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

Authors and Affiliations

Karoline Krane-Gartiser [a, b *], Tone E. G. Henriksen [c, d, e], Gunnar Morken [a, b], Arne E. Vaaler [a, b], Ole Bernt Fasmer [c, d]

[a] Department of Mental Health, NTNU, Norwegian University of Science and Technology, Trondheim, Norway

[b] Department of Psychiatry, St. Olav's University Hospital, Trondheim, Norway

[c] Department of Clinical Medicine, Section for Psychiatry, Faculty of Medicine and Dentistry, University of Bergen, Bergen, Norway

[d] Division of Psychiatry, Haukeland University Hospital, Bergen, Norway

[e] Division of Mental Health Care, Valen Hospital, Fonna Local Health Authority, Valen, Norway

*** Corresponding author:**
Karoline Krane-Gartiser, M.D., Ph.D. Address: Department of Mental Health, NTNU, Norwegian University of Science and Technology. P.O. box 3250 Sluppen, 7006 Trondheim, Norway. Telephone number (+47) 41 26 46 20. Fax number: (+47) 72 82 30 46. E-mail: karoline.krane-gartiser@ntnu.no

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ABSTRACT (word count: 214 words)

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

Keywords: actigraphy, non-linear analysis, psychosis, schizophrenia, affective disorders, diagnosis

1. INTRODUCTION

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

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

In several publications on acutely ill inpatients with affective disorders, we have applied linear and nonlinear analytical methods to 24-hour actigraphy recordings (Krane-Gartiser et al., 2015; Krane-Gartiser et al., 2014; Krane-Gartiser et al., 2016). For mania, we found irregular activity patterns that are stable within 24 hours, whereas depressed subgroups demonstrated low total activity, higher variability between active and inactive periods and several changes in activity parameters within 24 hours (Krane-Gartiser et al., 2014; Krane-Gartiser et al., 2017). As schizophrenia cases in other studies have shown motor features that resemble our findings for both mania and depression, the aim of the current study was two-fold: first, to characterize 24-hour motor activity patterns in a new group of inpatients with schizophrenia and psychotic

disorders, and second, to compare them to inpatients from the same setting with bipolar mania and motor-retarded unipolar depression and to a non-hospitalized group of healthy individuals. We hypothesized that cases with depression would have lower activity levels and more regular patterns compared to the other groups, and that cases with mania and schizophrenia would show similar features of irregularity in activity patterns. Because our application of linear and nonlinear dynamics in between-group comparisons as well as in within-group analyses from morning to evening has proven valuable, we wanted to undertake the same procedure for the group with schizophrenia and psychotic disorders.

2. MATERIALS AND METHODS

2.1. Sample

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

patients with unipolar depression were in a mild depressive episode (F32.0 or F33.0), 15 in a moderate episode (F32.1 or F33.1) and 7 in a severe episode without psychotic symptoms (F32.2 or F33.2).

2.2. Recordings of motor activity

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

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

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

2.3. Mathematical analyses

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

a) the standard deviation (SD) as an intra-individual measure of fluctuations from the mean

b) the root mean squared successive difference (RMSSD), which describes the difference in successive counts from minute to minute

c) the RMSSD/SD ratio

For the 64-minute periods we further assessed:

d) sample entropy as a measure of complexity or irregularity

e) autocorrelation (lag 1)

f) ratios between high-frequency and low-frequency variance in a Fourier analysis

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

2.3.1. Sample entropy

Sample entropy is a nonlinear measure that indicates the degree of regularity (complexity) of a time series. A low sample entropy value corresponds to a more regular series. It is the negative natural logarithm of an estimate of the conditional probability that subseries of a certain length (m) that match point-wise, within a tolerance (r), also match at the next point. We chose the following values, m = 2 and r = 0.2. Data were normalized by transforming the time series to have sample mean 0 and sample variance 1 (Richman and Moorman, 2000).

2.3.2. Autocorrelation at lag 1

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

2.3.3. Fourier analysis

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

2.4. Statistics

Statistical analyses were planned in advance, based on previous studies (Krane-Gartiser et al., 2017) and carried out using SPSS version 24.0. For comparison of counts of categorical data

we used chi-square tests, and for comparison of means, we used one-way analyses of variance (ANOVAs) with Least Significant Difference (LSD) post-hoc tests to obtain differences between groups. In covariance analyses (ANCOVAs), we controlled for antipsychotic medication treatment. To obtain within-group differences between variables in the morning and evening, we used paired samples T-tests. Finally, we tested group differences in changes from morning to evening using linear mixed models for patient groups only. A p-value ≤ 0.05 was considered significant.

2.5. Ethics statement

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

3. RESULTS

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

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

In the 64-minute periods of continuous motor activity, there were more between-group differences in the morning than in the evening period (Table 4). Patients were significantly less active in the morning compared to healthy individuals. Again, the UP cases showed an increased SD/min compared to other groups in both the morning and evening periods. The schizophrenia and UP groups had higher RMSSD values than healthy individuals in the morning, indicating more minute-to-minute differences in activity counts. With regards to the relationship between RMSSD and SD, cases with mania or schizophrenia had increased RMSSD/SD ratios compared to UP cases and healthy individuals in the morning and compared to healthy individuals only in the evening. Variation in the high-frequency part of the spectrum relative to the low-frequency part in the Fourier analysis in the morning was higher for the schizophrenia group compared to UP cases and healthy controls. The mania group also had a significantly increased Fourier finding compared to healthy controls. The cases with schizophrenia and mania further showed more irregular patterns in the morning period, as given by increased sample entropy levels and lower autocorrelation compared to the two other groups.

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

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

In group-by-time analyses for the three patient groups only, there were no significant differences in any of the activity variables, but trend findings (p<0.1) for Fourier analysis (p=0.065) and autocorrelation (p=0.095). (Supplementary table S3.) Adjusting for antipsychotic medication treatment did not alter the results of morning to evening activity differences for any of the patient groups (data not shown).

4. DISCUSSION

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

Activation has gained renewed attention as a central phenomenon of bipolar disorder in particular, but remains understudied in psychiatric research as a whole (Scott et al., 2017a). Activation seems to represent a distinct dimension according to a recent meta-analysis of factor analytic studies, and actigraphy as an objective measure may provide more knowledge about the dynamics of motor activation (Scott et al., 2017a). Along these lines, actigraphy analyses may help identify similarities and differences between functional psychiatric disorders. Ultimately, classification according to activity characteristics may complement current diagnostics of psychiatric disorder subcategories (Scott et al., 2017b). The current study is yet another contribution to decipher the linear and non-linear dynamics of motor activity between prevalent psychiatric conditions, this time with a particular emphasis on schizophrenia.

All patient groups were less active than healthy individuals, even the mania cases, which is a consistent finding in comparisons of hospitalized to non-hospitalized individuals (Burton et al.,

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

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

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

disorganization that prevents proper action planning, and future studies that combine imaging and actigraphy can provide more insight into the correlation between brain activity and motor behavior (Farrow et al., 2005).

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

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

A possible mechanism for the normal fluctuation in motor activity in healthy people and the pathological activity patterns seen in the patients, could be found in the interplay between the circadian (near 24 hours) and ultradian (near 4 hours) rhythms of arousal and motor activity (Blum et al., 2014). In nearly all species, there are regular fluctuations in arousal and motor activity influenced by endogenous chronobiologic rhythms. The most striking of these rhythms

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

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

Obviously, we need to take into account that medications could confound the results through effects on motor activation. In an effort to meet this problem, analyses where repeated with adjustment for antipsychotic medication. Most antipsychotics are antidopaminergic compounds with potential to influence motor activity. The main findings in the study remained unaltered after controlling for effect of antipsychotics. In our view, this strengthens the validity

of results, having in mind the relatively small sample and the likelihood of correlation between use of antipsychotics and severity of illness. The patient groups in our study differed somewhat with regard to medication, most importantly the unipolar depression cases compared to cases with mania or schizophrenia. The unipolar depressed group received more antidepressants, less antipsychotics and less anticonvulsants. It is however less likely that the lower activity for the unipolar depressed group is caused by these differences in medication alone for the following reasons: Antidepressants can be activating (e.g. venlafaxine) or sedative (e.g. mianserin). The sedative antidepressants are usually prescribed for the nighttime in the subjects' resting phase, so the impact on mean activity would be small. If any effect of the higher percentage of antidepressant users in the unipolar depressed group, one would expect a moderating effect toward normalized activity with higher mean activity and normalized activity patterns. Also, any confounding effects from less antipsychotics and less anticonvulsants in the unipolar depressed group would make group differences of mean activity smaller since these substances are usually sedative and not activating (except for aripiprazole). With regards to potential effects of medication on mean activity in the patients with mania, a previous study of recovered bipolar I patients still using medication found no relation between type or dose of psychotropic medication and actigraphic measures (mean activity and measures of circadian rhythm) compared to during the illness episode (Salvatore et al., 2008). Also, among the few investigations of the relative contribution of psychiatric symptoms and psychotropic medications on the sleep-wake cycle, one study found that mania symptoms were predictive of lower circadian amplitude and rhythmicity, independently of medications (Robillard et al., 2016). Antipsychotics and certain antidepressant agents had an effect on several sleep parameters, but not on activity rhythms. Moreover, lower activity in mania is in line with other studies (De Crescenzo et al., 2017). In the patients with schizophrenia, the percentage of potentially sedative medications (antipsychotics, hypnotics/anxiolytics and antihistamines) was the same or lower than in the mania group and higher than in the unipolar depressed group (except for slightly fewer patients receiving hypnotics/anxiolytics than in the UP group). Therefore, this cannot explain the second lowest mean level compared to the other patient groups. Effects of medication on other aspects of activity patterns cannot be ruled out. Given that certain antidepressants and antipsychotics alter dopaminergic tone, they could influence on ultradian rhythms that are potentially generated by the dopamine oscillator (Blum et al., 2014). Our findings are in line with previous studies on motor activity patterns in psychotic and affective disorders (Walther et al., 2014, Hauge et al., 2011). Also, there is extensive overlap of medication used for psychotic and affective disorders and much heterogeneity of

psychotropic medication as well. All in all, we consider that the medication profile of the subgroups suggests that there are disorder-specific motor activity markers that cannot be fully explained by psychotropic medication. However, we also acknowledge that there is a general lack of large studies that could provide valid answers on the moderating effects of different psychotropic drug classes on motor activity patterns. Our study was too small to allow for further stratification of the sample and cannot resolve to which extent medication influenced on different patterns between separate acute psychiatric states.

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

The main finding of this study is that schizophrenia and psychotic disorders can be separated from motor-retarded unipolar depression and healthy individuals by detailed analysis of motor activity patterns. Using linear and nonlinear analytics, the activity patterns for a group of

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

Conflicts of interest

All authors declare that they have no conflict of interest.

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Table 1: Demographic data

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

Table 2: Medical treatment

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

All values are shown as *n* (%).

Table 3: 24-hour actigraphy recordings of motor activity

Variable	Schizophrenia (SCZ)	Mania	Unipolar depression (UP)	Healthy controls (HC)	*p*-value[a]	Post hoc test[b]
Duration of recording in minutes	1381 ± 129	1344 ± 244	1363 ± 207	1440 ± 0	0.188	
Mean activity count/minute	139 ± 81	157 ± 84	91 ± 47	203 ± 71	**<0.001**	SCZ vs. UP: 0.015; SCZ vs. HC: 0.001; Mania vs. HC: 0.036; Mania vs. UP: 0.004; UP vs. HC: <0.001
SD/min in % of mean	169.7 ± 49.7	145.1 ± 39.1	206.1 ± 49.0	147.3 ± 29.8	**<0.001**	SCZ vs. UP: 0.003; Mania vs. UP: <0.001; UP vs. HC: <0.001
RMSSD/min in % of mean	137.5 ± 55.5	113.7 ± 41.8	160.7 ± 54.8	99.1 ± 21.5	**<0.001**	SCZ vs. HC: 0.002; Mania vs. UP: 0.001; UP vs. HC: <0.001
RMSSD/SD	0.794 ± 0.121	0.774 ± 0.094	0.772 ± 0.133	0.675 ± 0.077	**<0.001**	SCZ vs. HC: <0.001; Mania vs. HC: 0.003; UP vs. HC: 0.002

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

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

Activity variable	Sequence	Schizo-phrenia (SCZ)	Mania	Unipolar depression (UP)	Healthy controls (HC)	Between - group *p*-value[a]	Post hoc test[b]
Mean activity count/ minute	Morning	232 ± 112	215 ± 144	200 ± 103	391 ± 139	**<0.001**	SCZ vs. HC: <0.001; Mania vs. HC: <0.001; UP vs. HC: <0.001
	Evening	195 ± 93	213 ± 122	162 ± 109	247 ± 137	0.080	
SD/min in % of mean	Morning	96.8 ± 34.7	87.3 ± 21.7	113.7 ± 26.4	89.4 ± 24.3	**0.009**	SCZ vs. UP: 0.035; Mania vs. UP: 0.005; UP vs. HC: 0.003
	Evening	112.8 ± 32.5	97.4 ± 37.8	136.1 ± 48.9	112.5 ± 41.7	**0.025**	SCZ vs. UP: 0.046; Mania vs. UP: 0.003; UP vs. HC: 0.043
RMSSD/min in % of mean	Morning	96.4 ± 43.4	86.1 ± 28.6	97.5 ± 29.7	74.7 ± 23.1	**0.043**	SCZ vs. HC: 0.015; UP vs. HC: 0.015
	Evening	109.7 ± 40.6	99.1 ± 46.9	128.2 ± 51.0	96.4 ± 39.0	0.066	
RMSSD/SD	Morning	0.988 ± 0.165	0.980 ± 0.178	0.857 ± 0.174	0.844 ± 0.140	**0.002**	SCZ vs. UP: 0.006; SCZ vs. HC: 0.001; Mania vs. HC: 0.009; Mania vs. UP: 0.023
	Evening	0.970 ± 0.156	1.011 ± 0.171	0.953 ± 0.191	0.866 ± 0.166	**0.033**	SCZ vs. HC: 0.028; Mania vs. HC: 0.006
Sample entropy (m = 2, r = 0.2)	Morning	1.471 ± 0.681	1.474 ± 0.624	0.911 ± 0.432	1.114 ± 0.407	**0.001**	SCZ vs. UP: <0.001; SCZ vs. HC: 0.016; Mania vs. HC: 0.037; Mania vs. UP: 0.002
	Evening	1.038 ± 0.507	1.309 ± 0.703	0.919 ± 0.627	0.976 ± 0.516	0.166	
Fourier analysis	Morning	0.98 ± 0.59	0.87 ± 0.48	0.60 ± 0.32	0.55 ± 0.27	**0.001**	SCZ vs. UP: 0.003; SCZ vs. HC: <0.001; Mania vs. HC: 0.024
	Evening	0.81 ± 0.40	1.08 ± 0.71	0.88 ± 0.58	0.72 ± 0.59	0.203	
Autocorrelation	Morning	0.475 ± 0.164	0.494 ± 0.163	0.618 ± 0.148	0.628 ± 0.116	**<0.001**	SCZ vs. UP: 0.001; SCZ vs. HC: <0.001; Mania vs. HC: 0.005; Mania vs. UP: 0.011
	Evening	0.508 ± 0.147	0.470 ± 0.171	0.519 ± 0.170	0.538 ± 0.167	0.131	

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

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

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

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

Supplementary Table S1: 24-hour actigraphy recordings of motor activity after adjustment for antipsychotic treatment

Variable	Schizophrenia (SCZ)	Mania	Unipolar depression (UP)	Healthy controls (HC)	*p*-value[a]	Post hoc test[b]
Duration of recording in minutes	1381 ± 129	1344 ± 244	1363 ± 207	1440 ± 0	0.188	
Mean activity count/minute	139 ± 81	157 ± 84	91 ± 47	203 ± 71	**<0.001**	SCZ vs. HC: 0.001; Mania vs. HC: 0.019; Mania vs. UP: 0.046; UP vs. HC: <0.001
SD/min in % of mean	169.7 ± 49.7	145.1 ± 39.1	206.1 ± 49.0	147.3 ± 29.8	**<0.001**	SCZ vs. UP: 0.011; Mania vs. UP: <0.001; UP vs. HC: <0.001
RMSSD/min in % of mean	137.5 ± 55.5	113.7 ± 41.8	160.7 ± 54.8	99.1 ± 21.5	**<0.001**	SCZ vs. HC: 0.007; Mania vs. UP: 0.010; UP vs. HC: <0.001
RMSSD/SD	0.794 ± 0.121	0.774 ± 0.094	0.772 ± 0.133	0.675 ± 0.077	**0.001**	SCZ vs. HC: <0.001; Mania vs. HC: 0.004; UP vs. HC: 0.001

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

Supplementary Table S2: Actigraphy variables from 64-minute periods of continuous motor activity in the morning and evening after adjustment for antipsychotic treatment

Activity variable	Sequence	Schizo-phrenia (SCZ)	Mania	Unipolar depression (UP)	Healthy controls (HC)	Between - group *p*-value[a]	Post hoc test[b]
Mean activity count/ minute	Morning	232 ± 112	215 ± 144	200 ± 103	391 ± 139	**<0.001**	SCZ vs. HC: <0.001; Mania vs. HC: <0.001; UP vs. HC: <0.001
	Evening	195 ± 93	213 ± 122	162 ± 109	247 ± 137	0.076	
SD/min in % of mean	Morning	96.8 ± 34.7	87.3 ± 21.7	113.7 ± 26.4	89.4 ± 24.3	**0.009**	Mania vs. UP: 0.041; UP vs. HC: 0.001
	Evening	112.8 ± 32.5	97.4 ± 37.8	136.1 ± 48.9	112.5 ± 41.7	0.114	
RMSSD/min in % of mean	Morning	96.4 ± 43.4	86.1 ± 28.6	97.5 ± 29.7	74.7 ± 23.1	**0.013**	SCZ vs. HC: 0.005; UP vs. HC: 0.005
	Evening	109.7 ± 40.6	99.1 ± 46.9	128.2 ± 51.0	96.4 ± 39.0	0.059	
RMSSD/SD	Morning	0.988 ± 0.165	0.980 ± 0.178	0.857 ± 0.174	0.844 ± 0.140	**0.003**	SCZ vs. UP: 0.003; SCZ vs. HC: 0.001; Mania vs. HC: 0.004; Mania vs. UP: 0.010
	Evening	0.970 ± 0.156	1.011 ± 0.171	0.953 ± 0.191	0.866 ± 0.166	**0.013**	SCZ vs. HC: 0.006; Mania vs. HC: 0.002
Sample entropy (m = 2, r = 0.2)	Morning	1.471 ± 0.681	1.474 ± 0.624	0.911 ± 0.432	1.114 ± 0.407	**0.015**	SCZ vs. UP: 0.002; Mania vs. UP: 0.009
	Evening	1.038 ± 0.507	1.309 ± 0.703	0.919 ± 0.627	0.976 ± 0.516	0.312	
Fourier analysis	Morning	0.98 ± 0.59	0.87 ± 0.48	0.60 ± 0.32	0.55 ± 0.27	**0.002**	SCZ vs. UP: 0.001; SCZ vs. HC: <0.001; Mania vs. HC: 0.012; Mania vs. UP: 0.022
	Evening	0.81 ± 0.40	1.08 ± 0.71	0.88 ± 0.58	0.72 ± 0.59	0.181	
Autocorrelation	Morning	0.475 ± 0.164	0.494 ± 0.163	0.618 ± 0.148	0.628 ± 0.116	**<0.001**	SCZ vs. UP: <0.001; SCZ vs. HC: <0.001; Mania vs. HC: 0.001; Mania vs. UP: 0.002
	Evening	0.508 ± 0.147	0.470 ± 0.171	0.519 ± 0.170	0.538 ± 0.167	0.060	

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

Supplementary table S3: Group by time analyses for activity variables in patient groups only

	***p*-value[a]**
Mean activity	0.464
SD in %	0.654
RMSSD in %	0.293
RMSSD/SD	0.188
Sample entropy	0.163
Fourier analysis	0.065
Autocorrelation	0.095

[a] Linear mixed models with patient group and time as fixed effects and participant as a random effect. Individual activity parameters as the dependent variable.

Figure legend:

Figure 1. 24-hour actograms from a representative subject in each group.

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

Figure 1