Chapter 2

Using Behavioral Patterns Across Species in Mood Disorder Research

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Abstract

Measuring motor activity has been one of the most commonly used tools to assess behavior in rodents. The macroscopic measure of behavior called motor activity is actually composed of assemblies of microscopic responses however. These microscopic responses can be measured simultaneously producing multivariate profiles that reveal differential and specific patterns of effects of pharmacological, genetic, or environmental manipulations. Thus, while stimulants increase the amount of motor activity irrespective of their varying neurotransmitter effects, they produce very different behavioral patterns of exploration. Given the utility of this approach for understanding the effects of manipulations in rodents, we have recently begun measuring behavioral patterns of exploration in humans using the same microscopic measures. Unlike rating scales, this technique has yielded information on quantitative differences of exploration in multiple psychiatric populations, including bipolar disorder, methamphetamine dependence, and schizophrenia. While the exploratory patterns of the three groups differ from controls, they also differ from each other, providing us with quantitative differences which we have used to produce more patient population-specific animal models. Thus utilizing quantitative measurement of exploration in humans may provide us with (1) more specific animal models for disease states, (2) valuable insight into neural abnormalities in patient populations, and (3) quantitative assessment on the effects of treatments.

Key words: Behavioral pattern monitor, Bipolar disorder, Mania, Motor activity, Locomotion, Mouse, Exploration patterns, Cross-species assessment

1. Background and Overview

In order to develop a greater understanding of mood disorders that result in abnormal behavior, we must first understand behavior. While there are many forms of behavior, measuring unconditioned motor activity remains the most commonly utilized tool in rodents. Motor activity does not constitute a unitary class of behavior however, but in fact is composed of multiple aspects of behavior.

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This macroscopic nature of motor activity means that a univariate assessment would be overly simplistic given that it consists of assemblies of microscopic responses (1). These microscopic responses could be measured separately given appropriate definitions, criteria, and measurement tools. Multivariate assessment of behavior provides measurements that may therefore be altered by orthogonal, synergistic, or competing physical systems. Differentially affecting these systems may therefore produce varying changes in these measures, resulting in different patterns of behavior. Hence, from a macroscopic level, motor activity may be viewed as chaotic, but what we call chaos can also be viewed simply as patterns we have not yet recognized.

Generating patterns of behavior can therefore provide greater information on experimental effects than examining single measurements alone. Using multivariate assessment tools has been recognized for some time by various researchers, with different approaches proposed to quantify the various components of motor activity (2–6). Some of these approaches are based on observer ratings, while others have attempted to automate the entire measurement process (7–10). The behavioral pattern monitor (BPM; Fig. 1) is a computerized activity system created to incorporate multivariate measures of exploration. Equipped with rearing sensors (both touchplates and infra-red beams) and 11 holes in the floors and walls (that serve as discrete stimuli for rodents to investigate; Fig. 2), the BPM measures activity, specific exploration, and path patterns at high levels of temporal and spatial resolution (11). This equipment produces >50 measures of exploration (Table 1) which can be used to differentiate pharmacological, genetic, and environmental influences on exploration (see below). While these measurements are disparate, many converge on hypothetical concepts. To explore the similarities between these measurements and the fundamental dimensions reflected in these multivariate

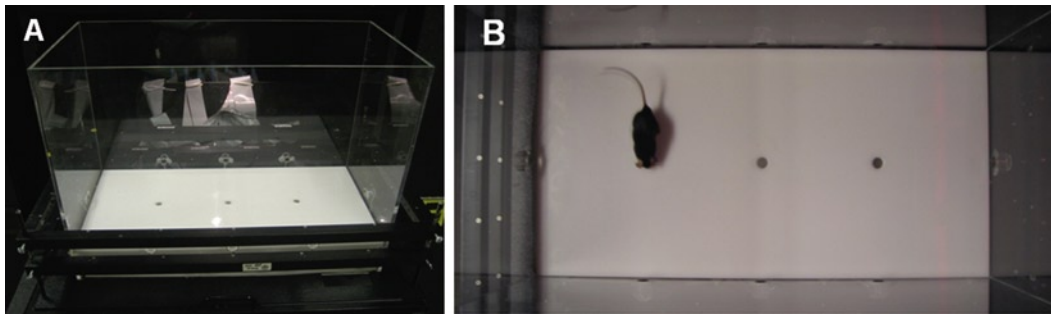

Fig. 1. The mouse behavioral pattern monitor (BPM). The mouse BPM is an activity chamber (30.5 × 61 cm). A 2.5 D view of a mouse BPM chamber in which the 11 investigatory holes (three on the near long wall, three on the far long wall, three on the floor, and one on each short wall) are visible (**a**). A top down view of mouse BPM in which the floor investigatory holes are clearly visible, as is a mouse holepoking into one of these holes (**b**).

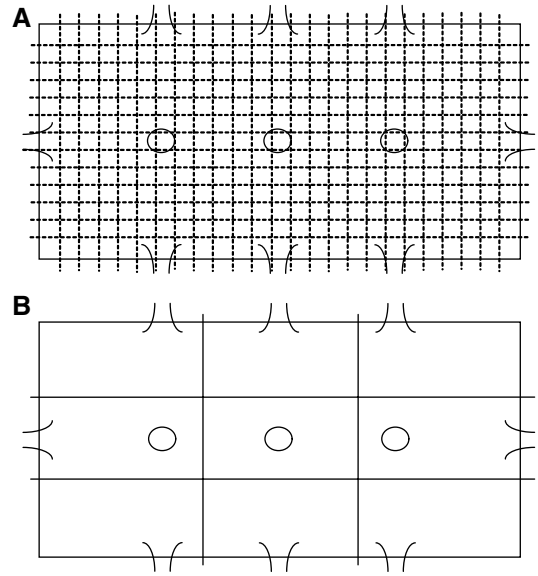

Fig. 2. Schematic of the mouse BPM. The mouse BPM records the spatial location of the mouse using a grid of 12 × 24 photobeams (*dashed lines*) located 1 cm above the floor (**a**). The chamber contains eleven 1.4 cm diameter holes (three in the floor, three on each long wall, one on each short wall), each provided with an infrared photobeam to detect investigatory holepokes (**b**). For analysis, the chamber is divided into nine unequal regions (**b**), with transitions between regions utilized as a measure of investigatory activity.

characterizations, we conducted factor analyses on the exploratory behavior of 137 rats (12). The analyses identified three primary factors (Table 1) onto which the various automated assessments of exploration loaded: the amount of activity (e.g., distance traveled, transitions, and counts); specific exploration (e.g., rearing and holepoking); and path patterns that involve novel quantitative measures based on nonlinear dynamical systems methods and fractal geometry to assess important aspects of the hierarchical and sequential organization of behavior (spatial scaling exponent d, dynamical entropy h, spatial CV, temporal CV) (2, 9, 13, 14). Together, these three factors accounted for 77% of the variance in the measures. These studies confirmed that composite variables composed of the weighted measures for each factor are highly effective in discriminating receptor subtype-specific drug effects in rats (15). While the measurements of activity levels and specific exploration are largely self-explanatory, we have provided a more in-depth explanation of path patterns below.

1.1. Linear Dynamics vs. Predefined Response Categorization

Behavior is traditionally categorized in terms of predefined response categories, even in some multivariate assessments (e.g., the OFT; (6)). Stimulant drugs disrupt normal behavioral responses however, fragmenting behavioral sequences and introducing novel elements into the normal repertoire. Thus, drug-specific categorical

Table 1
Measurements and their associated factors in the mouse behavioral pattern monitor (12)

Factor	Measure	Description
Activity measures	Counts	The cumulative number of distinct behaviors to occur during testing
	Transitions	The number of movements from one predefined area to another
	Center entries	The number of entries into the area defined as the center
	Distance traveled	Total distance traveled while exploring the chamber measured in cm
Specific exploration	Hole pokes	The total number of investigatory holepokes across all 11 holes
	Repeated poking	The number of times a hole was repeatedly poked before moving to the another hole
	Varied poking	The number of times the mouse holepoked into different holes
	Rear	The number of times the mouse reared into the air or against the side walls
	Center duration	The amount of time (s) spent in the area designated as the center of the chamber
Locomotor patterns	Spatial d	Spatial scaling exponent d measures the hierarchical and geometric organization of behavior
	Entropy h	Quantifies the sequential aspects of sequences of behavior, specifically measuring the degree to which behavior is observed along a continuum between complete order and disorder
	Spatial CV	Measures the consistency by which the animal moves from one region to another
	Temporal CV	Measures the consistency of the dwell time in each of the regions

rating scales (e.g., amphetamine stereotypy) have evolved, reflecting the fact that the arbitrary definitions of responses appropriate for normal behavior are often inadequate for the characterization of drug-manipulated behavior. Such rating scales designed for one drug (e.g., amphetamine) are often inappropriate for another drug however, even for drugs with related chemical structure such as MDMA (16). Traditional measures have fundamental problems therefore as they are (1) constrained to support inferences about the relationship of drug effects to the normal behavioral repertoire of the animal, (2) insufficient in quantifying the sequential arrangement of behavioral elements, (3) inadequate for assessing the temporal and spatial resolution of behavior, and (4) insufficient to provide comparison to other drugs. Numerous investigators acknowledge the need to quantify the sequential arrangement of

behavioral elements, yet evaluation techniques have not evolved far beyond descriptively categorizing and enumerating predefined behavioral sequences. Most of the quantitative analyses are rooted in the theory of Markov processes or involve run statistics or time-series analyses. Although these approaches have confirmed that sequences of motor acts are not independent random events but show varying degrees of interdependency, they have demonstrated only limited utility, particularly in the characterization of drug effects (1). Finally, in traditional approaches, the temporal and spatial resolution used to define the measures is chosen arbitrarily. This choice is based frequently on the qualitative separation of temporal and spatial scales. As our studies indicate, however, there appears to be no distinct separation of temporal scales. Instead, "pauses" and "behavioral actions" are found on all time scales. Moreover, this separation fundamentally neglects the hierarchical nature of behavioral organization.

To quantify behavioral patterns in sequences of locomotor behavior, we began with the following premise: behavior consists of purposefully organized sequences of acts that can be observed by the motor output of an animal or human subject. Accordingly, behavioral organization can be defined as the selection, ordering, and sequencing of behavioral elements in response to external or internal stimuli to form flexible, yet stable, macroscopic patterns of behavior. The assessment of behavioral organization, as in the case with locomotor behavior, can be approached from both hierarchical and sequential points of view. Hierarchically, behavioral elements are thought to form organized behavioral components on successively larger spatial or temporal scales. Accordingly, the evaluation should quantify the scale-invariant properties of the behavioral organization. Sequentially, behavioral elements are thought to be arranged serially into organized behavioral patterns. Thus, the evaluation should quantify the sequence length-independent properties of the behavioral organization. The path pattern measures described below were originally developed for studies of rodent locomotor activity and are now being extended for studies of humans. Two of the measures, the spatial scaling exponent d, and the dynamical entropy h, quantify the hierarchical and sequential properties of behavioral organization, respectively. These measures have several advantages over traditional rating scales and other scale-dependent assessments of motor behavior. Specifically, this approach does not depend on response categories that are defined a priori, is resolution and sequence-length independent, can be extended to include time-dependent characteristics, and allows one to obtain detailed statistical evaluations.

1.1.1. Spatial d

The spatial scaling exponent, 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 by the animal is one-dimensional or two-dimensional. Spatial d is measured by the distance traveled plotted against the number of micro-events (smallest change that can be observed) using a double-logarithmic coordinate system, generating a line of fit between these two variables (17). Spatial *d* typically varies between one (a straight line) and two (a filled plane), with values closer to one reflecting straight movements and values closer to two reflecting highly circumscribed, local movements. At both ends of this spectrum, the geometric pattern of movement around the BPM is highly predictable and can exhibit the same level of activity but describe almost straight line or highly circumscribed geometrical patterns.

1.1.2. Entropy h

Entropy *h* quantifies the sequential aspects of sequences of behavior, specifically measuring the degree to which behavior is observed along a continuum between complete order and disorder (18). Briefly, a given sequence of activity is compared to 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. Thus, there are commonalities in the sequences of activities being compared and future sequences could be predicted based on earlier sequences. Higher values (high entropy) suggest a greater variety, or disorder, in the level of motor activity, where the sequences being compared are not similar and are thus unpredictable from one sequence to another (see (19)).

1.1.3. Spatial CV

The spatial CV statistic describes another aspect of the spatial pattern of the animal's movement. Spatial CV measures the degree to which an animal makes the same repetitive transitions from one area to another. A transition matrix can be made of the transitions between different regions of the chamber, e.g., the corners, walls, and center. A preferential exhibition of a subset of transitions results in a high coefficient of variation (CV), reflecting the repetitive preference of certain transitions, i.e., repeatedly following the same path. A highly varied pattern transition lowers CV, i.e., different paths chosen (17, 20).

1.1.4. Temporal CV

Analogously, the length of time spent in each of the regions can also be quantified and used to calculate a CV statistic in the temporal domain. Thus, temporal CV defines the degree to which the animal remains in one area or distributes its time across multiple areas (high vs. low temporal CV respectively; (20)).

Collectively, such descriptors as spatial scaling exponent d, dynamical entropy h, spatial CV, and temporal CV assess various aspects of the hierarchical and sequential organization of behavior at a temporal macroscopic level (see e.g., Fig. 3 of paths that generate variations in these measures). This approach using nonlinear measures has provided a useful complement to the more traditional

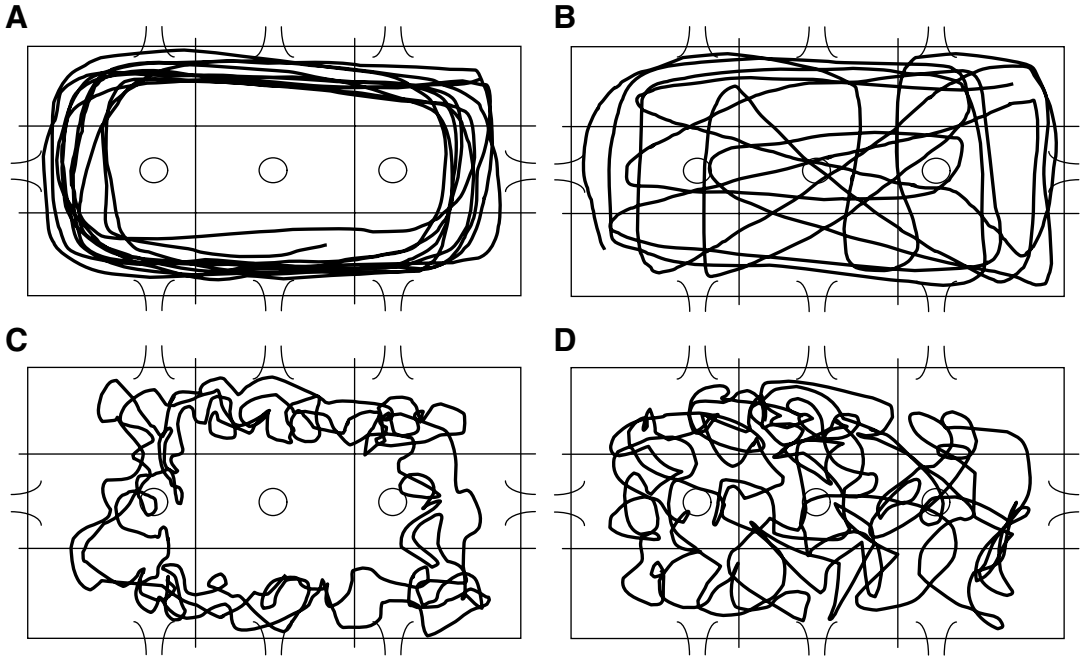

Fig. 3. Hypothetical examples of locomotor path patterns that can be measured in the mouse BPM. The spatial location of the mouse during exploration of the BPM is recorded using banks of photobeams. The path of the mouse as it moves through the BPM is continuously recorded and can be recreated for path analysis. The path of a mouse that was recorded to exhibit a low spatial d (long linear movements through space), high spatial CV (transitions made from one region to another consistently), and a low entropy h (predictable pattern of behavior) would resemble (**a**). The path of a mouse that was recorded to exhibit low spatial d, low spatial CV (transitions from one region to another that are random), and low entropy h would resemble (**b**). The path of a mouse that was recorded to exhibit a high spatial d (localized meandering movements in the chamber), high spatial CV, and low entropy h would resemble (**c**). The path of a mouse that was recorded to exhibit a low spatial d, spatial CV, and entropy h would resemble (**d**).

behavioral profiles based on a priori definitions of categorical events (10, 21).

1.2. Differentiating Stimulant Effects Using a Multivariate Approach

The multivariate approach of assessing activity, specific exploration, and path patterns has provided us with greater clarity on the differential effects of manipulations on exploratory behavior. We and others have used a multivariate approach to elucidate the behavioral characteristics and neuropharmacological mechanisms of psychoactive drugs (22, 23). Stimulants such as amphetamine, apomorphine, caffeine, 3-4-methylenedioxymethamphetamine (MDMA), nicotine, and scopolamine induce similar increases in the amount of activity (albeit dose-dependent), as measured in either the Open Field, photobeam activity chambers, or the BPM (11, 16, 24–32). Differential effects have been noted however, when even the simplest of multivariate assessments is used. For example, caffeine increases activity but also increases specific exploration as measured by rearing behavior in the Open Field and BPM, as well as holepoking in the holeboard and BPM (11, 25, 30, 33).

Nicotine had no effect on rearing behavior in the Open Field or BPM however, (11, 30), with higher doses of nicotine reducing activity and holepoking behavior (34, 35), likely due to hypothermic effects. The direct dopamine agonist apomorphine inhibits holepoking behavior (11, 36), consistent with MDMA, which releases presynaptic serotonin rather than dopamine (16). Stereotypy is observed in conjunction with both amphetamine- and apomorphine-induced hyperactivity (11, 37–39). Higher doses are required for amphetamine-induced stereotypy however, (36), and the nature of the stereotypy induced varies, with amphetamine at low doses simply producing an exaggerated wide range of activities, while apomorphine produces a more restricted behavioral repertoire (37, 40), and MDMA produced repetitive behaviors that could not be readily scored using the rating scales defined for amphetamine-treated animals (16). Multivariate assessments of behavioral patterns are therefore required, where fine discriminations can be made as to the distinctive characteristics of the behavioral profiles and thus potentially unique effects of compounds.

These stimulants also vary in their effects on path patterns. While apomorphine, MDMA, and scopolamine increased spatial CV, reflecting the generation of more repetitive patterns of movements, amphetamine increased the variety of movements, lowering spatial CV, while neither nicotine nor caffeine had any significant effect on spatial CV (11, 16). Differing effects are observed using the spatial d measure: apomorphine and scopolamine lowered spatial d, suggestive of path patterns with straighter lines; amphetamine increased spatial d at low doses and had variable effects at higher doses; neither nicotine nor caffeine affected spatial d (11, 41). Amphetamine and MDMA increased entropy h, suggesting increasingly disordered movement, while higher doses of MDMA lowered entropy h, suggesting more ordered and predictable paths (19). Temporal CV is the only path pattern measure that is consistently affected by all these psychostimulants, with amphetamine, apomorphine, scopolamine, nicotine, and caffeine all lowering temporal CV. In general, unlike the other measures of path patterns, the temporal CV measure is strongly and inversely related to the amount of activity.

Thus, despite the common psychostimulant label for all these compounds, they produce distinctive behavioral patterns that can be readily differentiated using multivariate assessments. Such differentiation should not be surprising given the different mechanisms of actions of each of these drugs. It is reassuring to know that behavioral analysis of spontaneous locomotion and exploration can differentiate between these drugs in a manner that is consistent with their differential pharmacological mechanisms. For example, amphetamine-induced blockade of norepinephrine, dopamine, and serotonin transporters increases extracellular levels of these neurotransmitters throughout the CNS leading to the myriad of effects observed, while scopolamine primarily acts as a muscarinic receptor

antagonist. Hence, other drug-induced manipulation of these neurotransmitter systems can also cause hyperactivity and altered exploratory behavior and locomotor patterns.

Numerous neurotransmitter systems have been implicated in the pathophysiology of mood disorders. These systems can be investigated specifically using this multivariate approach in animals. For example, a reduction of norepinephrine in the locus coeruleus reduced specific exploration in rats, as measured by holepoking and rearing behavior (11, 42). Because either intra-ventricular or intra-hippocampal infusions of norepinephrine increase locomotor and specific exploration (43, 44), norepinephrine is likely to assist in maintaining normal exploratory behavior. Moreover, evidence suggests that β-adrenergic receptors may play a role in these noradrenergic effects (45). Such findings demonstrate the utility of the BPM because patients with mood disorders exhibit reduced volumes of brain regions that are major sources of norepinephrine in the CNS (46). Moreover, the turnover rate of norepinephrine in BD patients is increased compared to controls as measured by urinary and plasma levels, as well as postmortem analyses (47–50). Recently, we demonstrated that patients with BD mania exhibit increased activity, specific exploration, and more linear movement in the human BPM ((51) see below). Therefore, investigating the links between neuropathology in mood disorders and the mechanisms that subserve exploration in rodents may provide an avenue for the development of novel therapeutics to treat BD.

Other neurotransmitter system abnormalities may contribute to mood disorders but have received limited investigation. For example, the mAChR antagonist scopolamine increases locomotor and exploratory activity, while lowering spatial CV, temporal CV, and spatial *d* (11, 52). Depending upon dose and timecourse, the nicotinic acetylcholine receptor (nAChR) agonist nicotine can increase or decrease locomotor activity, presumably via actions at the α4β2 nAChR, but has limited effects on other domains of exploration. Noncompetitive NMDA antagonists, such as dizocilpine and phencyclidine, also act as stimulants (53), increasing and decreasing holepoking activity at low and high doses respectively, and inducing perseverative path patterns. Phencyclidine administration results in animals running in circles or figure of eight patterns while dizocilpine increases small localized movement activities in the corners (20). This list is not intended to be exhaustive since the primary goal of this chapter is to provide information on the cross-species translational utility of exploratory behavior. Thus, while the majority of these studies to date have been conducted in rats, we have since extended this exploratory paradigm into other species.

1.3. Cross Species Translation of the BPM

1.3.1. Rat to Mouse

The development of a mouse BPM was important on several levels: (1) since mice are more readily modified genetically, mutant disease models or knockout (KO) animals can be generated (51, 54) and utilized to complement pharmacological studies of receptor

subtypes (55–58); (2) evidence for cross-species generalization increases the likelihood that findings will be of relevance across other species including humans (51, 59, 60).

Initial studies in the mouse BPM investigated which dopamine receptors contributed to the exploratory effects of MDMA using various dopamine receptor KO mice. MDMA increased activity, lowered spatial d, and increased spatial CV in wild-type mice (56) consistent with rats (16). Dopamine D1 KO mice exhibited an exaggerated responsiveness to the MDMA-induced increases in locomotor activity, while dopamine D2 KO mice exhibited a reduced amount of MDMA-induced activation (56). Although MDMA-induced hyperactivity was unaffected in dopamine D3 KO mice, these mice did not exhibit the same immediate MDMA induced-increase in perseverative locomotor path patterns (spatial CV). Altered exploration in these mice also suggested that D1 receptors may contribute to the locomotor pattern quality, i.e., linear vs. circumscribed movement (spatial d), while D2 receptors may contribute to perseverative or thigmotactic locomotor effects of MDMA (spatial CV). Thus, by utilizing genetic mutations, the mouse BPM provided information on receptors that (a) contribute to basic exploratory behaviors, and (b) mediate drug effects on exploration.

The mouse BPM has since been used to examine the contribution of the corticotropin releasing factor (CRF) receptor subtype 2 (CRF2) to alterations in exploration induced by isolation rearing during development (55). CRF2 KO mice exhibited a hypersensitivity to isolation rearing, with increased activity, holepoking, and temporal CV observed in these mice relative to isolation-reared wild-type mice (55). In another application of the mouse BPM, the hallucinogen 1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane (DOI) increases activity at low, while reducing activity at high doses. DOI-induced hyperactivity was absent in 5-HT2A KO mice however, while DOI-induced decreases in activity were attenuated with coadministration of a 5-HT2B antagonists, suggesting that these receptors mediate different aspects of DOI-induced alterations in activity (57). Other hallucinogens such as psilocin are affected by 5-HT2A, 5-HT2C, as well as 5-HT1A receptors also (61). Interactions between hallucinogens and other neurotransmitter systems can also be investigated, e.g., metabotropic glutamate receptor 5 KO mice exhibit an increased behavioral response to the 5-HT2A agonist hallucinogen DOM (2,5-dimethoxy-4-methylamphetamine) (58).

The exploratory profiles of genetic mouse models of mood disorders have also been assessed in the mouse BPM (51, 54). Using a traditional open field test, we found that mice with reduced (10% compared to WT littermates) dopamine transporters (DAT) exhibit increased activity and more linear movement (reduced spatial d) (62). Moreover, acute doses of the mood stabilizer valproate (200 mg/kg) reversed these effects (62). We have since confirmed

in the mouse BPM that in addition to their locomotor hyperactivity, DAT KD mice also exhibit increased specific exploration (hole-poking) and reduced spatial d (51, 54). This pattern of exploratory behavior is consistent with mice administered the selective DAT inhibitor GBR 12909 (51, 54, 63). Given evidence that the DAT polymorphisms associated with BD result in reduced number and/or function of the DAT (64, 65), we recognized that gaining knowledge of the exploratory behavior of patients using a similar multivariate approach was paramount.

Importantly however, the mouse studies described here provide evidence for the utility and cross-species generalizability of the BPM.

1.3.2. Rodents to Humans

As reviewed here, multivariate assessment of exploratory behavior has borne a richness of results in terms of elucidating the underlying neural mechanisms of drugs in rodents. To date however, the extent of this work has not been paralleled by similar studies in humans. Consistent with early studies in rodents, initial activity studies in humans were limited to measuring motor activity only, using a wrist or leg actigraph (66–68). While these reports in psychiatric populations are consistent with expectations (increased activity in patients with attention deficit hyperactivity disorder and BD), these data are limited by their univariate assessment. Pierce and Courchesne (69) attempted a multivariate assessment of exploratory behavior in autistic children by rating videotapes of subjects left in a room with colorful and interactive objects for 8 min. The observers' ratings of decreased exploration were correlated with MRI-based measures of altered brain volumes in children with autism. These data support the hypothesis that a human exploratory paradigm would be useful in detecting behavioral deficits that are associated with brain dysfunction. The vast majority of studies on hyperactive behavior in these patient populations, however, have been limited to observer-rated and self-report scales. As discussed above, such scales: (a) may not be optimal in detecting potentially subtle alterations in activity levels; (b) are minimally effective in distinguishing psychiatric populations; and (c) do not provide the opportunity for cross-species comparisons.

In light of the paucity of quantitative multivariate assessment tools in psychiatry despite the number of disorders described as having altered motoric behavior, we recently developed a human version of the BPM. This human BPM was designed to be analogous to the rodent BPMs described above in which we would be able to rapidly and sensitively quantify activity, specific exploration, and path patterns in humans (59). The apparatus for the human BPM is described in detail below but is essentially a room that the human participant has not been exposed to and therefore, consistent with the rodent BPM, is a novel and unfamiliar environment. Eleven objects deemed to be safe, colorful, tactile, and manipulable

and are placed dispersed throughout the room on items of furniture. These objects provide an analog of the exploratory holes in the walls and floor of the rodent BPM chambers. Participants are directed into the room and are asked to wait for the experimenter to return. The human BPM session has been 15 min long in our studies to date. Using a camera mounted in the ceiling and automated tracking software, we are able to generate X-Y coordinate locations for the subject in the room. The precise measurements and their collection are described below. In brief however, we are able to capture information on the activity, specific exploration, and path patterns of human subjects, consistent with that of the rodent studies described above.

To date, we have quantified the spontaneous exploration of acutely ill patients with BD mania and schizophrenia, as well as subjects dependent upon methamphetamine (MD) (51, 70–72). These three groups demonstrate strikingly different exploratory patterns of behavior, once again highlighting the importance of multivariate assessment of activity, where measurement of multiple parameters may yield distinct "signatures" of exploration that characterize and differentiate these disorders. From a diagnostic perspective, these signatures of exploration may provide an obvious and meaningful difference between acutely ill populations who are difficult to distinguish because they present with psychotic and mood symptoms (73).

Consistent with the differentiation of stimulants in rodents described above, patients with schizophrenia, BD, and MD exhibit unique patterns of exploratory behavior. For example, patients with BD exhibit hyperactivity in the first 5 min in the hBPM, with rapid habituation, patients with schizophrenia exhibit hyperactivity only in the last 5 min (51), while MD subjects do not exhibit hyperactivity at any timepoint (72). Interestingly, both patients with BD and schizophrenia exhibit increased entropy h and reduced spatial d, the latter being more prominent in patients with BD (51). These data suggest that both schizophrenia and BD patients exhibit more disorganized but straighter line movement through space when compared to controls (51), while MD subjects did not differ from control subjects (51). Both BD patients and MD subjects exhibited increased specific exploration (object interactions), while patients with schizophrenia did not differ from healthy comparison subjects (51, 71). These specific abnormal patterns and the availability of an animal version therefore provide the opportunity to dissect the abnormal neuroanatomy that underlies these changes.

Interestingly, the increased object interaction of MD subjects correlated with a number of perseverative errors they made on the Wisconsin Card Sorting Task, a cognitive task mediated by the frontal lobes (72). Subjects whose frontal lobes were lesioned exhibit inappropriate "grasping" behavior of objects that are within reach (74). There may therefore be a link between this simplistic

measure of exploratory behavior and frontal functioning, which could be useful given that frontal dysfunction is associated with mood disorders (75–77). Recently, we also demonstrated that DAT KD mice exhibit increased risk taking behavior in a rodent model of the human Iowa Gambling Task, a frontally mediated behavior (78), that also correlated with increased specific exploration (holepoking) in these mice (79). The evidence for the utility of assessing behavioral patterns of exploratory behavior across species is therefore growing.

2. Equipment, Materials, and Setup

2.1. Rodent Behavioral Pattern Monitors

Both rat and mouse BPMs (Fig. 1) exist that can quantify exploratory behavior. Each chamber consists of a 30.5 × 61 × 38-cm area with a hole board floor equipped with three floor holes and eight wall holes (three along each side of the long walls, and two holes in the front and back walls). Each hole (rat = 2.5 cm, mouse = 1 cm) is equipped with an infrared photobeam to detect nose poking behavior. Each chamber is illuminated from a single light source above the arena (producing 350 lux in the center, and 92 lux in the 4 corners). For the mouse BPM, a grid of 12 × 24 infrared photobeams 1 cm above the floor records the location of the mouse every 0.1 s (Fig. 2). For the rat BPM, a 4 × 8 grid records the rat's X-Y position. To measure rearing behavior, the mouse BPM has an array of 16 infrared photobeams 2.5 cm above the floor and aligned with the long axis of the chamber, while the rat BPM has touchplates located 15.2 cm high on the walls. The position of the mouse and rat is defined across nine unequal regions (four corners: 9.375 × 16.875 cm, four wall regions: long, 9.375 × 26.25 cm, short, 11.25 × 16.875 cm, and a center: 11.25, 26.25 cm (11, 56)). At the start of each test session, the rodent is placed in the bottom left hand corner of the chamber, facing the corner and the test session started immediately.

2.2. Human Behavioral Pattern Monitor

The human BPM takes place in a room that, at least for the initial test of a subject, is novel and unfamiliar environment to the human participant. Subjects wear an ambulatory monitoring vest that measures accelerometry in digital units at 10 Hz, stored in an onboard PDA. Currently, we have used both 2.7 × 4.3 and 3.5 × 4.9 m rooms. To date, no discernible differences between these rooms have been observed. The rooms are furnished with a desk, two bookcases, a small file cabinet, and a large file cabinet. On these furnishings are placed 11 small but visually engaging objects. These objects were chosen using the criteria that they be safe, colorful, tactile, and manipulable and thus may promote human exploration. The toys are used as an analog of the exploratory

holes in the walls and floor of the rodent BPM chambers. Specific exploration is also counted for exploration of drawers in a cabinet, manipulation of blinds over the window, and the accelerometer's recording device housed in the fanny-pack around the subject's waist. Participants are escorted into the room and are asked to wait for the experimenter to return after setting up testing equipment elsewhere. The subject is then left alone in the room and so far all sessions have been 15 min long.

Data in the human BPM are gathered using three sources of measurement: (1) x-y coordinates of the subject's spatial location in the BPM, extracted from digital video recording (a video camera is embedded in the ceiling (51)); (2) experimenter ratings of exploratory activity, obtained by carefully scoring the video recording of the BPM session and measuring events such as interactions with objects (51, 71); and (3) motor activity of the subject's torso, using an accelerometer embedded in an ambulatory monitoring device that the participant wears (51, 70). It is hypothesized that similarly to the rat and mouse BPMs, three main independent factors will emerge, describing activity (counts, transitions, accelerometry), specific exploration (object interactions), and sequential organization of behavior (spatial d and spatial CV).

The digital videos of subject activity in the human BPM are subjected to frame-by-frame analysis with proprietary software (Clever Systems, Inc.1999), which generates x- and y-coordinates of the subject's location at the rate of 30 Hz. Activity can be measured by total distance traveled or transitions across nine regions of the human BPM. These regions are analogous to our definition of nine areas of the rodent BPM, the four corners, four walls, and the center (11). These data therefore enable us to obtain a distribution of amount of time spent in each region as well as to measure the number of transitions, consistent with the rodent work as movement from one region to an adjacent one. In any event, transitions between regions and dwell times within specific regions can serve as additional measures to describe different aspects of locomotor activity (51).

The video footage also enables the assessment of specific exploratory behaviors of the participant. Trained observer rating analysis is conducted on (1) total object interaction, (2) total amount of time spent with all objects, (3) multiple object interactions, (4) percent of perseverative interactions, (5) wear mask/glasses, and (6) explore drawer (for measurements and definitions see Table 2) (71).

Accelerometry data are generated using the LifeShirt System (80), an ambulatory, multisensor, continuous monitoring system that also collects data using respiratory inductive plethysmography bands, which measure pulmonary function, electrical activity of the myocardium via a three-lead EKG, and activity/posture via a two-axis accelerometer (51, 70, 81). To measure activity levels, a two-axis

Table 2
Observer rating of subjects behavior in the room – focus on object interaction (71)

Measure	Description
Object interaction	When subject makes any physical contact with the object, including when the object is in the hand, on the foot, becomes a physical extension of the body, or is used to push, poke, prod, or otherwise make physical contact with any other object or item of furniture
Mean time spent with objects	Totaling the number of seconds a subject spent interacting with objects during the 15-min period and dividing by the total object interactions
Multiple object interaction	Any instance a subject interacts with more than one object at the same time. Should a subject pick up a new object, it is scored as another multiple object interaction; however, if that same object (or one of the other objects the subject is interacting with) is put down, a new MOI is not scored
% perseverative interaction	The total number of objects a subject touched more than once divided by the total number of objects in the room
Wear mask/glasses	Subject places the mask or glasses on head (or arm, waist, leg, etc.) and releases the object completely – but the object is still on subject
Explore drawer	The instant a subject first opens a drawer to the instant they close it and release the drawer
Time spent walking	Time the subject takes one or more steps in any direction, (forward, backward, sideways, or diagonal) or when the subject shifts weight from one foot to another
Time spent sitting	Time the subject sits at the desk, cabinets, or floor

accelerometer is placed onto the shirt over the sternum, and the rectified and integrated accelerometer signal detects periods of physical activity and rest. An on-board PDA continuously encrypts and stores the patient's activity and postural physiologic data on a compact flash memory card. Accelerometry data are sampled at 10 Hz and stored numerically in digital units.

2.3. Data Acquisition

The primary dependent variables of interest were locomotor activity as measured by transitions (calculated as a movement across a defined region) and center entries (cumulative entries into the center region); specific exploration as measured by holepoking, rearing, and center duration (cumulative time spent in the center); and locomotor exploratory pattern as measured by spatial *d*. Spatial *d* uses analyses based on fractal geometry to quantify the geometrical structure of the locomotor path, where a value of 2 represents highly circumscribed localized movement, 1 represents straight line distance covering movements (17).

2.4. Troubleshooting

With sufficient resolution, multivariate assessment of exploratory behavior is possible. The patterns of behavior of animals with experimental manipulation do not apparently change with chamber size (82), or whether the chamber is square, rectangular, or circular (83). Consistent with other tests of exploratory activity in rodents, rats and mice habituate with repeated exposure to the same environment, displaying less exploration when compared with previous exposures (54). Altering the environment at the time of repeated testing can reinstate exploration patterns however. The environment can be altered by altering the floor (e.g., changing from acrylic to sandpaper), or adding odorant objects (with or without odors) in the holes (encourages specific exploration) (43, 54). When assessing behavior across strains, the shape of the animal may contribute toward strain differences. For example, the lower levels of holepoking of 129 compared to C57BL mice may be due in part to the shorter nose of the former strain. GBR12909-induced increases in specific exploration can be observed in both groups however, suggesting that selective DAT inhibition increases specific exploration irrespective of the background strain (63). Finally, because of the use of infra-red beams to detect movement in the BPM, the size of the animal may make a difference in the level of activity recorded. For example, mice that are 20 g may appear less active in terms of distance traveled than mice of 45 g because the latter mouse would break more beams as it moves through space. If size differences are an issue, performance can be analyzed using weight as a co-varying factor.

2.5. Cleaning

The rodent BPM chambers should always be cleaned between testing cohorts using water and wipes (leaving no odor of a cleaning product). The pattern of cleaning should not be repetitive, e.g., do not clean in a circle, spiral figure eight etc., in order to avoid laying an odor trail of the previous animal. When cleaning between testing subjects, clean at least in all areas that the animal can conceivably touch. When time allows (at least 12 h before testing a new cohort), clean all chambers with a cleaning product and after cleaning air out as much as possible. When cleaning between cohorts, clean the whole chamber thoroughly. The human BPM must simply be kept clean and clear of any objects other than those strategically placed there.

3. Procedure

The rat, mouse, and human BPMs follow very similar procedures. The subject is introduced to the chamber with little to no guidance on what behavior is expected. In the rat and mouse BPMs, the subject is placed in the bottom left corner facing the wall and

behavior is recorded immediately. In the human BPM, the subject is asked to wait while other equipment is set up and the experimenter will return soon. When the door is closed, the recording of their exploratory behavior begins. The video recording is monitored at all times to ensure the subject is not doing anything that may hurt themselves or damage anything in the room. At the end of the allotted time (rodent BPM has run anything from 15 to 180 min, human BPM 15 min to date only), the subject is removed from the chamber/room.

Exploration in the rodent BPM can be assessed under white, red, or no light conditions. Moreover, the lighting in the holding area of the rodents can be under white or red lighting. Although never directly assessed, the primary difference of white or red lighting in the rodent BPM is the amount of activity in the center of the chamber, decreased vs. increased activity respectively. To date, the human subjects have always been tested under white lighting.

4. Anticipated Results

Certain results can be expected in the rodent BPMs. Within a 60-min session, the subject will habituate to the testing chambers and the level of activity will reduce over time. The spatial scaling exponent d typically increases over time, suggesting that animals start to meander and perform localized investigatory movement as time goes on. Consistent with some of these behaviors, the rate of investigation of objects by humans does not alter over time, while spatial d does increase over time.

As described above, multiple assessments of the same subject in the BPM will result in lower activity and specific exploration levels with increased spatial d and a more rapid within-session habituation compared to BPM-naïve animals. Altering the environment (e.g., sandpapered floors or objects in the holepoke areas) can reinstate initial exploration levels in rats and mice however. Repeated testing analysis has yet to be fully quantified in the human BPM but data are being generated.

5. Discussion

In conclusion, using the BPM to provide a multivariate assessment of exploration is an important example of cross-fostering translational research. Exploratory behavior in rodents is a complex phenotype that is not sufficiently characterized by univariate approaches. Instead, measures that quantify its temporal, spatial, and dynamic organization have proven to be valuable tools to differentiate the

contributions of different neural transmitter systems on locomotor and exploratory behavior. Similarly, multivariate approaches to human exploratory behavior have provided powerful insights into the different patterns exhibited by clinical populations that are often difficult to distinguish from one another during acute illness. The identification of these patterns in a cross-species task provides an opportunity to (a) develop better animal models of these disorders, (b) investigate the neural bases of these behaviors, (c) quantitatively assess current and developing treatment effects, and (d) may provide new biomarkers as targets for the development of novel therapeutics.

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