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Authors

Gershon, Anda
Ram, Nilam
Johnson, Sheri L
et al.

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Daily Actigraphy Profiles Distinguish Depressive and Interepisode States in Bipolar Disorder

Anda Gershon, Ph.D.[1], **Nilam Ram, Ph.D.**[2], **Sheri L. Johnson, Ph.D.**[3], **Allison G. Harvey, Ph.D.**[3], and **Jamie M. Zeitzer, Ph.D.**[1,4]

[1]Department of Psychiatry and Behavioral Sciences, Stanford University School of Medicine

[2]Department of Human Development and Family Studies, The Pennsylvania State University

[3]Department of Psychology, University of California, Berkeley

[4]Mental Illness Research Education and Clinical Center, VA Palo Alto Health Care System

Abstract

Disruptions in activity are core features of mood states in bipolar disorder (BD). This study sought to identify activity patterns that discriminate between mood states in BD. Locomotor activity was collected using actigraphy for six weeks in participants with inter-episode BD type I (n=37) or participants with no lifetime mood disorders (n=39). The 24-hour activity pattern of each participant-day was characterized and within-person differences in activity patterns were examined across mood states. Results show that among participants with BD, depressive days are distinguished from other mood states by an overall lower activity level, and a pattern of later activity onset, a midday elevation of activity, and low evening activity. No distinct within-person activity patterns were found for hypomanic/manic days. Since activity can be monitored non-invasively for extended time periods, activity pattern identification may be leveraged to detect mood states in BD, thereby providing more immediate delivery of care.

Keywords

Bipolar disorder; depression; activity; actigraphy; circadian rhythms

Introduction

Bipolar disorder (BD) is a severe and recurrent psychiatric disorder that is associated with significant impairments in functioning (Gitlin, Swendsen, Heller, & Hammen, 1995; Judd et al., 2002). Despite receiving treatment, many persons with BD spend a substantial proportion of their time unwell, with depression being the most common mood state (Kupka et al., 2007).

Disruptions in physical activity are diagnostic features of both mania and depression. The fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) includes

Correspondence: Anda Gershon, Ph.D. Stanford University School of Medicine, Department of Psychiatry and Behavioral Sciences, 401 Quarry Road, Stanford, CA 94304, United States. Phone: (650) 862-6172. gershon@stanford.edu.

increases in activity and psychomotor agitation as part of the diagnostic criteria for mania and hypomania and, in parallel, the criteria for depression include diminished activity and psychomotor retardation (American Psychiatric Association, 2013). Consistent with the central placement of these symptoms in the DSM, research has suggested that indices of physical activity may be highly relevant for understanding the course of disorder (Gonzalez, Tamminga, Tohen, & Suppes, 2014; Klein, Lavie, Meiraz, Sadeh, & Lenox, 1992; Salvatore et al., 2008).

While studies using actigraphy (non-invasive, wrist-worn accelerometry) have shown that increases in daytime activity are predictive of mania recurrence (Klein et al., 1992), actigraphy studies also suggest that mania is characterized by a more nuanced profile of disruption than a simple increase in physical activity. As compared to persons with BD who are experiencing an inter-episode state as well as to healthy controls, persons with BD who are experiencing manic symptoms show a diminished rhythmicity of their diurnal rhythms, with less difference in activity levels during the day versus night (Gonzalez et al., 2014; Salvatore et al., 2008; Wehr et al., 1985).

In contrast to this manic profile of diminished rhythmicity, studies using actigraphy indicate that during bipolar depression, activity is both diminished and more variable as compared to inter-episode states (Janney et al., 2014; Krane-Gartiser, Henriksen, Morken, Vaaler, & Fasmer, 2014), although see (Gonzalez et al., 2014) for a non-replication. Some studies, using telemetry and nurses' ratings of patients' behavior, suggest that activity levels are lower in bipolar depression than in unipolar depression (Beigel & Murphy, 1971; Kupfer, Weiss, Foster, Detre, & McPartland, 1974). In addition, greater variability in activity has been documented during depressive states relative to controls (Krane-Gartiser et al., 2014).

The inter-episode state of BD has also been characterized by diminished and more variable activity levels relative to the activity levels of healthy controls (Harvey, Schmidt, Scarna, Semler, & Goodwin, 2005; Jones, Hare, & Evershed, 2005; McKenna, Drummond, & Eyler, 2014). With regard to actigraphic measures of sleep, studies have noted more variability in sleep and wake duration during the inter-episode state of BD relative to healthy control (Millar, Espie, & Scott, 2004). In addition, a recent meta-analysis of actigraphic studies found that relative to controls, the inter-episode period of BD is characterized by significantly longer sleep latency, longer sleep duration, longer wake after sleep onset, and lower sleep efficiency (Geoffroy et al., 2015).

A closely related literature focuses on the timing of activity, which in some cases is a reliable index of circadian rhythms (Ancoli-Israel et al., 2003). Unipolar depression has been consistently related to a delay (latening) of circadian timing (Lewy, 2009), and there is some evidence suggesting that a delay in the sleep-wake cycle, as indexed by actigraphy-measured wake times, may be more prevalent in bipolar depression than in unipolar depression (Robillard et al., 2013). Congruently, among those with BD, self-reported "eveningness" has been found to correlate with depressive symptoms (Wood et al., 2009). The converse has been observed during manic episodes; one study of physical activity suggested an *earlier* timing of the circadian sleep-wake cycle (phase advance) among participants with current

manic episodes, a feature that did not change significantly during the early phases of recovery (Salvatore et al., 2008).

To summarize, actigraphy research highlights low diurnal rhythmicity (*e.g.,* reduced difference between day and night activity levels) during manic states, and diminished, more varied, and delayed patterns of activity during depressive states of BD. There is some evidence that diminished and more varied activity levels also occur during inter-episode states of BD. Research thus highlights the importance of considering a set of activity parameters in BD that includes the amplitude, variability, and the 24-hour patterning of activity. To date, few studies have jointly considered these activity parameters within a diagnosed BD sample. This is a major goal of the present study. To achieve this goal, we used functional data analysis to identify a number of statistically distinct 24-hour patterns that could be derived from actigraphy data. Based on prior literature, we expected that manic states, as compared to inter-episode states in BD, would be characterized by reduced difference between day and night activity levels (Gonzalez et al., 2014; Salvatore et al., 2008; Wehr et al., 1985). Diminished and more varied levels of activity have been found to characterize depressive states, but similar features have been noted during inter-episode states (Janney et al., 2014; Krane-Gartiser et al., 2014; Robillard et al., 2013). Depressive states have been more uniquely tied to delay in the timing of daily activity, and so we hypothesized that this pattern would differentiate depressive states from inter-episode states.

An important limitation to previous modeling efforts is that they used algorithms that assume the pattern of activity has a specific shape, most typically a modification of a sine wave. Because an abnormal shape of the 24-hour activity pattern has been reported to occur in those with BD (Salvatore et al., 2008), it is critical not to presuppose a specific pattern. As such, the use of a shape-naive technique, such as functional data analysis, is important as an analytic approach (J. O Ramsay & Silverman, 2005; Zeitzer et al., 2013).

Another important limitation to prior research is that activity parameters have rarely been studied for a sufficient duration to examine these as potential indicators of mood states in BD. In one such study, researchers examined persons with mania as they achieved an inter-episode state. During the inter-episode state, previously noted deficits in the day-night rhythmicity of activity normalized (Salvatore et al., 2008). Less research is available concerning activity pattern differences between depression and inter-episode states. Accordingly, examining actigraphy-derived parameters across such states is a second major goal of this study.

Methods

Participants and Procedure

Participants, ages 18–64 years, were recruited from the San Francisco area through online advertisements and flyers posted in the community. Thirty-seven were diagnosed with BD type I or II and 39 controls had no history of mood disorders, psychotic disorders, anxiety disorders, eating disorders, or substance related disorders. After complete description of the study to the participants, written informed consent was obtained. Participants completed a demographics and medication questionnaire, and diagnostic and symptom interviews.

Eligible participants were then given an actigraph, a watch-like activity-monitoring device, to be worn continuously on the non-dominant wrist. After one month, participants returned for a second session. During this session, data were retrieved from the actigraph, and participants completed diagnostic and symptom interviews. Participants left the session wearing the actigraph on their wrist and were instructed to wear it for an additional month. At the final session, one month later, participants returned the actigraph, completed diagnostic and symptom interviews, and received their final compensation.

Study exclusion criteria included the presence of serious medical or neurological conditions known to influence daily activity patterns (*e.g.*, Alzheimer's disease, history of head trauma), alcohol or substance abuse or dependence in the past six months, shift work, an unstable living arrangement, or a primary sleep disorder, as assessed with the Duke Structured Interview for Sleep Disorders (DSISD (Edinger et al., 2004)). At study entry, participants in the bipolar group were selected to be inter-episode, defined as the absence of a depressive or hypomanic/manic episode in the preceding month, as assessed using the Structured Clinical Interview for DSM-IV (SCID (First, Spitzer, Gibbon, & Williams, 2007)), and no more than mild depressive or manic symptom severity, as assessed using the clinician-rated Inventory of Depressive Symptomatology (IDS-C; score ≤ 23 (Rush, Gullion, Basco, Jarrett, & Trivedi, 1996)) and the Young Mania Rating Scale (YMRS; score ≤ 11 (Young, Biggs, Ziegler, & Meyer, 1978)). Participants in the control group were selected to exhibit no more than mild symptom severity on the IDS-C and the YMRS. The University of California, Berkeley Institutional Review Board approved all study procedures.

Measures

Psychiatric Disorders—Lifetime and current psychological disorders were assessed at the initial lab session using the SCID, administered by clinical psychology doctoral students or a post-doctoral fellow. At each subsequent monthly lab session, the mood disorder module of the SCID was re-administered to assess for any potential mood episodes occurring in the preceding month. Diagnostic rater reliability for a randomly chosen subset of participants ($n = 17$) in the current study was excellent ($k = 1.00$).

Sleep Disorders—Sleep disorders were assessed at the initial lab session using in-person interviews (Edinger et al., 2004), administered by clinical psychology doctoral students or a post-doctoral fellow. The DSISD assesses for sleep disorders based on Research Diagnostic Criteria (Edinger et al., 2004) and the nosologies of the DSM–IV–TR (American Psychiatric Association, 2000). The DSISD has been shown to have good reliability and validity.

Symptom Severity—Symptom severity was measured using the IDS-C and the YMRS, administered in-person by clinical psychology doctoral students or a postdoctoral fellow at the initial lab session and at each of the two subsequent monthly sessions. A score of 23 or lower on the IDS-C indicates mild symptoms and a score of 24 or higher indicates moderate to severe symptoms (Rush et al., 1996). A score of 11 or lower on the YMRS indicates mild symptoms, a score of 12 or higher indicates moderate to severe symptoms (Suppes et al., 2005). In this sample, intra-class correlations between the original interviewer and an

independent rater for a randomly chosen subset of participants ($n = 42$) were strong ($r = 0.90$ for IDS-C and $r = 0.84$ for YMRS).

Mood State Status—Depressive, manic/hypomanic, mixed, or inter-episode states of BD participants were determined based on information obtained during the monthly diagnostic and symptom severity interviews. Specifically, a depressive state was identified if the participant either met DSM diagnostic criteria for a major depressive episode in the past month according to the SCID, and/or received a score of 24 or higher on the IDS-C. A manic/hypomanic state was identified if the participant either met DSM diagnostic criteria for a manic or hypomanic episode in the past month according to the SCID, and/or scored 12 or higher on the YMRS. A mixed episode was identified if the participant met DSM diagnostic criteria for a mixed mood episode in the past month according to the SCID, and/or simultaneously scored 24 or higher on the IDS-C and scored 12 or higher on the YMRS. Finally, an inter-episode state was identified if the participant neither met DSM diagnostic criteria for any mood episode in the past month (depressive, manic/hypomanic, nor mixed) and scored 23 or below on the IDS-C and 11 or below on the YMRS. Based on these definitions, 12 participants with BD were coded as having experienced a conversion from an inter-episode state (all participants with BD were selected to be inter-episode at study entry) to another mood state during the study period. More specifically, seven participants experienced a conversion to a depressive state; all seven met DSM criteria for a depressive episode. Four participants experienced a conversion to a hypomanic/manic state: two met DSM criteria for a hypomanic episode, one met DSM criteria for a hypomanic episode, and following a two-month pause in participation and a 3-week inter-episode state, met DSM criteria for a full manic episode, and one received a moderate severity score on the YMRS. One participant was coded as having experienced a mixed state; this participant simultaneously received moderate to severe scores on both the IDS-C and the YMRS for 27 days. Given the small amount of data and unclear status, mixed-episode days were grouped with inter-episode days as a conservative approach (increasing the baseline variance slightly; parallel analyses with these days removed produced an identical pattern of results).

Medication Use—Participants provided the name, dosage, and frequency of use for all current medications. Lithium and valproate levels were scaled by dividing reported dose by maximum recommended dose (mg/day). Doses for antidepressants, atypical neuroleptics, and benzodiazepines were converted to imipramine, risperidone, and diazepam dose equivalencies (mg/day), respectively, using standardized conversion tables (Bauer et al., 1997). For each medication class, dose scores were coded as 0 if an individual was not taking the medication.

Activity Patterns—Movement data were collected by Actiwatches (AW64, Respironics Inc., Bend OR) worn continuously on the wrist of the non-dominant hand (Sadeh, Hauri, Kripke, & Lavie, 1995). To improve assessment of sleep and wake times, participants recorded bedtimes, wake times, and naps using a daily diary (Morin & Espie, 2003).

Embedded within each actiwatch is a piezoelectric sensor to detect movement acceleration, a processor to convert this information to a unitless activity count over a specified time interval (one minute intervals were used for this study), and memory to store the

information. Minute-to-minute movement data were downloaded and preprocessed using Actiware software (v.5.5, Respironics, Inc.). Daily activity graphs were examined for completeness. Periods of no movement for 10 or more minutes during non-sleep hours (as determined from daily sleep diaries) were flagged as times when the device had been removed (*n.b.,* even during sleep, there is typically occasional movement). Then, data were parsed into 24-hour (daily) epochs that ran from 00:00 (midnight) to 23:59. Periods of missing data less than 60 minutes in duration were imputed using linear interpolation. Periods of missing data greater than 60 minutes in duration were deleted. A total of 167 days (90 in the bipolar group, 77 in the control group) contained segments of less than 60 missing minutes that were imputed, equivalent to < 5% of the total days available for analysis. A total of 547 days (308 in the bipolar group, 239 in the control group) contained segments of more than 60 missing minutes that were deleted, equivalent to 13% of the total days available for analysis. After processing, data provided minute-to-minute activity frequency counts for a total of 3,551 days.

Activity Patterns Components Analysis—Minute-to-minute data were analyzed using functional principal components analysis (*fPCA*), a variant of standard PCA that extracts orthogonal components from semi-continuous data (J. O Ramsay & Silverman, 2005). In brief, the daily epochs of minute-to-minute activity data are first re-represented using a set of nine Fourier-based functions that effectively capture the major trends in daily activity patterns with reduced noise (Ding et al., 2011; Zeitzer et al., 2013). The resulting continuous functions are then summarized for interpretation as a smaller set of (functional) principal components that are used in subsequent analysis. The principal components derived from this analysis correspond to eigenvectors; the variance explained by these components corresponds to the eigenvalues. Eigenvectors provide for interpretation of the activity patterns captured by each component, and daily component scores indicate the extent to which each component pattern is reflected in a specific participant's activity on a specific day. In sum, the analysis, run using the fda library in R (J. O. Ramsay, Hooker, & Graves, 2009), effectively and efficiently summarizes the 1440 minutes of each day's activity as a small set of daily $fPCA_{it}$ scores.

Between-group and Mood State Differences in Activity Patterns—Our main interest was to determine if and how daily activity patterns, as quantified by individuals' daily *fPCA* scores, differed between groups (BD, control) and mood states (depressive, hypomanic/manic, inter-episode). To accommodate the nested nature of the data (days nested within persons), analyses were conducted in a multilevel modeling framework (Snijders & Bosker, 1999). Specifically, the daily measures of activity and episode were modeled as:

$$fPCA\#_{it}=\gamma_{00}+\gamma_{01}*group_i+\gamma_{10}*depression\_day_{it}+\gamma_{20}*mania\_day_{it}+u_{0i}+e_{it} \quad \text{(eq. 1)}$$

where the *fPCA* scores obtained above for person *i* on day *t*, $fPCA\#_{it}$, are modeled separately as a function of between-person and within-person differences. Specifically, γ_{00}, indicates the expected *fPCA* activity score for a prototypical person in the BD group on a prototypical inter-episode day (the reference category); γ_{01} captures between-group

differences in inter-episode day activity (BD group vs. control group); γ_{10} and γ_{20} indicate extent of within-person differences between inter-episode days and mood-episode days (depressive- or hypomanic/manic-, respectively); and u_{0i} and e_{it} capture additional between-person and occasion-specific differences not otherwise explained. All models were fit using SAS 9.4 (proc mixed (Littell, Miliken, Stoup, & Wolfinger, 1996)) with restricted maximum likelihood estimation. Statistical significance was evaluated at $\alpha = 0.05$ with conservative degrees of freedom (of $N - 1 = 74$ or $N - 2 = 75$ for all fixed effects). Effect size was evaluated with respect to proportional reduction in unexplained variance from an informative baseline model (*pseudo-*R^2 (Snijders & Bosker, 1999)).

Results

Demographic and clinical characteristics of the sample are shown in Table 1. The 37 participants in the BD group each contributed, on average, 45.6 days (SD = 12.2, range = 24–72) of useable activity data. Of these 1,719 total days, 245 were mood state days, with 140 depressive days, and 105 hypomanic/manic days. The 39 participants in the control group each contributed, on average, 47.0 days (SD = 13.3, range = 10–67) of useable activity data. All of these 1,832 days were non-episode days.

Activity Patterns Components Analysis

As described above, fPCA was used to characterize daily activity patterns across all participants. The first four functional principal components were retained, which together accounted for 80.1% of the variance in the minute-to-minute movement data. Visual representations of the eigenvectors describing the shapes of these functions are shown in Figure 1. The shape of first component, *fPCA1,* or *Overall Amount of Activity* (35.3% of total variance) captures a general sleep-wake-sleep pattern typical of most days across all participants. The bold red and blue lines are interpreted in relation to the average daily pattern shown by the thin, gray line. Curves with high (bold red line) and low (bold blue line) component scores illustrate differences in amount of overall activity. The shape of the second component, *fPCA2, or Morningness vs. Eveningness* (20.6% of total variance), captures shifts in the timing of activity such that days with higher component scores (red line) have a *later* onset and offset of activity and days with lower component scores (blue line) have an *earlier* onset and offset of activity. The shape of the third component, *fPCA3, or Afternoon vs. Late Evening Activity* (14.0% of total variance) is more complex, such that days with higher component scores are characterized by an earlier activity onset, an early afternoon decrease in activity, and a late evening peak in activity. In complement, days with lower component scores are characterized by a later activity onset, a slightly elevated midday peak, and low levels of activity in the evening. The shape of the fourth component, *fPCA4, or Early Evening Rest vs. Activity* (10.2% of total variance) is also complex, such that higher component scores indicate peaks of activity at noon and in the late evening that frame a midday decrease in activity and lower component scores indicate a steady rise of activity that peaks in the evening and is followed by a relatively early activity offset. Any given day's activity pattern is a weighted sum of these four component functions, with each day having more or less of each pattern embedded in it. None of the medication variables were significantly related to the four activity parameters (r's < 0.27, p's > 0.10).

Between-group Differences in Activity Patterns

Results from the multilevel models are shown in Table 2. There was no evidence of systematic between-group differences (BD vs. control) in any of the fPCA scores. For example, although the expected level of *fPCA1* for the BD group on inter-episode days was $\gamma_{00} = -298.10$ ($p = 0.50$), with the control group differing by $\gamma_{01} = +462.16$ ($p = 0.45$), this difference was not significant in the context of between-person variance of $\sigma^2_{u0} = 6984460$. Across all four components, the extent of between-person heterogeneity, even within group, is very large in comparison to the size of systematic group differences ($p \geq 0.45$ for all γ_{01}).

Mood State Differences in Activity Patterns

Within-person analyses indicated that mood-episode days differed significantly from inter-episode days. Specifically, BD depressive-episode days were characterized by significantly lower *fPCA1* values relative to BD inter-episode days, $\gamma_{10} = -849.49$ ($p = 0.01$). Within the sample of individuals who experienced depressive episodes ($n = 7$), this difference accounted for [(8161856 − 8040344)/8161856] = 1.5% of day-to-day variance in *fPCA1* (i.e., small but statistically significant effect). Similarly, BD depressive-episode days were characterized by significantly lower *fPCA3* values relative to BD inter-episode days, $\gamma_{10} = -489.75$ ($p = 0.05$). Within the sample of individuals who experienced depressive episodes ($n = 7$), this difference accounted for [(5726424 − 5706668)/5726424] = 0.35% of day-to-day variance in *fPCA3* (i.e., small but statistically significant effect). Differences between inter-episode days and depressive-episode days were not apparent in *fPCA2* ($\gamma_{10} = -298.76$, $p = 0.25$) or *fPCA4* ($\gamma_{10} = -236.66$, $p = 0.26$). There was no evidence of within-person differences in activity patterns for any of *fPCA* parameters between inter-episode and hypomanic/manic-episode days ($p \geq 0.12$ for all γ_{20}).

Discussion

The present study examined how motor activity patterns measured using actigraphy over a six-week period could be used to differentiate mood states in BD. We found that depressive episode days are distinguished from inter-episode states by significantly lower overall activity levels (*fPCA1*), and by a later daily onset of activity, a slightly elevated midday peak, and less evening activity (*fPCA3*). Given that patients with BD spend most of their lives symptomatic, largely with depressive symptoms (Kupka et al., 2007), these findings highlight the potential for developing better methods for detecting, understanding, and treating bipolar depression via activity patterns.

Change in activity has long been proposed to be a more reliable marker of mood states in BD relative to subjective reports (Akiskal et al., 2001; Bauer et al., 1991). However, previous research has not followed participants with BD for enough time to observe cycles between depressive and inter-episode states. More specifically, although previous research suggested that patients with unipolar depression showed diminished activity relative to healthy controls (Burton et al., 2013) and that depressive symptoms in BD were correlated with diminished activity and with delayed timing (Krane-Gartiser et al., 2014; Wood et al., 2009), this previous research had not followed individuals over time to differentiate whether these were person-level characteristics, or were more specific to the shifts that occur with the

onset of depressive symptoms. Our findings clarify that this profile of activity appears to be a specific marker of depressive symptoms in BD. The findings also suggest that it is important to consider both activity levels and diurnal profiles, and extend the growing literature on the importance of circadian rhythms in bipolar depression (Robillard et al., 2013).

Our findings may have implications for understanding sleep disturbances in studies of BD. For example, a recent meta-analysis of studies with inter-episode BD samples found a trend-level association between lower levels of residual depression symptoms and longer sleep duration (Geoffroy et al., 2015). When considered in the context of the 24-hour activity patterning of depressive states in BD, as found in the current study, it may be the case that a relatively reduced and delayed 24-hour activity pattern is related to more sleep disturbance (shorter sleep duration) during depressive states.

If replicated, the results raise the possibility that patients with bipolar depression may benefit from treatments that include a focus on increasing physical activity levels overall and advancing the onset of activity to earlier in the day. Indeed, a recent literature review to examine the relationship between depression and activity suggests that daytime activity is significantly increased in unipolar depressed samples following treatment (Burton et al., 2013). The relatively low and delayed activity patterns found for depressive days may respond to interventions designed to increase the level of activity, such as behavioral activation (Martell, Addis, & Jacobson, 2001) and those designed to increase the regularity of activity, such as interpersonal and social rhythm therapy (Frank, Swartz, & Kupfer, 2000). Taken together, current findings provide novel insight into potential new ways to consider treatment targets in bipolar depression.

Although we identified activity level parameters that differentiated depressive and inter-episode days, none of the activity patterns identified in this study differentiated those with BD from the healthy controls when findings across mood states were considered. The absence of significant between-group differences may be due to the limited statistical power. Given that activity patterns were quite heterogeneous across the BD group until mood state was considered, it may also be that simple between-group study designs are not well-poised to understand the nature of activity disruptions in BD. Our findings suggest that designs that allow for a consideration of within-person fluctuations in mood state are particularly likely to be helpful.

Several limitations should be noted. First, manic episodes are relatively rare (Bopp et al., 2010). Accordingly, even with the six-week study period, power was limited to examine within-person changes in activity as markers of hypomanic/manic states. Future research would do well to recruit participants during manic states, as has been done in previous actigraphy research (Salvatore et al., 2008). Second, whereas activity was evaluated minute-by minute, symptoms were evaluated monthly. Fluctuations in mood state within the month may not have been recalled reliably. Past research shows that mood can change on a weekly basis (Judd et al., 2002). Given this, more frequent assessment of mood states would improve our ability to differentiate between mood states based on activity patterns. Third, we relied on a naturalistic assessment of activity. Recent research suggests that heightened

activity during mania may be more readily observed in reward-rich or novel environment (Johnson, Edge, Holmes, & Carver, 2012; Perry et al., 2010). Finally, most of our bipolar group participants and none of our control group participants were taking medications. Nevertheless, medication levels were not significantly related to any activity parameter within the bipolar group.

Despite these limitations, the current findings have promise for informing our understanding of the nature of the pathophysiology of BD as well as aiding treatment interventions for BD. Capitalizing on the advantages of within-subject designs and considering multiple aspects of activity disruptions, the current findings identify the precise activity patterns which differentiate depressive from inter-episode states in BD. Although there has been substantial progress in the development of treatments for BD, interventions are frequently not applied in time to prevent an emerging episode or to reduce the damage of a current episode. If distinct activity patterns correspond to distinct mood states, this correspondence can be leveraged by continuously tracking activity to provide ongoing information about the person's current mood state, thereby affording the opportunity for more immediate delivery of care.

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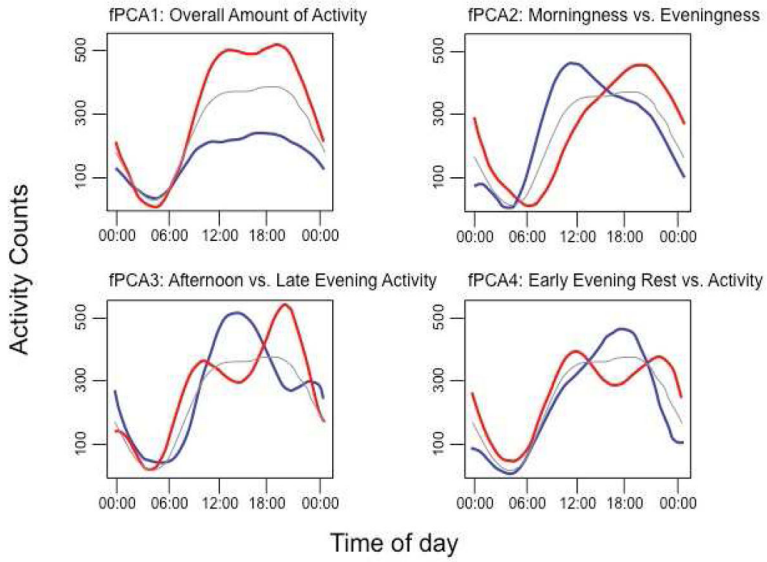

Figure 1.

fPCA of daily activity profiles in all participants combined (control and bipolar groups, N=3,551 days). The first four components of the fPCA are presented. High eigenvectors are shown by the red curve and low eigenvectors are shown by the blue curve. The grey curve is identical in all four plots and represents the average profile of activity over time.

Table 1

Sample Demographic and Clinical Characteristics

	Bipolar (n=37)	Control (n=39)
Demographic characteristics		
Female, n (%)	23 (62)	20 (51)
Caucasian, n (%)	24 (65)	17 (44)
Mean age (SD)	34.4 (10.4)	32.8 (12.5)
Married, n (%)	2 (5)	14 (36)
Employed, n (%)	22 (60)	25 (64)
Annual income of $50,000 or below, n (%)	26 (70)	26 (74)
Clinical characteristics		
Age at illness onset in years, Mean (SD)	17.9 (8.70)	--
Number of hypomania/manias, Mean (SD)	24.4 (74.0)	--
Number of depressive episodes, Mean (SD)	10.3 (13.5)	--
History of psychiatric hospitalization, n (%)	23.0 (62.2)	--
Number of psychiatric hospitalizations, Mean (SD)	1.8 (2.9)	--
GAF at study entry	72.5 (8.40)	--
Symptom severity		
IDS-C total score		
Initial lab session, Mean (SD)	8.7 (4.5)	2.3 (2.0)
Second lab session, Mean (SD)	12 (5.6)	3.1 (2.9)
Third lab session, Mean (SD)	11 (6.1)	4.1 (2.5)
YMRS total score		
Initial lab session, Mean (SD)	3.6 (3.2)	0.8 (1.3)
Second lab session, Mean (SD)	4.0 (3.8)	1.1 (1.5)
Third lab session, Mean (SD)	4.2 (4.6)	1.1 (1.4)
Current medications		
Lithium, n (%)	6.0 (16)	--
Lithium adjusted dose, Mean (SD), Range	0.13 (.309), 0–1.13	--
Valproate, n (%)	5.0 (14)	--
Valproate adjusted dose, Mean (SD), Range	0.10 (0.28), 0–1.17	--
Antidepressants, n (%)	16 (43)	--
Imipramine equiv, Mean (SD), Range	111 (163), 0–600	--
Atypical neuroleptics, n (%)	18 (49)	--
Risperidone equiv, Mean (SD), Range	1.8 (3.4), 0–15	--
Lamotrigine, n (%)	15 (41)	--
Lamotrigine adjusted dose	0.4 (0.5), 0–2.4	
Benzodiazepines, n (%)	6.0 (16)	--
Diazapam equiv, Mean (SD), Range	10.2 (49.5), 0–300	
Two or more classes of medications, n (%)	24 (69)	--

Note. Four control participants had missing data for annual income. Eight participants with bipolar disorder had missing data for number of hypomania/manias, seven had missing data for number of depressive episodes. One participant with bipolar disorder did not complete the second in-person session and therefore has missing data for symptom severity at this time point. IDS-C = Inventory of Depressive Symptomatology –

Clinician Rating; YMRS = Young Mania Rating Scale. Lithium, valproate, and lamotrigine doses are calculated as reported dose divided by maximum recommended dose (mg per day). Antidepressants, atypical neuroleptics, and benzodiazepines are converted to imipramine, risperidone, and diazapam dose equivalencies (mg per day), respectively. Two participants with bipolar disorder were not taking medications

Table 2

Results for Multilevel Models Examining Between-Group and Within-Person Differences in Four fPCA Components.

	*fPCA*1		*fPCA*2		*fPCA*3		*fPCA*4	
	Estimate	**(SE)**	**Estimate**	**(SE)**	**Estimate**	**(SE)**	**Estimate**	**(SE)**
Fixed effects								
Intercept, γ_{00}	−298.10	(441.23)	179.86	(324.34)	−4.38	(161.05)	113.04	175.23
Group (BD vs. Control), γ_{01}	462.16	(615.55)	−312.38	(452.43)	55.54	(223.97)	−139.95	244.14
Depressive-episode days, γ_{10}	**−849.49** *	(324.50)	−298.76	(259.03)	**489.75** *	(251.07)	−236.66	209.53
Hypomanic/m anic episode days, γ_{20}	−579.77	(369.68)	47.31	(294.93)	−281.79	(286.58)	−217.24	238.38
Random effects								
Intercept, σ^2_{u0}	6984460	(1177484)	3752813	(639936)	822488	(152845)	1043052	(186261)
Residual, σ^2_e	7953418	(190853)	5074871	(121795)	5041097	(120936)	3400797	(81621)
Fit Statistics								
−2LL	66721.0		65115.0		64987.3		63633.3	
AIC	66725.0		65119.0		64991.3		63637.3	

Note. Unstandardized estimates are used. Model based on 3,551 days nested within 76 participants. Estimates for depressive-episode days represent the difference between an inter-episode day and a depressive episode day for a participant with bipolar disorder (within-person effect). Estimates for hypomanic/manic episode days represent the difference between an inter-episode day and a hypomanic/manic day for a participant with bipolar disorder (within-person effect). SE = standard error; *AIC* = Akaike Information Criterion; *−2LL* = −2 Log Likelihood, relative model fit statistics.

* $p < .05$