A Reverse-Translational Study of Dysfunctional Exploration in Psychiatric Disorders

From Mice to Men

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Context: Bipolar mania and schizophrenia are recognized as separate disorders but share many commonalities, which raises the question of whether they are the same disorder on different ends of a continuum. The lack of distinct endophenotypes of bipolar mania and schizophrenia has complicated the development of animal models that are specific to these disorders. Exploration is fundamental to survival and is dysregulated in these 2 disorders. Although exploratory behavior in rodents has been widely studied, surprisingly little work has examined this critical function in humans.

Objectives: To quantify the exploratory behavior of individuals with bipolar mania and schizophrenia and to identify distinctive phenotypes of these illnesses.

Design: Static group comparison by the use of a novel human open field paradigm, the human Behavioral Pattern Monitor (BPM).

Setting: Psychiatric hospital.

Participants: Fifteen patients with bipolar mania and 16 patients with schizophrenia were compared with 26 healthy volunteers in the human BPM. The effects of amphetamine sulfate, the selective dopamine transporter inhibitor GBR12909, and the genetic knockdown of the dopamine transporter were compared with controls in the mouse BPM.

Main Outcome Measures: The amount of motor activity, spatial patterns of activity, and exploration of novel stimuli were quantified in both the human and mouse BPMs.

Results: Patients with bipolar mania demonstrated a unique exploratory pattern, characterized by high motor activity and increased object exploration. Patients with schizophrenia did not show the expected habituation of motor activity. Selective genetic or pharmacologic inhibition of the dopamine transporter matched the mania phenotype better than the effects of amphetamine, which has been the criterion standard for animal models of mania.

Conclusions: These findings validate the human open field paradigm and identify defining characteristics of bipolar mania that are distinct from those of schizophrenia. This cross-species study of exploration calls into question an accepted animal model of mania and should help to develop more accurate human and animal models, which are essential to the identification of the neurobiological underpinnings of neuropsychiatric disorders.

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Traditionally, bipolar mania and schizophrenia were considered unrelated conditions. More recent evidence, however, indicates that these disorders share genetic, symptom-related, and epidemiologic characteristics and that both respond to medications that act via blockade of dopamine receptors. These similarities have prompted some to suggest that bipolar mania and schizophrenia are 1 illness that varies along a continuum of mood and psychotic symptoms.

Animal models are highly useful in the understanding of the neurobiological substrates of psychiatric conditions. The unique features of bipolar mania and schizophrenia have, however, been difficult to model, largely because the symptoms that reflect the cardinal features of these conditions are challenging to produce and measure in laboratory animals. The lack of distinctive animal models of bipolar mania has limited the ability to identify the neurobiological underpinnings and potential treatments for this condition. Paradigms that can be used in both humans and animals are essential to the elucidation of the neurobiology of neuropsychiatric diseases. We recently developed and used a reverse-translational paradigm to characterize exploratory activity in humans that parallels our work with the rodent Behavioral Pattern Monitor (BPM).
Exploratory behavior is the act of making the unknown known and is a fundamental function found among all living species. Measures of exploratory motor activity in rodents in open fields have a rich tradition that has revealed the complexity of the behavior and its use in the fostering of drug discovery efforts. The BPM is an elaboration of the traditional rodent open field and provides measures of the 3 fundamental dimensions of exploratory behavior: the amount of motor activity, the sequential structure of this activity, and the exploration of novel stimuli. In rodents, the multivariate behavioral profiles assessed in the BPM have enabled us to distinguish and quantify effects of different pharmacologic, neurobiological, and genetic manipulations. Multivariate assessment of motor activity has been used to identify optimal doses of medication for the treatment of neuropsychiatric disorders. Nevertheless, surprisingly little experimental assessment of human exploratory behavior has been conducted (but see ). This paucity of research is particularly astounding given that abnormal exploratory behavior is characteristic of a number of major neuropsychiatric conditions, such as excessive activity observed in bipolar mania and prominent inactivity and withdrawal as observed in schizophrenia. Furthermore, an increasing amount of literature suggests that overactivity (i.e., increased motor behavior) is a core criterion for manic states and is as important as elevated and/or irritable mood for the diagnosis of mania.

The aims of this study were to validate our human BPM (hBPM), to establish quantifiable and distinct endophenotypes of bipolar mania and schizophrenia, and to empirically validate corresponding animal models. Specifically, we tested patients hospitalized with bipolar mania and those with schizophrenia as well as healthy volunteers in the hBPM to determine whether these psychiatric disorders exhibit distinctive signature patterns of exploratory behavior. In parallel, we tested potential candidate rodent models of these disorders in the mouse BPM (mBPM). Because amphetamine sulfate has been the criterion standard animal model of bipolar mania and has also been used to model aspects of schizophrenia, we examined the behavioral profile of mice treated with amphetamine. Furthermore, given that mutations and other abnormalities relevant to the function of the dopamine transporter (DAT) have been linked to both bipolar mania and schizophrenia and that amphetamine preferentially inhibits the norepinephrine transporter, we assessed the potential of genetic and selective pharmacologic manipulations of the DAT to mimic the patterns exhibited by patients with mania and/or schizophrenia. Specifically, we assessed the behavioral profiles of mice tested in the mBPM after administration of the selective DAT inhibitor GBR12909 and in DAT knockout (KD) mice that had 90% reduced expression of the DAT.

### METHODS

**HUMANS**

Patients 18 through 55 years of age who were hospitalized with “bipolar disorder, current episode manic” (n = 15; 9 men) or schizophrenia (n = 16; 10 men), as defined by the Structured Clinical Interview for DSM-IV, participated in this study. Healthy volunteers who had never met the criteria for an Axis I disorder as determined by the Structured Clinical Interview for DSM-IV were recruited from the community (n = 26; 13 men). Participants were excluded if they had met the DSM-IV criteria for abuse or dependence on alcohol or other substances within the past month, had a positive result on a urine toxicology screen, had a neurologic condition, or had a condition that impaired motor functioning. The table lists demographic and illness factors.

All patients with bipolar mania and all but 3 patients with schizophrenia were prescribed psychotropic medication during the time of testing; the patients with bipolar mania were typically treated with a combination of mood-stabilizing and atypical antipsychotic medications, whereas those with schizophrenia were prescribed an antipsychotic medication alone. The most common antipsychotic medication prescribed was risperdone, and the most common mood stabilizers prescribed were lithium carbonate and valproate sodium.

After participants consented to the study, the Brief Psychiatric Rating Scale (BPRS) and the Young Mania Rating Scale (YMRS) were administered to both groups. Participants were then fitted with an ambulatory monitoring device in the form of a wearable upper-body garment that resembles a sleeveless vest (LifeShirt; VivoMetrics, Inc, Ventura, California).

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**Table. Demographic and Illness Factors**

<table>
<thead>
<tr>
<th>Factor</th>
<th>Patients With Bipolar Mania (BD)</th>
<th>Patients With Schizophrenia (SCZ)</th>
<th>Healthy Volunteers (HV)</th>
<th>Group Differences</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>32.3 (12.6)</td>
<td>36.5 (12.7)</td>
<td>27.9 (8.9)</td>
<td>SCZ &gt; HV, P = .013</td>
</tr>
<tr>
<td>Sex, M/F</td>
<td>9/6</td>
<td>10/6</td>
<td>13/13</td>
<td>P = .59</td>
</tr>
<tr>
<td>Education, y</td>
<td>13.7 (2.2)</td>
<td>13.3 (2.8)</td>
<td>14.8 (1.7)</td>
<td>SCZ &lt; HV, P = .034</td>
</tr>
<tr>
<td>Age at Onset of Illness</td>
<td>23.0 (7.2)</td>
<td>28.8 (8.3)</td>
<td>NA</td>
<td>P = .98</td>
</tr>
<tr>
<td>Illness duration, y</td>
<td>9.4 (8.8)</td>
<td>9.3 (7.1)</td>
<td>NA</td>
<td>P = .19</td>
</tr>
<tr>
<td>Days in treatment, No</td>
<td>2.3 (1.8)</td>
<td>5.7 (10.8)</td>
<td>NA</td>
<td>P = .24</td>
</tr>
<tr>
<td>Illness subtype</td>
<td>Current episode manic</td>
<td>10 Paranoid, 2 disorganized,</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4 undifferentated</td>
<td></td>
<td></td>
</tr>
<tr>
<td>YMRS total score</td>
<td>25.7 (9.6)</td>
<td>18.3 (6.7)</td>
<td>NA</td>
<td>BD &gt; SCZ, P = .018</td>
</tr>
<tr>
<td>BPRS total score</td>
<td>41.2 (11.5)</td>
<td>36.1 (8.1)</td>
<td>NA</td>
<td>P = .16</td>
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<tr>
<td>Risperdone dose, mg</td>
<td>3.3 (2.3) [n = 6]</td>
<td>4.0 (1.6) [n = 11]</td>
<td>NA</td>
<td>P = .52</td>
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<tr>
<td>Valproate dose, mg</td>
<td>1916.7 (491.6) [n = 6]</td>
<td>2250.0 (333.6) [n = 2]</td>
<td>NA</td>
<td>P = .42</td>
</tr>
<tr>
<td>Lithium dose, mg</td>
<td>1180.0 (563.0) [n = 5]</td>
<td>NA</td>
<td>NA</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: BPRS, Brief Psychiatric Rating Scale; NA, not applicable; YMRS, Young Mania Rating Scale.

*For all entries except sex and illness subtype, values in the first 3 columns represent means (SDs).
trocardiogram leads were placed on the sternum of the participant and connected to the ambulatory monitoring vest for the measurement of cardiac parameters. A 2-axis accelerometer is embedded in the fabric of the garment. Once the patient was fitted with the ambulatory monitoring vest, he or she was directed into the hBPM and told that he or she would see the experimenter in a short period and was asked to wait in the room. No other instructions were provided.

The hBPM is a 2.7 × 4.3-m room to which the participant has not previously been exposed. It contains several items of furniture placed along the periphery of the room, including a desk, small and large filing cabinets, and 2 sets of bookshelves. There is no chair in the room. Dispersed evenly on items of furniture are 11 small objects. These objects were chosen using the criteria that they be safe, colorful, tactile, manipulable, and likely to invite human exploration. Participants were left in the hBPM for 15 minutes. They were monitored continuously by a digital video camera embedded in the ceiling; on 2 occasions a participant approached the door but was immediately met by the research team and asked to remain in the room.

Data in the hBPM reflect 3 sources of measurement: physiologic data, namely motor activity of the torso of the participant, using the accelerometer embedded in the ambulatory monitoring vest; x-y coordinates of the spatial location of the patient in the room, as extracted from digital video recording; and experimenter scoring of the video recordings to count exploratory events, such as interactions with objects, drawers, or window blinds. These measurements are the human analogs to the 3 dimensions of exploratory activity described in the work done with rodents by some of us.13–15

Accelerometer data from the ambulatory monitoring vest were sampled in digital units at 10 Hz, stored in an on-board PDA during data collection, and extracted and analyzed using Vivologic Software (VivoMetrics, Inc). The number of acceleration movements was assessed for each 5-minute epoch. In addition, the continuous high-frequency sampling of motor activity data enabled the calculation of dynamical entropy (h), which measures the degree to which behavior is observed along a continuum between complete order and disorder.30 To calculate h, a given sequence of activity is compared with similar preceding sequences, and this comparison is conducted for varying sequence lengths. Lower values of h (low entropy) suggest highly predictable or ordered sequences of motor activity across time, whereas higher values (high entropy) suggest a greater variety, or disorder, in the structure of motor activity across time.

To generate x-y coordinates, the digitized video images are stored at 30 frames per second (Figure 1) and subjected to frame-by-frame analysis with proprietary software (TopScan 1.0; Clever Systems Inc, Washington, DC) that generates x-y coordinates of the successive locations of the participant. The x-y coordinates can provide a measure of the amount of motor activity, quantified by counts, which are defined as the number of discrete instances of movement or the smallest measured change in x-y coordinates. From the x-y coordinates, the spatial scaling exponent d is also calculated. Spatial d measures the hierarchical and geometric organization of behavior. Specifically, d is based on the principles of fractal geometry and describes the degree to which the path taken within an enclosure by the participant is 1-dimensional or 2-dimensional. To obtain spatial d, the distance traveled is plotted against the number of counts using a double-logarithmic coordinate system, and a line of fit between these 2 variables is generated.36 Spatial d typically varies between 1 (a straight line) and 2 (a filled plane), with values closer to 1 reflecting straight movements and values closer to 2 reflecting highly circumscribed, local movements. At both ends of this spectrum, the geometric pattern of movement around the BPM is highly predictable but exhibits either an almost straight-line movement or a highly circumscribed geometrical pattern.30

In addition, the digitized video images enable detailed assessments of the interactions of the participant with the 11 objects placed in the room, in analogy to the investigatory behavior of the rodent directed toward the 11 holes placed in the walls and floors of the rodent BPM chambers. The number of discrete interactions with objects, drawers, or window blinds was hand-counted and recorded by experimenters who were masked to group membership. In many cases, several experimenters independently rated video recordings to ensure reliable ratings.

STATISTICAL ANALYSIS FOR HUMANS

Mean values for acceleration, entropy h, spatial d, counts, and object interactions were calculated for each of the three 5-minute epochs of the 15-minute hBPM session. Group differences on the hBPM measures were tested using a multivariate analysis of variance (MANOVA), with epoch as a repeated measure. The MANOVA was followed up by individual analyses of variance (ANOVAs) for each hBPM measure. Age and years of education were used as covariates in the ANOVAs because of group differences in these variables. Pearson r correlation coefficients were used to test for relationships between illness-related factors and hBPM measures and between symptom rating scores and hBPM variables. Items from the BPRS were clustered into 5 domains: negative symptoms, depression/anxiety, hostility/uncooperativeness, positive symptoms, and mania. These 5 domains, as well as the YMRS total score, were entered into a discriminant function analysis to classify the patients with schizophrenia and bipolar mania according to diagnosis. Another discriminant analysis was then conducted using only hBPM measures.

ANIMALS

The DAT KD condition in mice was generated by the insertion of embryonic stem cells of the 129/SvJ mouse strain into C57BL/6j blastocysts. One chimera was mated with 129/SvJ females to generate heterozygous mutants on a 129/SvJ genetic background.34 The DAT KD breeder mice were originally sent to our laboratory from Columbia University. All subsequent mice were derived from the breeding of heterozygous mice at the vivarium at the University of California, San Diego. The DAT KD and wild-type (WT) littermates assessed were from the 11th generation. At the time of first testing, the mice were between 5 and 6 months of age and weighed approximately 20 to 40 g each. To assess the pharmacologic models by the use of amphetamine or GBR12909 to inhibit the DAT, C57BL/6j mice were bought and were tested at approximately 4 months of age and weighed between 20 and 40 g each. All mice were housed in groups of a maximum of 4 per cage with a reversed day-night cycle (lights on at 8 PM and off at 8 AM) with unlimited access to water and food (Harlan Laboratories; Madison, Wisconsin) except during testing. Before the testing began, all mice were brought to the testing room for an acclimation period of at least 60 minutes. Testing occurred between 9 AM and 6 PM. All procedures were approved by the Institutional Animal Care and Use Committee of the University of California, San Diego. Mice were maintained in an animal facility at the University of California, San Diego, that meets all federal and state requirements for animal care.

DRUGS

d-amphetamine sulfate (Sigma-Aldrich Co; St Louis, Missouri) was dissolved in saline and injected at 5 ML/kg. GBR12909 di-
hydrochloride (Sigma-Aldrich Co) was dissolved in saline after sonication for 2 to 4 hours at 40°C. Because of the poor solubility of GBR12909 in saline, the injection volume was increased to 10 mL/kg. Drugs were administered by intraperitoneal injection.

MOUSE BEHAVIORAL PATTERN MONITOR

Spontaneous locomotor and exploratory behavior was examined for 60 minutes (unless otherwise stated) as described previously using the mBPM17 (Figure 1). The mBPM consists of a 30.5 × 61 × 38-cm plexiglas chamber equipped with 3 floor holes and 8 wall holes that serve as objects that engender frequent investigation by burrowing animals, such as mice (Figure 1). The location of the mouse is monitored by a grid of 12 × 24 infrared photobeams 1 cm above the floor and recorded every 55 milliseconds. Each hole is also equipped with an infrared photobeam to detect hole pokes. Rearing behavior is detected by an array of 16 infrared photobeams placed 2.5 cm above the

Figure 1. The human Behavioral Pattern Monitor (A) and mouse Behavioral Pattern Monitor (B) and sample x-y tracings.
MOUSE STUDIES IN THE mBPM

Naive male DAT KD (n=21) plus WT littermate mice (n=16) and female DAT KD (n=20) plus WT mice (n=14) were assessed in the mBPM for 40 minutes each. These mice were bred inhouse from heterozygote matings. The amphetamine study was conducted to determine a dose-response effect of D-amphetamine in C57BL/6J male mice at 0 (n=6), 0.5 (n=7), 1.25 (n=7), 2.5 (n=7), 5 (n=7), and 10 (n=7) mg/kg. A dose-response study of GRBR12909 was performed on C57BL/6J mice in the mBPM. Eighty male C57BL/6J mice were assessed in the BPM after short-term administration of GRBR12909 at 0 (n=14), 2.85 (n=14), 5 (n=13), 9 (n=13), 16 (n=13), or 28.5 (n=13) mg/kg. The mice were drug naive and had had 1 previous mBPM exposure 10 weeks earlier.

STATISTICAL ANALYSIS FOR ANIMALS

Data from each experiment were analyzed using 2- or 3-way ANOVAs, with sex, genotype, or treatment as between-subject factors and time as a within-subject factor. When no sex effect or interaction with sex was observed, data were collapsed across sex and reanalyzed. Statistically significant main effects were analyzed using Tukey post hoc analyses. The α level was set to .05. Data were analyzed in 10-minute epochs using the Biomedical Data Programs software (Statistical Solutions Inc, Saugus, Massachusetts).

RESULTS

HUMANS

Although bipolar mania and schizophrenia groups did not differ on BPRS total scores (F₂,₅₀=1.4; P=.16), patients with bipolar mania had higher YMRS scores than schizophrenic patients (F₂,₅₀=2.5; P=.02). The overall MANOVA that compared the 3 groups on all of the hBPM measures across all 3 epochs was statistically significant (time × group interaction F₄,₁₀₆=3.3; P=.02). Examination of overall activity (acceleration) showed that patients with bipolar mania were more active than schizophrenic patients initially and more active than healthy volunteers throughout the test (F₂,₅₀=7.6, P<.001; time × group interaction F₄,₁₀₆=3.4, P=.02) (Figure 2A). Moreover, the sequential accelerometer patterns of both patients with bipolar mania and those with schizophrenia were less predictable than those of healthy volunteers using a measure of dynamical entropy h²θ (F₂,₅₀=3.2; P=.047) (Figure 2B).

Reconstruction of the 2-dimensional (x-y) movements of each individual, collected by a video-tracking device, confirmed that manic patients moved around more than healthy volunteers early in the test session but also habituated more quickly over time. Healthy volunteers moved around the room at a relatively constant pace throughout the session, whereas patients with schizophrenia slightly increased their activity during the session (time × group interaction F₄,₁₀₆=3.4; P=.007) (Figure 2C). Relative to healthy volunteers, the spatial patterns of patients with bipolar mania were characterized by more direct straight paths, as evidenced by a decrease in the spatial scaling exponent d²θ (F₂,₅₀=5.1; P=.01) (Figure 2D). Visual inspection and scoring of the video recordings revealed that patients with bipolar mania interacted more with objects in the room than either patients with schizophrenia or healthy volunteers throughout the entire session (F₂,₅₀=18.5; P<.001) (Figure 2E). Whereas object interactions by patients with bipolar mania decreased as the hBPM session progressed, patients with schizophrenia and healthy volunteers interacted with objects in the room at a relatively constant but low level (time × group interaction F₄,₁₀₆=5.2; P<.001) (Figure 2E).

Patients with schizophrenia and higher scores on the BPRS negative symptoms domain engaged in more predictable sequential movement patterns (r=−.56; P=.03), whereas patients with schizophrenia who had higher scores on the BPRS manic symptoms domain (symptoms of excitability and agitation) engaged in more unpredictable movement patterns (r=.69; P=.003). These
correlations were not statistically significant for the patients with bipolar mania. Higher YMRS total scores were associated with increased object interactions ($r = 0.57; P < .001$). No relationships were found between hBPM measures and variables such as age of illness onset, duration of illness, and treatment duration.

To assess the potential impact of medications on the hBPM measures, we divided patients based on whether they were taking or not taking the most commonly prescribed medications: risperidone, valproate, and lithium. Patients taking risperidone did not have statistically significant differences in hBPM measures compared with patients not taking risperidone (for all $t_{29} = 0.14$ to $0.90$); the same was true for lithium (for all $t_{29} = 0.33$ to $0.98$). Patients taking valproate had statistically significantly more object interactions than those not taking valproate ($t_{29} = 1.5; P = .02$).

Finally, we conducted 2 discriminant function analyses to classify patients with bipolar mania and those with schizophrenia, the first using symptom domain scores from the BPRS and YMRS total scores and the second using the hBPM measures (acceleration, entropy, spatial d, and object interactions). Symptom domain scores correctly classified patients with bipolar mania with a sensitivity of 73% and a specificity of 75% and correctly classified patients with schizophrenia with a sensitivity of 75% and a specificity of 75%. The hBPM measures correctly classified patients with bipolar mania with a specificity of 80% and a specificity of 75% and correctly classified schizophrenic patients with a sensitivity of 75% and a specificity of 80%.

### ANIMALS

Using the mBPM,$^{17}$ we tested C57BL/6j mice for 1 hour after administration of various doses of d-amphetamine. As expected,$^9$ amphetamine increased activity ($F_{2,35} = 15.31; P < .001$) and decreased spatial d ($F_{2,35} = 4.27; P < .001$) but also statistically significantly reduced hole interactions ($F_{2,35} = 11.03; P < .001$) and had no effect on rearings (Figure 3A-D). Thus, across a wide dose range, amphetamine treatment failed to mimic the most striking of the 3 dimensions of abnormal exploration seen in bipolar mania: exaggerated investigatory behavior. Because amphetamine acts at multiple monoamine transporters, we conducted an identical study of mice treated with a more specific DAT inhibitor, GBR12909. Across multiple doses, GBR12909 increased activity ($F_{5,67} = 12.68; P < .001$) and rearings ($F_{5,67} = 2.73; P = .03$) while decreasing spatial d ($F_{5,67} = 6.83; P < .001$), with the most consistent effects being observed after the 16 mg/kg dose (Figure 3A, B, and D). Hole interactions were statistically significantly affected ($F_{5,67} = 3.17; P = .013$) (Figure 3C) because of a trend increase at 16 mg/kg and a reduction at the highest dose of GBR12909 (28.5 mg/kg) that was similar to the effect of all active doses of amphetamine and may not be selective for DAT over the norepinephrine transporter. This profile of behavior matches that seen in the bipolar group in that corresponding changes were seen in all 3 of the independent dimensions of exploratory behavior. To evaluate whether this profile of behavior seen after an acute inhibition of the DAT could be mimicked in mice that have a genetically associated with increased object interactions ($r = 0.57$).

In the present study, we demonstrate that the hBPM can characterize exploration and motor activity in patients with bipolar mania and can differentiate these patients from those with schizophrenia. In addition, the behavioral patterns exhibited by the patients with bipolar mania or those with schizophrenia in the hBPM paradigm clearly differed from those of healthy volunteers. Furthermore, each patient group exhibited a unique behavioral profile, quantitatively dis-

![Figure 3. Mouse models in the mouse Behavioral Pattern Monitor: amphetamine (AMP); dopamine transporter knockdown (KD); and GBR12909 (GBR). Activity levels (A), locomotor patterns (B), hole interactions (C), and rearing behaviors (D) are presented. Data are presented as mean ± SE for control (vehicle, DAT wild-type mice, and vehicle) and treatment (AMP at 2.4 mg/kg, DAT KD mice, GBR at 16 mg/kg) groups. *P < .05 compared with respective control group.](https://www.archgenpsychiatry.com/article.aspx?doi=10.1001/archgenpsychiatry.2009.243)
distinct from each other. The hBPM, however, was considerably more effective in the demonstration of behavioral abnormalities in patients with bipolar mania than in those with schizophrenia, relative to healthy volunteers. Motoric hyperactivity is widely expected as a feature of bipolar mania.\textsuperscript{22,43,44} The present work extends and complements early reports on actigraphy in psychiatric populations\textsuperscript{45,46} and provides an objective quantification of hyperactivity in patients with bipolar mania. In addition, the hBPM revealed that patients with bipolar mania are characterized by abnormalities in all 3 main dimensions of exploratory behavior that have been described in rodent studies. Factor analyses that converge with extensive pharmacologic studies in rodents demonstrate that exploratory behavior is composed of 3 independent domains: the amount of activity, the structure of the activity, and investigatory behavior.\textsuperscript{45-42} The present study reveals that patients with bipolar mania exhibit not only increased levels of activity but also abnormally straight and predictable patterns of activity and excessive specific investigatory activity as reflected by object interactions. It appears that such investigatory exploration most sensitively differentiated individuals with bipolar mania from the other groups. Specifically, patients with bipolar mania gathered up multiple objects and most picked up and wore a face mask that was among the objects placed in the room, in contrast to the healthy participants or patients with schizophrenia. Thus, the hBPM provides an objective means to assess overt disinhibition, a hallmark of bipolar disorder, because the act of entering a novel environment and engaging with the belongings of a stranger reflects a failure of behavioral fitness as reflected by object interactions. It appears that such investigatory exploration most sensitively differentiated individuals with bipolar mania from the other groups. Specifically, patients with bipolar mania gathered up multiple objects and most picked up and wore a face mask that was among the objects placed in the room, in contrast to the healthy participants or patients with schizophrenia. Thus, the hBPM provides an objective means to assess overt disinhibition, a hallmark of bipolar disorder, because the act of entering a novel environment and engaging with the belongings of a stranger reflects a failure of behavioral filtering processes that modulate appropriate social conduct. In contrast to this multidimensional profile of abnormalities in patients with bipolar mania, patients with schizophrenia exhibited normal levels of object interactions and differed from healthy volunteers primarily in their failure to exhibit the normal habituation of motor activity across time in the novel environment. This abnormality is consistent with previous reports of failures of habituation in schizophrenia in other behavioral paradigms.\textsuperscript{47-49}

One criterion for the usefulness of this reverse-translational approach is its ability to classify individuals into different diagnostic groups. The discriminant functional analyses revealed that the hBPM measures correctly classified patients with bipolar mania and those with schizophrenia better than did symptom domain scores. Bipolar mania and schizophrenia share many symptoms, particularly during highly symptomatic states when psychosis is a prominent feature of both illnesses. Still, there are cardinal features that help to differentiate these 2 disorders, namely the hypermotoric behavior of people with bipolar mania and the prominent withdrawal observed among patients with schizophrenia. Surprisingly, this distinction has been understudied. The current data support the position that the disorders share many symptoms, as indicated by the similar BPRS scores, but that patients with bipolar mania have the distinct characteristics of hyperexploration and increased motor activity. It remains unclear whether these features are enduring characteristics of bipolar mania or whether they are specific to the manic state. Therefore, an obvious next question is whether this signature of inhibitory deficits persists during other phases of bipolar disorder (eg, during euthymic, depressed, and hypomanic states).

Because almost all the patients with bipolar mania and schizophrenia in this study were treated with a variety of medications, potential medication effects on the hBPM measures are difficult to quantify, which is a limitation of this investigation. Nevertheless, treatment with antidepressants or mood stabilizers did not appear to reduce activity for patients with either bipolar mania or schizophrenia. The observation that patients taking valproate had increased object interactions is likely because these patients had bipolar mania. The increase in object interactions was not seen in patients taking lithium, which may be cause for some speculation that lithium may have had more of a dampening effect on activity than did valproate. This speculation is tempered, however, by the fact that patients with bipolar mania were tested after an average of 2 days of treatment, before steady-state blood levels of lithium were reached. Medication effects on exploratory behavior can be better addressed in longitudinal studies in which patients are tested in an unmedicated state and retested after several weeks of treatment; such studies are ongoing in our laboratory.

With respect to the candidate mouse models tested, the genetically induced lack of DAT function produced a behavioral profile that matched that seen after pharmacologic inhibition of DAT function in mice. Furthermore, both of these multivariate profiles were consistent with that observed for bipolar mania. In particular, the similarity between bipolar mania and these 2 models in the spatial patterns of locomotion was striking (Figure 4). The shared mechanism of these 2 rodent models therefore suggests possible neurobiological underpinnings of bipolar mania and a putative target for the development of novel therapeutics. It has been suggested that DAT KD mice may be suitable as a model for attention-deficit/hyperactivity disorder.\textsuperscript{50} On the basis of the present data and their hypersensitivity to stimulants,\textsuperscript{51} (although see\textsuperscript{34}), DAT KD mice may prove to be more suitable as a model of bipolar mania. These data provide support for studies that have implicated DAT polymorphisms\textsuperscript{52} and lower levels of DAT binding\textsuperscript{28} as being important for the bipolar disorder phenotype.

Importantly, the multivariate profile of novel environment exploration that characterized patients with schizophrenia was not reproduced by any of the animal models assessed herein. Although this observation may reflect the complexity and multifactorial origin of schizophrenia, it remains surprising given the widespread use of amphetamine-induced hyperactivity in animal models of schizophrenia.\textsuperscript{25,27} Nonetheless, it should be recognized that amphetamine-induced motor hyperactivity remains a highly predictive model that identifies existing antipsychotic treatments that act as antagonists at dopamine receptors. When one considers the fact that antipsychotic medications are used to treat both schizophrenia and bipolar mania, the amphetamine hyperactivity model may be seen as more applicable to the study of antipsychotics and less as a mimic of schizophrenia or mania specifically. Hence, this cross-species characterization of exploratory behavior has allowed us to empirically assess and challenge the widely used animal
model of amphetamine administration for bipolar mania or schizophrenia; it suggests that more specific genetic or pharmacologic manipulations of the DAT might provide more appropriate models.

In contrast to the typical approach that starts from the human and attempts to model behaviors in animals, we adopted the reverse strategy, which has been fruitful in other contexts, such as the virtual water maze for humans. The translation of animal behavior models to humans has allowed us to differentiate groups of patients with neuropsychiatric conditions through the unique signatures of their patterns of exploration. Compared with healthy volunteers and patients with schizophrenia, patients with bipolar mania exhibit hyperexploration but do so in a highly predictable fashion. This finding is not surprising given that, clinically, individuals with bipolar mania do not classically demonstrate aimless overactivity but rather are driven by a persistent and highly focused attraction to novel, often risky situations. Furthermore, despite relatively modest sample sizes, the hBPM successfully distinguished between patients with bipolar mania and those with schizophrenia better than the symptom presentation of each of these 2 groups. This distinction between bipolar mania and schizophrenia in humans is consistent with the parallel studies in mice. Consequently, the quantification of behavior in the hBPM provides a behavioral marker of psychiatric disorders that can be directly modeled in animals. These markers may provide quantifiable indicators of the efficacy of putative therapeutic treatments that are likely to be more readily predicted by preclinical rodent screens than are standard clinical measures based on symptom rating scales.

The present findings also support the use of the hBPM in the identification of differences between patients with bipolar mania and those with schizophrenia. Although these disorders appear to share many commonalities, from risk factors, pathophysiologic features, and genetics to clinical manifestation, there are clear behavioral manifestations that have eluded empirical characterization. Thus, future use of the hBPM may assist in the discovery of novel therapeutics via guided research as opposed to current treatments of bipolar disorder, which have been discovered largely via serendipity or by the testing of medications previously approved for other disorders.

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Figure 4. The x-y plots of the tracking movements in the human and mouse Behavioral Pattern Monitors. Case examples of a healthy volunteer, a patient with bipolar disorder, a dopamine transporter wild-type (DAT WT) mouse, and a dopamine transporter knockdown (DAT KD) mouse.