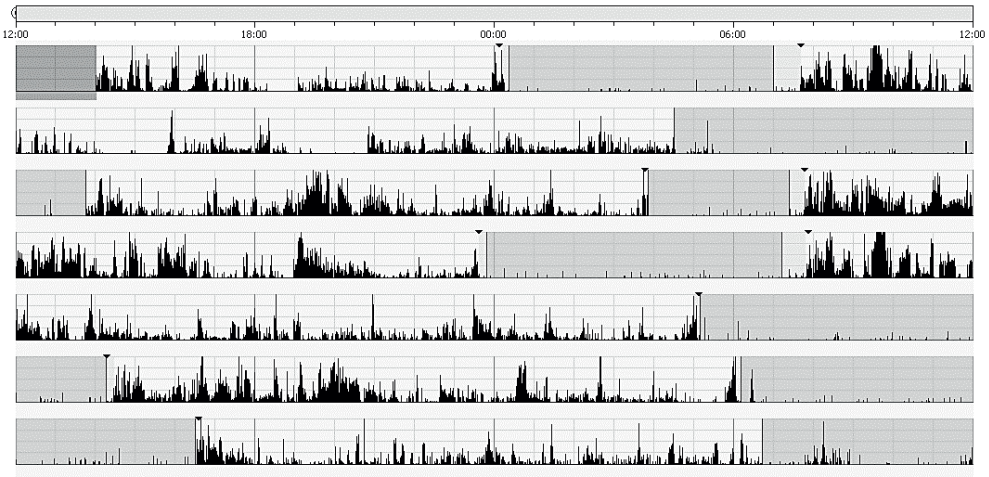

Figure 13. An example of a 1-week actigraphy recording from a patient in the unstable rest-activity cycles group. The time scale from left to right is from 12h to 12h the next day. Activity counts are shown in black on a scale from 0 – 500. Gray-colored time periods are sleep intervals calculated from the rest intervals by the actigraphy software program.

	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
+ 3							
+ 2							
+ 1							
Neutral							
- 1							
- 2							
- 3							

	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6
+ 3						
+ 2						
+ 1						
Neutral						
- 1						
- 2						
- 3						

Figure 14. Two examples of 1-week mood diaries from patients displaying mood variability. 3 levels of elevated mood above the neutral level in the middle and 3 levels of depressed mood below.

Errata

Erratum 1:

The tables of Paper I were omitted in the version sent to the opponents and were later forwarded to them. The tables have now been included.

Erratum 2:

The tables of Paper IV were omitted in the version sent to the opponents and were later forwarded to them. The tables have now been included.

Erratum 3:

The gender distribution numbers given in Table 1 of Paper IV are incorrect. The correct numbers are:

19 females (86.3 %) in the stable rest-activity cycles group, and 13 females (61.9 %) in the unstable rest-activity cycles group. The revised result of the chi-square test is $p = 0.07$.

Original Papers I – IV

Paper I

Is not included due to copyright

Paper II

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Paper III

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PLOS ONE

Actigraphic Assessment of Motor Activity in Acutely Admitted Inpatients with Bipolar Disorder

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Abstract

Introduction: Mania is associated with increased activity, whereas psychomotor retardation is often found in bipolar depression. Actigraphy is a promising tool for monitoring phase shifts and changes following treatment in bipolar disorder. The aim of this study was to compare recordings of motor activity in mania, bipolar depression and healthy controls, using linear and nonlinear analytical methods.

Materials and Methods: Recordings from 18 acutely hospitalized inpatients with mania were compared to 12 recordings from bipolar depression inpatients and 28 healthy controls. 24-hour actigraphy recordings and 64-minute periods of continuous motor activity in the morning and evening were analyzed. Mean activity and several measures of variability and complexity were calculated.

Results: Patients with depression had a lower mean activity level compared to controls, but higher variability shown by increased standard deviation (SD) and root mean square successive difference (RMSSD) over 24 hours and in the active morning period. The patients with mania had lower first lag autocorrelation compared to controls, and Fourier analysis showed higher variance in the high frequency part of the spectrum corresponding to the period from 2–8 minutes. Both patient groups had a higher RMSSD/SD ratio compared to controls. In patients with mania we found an increased complexity of time series in the active morning period, compared to patients with depression. The findings in the patients with mania are similar to previous findings in patients with schizophrenia and healthy individuals treated with a glutamatergic antagonist.

Conclusion: We have found distinctly different activity patterns in hospitalized patients with bipolar disorder in episodes of mania and depression, assessed by actigraphy and analyzed with linear and nonlinear mathematical methods, as well as clear differences between the patients and healthy comparison subjects.

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Competing Interests: The authors have declared that no competing interests exist.

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Introduction

Alterations in motor activity are important clinical features of acute bipolar disorder; mania is associated with overactivity, whereas depression usually is characterized by a reduction in activity [1]. Today, changes in psychomotor activity are assessed by the clinician, but objective recordings of activity could be useful for monitoring symptom severity and phase shifts in bipolar disorder.

In bipolar depression, psychomotor retardation and low mood are often more pronounced in the morning than in the evening [2], [3], implying a phase-delayed peak of activity [4]. Psychomotor agitation can occur in both depression and mania [5] and can be defined as motor restlessness with either goal-directed movements or sustained fidgeting and frequent position changes [6].

With the ongoing debate on the classification of bipolar disorders including bipolar spectrum disorders [7], psychomotor activation may become a key factor in separating subtypes. Actigraphy is a method of activity monitoring used in several studies in psychiatric populations [8]-[10]. An actigraph is a wrist-worn, relatively cheap and handy device, clinically useful in the evaluation of sleep disorders [11], [12]. Its role as an indicator of mood state is uncertain, but promising research findings [13]-[16]

suggest that actigraphs might become a valuable supplement to clinical diagnostics.

However, little is known about actigraphically registered activity characteristics across different phases of bipolar disorder. The activity patterns in patients with major depression seem to be different from those of patients with schizophrenia and healthy controls [14], [17]. Other actigraphy studies have confirmed the clinical impression that patients with depression are less active during daytime, and that activity increases with treatment [10], but to our knowledge no studies have investigated differences in activity by actigraphy in acute episodes of bipolar disorder. Also, very few actigraphy studies have used adequate analytical methods to extract all relevant features from actigraphy data, irrelevant of study population [10]. In recent years it has been found that mathematical techniques with a theoretical basis in nonlinear dynamics may be used to describe the complexity seen in behavioral patterns [15], [18], [19].

For these reasons we aimed to compare patterns of motor activity during psychiatric hospitalization due to either mania or depression in bipolar disorder with healthy controls. Using 24-hour actigraphy recordings, we wanted to describe overall patterns of activity in these three groups and compare active periods in the morning and evening, by employing linear and non-linear mathematical methods [15].

Materials and Methods

Patients

Consecutively, acutely admitted inpatients at the Department of Psychiatry, St. Olav's University Hospital, Trondheim, Norway, were asked to participate in a study assessing symptoms of agitation during admission. All Norwegian acute psychiatric services are public. All patients above 18 years in the catchment area who suffer from any acute psychiatric condition and are in need of acute admittance are admitted to this department. The only exclusion criterion was inability to give an informed consent in the primary examination by a senior psychiatrist or specialist in clinical psychology the first day after admittance. A total of 424 admissions were included in the study. If patients were admitted more than once, up to three admissions could be included. The patients with an inpatient stay of more than one day after inclusion were asked to wear an actigraph for 24 hours. In total, 280 actigraphy recordings were effectuated during hospitalizations between September 1st, 2011 and March 31st, 2012. The largest diagnostic group was affective disorders, which included 110 admissions (39.3% of the 280 admissions). Of these, 33 admissions were due to a primary ICD-10 diagnosis of bipolar disorder (F31.1–F31.5, current episode manic or depression). The sample excluded patients in mixed episodes (F31.6), patients in remission (F31.7) and patients with other bipolar affective disorders (F31.8 and F31.9, bipolar II disorder and unspecified bipolar disorder).

20 admissions were due to a current manic episode (F31.1, current episode manic without psychotic symptoms, and F31.2, current episode manic with psychotic symptoms), and 13 admissions were due to a current episode of depression (F31.3, current episode mild or moderate depression, F31.4, current episode severe depression without psychotic symptoms, and F31.5, current episode severe depression with psychotic symptoms). Two patients were admitted twice; one patient was first admitted in an episode of depression, then in an episode of mania, and one patient was admitted twice with mania. Second admissions were excluded from analysis, so that all patients are represented with only one admission. One recording was incomplete and therefore excluded. Finally, a total of 18 recordings from patients with bipolar disorder in a manic episode were compared to 12 recordings from patients with bipolar disorder in an episode of depression.

Comparison Subjects

The comparison group (n = 28) primarily consists of employees at the Department of Psychiatry, Fonna Regional Health Authority in a western region of Norway, who were recruited through oral and written presentations approved by the Regional Committee for Medical and Health Research Ethics of Western Norway. None of the subjects were diagnosed with an affective disorder, nor were any of them prescribed psychopharmacological drugs, and they had no disposition to psychiatric disorders in general. They wore an actigraph for at least 24 hours during the period March 13th, 2012 - June 6th, 2013, and this 24-hour recording was included in the current study. 18 of them wore the actigraph in spring or summer months (April – August). 15 healthy controls wore the actigraph on a weekday, 11 healthy controls during the weekend, and 2 were retired. Comparison subjects are from now on referred to as healthy controls, although they were not age- nor gender-matched to the patients. No information about the weight of the healthy controls is available, and the samples could therefore not be matched by BMI.

Recordings of Motor Activity

Motor activity was recorded using an actigraph (Actiwatch Spectrum, Philips Respironics Inc., Murrysville PA, USA), which contains a piezoelectric accelerometer programmed to record the integration of intensity, amount and duration of movement in all directions. A corresponding voltage is produced and stored as an activity count in the memory unit of the actigraph. Patients and healthy controls wore the actigraph around the wrist of their choice and were instructed not to take it off during the next 24 hours. Which wrist was not noted, but previous studies have found only small differences between the left and right wrist [20], [21]. Patient recordings contained an average of 1364.8±203.5 minutes for analysis, ranging from 435 to 1446 minutes. All starting times were in the daytime hours, between 09h14 and 19h51 (mean 12h41±2h35). Healthy control recordings contained 1440 minutes from midnight to midnight, as they were 100% compliant in wearing the actigraph for 24 hours.

Activity counts were recorded for one minute intervals during 24 hours. Data were analyzed for the total time of recording. From each patient and healthy control we also selected actigraphy data from 6 AM to midnight and separated this time period in morning and evening epochs. Morning epochs were defined to occur between 6 AM and 3 PM, and evening epochs between 3 PM and midnight. Because many of the recordings contained periods of inactivity, we searched each recording for periods of continuous motor activity in the morning and evening. The active morning period was searched from the start of the series, and the active evening period from the end of the series. From each participant we selected the first period of 64 minutes not containing more than two consecutive minutes of zero activity counts. If there was no such period, we searched for sequences with no more than 3 consecutive minutes with zero activity, and if that was not found, sequences with at most 4 consecutive minutes with zero activity. In this way we were able to obtain 64-minute sequences from almost all of the participants. 64 minutes were chosen due to the Fourier analysis, which requires sequence lengths to be potencies of 2 (32, 64, 128…).

One patient with mania did not have a valid recording in the morning, and consequently no active 64-minute period could be calculated. Another patient with mania lacked a 64-minute

sequence with at most 4 consecutive minutes with zero activity in the morning. Both patients were omitted from morning series analyses, reducing the group with mania to 16 patients. One healthy control lacked a 64-minute sequence with at most 4 consecutive minutes with zero activity in the evening and was therefore excluded from evening series analyses.

Mathematical Analyses

From the activity counts in the actigraph software program (Actiware, version 5.70.1) we calculated means for the whole recording period and the 64-minute periods of continuous motor activity. We further calculated the standard deviation (SD) for each time series, which is an intra-individual measure of fluctuations in activity, the root mean square successive difference (RMSSD), which describes the difference in successive counts from minute to minute, and the RMSSD/SD ratio. For the 64-minute time periods we additionally calculated autocorrelation (lag 1) and performed a Fourier analysis. We also used two measures of complexity: sample entropy and symbolic dynamic analysis. All techniques represent distinct means of characterizing a series of data in time. The software used for the estimation of sample entropy and for the Fourier analysis was obtained from the Physio Toolkit Research Resource for Complex Physiologic Signals [22], see http://www.physionet.org.

Autocorrelation at Lag 1

An autocorrelation function is a mathematical tool to measure the degree of relationship between observations that are k lags apart. The autocorrelation at lag 1 is the correlation of a time series with itself lagged one step, in this case from minute to minute. As such, values closer to one indicate a stronger correlation. Autocorrelation analyses were performed using SPSS version 20.0.

Sample Entropy

For the analysis of sample entropy the data were normalized by transforming the time series to have sample mean 0 and sample variance 1. Sample entropy is a nonlinear measure, which indicates the degree of regularity (complexity) of a time series, and 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 $r = 0.2$. Sample entropy was used since it can be employed with comparatively short time series (>50) and is robust with regard to outliers [23].

Symbolic Dynamics

The time series were transformed into series of symbols according to the method described by Guzzetti et al. [24] and Porta et al. [25]. For the analyzed active morning and evening sequences, the difference between the maximum and minimum value was divided into 6 equal portions (1–6) and each value of the series was assigned a number from 1–6, such that the transformed time series consisted of a string of numbers from 1–6. To avoid the problem with outliers the maximum value was set at no more than the mean +3 times the SD, and the minimum value was set at no less than the mean –3 times the SD. The series were then divided into overlapping sequences of three consecutive numbers. The series thus contained 62 such sequences, and the number of different sequences was counted, giving an indication of the complexity of the time series [26].

For the symbolic dynamic analyses we also used an alternative method to analyze the data, described by the same authors [24], [25]. Each sequence of three consecutive numbers was assigned one of four symbols, according to the following rule: 1) a pattern with no variation (e.g. 333), 2) a pattern with only one variation: two consecutive symbols are equal and the remaining symbol is different (e.g. 331), 3) a pattern with two like variations, such that the 3 symbols either ascend or descend (e.g. 641 or 235) and 4) a pattern with two unlike variations, both ascending and descending values (e.g. 312 or 451). The rates of occurrence of these four patterns were counted and the results given as the percentage of the total number of sequences analyzed ($n = 62$).

Fourier Analysis

Data were normalized before analysis. No windows were applied. 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 minutes) and the low frequency part (0.00026 - 0.0021 Hz, corresponding to 8–64 minutes).

Statistics

Statistical analyses were carried out using SPSS version 20.0. Means and standard deviations were calculated for the continuous variables, and proportions for the categorical variables. For comparison of means between patients we used t-tests, and for comparison of counts of categorical data chi-square tests. For comparison of subject characteristics and activity variables in all three groups, we used one-way ANOVAs with Bonferroni post-hoc tests to obtain differences between groups. A P-value ≤ 0.05 was considered significant.

Ethics Statement

The patient study has been approved by the Regional Committee for Medical and Health Research Ethics of Central Norway, and the healthy control study by the Regional Committee for Medical and Health Research Ethics of Western Norway. All participants signed a written informed consent form prior to inclusion. The patients' capacity to consent was established by a senior psychiatrist or specialist in clinical psychology, and patients who were unable to consent were not included in the study.

Results

Subject characteristics are shown in table 1 and table 2. A significantly larger proportion of the group with mania than with depression was admitted to a psychiatric intensive care unit (PICU). Psychotropic drug treatment for both groups is summarized in table 2. Controls were more often employed and had a higher level of education than both patient groups (table 1). Controls and patients with depression were younger than the patients with mania (table 1).

24-hour actigraphy recordings for a patient with depression, a patient with mania and a healthy control subject are shown in Figure 1. Analysis of the 24-hour recording shows a lower mean activity level for the patients with depression compared to the healthy controls (table 3), and the RMSSD in percent of mean activity is higher for the depression group compared to the controls. Both patient groups also have a significantly higher RMSSD/SD ratio compared to healthy controls.

Activity variables for the 64-minute period of continuous motor activity in the morning, also referred to as the active morning period (Figure 2), are shown in table 4. The motor activity is significantly lower in patients with mania and depression compared to healthy controls. The SD in percent of mean activity

Table 1. Demographic data, all groups.

Variable	Mania	Depression	Healthy controls
Number of subjects (n)	18	12	28
Age (years) (mean ± SD)	51.2±15.4	39.9±15.6	41.7±11.6*
Gender (female)	11 (61%)	7 (58%)	13 (46%)
Unemployment (incl. sick leave, retirement)	16 (89%)	9 (75%)	0###
Higher education (above high school)	6 (33%)	3 (25%)	19 (68%)###

If not mentioned otherwise, values are number of subjects, n (%).
*p≤0.05 one-way ANOVA. No significant differences between groups with Bonferroni post hoc test.
###p≤0.001 chi-square test where both patient groups were compared to healthy controls.
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is significantly higher in the depression group compared to both patients with mania and healthy controls. The RMSSD in percent of mean activity is also higher in the patients with depression compared to both other groups, but only significantly different from the healthy controls. Patients with mania have the highest RMSSD/SD ratio, also significantly different from the healthy controls. Compared to the healthy controls, patients with mania have a significantly lower autocorrelation in the first lag, and a significantly higher ratio between variance in the high-frequency and the low-frequency parts of the spectrum, as shown by the Fourier analysis (Figure 2). The symbolic dynamic analysis shows the highest number of unique sequences in the mania group, and the difference between the two patient groups is significant. The alternative method of symbolic dynamic analysis also shows the highest complexity in patients with mania, but the differences between the groups are not significant (data not shown). Similarly, the patients with mania have the highest value for sample entropy (table 4).

Regarding the active evening period (table 5), the only significant difference is a higher RMSSD/SD ratio in the patients with mania compared to healthy controls.

When the patients with mania are separated into two groups; one including patients admitted to a PICU (n = 10) and one including patients admitted to an ordinary ward (n = 8), the patients in the PICU have a significantly increased RMSSD/SD ratio, lower autocorrelation in the first lag and higher variance in the high frequency part of the spectrum in the Fourier analysis, in the active morning period only. Also, in the 24-hour recording they have an increased SD in percent of mean activity compared to patients on an open ward (data not shown).

Table 2. Patient characteristics, groups according to current episode.

Variable	Mania	Depression
Number of patients (n)	18	12
Days admitted (mean ± SD)	22.9±17.2	22.2±24.6
Number of days between admission and actigraphy recording (mean ± SD)	2.1±1.1	3.5±2.7
Compulsory admission	9 (50%)	2 (17%)
Intensive care unit	10 (56%)	1 (8%)**
Body Mass Index (mean kg/m^2± SD)	27.0±5.8	23.6±3.2
ICD-10 primary diagnosis	**n (%)**	**n (%)**
F31 Bipolar affective disorder		
- F 31.1, current episode manic without psychotic symptoms	7 (39)	–
- F 31.2, current episode manic with psychotic symptoms	11 (61)	–
- F 31.3, current episode mild or moderate depression	–	6 (50)
- F 31.4, current episode severe depression without psychotic symptoms	–	5 (42)
- F 31.5, current episode severe depression with psychotic symptoms	–	1 (8)
Treatment	**n (%)**	**n (%)**
- Antipsychotics	15 (83)	5 (42)
- Hypnotics/anxiolytics	9 (50)	6 (50)
- Anticonvulsants	7 (39)	4 (33)
- Lithium	2 (10)	1 (8)
- Antidepressants	1 (5)	1 (8)
- No psychotropic drug treatment	1 (5)	1 (8)

If not mentioned otherwise, values are number of patients, n (%).
**p≤0.01 chi-square test.
doi:10.1371/journal.pone.0089574.t002

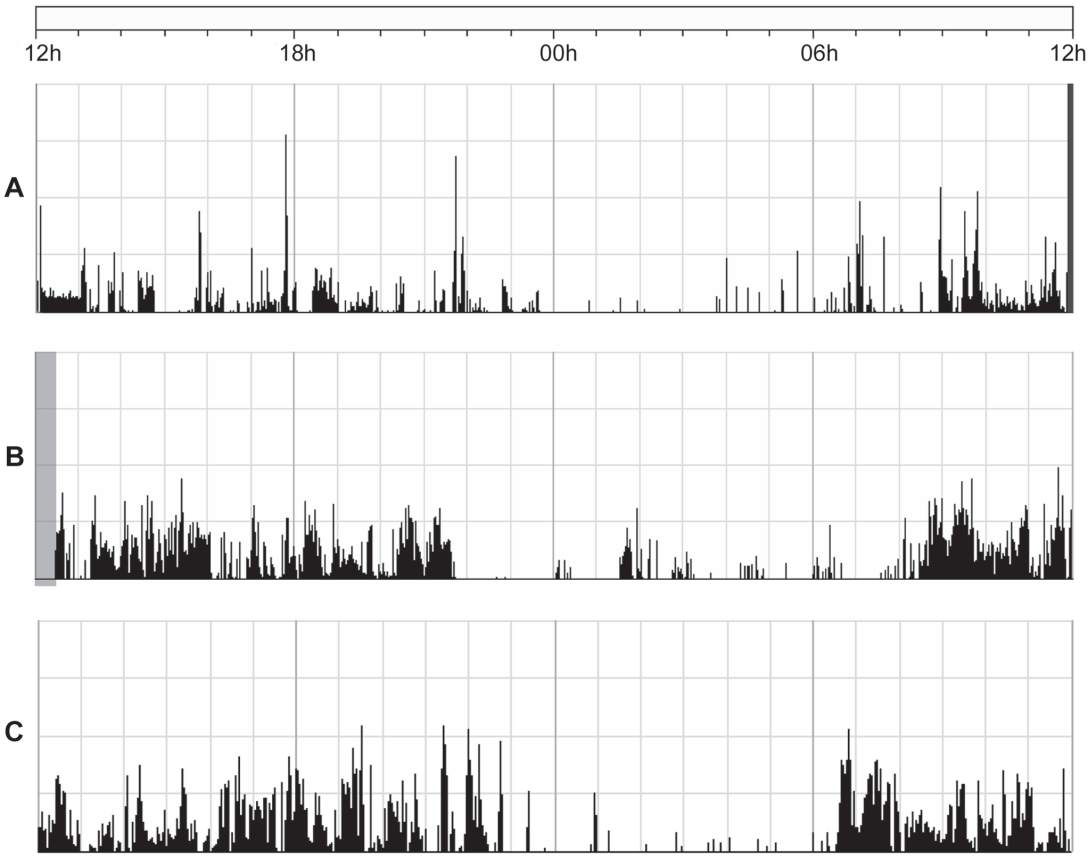

Figure 1. 24-hour actigraphy recordings for all three groups. Activity counts from a patient with depression (A), a patient with mania (B) and a healthy control (C). The figure shows the activity counts in black during 24 hours from 12 h to 12 h the next day. The dark gray area at the end of recording A and the gray area at the beginning of recording B represent excluded periods, when the subject was not wearing the actigraph.
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Discussion

The main findings of our study are distinct differences in motor activity parameters between acutely hospitalized patients with bipolar disorder in an episode of mania or depression. Compared to healthy controls there are also clear differences. In addition we find a distinct diurnal pattern, with the most pronounced differences during periods with continuous activity in the morning.

Table 3. Results from the 24-hour recording of motor activity.

Variable	Mania	Depression	Healthy controls	p-value
Number of subjects (n)	18	12	28	
Mean/minute	157±84	128±76^{+}	203±71	**0.014**
SD/min in % of mean	145.1±39.1	179.4±56.9	147.3±29.8	**0.043**
RMSSD/min in % of mean	113.7±41.8	150.5±62.4^{+} (T)	99.1±21.5	**0.002**
RMSSD/SD	0.774±0.094***	0.828±0.098^{+++}	0.675±0.077	**<0.001**

All data are given as mean ± SD. p-values obtained in a one-way ANOVA. Post hoc Bonferroni tests:
***p≤0.001, mania compared to healthy controls.
$^{+}$p≤0.05, depression compared to healthy controls.
$^{+++}$p≤0.001, depression compared to healthy controls.
(T): Tamhane's T2 post hoc test was used when unequal variances were assumed.
doi:10.1371/journal.pone.0089574.t003

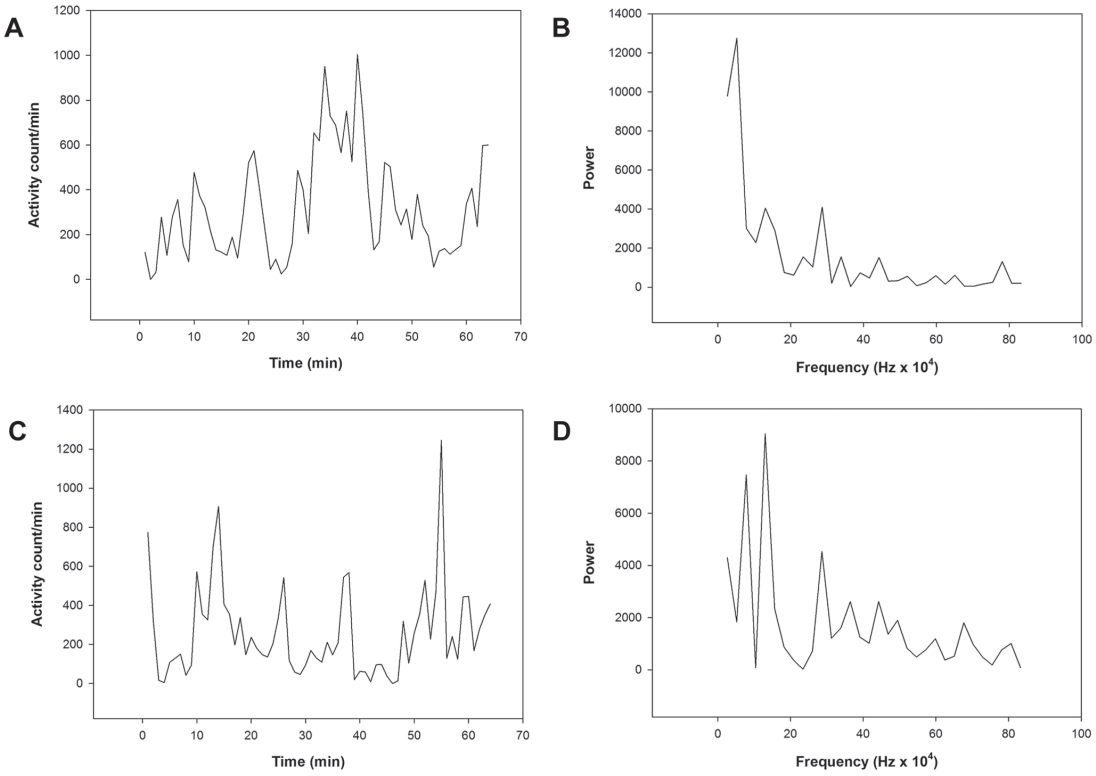

Figure 2. Actigraphy recordings of 64-minute periods of continuous motor activity in the morning. Activity counts and Fourier analysis from a healthy control (A and B) and a patient with mania (C and D).
doi:10.1371/journal.pone.0089574.g002

The patients with depression are less active than healthy controls over 24 hours, which corresponds with low activity being a common factor in depression [10]. Also, both patient groups are less active than the healthy controls during a 64-minute period of

Table 4. Results from the 64-minute period of continuous motor activity in the morning.

Variable	Mania	Depression	Healthy controls	p-value
Number of subjects (n)	16	12	28	
Mean/minute	215±144***	235±101^{++}	391±139	**<0.001**
SD/min in % of mean	87.3±21.7	117.0±41.9$^{+\#}$	89.4±24.3	**0.012**
RMSSD/min in % of mean	86.1±28.6	107.4±46.3^{++}	74.7±23.1	**0.012**
RMSSD/SD	0.980±0.178*	0.919±0.172	0.844±0.140	**0.026**
Sample entropy (m = 2, r = 0.2)	1.474±0.624	1.032±0.481	1.114±0.407	**0.034**
Symbolic dynamics	36.81±6.25	30.08±6.54$^{\#}$	33.61±6.57	**0.031**
Fourier analysis	0.87±0.48*	0.70±0.34	0.55±0.27	**0.025**
Autocorrelation Lag 1	0.493±0.163**	0.561±0.163	0.628±0.116	**0.013**

All data are given as mean ± SD. p-values obtained in a one-way ANOVA. Post hoc Bonferroni tests:
*p≤0.05, mania compared to healthy controls.
**p≤0.01, mania compared to healthy controls.
***p≤0.001, mania compared to healthy controls.
$^{+}$p≤0.05, depression compared to healthy controls.
$^{++}$p≤0.01, depression compared to healthy controls.
$^{\#}$p≤0.05, depression compared to mania.
doi:10.1371/journal.pone.0089574.t004

Table 5. Results from 64-minute period of continuous motor activity in the evening.

Variable	Mania	Depression	Healthy controls	p-value
Number of subjects (n)	18	12	27	
Mean/minute	213±122	177±74	247±137	0.245
SD/min in % of mean	97.4±37.8	123.8±44.0	112.5±41.7	0.216
RMSSD/min in % of mean	99.1±46.9	117.1±47.4	96.4±39.0	0.379
RMSSD/SD	1.010±0.171*	0.949±0.142	0.866±0.166	**0.017**
Sample entropy (m = 2, r = 0.2)	1.309±0.703	1.083±0.440	0.976±0.516	0.165
Symbolic dynamics	33.72±7.51	28.92±7.53	31.30±8.65	0.281
Fourier analysis	1.08±0.71	0.77±0.34	0.72±0.59	0.126
Autocorrelation Lag 1	0.470±0.171	0.538±0.128	0.538±0.167	0.080

All data are given as mean ± SD. p-values obtained in a one-way ANOVA. Post hoc Bonferroni test:
*p≤0.05, mania compared to healthy controls.
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continuous activity in the morning, which probably partly reflects a natural consequence of staying on a hospital ward within a limited area, and partly the effect of psychotropic drug treatment. Without these constraints the patients with mania would be expected to be more active than the healthy controls [27], [28].

Thus, while the total activity counts do not distinguish between patients in a manic and a depressive phase, other parameters show differences in regulation of motor activity in bipolar mania and depression. For the patients with depression the reduced activity level seems to be characterized by increased variability, as shown by the significantly increased standard deviation (SD) in an active period in the morning compared to both patients with mania and healthy controls. In addition, the patients with depression have a significantly higher root mean square successive difference (RMSSD) over 24 hours and in the active morning period compared to healthy controls. These findings are in agreement with a previous study on motor activity of patients with depression [15], and increased intra-individual variability has also been found in actigraphy studies of ADHD patients [29].

Interesting is also the increased RMSSD/SD ratio in the patient groups compared to the healthy controls, meaning that the alteration between successive activity counts increases relative to overall variability. For the patients with depression this ratio is only significantly different from healthy controls in the 24-hour recording, whereas the patients with mania have a higher ratio compared to healthy controls in all analyzed time series. An increased RMSSD/SD ratio has been found in patients with schizophrenia [15] and in healthy individuals treated with the glutamatergic N-methyl-D-aspartate (NMDA) antagonist memantine [30].

Autocorrelation in the first lag was significantly lower in the patients with mania compared to controls in the active morning period, which indicates less correlation of activity counts from minute to minute and corresponds well with the increased RMSSD/SD ratio. A lower autocorrelation between adjacent activity recordings has also been associated with memantine and was in addition found in a sample of patients with schizophrenia [30].

The Fourier analysis shows that the patients with mania demonstrate an increased variance in the high frequency part of the spectrum in the active morning series, corresponding to the period from 2–8 minutes. This was also found in a sample of patients with schizophrenia [15], and although it was considered to reflect a fundamental difference between schizophrenia vs. depression and no mental illness, our results indicate that it could be a common factor of both schizophrenia and mania. In the memantine-treated individuals a higher variance in the high frequency compartment of the spectrum was found as well [30].

The pattern that thus emerges from these different analyses related to variability is that bipolar depression is characterized by generally increased variability, reflected in the SD and RMSSD analyses, while mania is characterized by increased variability in the high frequency part of the spectrum, corresponding to the 2–8 minute period in the Fourier analysis, and is also seen in the increased RMSSD/SD ratio and the reduced autocorrelation (lag 1).

The group with mania also show increased complexity compared to patients with depression in the symbolic dynamic analyses of the active morning periods. The results from the sample entropy analyses closely correspond to this finding, supporting the notion that a manic state is accompanied by increased complexity of motor activity patterns. An increase in entropy indicates a higher level of disorder and unpredictability in a time series. Again, a similar increase in sample entropy has been found in patients with schizophrenia [15] and was suggested to represent a partial breakdown in structured normal activities of everyday life. Reduced complexity in different physiological systems has been postulated to be characteristic of both diseases and aging processes [31]. However, this may depend on the dynamics of the system under study. Vaillancourt and Newell [32] have postulated that in systems with intrinsic oscillations, disease processes may instead be accompanied by increased complexity. In addition to the findings from patients with schizophrenia referred to above, more random stride-interval fluctuations in aging and in patients with Huntington's disease has been reported by Hausdorff et al [33], and increased complexity has been described in the EEG patterns of patients with mania [34].

Our findings for the group with mania closely correspond to the findings in patients with schizophrenia in a study from Bergen, Norway, where the same mathematical analytical methods were employed to analyze actigraphy data of patients with schizophrenia and depression [15]. Also, an associated group of investigators found that memantine induced movement patterns which partly resembled those found in patients with schizophrenia and suggested that the NMDA receptor could be involved in movement disturbances in schizophrenia [30]. Bipolar disorder has also been associated with a dysfunctional frontal glutamate system [35]. Based on the present study the question of how the

NMDA receptor may be involved in mania-associated activity patterns should be further explored.

Although the patients with depression demonstrate reduced complexity compared to the patients with mania, using symbolic dynamic analyses, the values are not significantly lower when compared to healthy controls. It would, however, be interesting to study this further in other groups of patients with depression, since Friedman et al [36] found reduced complexity of mesolimbic dopaminergic activity in a rat model of depression.

The highly significant differences between the three groups despite only 12 and 18 patients in the patient groups and 28 healthy controls indicate clear differences in the regulation of motor activity between the three groups.

There are some limitations to our study which may restrict the findings: The number of participants is rather small, and psychotropic drug treatment may have biased the results; a greater proportion of the patients in an episode of mania were prescribed antipsychotic medication. On the other hand, the marked diurnal variation observed, with significant differences between the groups mainly in the active morning sequences argue against drug treatment as a main reason for the present results.

The fact that more patients with mania were admitted to a psychiatric intensive care unit (PICU), may have affected the results. This could be an alternative explanation of the similarities between our patients in an episode of mania and the patients with schizophrenia described previously, and is supported by the finding that the patients in a PICU, compared to the patients on an ordinary ward, have values of RMSSD/SD, autocorrelation and Fourier analysis which are similar to results from patients with schizophrenia. A PICU implies a single room under regular surveillance, and all patients are allowed to move about freely, but within a more limited space in the intensive care unit than on an open ward.

It is possible that hospitalization in itself can explain the differences in activity between patients, as hospital programs and schedules may have increased activity for the patients with depression and restricted the patients with mania. However, because the total 24-hour activity counts do not separate the patients with mania and depression, the differences found in other measures seem all the more significant, as they cannot be attributed to differences in total activity levels.

Activity is expected to differ between workdays and weekends for non-hospitalized individuals. Dividing the healthy controls in 15 who wore the actigraph on a weekday and 13 who were monitored in the weekend or were retired, produces only one significant difference in all analyses: RMSSD/SD for the 24-hour period. We therefore assume that the day when the actigraph was worn cannot account for the differences in activity between the controls and the patients.

The seasons when the groups were monitored may also have biased the results, since 18 of the 28 healthy controls were monitored in spring or summer months, as opposed to the patients who were all monitored in fall or winter months. The healthy controls have completed the Seasonal Pattern Assessment Questionnaire (SPAQ) [37], and the majority of controls report a moderate seasonal change in energy level, with the most energy during spring or summer. On the other hand, studies suggest that activity may not show seasonal variation, possibly because activity seems to be less influenced by light exposure than mood [38], [39].

Patients were all hospitalized in an acute state of their bipolar disorder, and results should therefore not be generalized to this diagnostic group as a whole. It is possible that hospitalized patients will have different activity profiles than outpatients with a less severe course of illness.

In tables 3 to 5, several ANOVA tests were conducted on activity measures from the data. A correction for multiple comparisons adjusting for the total number of statistical tests has not been done since the analyses were planned before they were conducted [15], [30], [40].

Despite the limitations mentioned, the main findings of our study remain well-founded: episodes of bipolar depression are associated with reduced 24-hour activity and an activity pattern characterized by high intra-individual variability. Acute bipolar mania is also associated with lower mean activity levels than non-hospitalized healthy individuals, but less variance in activity compared to patients with depression. In addition, a more complex activity pattern is found in patients with mania, and at the same time Fourier analysis shows increased variability in the high frequency part of the spectrum, and probably related to this, an increased RMSSD/SD ratio and reduced autocorrelation (lag 1).

Our results provide strong indications that psychomotor function shows opposite symptom manifestations in acutely admitted patients with bipolar depression and mania, and that these manifestations can be identified by actigraphy recordings analyzed with linear and nonlinear methods. Further research on larger samples and other psychiatric populations is warranted, as it could establish the role of actigrahy as a diagnostic and therapeutic marker of psychiatric disorders in clinical practice.

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Author Contributions

Conceived and designed the experiments: KKG TEGH GM AV OBF. Analyzed the data: KKG GM OBF. Contributed reagents/materials/analysis tools: OBF. Wrote the paper: KKG TEGH GM AV OBF. Final approval of version to be published: KKG TEGH GM AV OBF. Acquisition of data: TEGH AV.

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Paper IV

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