Published in final edited form as:

Psychiatry Res. 2016 March 30; 237: 166–174. doi:10.1016/j.psychres.2016.01.047.

State-related differences in the level of psychomotor activity in patients with bipolar disorder-Continuous heart rate and movement monitoring

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Abstract

Measuring changes in psychomotor activity is a potential tool in the monitoring of the course of affective states in bipolar disorder. Previous studies have been cross-sectional and only some have used objective measures. The aim was to investigate state-related differences in objectively-measured psychomotor activity in bipolar disorder. During a 12 weeks study, repeated measurements of heart rate and movement monitoring over several days were collected during different affective states from 19 bipolar disorder outpatients. Outcomes included activity energy expenditure (AEE) and trunk acceleration (ACC). Symptoms were clinically rated using Hamilton Depression Rating Scale (HDRS-17) and Young Mania Rating Scale (YMRS). Compared to patients in a euthymic state, patients in a manic had significantly higher AEE. Compared to patients in a depressive state, patients in a manic state had significantly higher ACC and AEE. There was a significant diurnal variation in ACC and AEE between affective states. Finally, there was a significant correlation between the severity of manic symptoms and ACC and AEE, respectively. This first study measuring psychomotor activity during different affective states using a combined heart rate and movement sensor supports that psychomotor activity is a core symptom in bipolar disorder that is altered during affective states.

Keywords

Bipolar disorder; psychomotor activity; combined heart rate and movement sensor; affective state; intra-individual variation; diurnal variation

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Contributors

MFJ, SB and LVK performed the statistical analyses. MFJ and LVK wrote the first draft of the manuscript. All authors contributed to and have approved the final version of the manuscript.

Conflicts of interest and financial disclosures

MFJ has been a consultant for Eli Lilly and Lundbeck. SB has no conflicts of interests and is funded by the UK Medical Research Council (MC_UU_12015/3). MV has been a consultant for Eli Lilly, Lundbeck, Astra Zeneca and Servier. LVK has within recent three years been a consultant for Lundbeck and Astra Zeneca.

1 Introduction

A central feature in bipolar disorder is abnormalities in psychomotor activity, and psychomotor retardation during bipolar disorder depression as well as increased motor activity during mania has been described in the literature (Beigel and Murphy, 1971; Kupfer et al., 1974; Kuhs and Reschke, 1992; Goodwin, and Jamison, 1996; Sobin and Sackeim, 1997; Goldberg et al., 2009; Mitchell et al., 2011; Judd et al., 2012). Changes in the level of psychomotor activity could be a useful tool in the monitoring of the course of affective states in patients with bipolar disorder (Kupfer et al., 1974). A number of different studies have investigated the level of psychomotor activity in affective disorders using clinical assessments and self-reporting (Blackburn, 1975; Dunner et al., 1976; Popescu et al., 1991; Salvatore et al., 2008), while other studies have used different types of accelerometers/movement sensors as an objective monitoring method (Kupfer et al., 1974; Foster and Kupfer, 1975; Kuhs and Reschke, 1992; Jones et al., 2005; Minassian et al., 2010; Krane-Gartiser et al., 2014). The use of clinical assessments and self-reporting as monitoring tools of psychomotor activity is based on subjective data, often collected retrospectively, introducing the risk of poor validity and recall bias. However, measuring the level of psychomotor activity using objective methods may be a tool for collection of real-time data on behavior.

Over time accelerometers of varying size/weight and intrusiveness, either worn on the wrist or on the thorax, have been used as objective monitoring methods for estimating the level of psychomotor activity in patients with bipolar disorder (Kupfer et al., 1974; Kuhs and Reschke, 1992; Jones et al., 2005; Krane-Gartiser et al., 2014). Results from these studies have been divergent and estimation of energy expenditure and other physiological constructs such as heart rate have not been possible. Most studies using accelerometers have monitored the level of psychomotor activity during hospitalization (Kupfer et al., 1974; Foster and Kupfer, 1975; Kuhs and Reschke, 1992; Minassian et al., 2010; Krane-Gartiser et al., 2014), and thus do not reflect the amount of movement in naturalistic settings during everyday life. Furthermore, most studies have monitored the level of psychomotor activity at a single time-point not including patients with bipolar disorder in different affective states and have not investigated intra-individual alterations of the level of psychomotor activity between a depressive, manic and euthymic state. One cross sectional study investigated the level of motor activity in acutely hospitalized patients with bipolar disorder in different affective states using an accelerometer, finding differences in levels of motor activity between a depressive state versus a manic state (Krane-Gartiser et al., 2014). Thus, the potential information on individual state-related alterations in the level of psychomotor activity has not been fully investigated.

Using combined heart rate and movement monitoring offers higher precision for estimating the level of physical activity energy expenditure (AEE) in everyday life settings, and we have previously reported that patients with bipolar disorder have significantly lower acceleration (ACC) and AEE than patients with unipolar disorder during a remitted to mild/moderate depressive state (Brage et al., 2004; Faurholt-Jepsen et al., 2012). Our group has previously reported that the sleeping heart rate (SHR) correlated with the severity of depressive symptoms measures using the Hamilton Depression Rating Scale 17-item

(HDRS-17) and may indicate the presence of insomnia and/or lower cardiorespiratory fitness (Hamilton, 1967; Faurholt-Jepsen et al., 2015).

Thus, using a combined heart rate and movement sensor as an objective supplementary tool for assessment of alterations the patients' affective state may provide important information of the affective state and level of symptoms in patients with bipolar disorder.

In the present study we monitored with such repeated objective measurements the level of psychomotor activity in naturalistic settings in different affective states in outpatients with bipolar disorder. The objectives were to investigate differences in the level of psychomotor activity during different affective states in a sample of patients with bipolar disorder.

2 Methods

2.1 Study participants and settings

The patients were recruited from The Copenhagen Clinic for Affective Disorders, Psychiatric Center Copenhagen, Denmark, during a period from October 2013 to December 2014. Treatment at the clinic comprises two years of combined evidence based psychopharmacological treatment and supporting therapy, including group psychoeducation. Further details about the treatment program at The Copenhagen Clinic for Affective Disorders and the effect of this have been described elsewhere (Kessing et al., 2013).

Inclusion criteria were: bipolar disorder diagnosis according to ICD-10 using the Schedules for Clinical Assessment in Neuropsychiatry (SCAN) interview (Wing et al., 1990).

Exclusion criteria were: pregnancy; lack of Danish language skills; severe physical illness; and schizophrenia, schizotypal or delusional disorders according to the SCAN interview.

The patients were followed for 12 weeks during their course of treatment at the clinic and therefore they received various types, combinations and doses of psychopharmacological treatment during the study period. The patients were invited to participate in the study following referral to the Copenhagen Clinic for Affective Disorders and clinical and socio-demographic data was collected at the beginning of the study. At the first day of every psychomotor activity monitoring the severity of depressive and manic symptoms were assessed according to clinical ratings using the HDRS-17 (Hamilton, 1967) and the Young Mania Rating Scale (YMRS) (Young et al., 1978), respectively.

A control group of healthy individuals aged 18-60 years without first-degree relatives with psychiatric disorders had previously been recruited from the Blood Bank at Rigshospitalet, Copenhagen as part of an earlier study (Faurholt-Jepsen et al., 2012), and serve as reference on the level of psychomotor activity among healthy individuals.

2.2 Monitoring of psychomotor activity

The height (kg) and weight (m) were assessed at baseline, and the body mass index (BMI) was calculated as weight/height^2 (kg/m^2). To monitor the level of psychomotor activity during everyday life a combined heart rate and movement sensor mounted at the thorax (Actiheart, Cambridge Neurotechnology Ltd, Papworth, UK) was used. The reliability and validity of the sensor have been described elsewhere (Brage et al., 2005). The sensor is

capable of monitoring the level of psychomotor activity (movement/acceleration (m/s^2) and heart rate (bpm)) during non-hospitalized everyday life settings for a prolonged period of time of up to 11 days, weighs 8 grams and should therefore not impede any kind of physical activity (Wickström and Bendix, 2000). As described by others, compared to indirect calorimetry, the method of estimating AEE from the combination of heart rate and movement monitoring has been shown to be valid (Thompson et al., 2006; Assah et al., 2011). As opposed to using accelerometers/movement sensors for monitoring, the combination of heart rate and movement monitoring gives the opportunity to estimate the amount of energy (kJ) spent on physical activity per day on the individual level.

The procedure of psychomotor activity monitoring

During the 12 weeks study period the patients visited the researcher (MFJ) for assessment of the severity of depressive and manic symptoms using clinical ratings and the heart rate and movement sensor was mounted on the thorax at the apex of the sternum and lateral to the left in a horizontal line using two ECG electrodes (Unomedical, Mona Vale, Australia) (Brage et al., 2006) during different affective states. The sensor was set up for long-term monitoring, collecting aggregated data every 30 second. Data on the heart rate and movement were monitored over a period of minimum three consecutive week days and nights. Patients were instructed to continue with their usual everyday life activities during the monitoring period and to wear the sensor 24 hours/day. Spare electrodes, including instructions on how to replace the electrodes, were provided to the patients. Patients did not provide individual calibration tests before the monitoring period and thus group calibration was used to calibrate heart rate to protocol-estimated physiological intensity. A quality examination of the sensor data was done when the patients returned to the researcher. If the recorded data was of poor quality the patients were invited to repeat the monitoring for another three days after clinical assessment of the severity of depressive and manic symptoms by the researcher (MFJ).

The sensor data was downloaded to a computer and the heart rate trace was processed using a robust Gaussian Process regression method to handle measurement noise (Stegle et al., 2008). Movement data did not require pre-processing.

AEE was estimated from a combination of heart rate and movement using a branched equation framework (Brage et al., 2007). Furthermore, data was summarized into quarter-daily data (from midnight- 6 am; 6 am-12 am; 12 am- 6pm; and 6 pm-12 pm). Periods of non-wear were inferred from the combination of non-physiological heart rate and prolonged periods of inactivity, which were taken into account when summarizing time-series data into quarter-daily estimates of ACC and AEE.

2.3 Statistical methods

For each analysis on different repeated measures of the level of psychomotor activity we considered a two-level linear mixed effects regression model. This model allows for both intra-individual variation and inter-individual variation of the dependent variables considered in the different regression analyses. In the analyses the first level of the model represented the repeated measurements of measures of psychomotor activity within

individuals. The second level of the model represented the between individuals variation of measures of psychomotor activity. All considered models included a patient specific random effect and all other covariates were specified as fixed effects.

In the analyses ACC and AEE were considered as the dependent variables reflecting levels of psychomotor activity and SHR as the dependent variable reflecting heart rate during sleep. We specified three sets of analyses according to the choice of independent variables. Firstly, we considered a model where differences in the dependent variables according to the patients' affective states (depressive, manic/mixed or euthymic) were investigated. Prior to inclusion of patients in the study a depressive state was defined as an ICD-10 diagnosis of bipolar disorder current episode depression combined with a HDRS-17 score ≥ 13 and an YMRS score ≥ 13 ; a manic or mixed state was defined as an ICD-10 diagnosis of bipolar disorder current episode hypomania, mania or mixed and an YMRS score ≥ 13 ; and a 'euthymic state' is consequently defined as remission or partial remission with a HDRS-17 score <13 and an YMRS score <13 .

Secondly, we considered models on differences in six hours intervals of the dependent variables according to the patients' affective states (depressive, manic/mixed or euthymic). Interactions between the six hours' time intervals and affective states were investigated for each of the considered models and reported accordingly. Thirdly, we considered models where we investigated differences in the above mentioned dependent variables according to the severity of depressive and manic symptoms measured using HDRS-17 and YMRS, respectively.

For the analyses we firstly employed an unadjusted analysis, and secondly an analysis adjusted for age; sex and body mass index (BMI) as possible confounding covariates. Model assumptions were checked visually by means of residuals and QQ plots. Data were entered using the data entry program Epidata® (The EpiData Association, Odense, Denmark, Europe) and the statistical software program STATA version 12.1 (StataCorp LP, College Station, TX, USA) was used for the statistical analyses. The significance level of the p-values in the statistical analyses was set to 0.05 (two-tailed).

2.4 Ethical considerations

The study was approved by the Regional Ethics Committee in the Capital Region of Denmark (H-2-2011-056) and the Danish Data protection agency (2013-41-1710). All potential participants were given both written and oral information about the study before informed consent was obtained. Participants were informed that they could withdraw from the study at any time without this having any effect on their course of treatment at the Copenhagen Clinic for Affective Disorder, Psychiatric Center Copenhagen, Denmark.

3 Results

3.1 Background characteristics

A total of 19 outpatients with bipolar disorder participated in the present psychomotor activity monitoring study. During the study period the level of psychomotor activity was monitored on 12 of the patients during a depressive state, on 8 of the patients during a manic

or mixed state (among which two episodes fulfilled the ICD-10 criteria for a mixed episode) and on 12 of the patients during a euthymic state. Nine patients were monitored during one affective state, seven patients were monitored during two affective states and three patients were monitored during all three affective states. Data on heart rate and movement were monitored over a period of minimum three consecutive week days and nights per patient in each affective state. Patients had a median age of 28.1 years [IQR: 20.8; 31.3] and a mean BMI of 25.6 kg/m² (SD 5.3) at inclusion. Further background characteristics of the patients are presented in Table 1.

3.2 Psychomotor activity analyses on daily data

The raw and unadjusted scores, not accounting for repeated measurements per patient, of depressive and manic symptoms and measures of psychomotor activity (SHR; ACC; and AEE) at the time of monitoring are presented in Table 2.

Unadjusted models and models adjusted for age, sex and BMI on differences in the levels of measures of psychomotor activity estimated as SHR; ACC; and AEE between affective states are presented in Table 3.

In both the unadjusted and the adjusted model compared to patients in a euthymic state, patients in a manic or mixed state had higher AEE (kJ/kg/day) (adjusted model: B= 14.79, 95% CI: 0.90; 28.68, p=0.037). Also, in both unadjusted and adjusted models, compared to patients in a manic or mixed state, patients in a depressive state had a lower ACC (m/s²) (adjusted model: B= -0.064, 95% CI: -0.005; -0.12, p=0.030) and AEE (kJ/day/kg) (adjusted model: B= -16.57, 95% CI: -30.80; -2.35, p=0.020). Patients in a manic or mixed state thus had higher levels of ACC and AEE on a daily basis compared to patients in a depressive state and higher levels of AEE on a daily basis compared to patients in a euthymic state. The exact values of AEE showed that during a euthymic state patients had a mean AEE of 42 kJ/kg/day, meaning that a patient weighing 70 kg would have a mean AEE of 2940 kJ/day. Thus, with a difference in AEE of approximately 16 kJ/kg/day (Table 3), compared to patients in a depressive state or euthymic state (table 3), means that a patient in a manic or mixed state weighing 70 kg had a mean AEE of 4060 kJ/day.

Box plot of differences in ACC and AEE in different affective states based on predicted values from linear mixed regression models adjusted for age, sex and BMI are shown in Figure 1.

3.3 Psychomotor activity analyses in six hours intervals per day

To investigate differences in measures of psychomotor activity (ACC and AEE) during time intervals during the day between affective states, intervals of six hours (0-6 am; 6-12 am; 12-6 pm; and 6-12 pm) were generated. Unadjusted models and models adjusted for age, sex and BMI on differences during six hours intervals in the levels of measures of psychomotor activity estimated as ACC and AEE between affective states are presented in Table 4. There were significant interactions between the six hours intervals and affective states on both ACC (p=0.005) and AEE (p<0.001), and thus data on each of the six hours intervals and affective states are reported (Table 4).

As can be seen, in both the unadjusted and the adjusted model compared to patients in a euthymic state, patients in a manic or mixed state had a higher ACC (m/s^2) between 12-6 pm (adjusted model: $B = 0.082$, 95% CI: 0.002; 0.16, $p = 0.043$), and a higher AEE (kJ/kg/day) between 12-6 pm (adjusted model: $B = 15.83$, 95% CI: 3.34; 28.31, $p = 0.013$). Furthermore, in both the unadjusted and the adjusted model compared to patients in a euthymic state, patients in a depressive state had a lower AEE (kJ/kg/day) between 12-6 pm (adjusted model: $B = -16.01$, 95% CI: -27.35; -4.68, $p = 0.006$). Finally, in both the unadjusted and the adjusted model compared to patients in manic or mixed state, patients in a depressive state had a lower ACC (m/s^2) between 6-12 am (adjusted model: $B = -0.081$, 95% CI: -0.16; 0, $p = 0.051$) and a lower AEE (kJ/kg/day) between 6-12 am (adjusted model: $B = -12.87$, 95% CI: -25.91; 0.002, $p = 0.050$).

3.4 Psychomotor activity and the severity of depressive and manic symptoms

To investigate correlations between psychomotor activity and the severity of depressive and manic symptoms we considered both unadjusted models and models adjusted for age, sex and BMI on associations between measures of psychomotor activity estimated as SHR; ACC; and AEE and the severity of depressive and manic symptoms measured using HDRS-17 and YMRS, respectively. Analyses are presented in Table 5. As can be seen, in both the unadjusted and the adjusted model there was a significant correlation between ACC and YMRS (adjusted model: $B = 0.005$, 95% CI: 0.001; 0.08, $p = 0.015$). Also there was a significant correlation between AEE and YMRS in both the unadjusted and the adjusted models (adjusted model: $B = 0.98$, 95% CI: 0.053; 1.91, $p = 0.038$), meaning that an increase on YMRS of 10 points would result in an increase in AEE of 9.8 kJ/kg/day which is roughly equivalent to 45 min. of moderate intensity activity such as brisk walking. For an individual weighing 70 kg that would mean an increase of 686 kJ/day .

There were no significant correlations between SHR and HDRS-17 and YMRS, respectively; ACC and HDRS-17 and AEE and HDRS-17 in the analyses.

4 Discussion

In the present study we investigated differences in psychomotor activity according to affective states using repeated measurements in outpatients with bipolar disorder. We found higher levels of AEE per day during a manic or mixed state compared to a euthymic state. Furthermore, we found higher levels of ACC and AEE per day during a manic or mixed state compared to a depressive state.

Analyses on correlations between psychomotor activity and levels of depressive and manic symptoms showed that there was a significant positive correlation between the severity of manic symptoms measured using YMRS and ACC and AEE, respectively.

In further analyses on six hours intervals we found that in the period between 12-6 pm ACC and AEE were higher during a manic or mixed state compared to during a euthymic state; in the period between 6-12 am ACC and AEE were higher during a manic state compared to a depressive state; and in the period between 12-6 pm AEE was lower in a depressive state compared to a euthymic state.

In the present study we found no differences between a depressive state compared to a euthymic state in the level of AEE per day and ACC per day. Also no correlations between the severity of depressive symptoms measured using HDRS and ACC and AEE, respectively were found.

This is the first study with repeated measurements investigating differences in the level of psychomotor activity during everyday life between affective states using a small combined heart rate and movement sensor, a monitoring method that allows for quantification of the amount of energy spent on movement at different time intervals during 24 hours and during everyday life settings. During manic states patients in the present study had higher levels of movement and activity energy expenditure compared to patients in depressive and euthymic states. For example a patient weighing 70 kg would spend 1120 kJ/day more on movement during a manic state than during a depressive and a euthymic state. Our study shows that it is possible to measure the level of psychomotor activity using a combined heart rate and movement monitor in an objective way reflecting changes in affective states in patients with bipolar disorder.

These findings confirm that during mania an increased psychomotor activity is a cardinal feature, and that mania is a highly stressful and energy consuming affective state. Further, this study shows that, as opposed to only using an accelerometer, using a combined heart rate and movement sensor allows for discrimination between a manic state and a euthymic state, provides information on the severity of illness activity during mania and a diurnal variation during depression compared to euthymia. Thus, it is the estimation of differences in AEE between affective states that provides information allowing for the discrimination of states rather the exact number kJ spent on movement/day per se.

Studies on rhythm disruptions in bipolar disorder have suggested that patients, compared to healthy control individuals, have a variable circadian activity and also have an evening preference for daily activities (Jones et al., 2005; Mansour et al., 2005; Ahn et al., 2008; Wood et al., 2009). Notably, these studies compared patients with bipolar disorder in a euthymic state to healthy control individuals and did not investigate differences in the level of rhythm disruptions in daily activities across affective states. In contrast to these studies, as can be seen from our analyses in the present study there were diurnal alterations in the level of psychomotor activity between affective states (both during a manic state and during a depressive state) and euthymia in the period between 12-6 pm.

Although the precise mechanism for alterations in these diurnal levels during different affective states are uncertain, these findings may provide indirect evidence supporting the hypothesis that circadian abnormalities may have a pathogenic role for bipolar disorder (Mitterauer, 2000; Manji et al., 2001).

Furthermore, as illustrated the severity of manic symptoms was reflected by the level of both ACC and AEE, and thus measuring the level of psychomotor activity using a combined heart rate and movement monitor could be an objective method to assess the severity of symptoms and serve as a supplementary tool to the subjective clinical assessments as well as clinical ratings of mania.

Findings from earlier studies by our group showed that patients with bipolar disorder during a remitted or mild/moderate depressive state had lower SHR, ACC and AEE compared to healthy individuals (Faurholt-Jepsen et al., 2012). Whether psychomotor retardation is a core feature of bipolar depression has been discussed, and findings from our prior and the present study as well as other studies (Goodwin, and Jamison, 1996; Parker et al., 2000; Mitchell et al., 2001) support the findings that alterations in the level of psychomotor activity is a signature symptom in bipolar disorder during affective states.

The present study investigated the level of psychomotor activity using repeated measurement on each patient during different affective states. In contrast to cross sectional designs, as used in most of the literature on psychomotor activity in patients with bipolar disorder, follow-up studies with repeated measurements allow for estimation of the influence of intra-individual alterations in the level of psychomotor activity according to the affective state. Furthermore, the level of psychomotor activity was monitored using a small heart rate and movement sensor mounted on the thorax in outpatients over several days during their everyday life. Due to the size and place of mounting of the sensor (weighs 8 grams) it should not impede any physical activity (Wickström and Bendix, 2000), and due to the location of the sensor on the thorax, the level of psychomotor activity monitored reflects “whole body” movement as opposed to using a wrist worn accelerometer typically used in other studies. Furthermore, the combined monitoring of both acceleration and heart rate allows for estimating the amount of energy spent on movement per day and hour and as opposed to using doubly labeled water (Speakman, 1998) the method allows for quantification of subcomponents such as hourly variations.

Other studies investigating the level of psychomotor activity in patients with bipolar disorder using accelerometers during different affective states have mostly monitored the patients during hospitalization, and data thus does not reflect the level of activity during everyday life (Kupfer et al., 1974; Foster and Kupfer, 1975; Kuhs and Reschke, 1992; Minassian et al., 2010; Krane-Gartiser et al., 2014). In contrast, the present study monitored the level of psychomotor activity during everyday life and not during hospitalization which is likely to influence the level of movement.

Furthermore, previous studies investigating the level of psychomotor activity at different affective states presented raw unadjusted analyses not considering adjusting the analyses for possible confounders such as age, sex and BMI (Foster and Kupfer, 1975, 1975; Kuhs and Reschke, 1992; Jones et al., 2005; Krane-Gartiser et al., 2014) which could influence the results of the statistical analyses. In one study, the analyses were adjusted for years of education and smoking status as possible confounders (Minassian et al., 2010), but not for BMI which is likely to influence the level of movement. Thus, it is difficult to conclude whether the association between the levels of psychomotor activity was due to illness activity or simply due to differences in other possible confounding factors, such as BMI and age, affecting the level of activity.

It has never been investigated whether psychomotor activity differs during a depressive state or during a hypomanic state in patients with bipolar disorder type I versus patients with bipolar disorder type II. In the present study we included patients with both bipolar disorder

type I (43.5%) and II, and exploratory analyses (data not shown) did not find any differences in diurnal variations of psychomotor activity during different affective states between bipolar disorder type I and II. However, the aim of the present study was not to investigate differences in psychomotor activity in bipolar disorder type I and II. Whether there is a difference in diurnal variation during different affective states between these two groups is unknown and would be of interest in future studies.

4.1 Limitations

A number of limitations to the present study should be mentioned. Firstly, the patients' affective states were defined according to clinical ICD-10 diagnoses of bipolar disorder current episode manic, mixed or depression combined with the total score of depressive and manic symptoms ≥ 13 according to HDRS-17 and YMRS, respectively. We chose a cut-off on the HDRS-17 and YMRS of 13, respectively to achieve a high validity of a current affective depressive or manic/mixed state. Consequently, euthymia was defined as a HDRS-17 and YMRS < 13 and in this way including states with partial remission also. In two cases the manic states also included depressive symptoms with a HDRS ≥ 13 , i.e. a mixed state. Conversely, during depressive episodes the severity of manic symptoms was low.

Secondly, the present study included a rather small sample of patients. However, this was a follow-up study with repeated measurements of the level of psychomotor activity in different affective states on each individual increases the statistical power, and allows for estimating intra-individual variation in psychomotor activity according to the affective state and level of symptoms. Thirdly, due to the small sample of this study our non-significant finding could be due to type II errors, and future studies should include more patients. As opposed to previous studies by the authors (Faurholt-Jepsen et al., 2015) in the present we did not find a significant correlation between SHR and the severity of depressive and manic symptoms, and this could be due to a type II error.

Fourthly, patients were followed during their course of treatment at a specialized mood disorder clinic and thus received different types, doses and combinations of psychopharmacological treatment. Due to the number of different possible treatment combinations and the given size of the study we did not adjust the statistical analyses for different categories and doses of psychopharmacological treatment. Thus, it cannot be excluded that the differences in objectively measured psychomotor activity between affective states and a euthymic state were not attributed to the affective states per se, but rather the effects of different dosages and combinations in psychopharmacological treatment. On the other hand, none of the patients participating in the study reported or were observed with any psychopharmacological treatment related movement side effect during the study.

The present study recruited patients from a specialized outpatient clinic, and it may be that the included patients represented a group of patients that was more motivated to participate in scientific studies than if the study was conducted in other settings. The patients were seen often (fourth nightly) by the researcher and only few patients took off the sensor during the

monitoring of psychomotor activity in a manic phase. In this case the monitoring was repeated if the patients still presented with manic symptoms.

Also, the individual heart rate and movement measurements were calibrated using group calibration and not individual calibration methods. Thus, a potential difference between groups could be masked due to differences in physical fitness. However, the study had a follow-up period of 12 weeks, and therefore changes in physical fitness are not believed to have happened to a large extent.

Finally, in contrast to earlier studies (Wood et al., 2009) the present study did not investigate the level of psychomotor activity in healthy control individuals and therefore was not able to investigate diurnal differences between patients and healthy control individuals.

4.2 Perspectives

The results from this study emphasizes that psychomotor activity is a core symptom in bipolar disorder that differs significantly between affective states. Thus, measuring the level of psychomotor activity using a combined heart rate and movement monitor may be used as a supplementary objective way to clinical assessment of alterations in affective states in patient with bipolar disorder.

Studies monitoring the level of psychomotor activity using combined heart rate and movement sensing during everyday life over several days and across changes in affective states on a larger sample of patients with bipolar disorder and accounting for possible confounders in the analyses are needed.

4.3 Conclusion

This is the first follow-up study investigating the level of psychomotor activity using a combined heart rate and movement monitor during affective state using statistical analyses allowing for both intra-individual and inter-individual variations over time. Findings from this study support that psychomotor activity is a core symptom in bipolar disorder that is altered during affective states and presents with diurnal variations. Thus, monitoring psychomotor activity may serve as a potential objective tool capable of monitoring the course of illness.

Acknowledgement

The authors would like to thank the patients for participating in the study. The EU 7th Frame Program funded the study together with the Mental Health Services, Copenhagen, Denmark, Trygfonden, the Gert Einar Joergensens foundation, and the A.P. Moeller and the Hustru Chastine Mc-Kinney Moellers foundation for general purposes. The funders had no role in the trial design, data collection, analyses and preparation of the manuscript.

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A

B

Figure 1.

Figure 1A and 1B: Box plot of acceleration (ACC) (m/s²) and Activity Energy Expenditure (AEE) (kJ/kg/day) (y axis) in different affective states (x axis) in patients with bipolar disorder based on predicted values from linear mixed regression models adjusted for age, sex and BMI. P-values indicating group differences. Error bars refer to standard deviation (SD).

Table 1Background characteristics of patients with bipolar disorder, n=19^I.

Age (years)	28.1 [20.8; 31.3]
Female sex, % (n)	57.9 (11)
Height (cm)	177.3 (10.6)
Weight (kg)	80.6 (18.1)
Body Mass Index (kg/m ²)	25.6 (5.3)
Number of depressive episodes	4 [2.5; 15]
Number of manic episodes	4 [3; 9]
Bipolar disorder type I, % (n)	43.5 (8)
Age at onset (years)	19.8 (6.8)
Illness duration (years)	9.2 (4.9)
Years of education after primary school	4.2 (2.3)
Psychopharmacological treatment	
Anticonvulsants, % (n)	69.6 (13)
Lithium, % (n)	21.7 (5)
Antipsychotics, % (n)	56.5 (11)
Antidepressants, % (n)	13.0 (2)

^I Data are mean (SD), median [IQR] or proportions (% , n) unless otherwise stated.

Table 2

Levels of affective symptoms and measures of psychomotor activity during different affective states in patients with bipolar disorder, N=32¹

	Depressive state, n= 12 ⁷	Manic or mixed state, n= 8 ⁸	Euthymic state, n= 12 ⁹
HDRS-17 ²	18.25 (3.54)	10.17 (3.54)	9.22 (3.23)
YMRS ³	3.38 (3.70)	16.10 (2.61)	3.89 (3.48)
SHR ⁴	58.45 (9.85)	60.63 (9.68)	56.18 (7.49)
ACC ⁵	0.10 (0.05)	0.17 (0.10)	0.12 (0.07)
AEE ⁶	41.76 (18.77)	59.42 (26.10)	42.40 (16.11)

¹ N represents the total number of measurements. Data are mean (SD), raw and unadjusted values not accounting for repeated measurements per patient.

² Hamilton Depression Rating Scale 17-item (total score)

³ Young Mania Rating Scale (total score)

⁴ Sleeping heart rate (beats/ minute)

⁵ Acceleration (m/s²)

⁶ Activity Energy Expenditure (kJ/day/kg)

⁷ Defined as HDRS-17 $\geq$ 13 and YMRS $\geq$ 13

⁸ Defined as YMRS $\geq$ 13

⁹ Defined as HDRS-17 < 13 and YMRS < 13

Table 3

Linear mixed regression models of psychomotor activity measures per day in patients with bipolar disorder according to the affective state, N=32

	Model 1 (unadjusted analyses)			Model 2 ¹		
	B ²	95% CI ³	P	B ²	95% CI ³	P
A: SHR⁴						
Depressive state/Euthymic state	0.43	-4.93; 5.81	0.87	0.72	-4.94; 6.38	0.80
Manic or mixed state/Euthymic state	4.08	-1.90; 10.05	0.18	4.12	-2.11; 10.34	0.19
Depressive state/manic or mixed state	-3.64	-2.16; 9.44	0.22	-3.39	-9.42; 2.63	0.26
B: ACC⁵						
Depressive state/Euthymic state	-0.009	-0.062; 0.043	0.73	-0.016	-0.072; 0.40	0.58
Manic or mixed state/Euthymic state	0.052	-0.004; 0.11	0.070	0.048	-0.010; 0.11	0.10
Depressive state/manic or mixed state	-0.061	-0.062; -0.004	0.030	-0.064	-0.005; -0.12	0.030
C: AEE⁶						
Depressive state/Euthymic state	0.68	-13.52; 14.52	0.93	-1.78	-15.22; 11.66	0.79
Manic or mixed state/Euthymic state	16.85	1.76; 31.94	0.029	14.79	0.90; 28.68	0.037
Depressive state/manic or mixed state	-16.17	-31.47; -0.89	0.038	-16.57	-30.80; -2.35	0.020

¹ Analyses adjusted for age, sex and body mass index (BMI)

² Parameter estimates

³ 95% confidence intervals

⁴ Sleeping heart rate (beats/ minute)

⁵ Acceleration (m/s²)

⁶ Activity Energy Expenditure (kJ/day/kg)

Table 4

Linear mixed regression models on six hours intervals per day of psychomotor activity measures in patients with bipolar disorder according to the affective state, N=32

	Model 1 (unadjusted analyses)			Model 2 ^I		
	B ²	95% CI ³	P	B ²	95% CI ³	P
A: ACC⁴ 0-6 am						
Depressive state/ Euthymic state	0.028	-0.025; 0.081	0.30	0.030	-0.025; 0.084	0.29
Manic or mixed state/ Euthymic state	0.031	-0.028; 0.090	0.30	0.032	-0.029; 0.093	0.31
Depressive state/ manic or mixed state	-0.003	-0.057; 0.063	0.91	-0.002	-0.063; 0.059	0.94
A1: ACC⁴ 6-12 am						
Depressive state/ Euthymic state	-0.035	-0.11; 0.035	0.33	-0.040	-0.11; 0.034	0.30
Manic or mixed state/ Euthymic state	0.045	-0.033; 0.12	0.26	0.041	-0.041; 0.12	0.32
Depressive state/ manic or mixed state	-0.081	-0.16; 0	0.052	-0.081	-0.16; 0	0.051
A2: ACC⁴ 12-6 pm						
Depressive state/ Euthymic state	-0.045	-0.11; 0.024	0.20	-0.047	-0.12; 0.025	0.20
Manic or mixed state/ Euthymic state	0.080	0.003; 0.16	0.040	0.082	0.002; 0.16	0.043
Depressive state/ manic or mixed state	0.034	-0.045; 0.11	0.39	0.035	-0.046; 0.12	0.40
A3: ACC⁴ 6-12 pm						
Depressive state/ Euthymic state	0.027	-0.042; 0.097	0.44	0.026	-0.047; 0.10	0.48
Manic or mixed state/ Euthymic state	0.060	-0.018; 0.14	0.13	0.059	-0.022; 0.14	0.15
Depressive state/ manic or mixed state	-0.033	-0.11; 0.048	0.43	-0.33	-0.12; 0.49	0.43
B: AEE⁵ 0-6 am						
Depressive state/ Euthymic state	5.46	-2.89; 13.81	0.20	5.38	-3.22; 13.98	0.22
Manic or mixed state/ Euthymic state	-0.33	-9.72; 9.07	0.99	-0.071	-9.69; 9.55	0.99
Depressive state/ manic or mixed state	5.78	-3.70; 15.27	0.23	5.45	-4.14; 15.05	0.27
B1: AEE⁵ 6-12 am						
Depressive state/ Euthymic state	-1.88	-13.06; 9.29	0.75	-1.43	-13.06; 10.19	0.81
Manic or mixed state/ Euthymic state	10.94	-1.46; 23.35	0.084	11.44	-1.40; 24.28	0.080
Depressive state/ manic or mixed state	-12.83	-25.68; 0.031	0.051	-12.87	-25.91; 0.0021	0.050
B2: AEE⁵ 12-6 pm						
Depressive state/ Euthymic state	-15.30	-26.21; -4.30	0.006	-16.01	-27.35; -4.68	0.006
Manic or mixed state/ Euthymic state	15.28	3.22; 27.34	0.013	15.83	3.34; 28.31	0.013
Depressive state/ manic or mixed state	0.020	-12.49; 12.45	0.99	-0.19	-12.83; 12.45	0.98
B3: AEE⁵ 6-12 pm						
Depressive state/ Euthymic state	4.14	-6.86; 15.14	0.46	3.50	-7.94; 14.94	0.55
Manic or mixed state/ Euthymic state	10.72	-1.60; 23.04	0.088	10.20	-2.55; 22.95	0.11

	Model 1 (unadjusted analyses)			Model 2 ¹		
	B ²	95% CI ³	P	B ²	95% CI ³	P
Depressive state/ manic or mixed state	-6.58	-19.32; 6.17	0.31	-6.70	-19.61; 6.22	0.35

¹ Analyses adjusted for age, sex and body mass index

² Parameter estimates

³ 95% confidence intervals

⁴ Acceleration (m/s²)

⁵ Activity Energy Expenditure (kJ/day/kg)

Table 5

Linear mixed regression models on measures of psychomotor activity and clinically rated depressive and manic symptoms in patients with bipolar disorder, N=19

	Unadjusted model			Adjusted model ¹		
	B ²	95% CI ³	P	B ²	95% CI ³	P
A: SHR⁴						
HDRS ⁵	-0.18	-0.69; 0.34	0.50	-0.23	-0.77; 0.30	0.39
YMRS ⁶	0.31	-0.062; 0.69	0.10	0.30	-0.089; 0.69	0.13
B: ACC⁷						
HDRS	-0.003	-0.008; 0.002	0.23	-0.004	-0.009; 0.001	0.12
YMRS	0.005	0.001; 0.008	0.006	0.005	0.001; 0.008	0.015
C: AEE⁸						
HDRS	0.31	-0.062; 0.69	0.10	0.30	-0.089; 0.69	0.13
YMRS	1.08	0.071; 2.08	0.036	0.98	0.053; 1.91	0.038

¹ Adjusted for age, sex and BMI

² Parameter estimates

³ 95% confidence intervals

⁴ Sleeping heart rate (beats/ minute)

⁵ Hamilton Depression Rating Scale 17-item (total score)

⁶ Young Mania Rating Scale score (total score)

⁷ Acceleration (m/s²)

⁸ Activity Energy Expenditure (kJ/day/kg)