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The quantitative assessment of motor activity in mania and schizophrenia

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Abstract

Background—Increased motor activity is a cardinal feature of the mania of Bipolar Disorder (BD), and is thought to reflect dopaminergic dysregulation. Motor activity in BD has been studied almost exclusively with self-report and observer-rated scales, limiting the ability to objectively quantify this behavior. We used an ambulatory monitoring device to quantify motor activity in BD and schizophrenia (SCZ) patients in a novel exploratory paradigm, the human Behavioral Pattern Monitor (BPM).

Method—28 patients in the manic phase of BD, 17 SCZ patients, and 21 nonpatient (NC) subjects were tested in the BPM, an unfamiliar room containing novel objects. Motor activity was measured with a wearable ambulatory monitoring device (LifeShirt).

Results—Manic BD patients exhibited higher levels of motor activity when exploring the novel environment than SCZ and NC groups. Motor activity showed some modest relationships with symptom ratings of mania and psychosis and was not related to smoking or body mass index.

Limitations—Although motor activity did not appear to be impacted significantly by antipsychotic or mood-stabilizing medications, this was a naturalistic study and medications were not controlled, thus limiting conclusions about potential medication effects on motor activity.

Conclusion—Manic BD patients exhibit a unique signature of motoric overactivity in a novel exploratory environment. The use of an objective method to quantify exploration and motor activity may help characterize the unique aspects of BD and, because it is amenable to translational research, may further the study of the biological and genetic bases of the disease.

Keywords

mania; Bipolar Disorder; motor activity; exploration; schizophrenia; inhibition

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Contributors

AM, MG, MP, and WP designed the study. AM, BH, and JY managed the literature searches and conducted the data analyses. All authors contributed to the original and final drafts of the manuscript and have approved the final draft.

Financial Disclosure/Conflict of Interest

AM reports a financial relationship with the manufacturer of the LifeShirt System, Vivometrics. BH, MP, MG, JY and WP report no biomedical financial interests or potential conflicts of interest.

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Introduction

Increased motor activity is a cardinal feature of mania, characterized in the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) as an “increase in goal-directed activity... or psychomotor agitation”(1994). Manic patients often report that they have more energy than usual and are observed to be physically restless, fidgeting, and changing posture and position frequently. Excessive motor behavior is a key manifestation of inhibitory failure in Bipolar Disorder (BD); individuals with BD have difficulty inhibiting inappropriate or excessive sensory responses, thought, and behaviors. As is thought to be true of inhibitory deficits in general, markedly increased motor activity probably reflects dysregulation of dopamine in the brain, particularly increased extracellular dopamine in subcortical structures which receive direct projections from frontal areas (Weissenborn and Winn, 1992).

Studies of motor overactivity in BD have typically used self-report and observer-rated symptom scales. Symptom ratings may not be the most sensitive means of measuring motor activity, as clinician observations and self-reports of physical activity can be unreliable (Sims et al., 1999). The use of an accelerometer to objectively measure physical activity has been informative in studying the circadian rhythms and everyday activity level of medical populations (Bussmann et al., 1998; Schasfoort et al., 2003; Sims et al., 1999; Sisto et al., 1998) including psychiatric patients (Dubbert et al., 2006; Faulkner et al., 2006; Teicher, 1995; Teicher et al., 1986). Recent advances in ambulatory monitoring such as the LifeShirt System (VivoMetrics, 2002) have made it possible to collect physical activity data via a 2-axis centrally mounted accelerometer. This approach has advantages over the more commonly used methods of wrist or ankle-mounted accelerometers because it measures “whole body” movements (Godfrey et al., 2008) and not just isolated motion of an arm or leg. Accelerometers “have become the preferred choice for continuous, unobtrusive, and reliable method in human movement detection and monitoring” (Godfrey et al., 2008) (p. 1369). In particular, the LifeShirt accelerometer has been previously shown to sensitively classify the unique locomotor activity pattern (shuffling gait) of patients with Parkinson’s Disease, supporting the utility of this technology in characterizing and distinguishing motor behaviors (Keenan and Wilhelm, 2005).

The aim of this investigation was to assess motor activity in BD patients who were hospitalized in the manic phase of their illness and compare them with acutely ill schizophrenia (SCZ) patients, as part of a larger investigation on exploratory behavior in human and animal models of psychiatric disease (Perry et al., in press). Motor behavior was assessed using ambulatory monitoring, while subjects were exposed to a novel environment designed to stimulate exploration. This newly developed paradigm, the Human Behavioral Pattern Monitor (BPM) (Perry et al., in press; Young et al., 2007), is a human analog of the classic animal “open field” test and is based upon the rodent BPM originally developed by our colleagues (Geyer et al., 1986). We hypothesized that manic BD patients would exhibit increased levels of motor activity compared to both SCZ patients and healthy volunteers. We also compared our physiologic measure of activity to scores from the Young Mania Rating Scale (YMRS) (Young et al., 1978), to assess the relationship between the objective activity measure and symptom ratings.

Method

Participants

The University of California, San Diego (UCSD) School of Medicine institutional review board approved the study. 28 individuals (15 M) with BD, Current Episode Manic participated, along with 17 individuals (11 M) with SCZ and 21 healthy comparison subjects (NC) (10 M). BD and SCZ patients were tested within an average of 96 hours of admission to the psychiatric

service at the UCSD Medical Center while they were highly symptomatic. Diagnosis of the BD and SCZ patients was obtained using the Structured Clinical Interview for DSM-IV Disorders (SCID) (First et al., 1994) administered by a trained clinician. NC subjects were recruited from the community with the use of advertisements, and were also assessed with the SCID. We previously established a 98 percent agreement for determining Axis I diagnoses using the SCID (Perry et al., 2001). Potential participants were excluded for: Axis I and II disorders as assessed by the SCID (apart from BD and SCZ for the psychiatric groups); neurological illness or head trauma; unstable medical illness; drug abuse or dependence within the past six months; treatment with electroconvulsive therapy; or a positive result on a toxicology screen. See Table 1 for demographic information. A subset of the sample in this study has been presented in Perry et al (in press); the current report is an elaboration of the motor activity findings that are mentioned in that manuscript, with the addition of new BD and SCZ subjects as well as more detailed analyses of potential correlates of motor activity.

The majority of BD and SCZ patients were taking atypical antipsychotic and/or mood stabilizing medications (see Table 2). The most common medications were risperidone ($n = 24$), valproate ($n = 13$), and lithium ($n = 8$). Doses of psychotropic medication did not significantly differ between BD and SCZ patients (see Table 1).

Procedure

Subjects were fitted with the LifeShirt, a monitoring device in the form of a wearable upper-body garment that resembles a sleeveless vest and is available in a range of sizes. Electrocardiogram (ECG) leads were placed on the subject's sternum and connected to the LifeShirt for the measurement of cardiac parameters. Two dual-axis accelerometers embedded in the fabric of the LifeShirt on the anterior surface of the abdomen are utilized to measure motor activity, oriented at right angles to one another to provide x, y, and z axis data. Following a brief calibration procedure, subjects were directed into the BPM, told that they would see the experimenter shortly, and instructed to wait in the room without any other direction.

The BPM is a 9' by 14' room to which the subject has not been previously exposed, containing several items of furniture placed along the periphery including a desk, small and large filing cabinets, two sets of bookshelves, but no chairs. Dispersed evenly in the BPM are eleven small objects that were chosen using the criteria that they be safe, colorful, tactile, and manipulable and therefore likely to invite exploration. Subjects remained in the BPM for fifteen minutes and were monitored by a digital videocamera embedded in the ceiling to ensure that they were not engaging in dangerous behaviors. During the informed consent process, subjects were told that they might be videotaped during a part of their examination, but were not specifically instructed that this recording would occur during the BPM session. Following the BPM session, subjects were returned to the laboratory where other testing, including administration of symptom rating scales, was completed. Because physiologic parameters can be impacted by body weight and nicotine use, height and weight were collected for the calculation of Body Mass Index (BMI), and subjects were asked about their smoking habits.

Data Collection

Accelerometer data from the LifeShirt were sampled in digital units at the rate of 10 hertz, stored in an on-board PDA during the phase of data collection, and extracted and analyzed using the Vivologic Software (Keenan and Wilhelm, 2005; VivoMetrics, 2002). Accelerometer values represent a filtered summation of motion on both the x and y axes that excludes acceleration forces due to gravity. Digital units of acceleration approximately correspond to the following intensities of movement: below 5 = resting, 2–5 = walking slowly, 7–10 = walking at a medium pace, 12–18 = walking fast (VivoMetrics, 2002).

Data Analysis

Mean acceleration in digital units was derived for each of the three five-minute epochs of the human BPM session; mean values of acceleration are a common and accepted method with which to determine static and dynamic motor activity (Godfrey et al., 2008). The data were inspected for normality and homogeneity of variance. Mean acceleration was analyzed using a mixed 3×3 Analysis of Variance (ANOVA), with epoch as the repeated measure and group as the between-subjects measure. Because education and smoking status were different across groups (see Table 1), years of education was used as a covariate in the ANOVA, and smoking status (daily smoker vs. non-smoker) was used as an additional between-subjects measure. Planned comparisons were conducted between the groups. Pearson r correlation coefficients measured the relationship between motor activity and symptom scores, as well as between motor activity and BMI.

The potential effect of psychotropic medications on motor activity was assessed in several ways; patients on the most commonly prescribed medications (risperidone, valproate, lithium) were compared to patients not on each of those medications using Independent Samples t -tests. Additionally, Pearson r correlation coefficients were conducted between dose of these medications and motor activity. Statistical analyses were conducted with SPSS (Chicago, USA).

Results

Motor Activity Across Groups

The mixed ANOVA on motor activity with education as a covariate revealed a strong main effect of diagnostic group [$F(2, 59) = 6.5, p = .003$], no main effect of session epoch, no main effect of smoking status, and a trend towards a group-by-epoch interaction [$F(4, 118) = 2.2, p = .08$]. No other two- or three-way interactions were statistically significant. Figure 1 shows a slight decrease in motor activity across the session in the BD group relative to the other two groups. Planned comparisons indicated that BD patients exhibited more motor activity during all three epochs compared to NC subjects [$p \leq .002$, Cohen's $d = .94$ to 1.4]. BD patients exhibited more activity than SCZ patients in the first two epochs [$p \leq .04$, Cohen's $d = .67$ to $.91$], but not the third [$p = \text{ns}$, Cohen's $d = .10$]. SCZ patients and NC subjects did not differ in any of the epochs [$p = \text{ns}$, Cohen's $d = .40$ to $.67$]. The exemplars in Figure 2 illustrate the typical motor activity patterns across the BPM session for each of the three groups, with the BD patient showing high levels of activity throughout most of the session and some attenuation towards the end, the SCZ patient showing relatively less activity, with slightly increased bursts of movement towards the end of the session, and the NC subject demonstrating consistent but relatively low activity throughout. Motor activity at any of the three epochs was not significant correlated with BMI for either the BD group (Pearson r range = $.06$ to $-.24$), the SCZ group (Pearson r range = $-.01$ to $-.24$), or the NC group (Pearson r range = $.01$ to $-.23$).

Relationship between Motor Activity and Symptom Scores

YMRS total scores and BPRS total scores were not significantly related to average motor activity in BD or SCZ patients. Some modest correlations were detected between motor activity and symptom ratings of elevated mood in the BD patients, and between motor activity and symptom ratings of increased motor activity in the SCZ patients (see Table 3). Only two correlations between motor activity and a BPRS item approached statistical significance; in SCZ patients, lower motor activity was related to higher ratings of blunted affect (Pearson $r = -.50, p = .05$) and to higher ratings of suspiciousness ($r = 0.47, p = .06$).

Effect of Patient Medication

Sample sizes for the medication effect analyses were small; however, treatment with risperidone did not have a significant effect on motor activity at any of the three epochs [$t(43) = .04$ to $.25$, ns]; nor did treatment with lithium [$t(43) = .003$ to 1.1 , ns] or valproate [$t(43) = 1.1$ to 1.3 , ns]. Additionally, there were no significant correlations between motor activity and dose of risperidone, lithium, or valproate at any of the three epochs.

Discussion

This study quantified motor activity in hospitalized manic BD patients and compared them to hospitalized SCZ patients, using ambulatory monitoring technology and a novel paradigm designed to measure human exploratory behavior, the BPM. BD patients showed markedly high motor activity throughout the majority of the exploratory session. Figure 1 shows that, unlike the two other groups, BD patients' activity appeared to decrease in the final five minutes, perhaps suggesting habituation to the novel environment, or alternatively fatigue or "rest" after a period of intense activity (also see exemplars of motor activity in Figure 2). Daily smoking and BMI did not appear to markedly influence motor activity levels.

Interestingly, motor activity as measured by the accelerometer showed only modest correlations with ratings of mania symptoms, supporting the notion that objective measures of activity may be more sensitive than self-report and observer ratings of psychomotor behavior (Bussmann et al., 1998; Dubbert et al., 2006; Sims et al., 1999). Furthermore, the measurement of motor activity in response to a novel environment may be qualitatively different than assessing for increased activity in the context of an interview, where patients are presumably seated and not confronted with novel stimuli that stimulate exploration.

Motor activity was not related to symptom ratings of general psychopathology, although several trends were observed: SCZ patients with higher ratings on the blunted affect item of the BPRS exhibited lower motor activity, as did SCZ patients with higher ratings on the BPRS suspiciousness item. These are not surprising findings given that a hallmark negative symptom that often accompanies blunted affect is a loss of volition, which in the BPM may manifest as a failure to engage with novel surroundings. Furthermore, an increased level of paranoia can certainly dampen a patient's willingness to explore a novel environment, particularly if that individual suspects that he or she is being watched. A similar negative correlation was reported between daily physical activity (as measured by caloric expenditure) and symptom ratings of hallucinations, in a cohort of severely mentally ill patients who wore an accelerometer for three days while they went about their daily activities (Dubbert et al., 2006).

While there are several older studies using wrist actigraphy to measure circadian rhythms in neuropsychiatric patients (Teicher et al., 1986; Wolff et al., 1985), and some more recent studies examining daily physical activity levels in schizophrenia patients (Dubbert et al., 2006; Faulkner et al., 2006), there is not a similar existing literature in psychiatric populations for whom altered motor activity is a hallmark symptom, e.g., BD or Attention Deficit/Hyperactivity Disorder (ADHD). Novel measures, however, such as the McLean Motion Analysis Test (M-MAT) (Faedda and Teicher, 2005) and ambulatory monitoring devices such as the LifeShirt now make it possible to precisely measure motor activity patterns and allow us to obtain signatures of activity that may be unique to certain disorders. For example, the M-MAT and actigraphy differentiated children with BD from those with ADHD (Faedda and Teicher, 2005), and our own work on spatial patterns of movement in the human BPM differentiates BD from ADHD adults (Paulus et al., 2007). The discrimination between manic BD and SCZ patients is often difficult to make with certainty in the acute phase of illness because both diseases can present with severe thought disorder, leading some to suggest that psychotic mood disorders and schizophrenia may not be distinct illnesses (Lake, 2007). Indeed

manic BD and SCZ subjects showed equivalent levels of general psychopathology as measured by the BPRS. The high motor activity seen in the manic BD patients, however, may be a unique signature, suggesting an interesting way to differentiate these two illnesses in an acute setting.

Animal models of mania have focused upon manifestations of hyperactivity, as this behavior is relatively straightforward to monitor in animals (Einat et al., 2003). Increased motor activity in an exploratory environment, such as in an open field test or rodent BPM, has been observed in rodents with genetically induced hyperdopaminergia (Ralph-Williams et al., 2003; Zhuang et al., 2001) as well as in rodents administered dopamine agonists such as amphetamine which has led some to suggest these as animal models for bipolar mania (Einat et al., 2003; Machado-Vieira et al., 2004). Allelic variation in the dopamine D₃ receptor gene appears to be associated with novelty-seeking in BD individuals (Staner et al., 1998). Additionally, some reports have associated polymorphisms of the dopamine transporter (DAT) gene (Greenwood et al., 2006) as well as altered levels of DAT binding (Amsterdam and Newberg, 2007) to BD. Clearly the link between mania and dopamine is complex, and hyperdopaminergic animals hold promise as a model for mania (Young et al., 2007).

Medication commonly used to treat psychiatric illness can affect motor activity, for example by having a sedating and psychomotor slowing effect, or as an effect of mood stabilization. One would certainly expect that pharmacological treatment of the manic phase of BD would eventually result in a decrease in inappropriate motor activity. The effects of mood-stabilizing agents in reducing cardinal symptoms of mania, including psychomotor agitation, are partially seen at one week, but more so at two weeks (Yatham et al., 2004). The BD patients in this study were tested after an average of only three days of treatment, while still experiencing manic symptoms as evidenced by high YMRS scores, and a marked effect of medications on dampening motor activity was not observed.

BD and SCZ patients in the current study were, however, prescribed a variety of medications at the time of testing and thus we cannot exclude the potential effect of pharmacological treatment on motor activity. For example, if SCZ patients were on higher doses of potentially sedating medications compared to manic BD patients, this could explain their relatively lower motor activity. In this sample, however, SCZ and BD patients were on comparable doses of antipsychotic medications, as well as mood stabilizers in the rare cases that a SCZ patient was prescribed one. We have attempted to address the medication issue partially by comparing subjects who were on and off risperidone, lithium, and valproate as these were most commonly prescribed medications in this sample, as well as to test for correlations between medication dose and motor activity. It is important to note that the sample size for these analyses was relatively small and this analysis does not account for the wide variety of medications administered to patients. Medication effects on motor activity can be better addressed in longitudinal studies where patients are tested in an unmedicated state and re-tested after several weeks of treatment; such studies are ongoing in our laboratory.

Using accelerometry technology provides a sensitive measure of the quantity of motor activity, and other methods can be informative as to the specific nature of that activity to assess whether the groups can be distinguished based upon factors such as walking or fidgeting, or the degree to which they interacted with the stimuli in the BPM. The video capture of the BPM session does allow for further examination of these qualities. For example, continuous digital recording of the subject's location makes it possible to examine sequential patterns of movement and distinguish short-range, localized movements (e.g., fidgeting) from long-range, distance-crossing movements (e.g., pacing). Furthermore, the nature of subjects' interactions with the BPM's objects (number of object interactions, time spent with objects, etc) can be quantified using ratings of the videos. These measures, together with quantification of motor activity, can help us develop unique signatures of exploratory behavior in psychiatric populations. Some of

our work in this arena is in press (Perry et al., in press), and additional reports elaborating on sequential patterns of activity and object interactions are in preparation.

In conclusion, manic BD patients exhibited significantly greater motor activity compared to both NC and the SCZ patients when exposed to a novel exploratory environment and assessed with quantitative methods. Further analysis of the components that comprise exploratory behavior, for example using non-linear dynamic analytical methods that are features of our colleagues' rodent version of the BPM (Geyer et al., 1986; Paulus and Geyer, 1996), may lead towards the development of a unique phenotypic "signature" of the mania of BD. This set of phenotypes may then be used to refine much-needed animal models of BD, to study biological and genetic bases of the disease, and to monitor treatment response and prognosis.

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Figure 1.

Motor activity in the human BPM for BD patients ($n = 28$), SCZ patients ($n = 17$), and NC subjects ($n = 21$). ** BD > SCZ and NC, $p < .01$; * BD > SCZ and NC, $p < .05$; † BD > NC, $p < .01$.

Figure 2.
Exemplars of motor activity in the human BPM for a BD patient (A), a SCZ patient (B), and a NC subject (C).

Table 1

Demographic and illness factors.

	Bipolar Mania (BD)	Schizophrenia (SCZ)	Nonpatient Comparison (NC)	Group differences
Age (years)	34.1 (13.3)	36.7 (12.4)	30.3 (9.5)	ns
Gender	15 M, 13 F	11 M, 6 F	10 M, 11 F	ns
Years of education	13.4 (2.0)	13.3 (2.7)	15.0 (1.3)	BD, SCZ < NC, p<.05
Age of onset of Illness	23.2 (8.6)	25.9 (8.8)	--	ns
Smoking Status	17 daily smokers	9 daily smokers	2 daily smokers	BD, SCZ > NC, p < .05
Body Mass Index	28.2 (7.4)	25.6 (5.3)	25.8 (5.8)	ns
Years of illness duration	11.5 (10.2)	10.4 (8.2)	--	ns
Number of days in treatment	2.7 (2.2)	5.9 (10.5)	--	ns
Illness subtype	All Current Episode Manic	11 paranoid, 2 disorganized, 4 undifferentiated	--	--
YMRS total score	27.9 (8.7)	19.1 (7.2)	--	BD > SCZ, p<.01
BPRS total score	40.9 (10.7)	36.5 (8.0)	--	ns
Risperidone dose (mg)	n = 13 3.0 (1.6)	n = 11 4.0 (1.6)	--	ns
Valproate dose (mg)	n = 11 2000.0 (447.2)	n = 2 2250.0 (353.6)	--	ns
Lithium Dose (mg)	n = 8 1075.0 (477.3)	--	--	--

Note: For all variables except gender, smoking status, and illness subtype, values in the first three columns represent means and standard deviations. YMRS= Young Mania Rating Scale, BPRS = Brief Psychiatric Rating Scale

Table 2

Frequencies of psychotropic medication classes for BD patients (n = 28) and SCZ patients (n = 17).

Medication Class	n of BD patients	n of SCZ patients
Antipsychotic alone	5	12
Mood stabilizer alone	3	0
Antipsychotic plus mood stabilizer	19	2
Not medicated	1	3

Table 3

Pearson r correlation coefficients between average motor activity during the exploratory session and YMRS items for BD patients (n = 28) and SCZ patients (n = 17).

	Average motor activity-BD patients	Average motor Activity-SCZ patients
YMRS Item 1: Elevated Mood	.43*	-.07
YMRS Item 2: Increased Motor Activity	.27	.48*
YMRS Item 3: Sexual Interest	-.10	.12
YMRS Item 4: Sleep	-.19	.31
YMRS Item 5: Irritability	.31	-.10
YMRS Item 6: Speech	.09	-.01
YMRS Item 7: Language-Thought Disorder	-.10	-.03
YMRS Item 8: Content	.08	-.17
YMRS Item 9: Disruptive-Aggressive Behavior	.18	.06
YMRS Item 10: Appearance	-.07	.09
YMRS Item 11: Insight	-.06	-.26
<i>YMRS Total Score</i>	.16	-.03

*
p < .05