

Modeling facets of mania – new directions related to the notion of endophenotypes

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Abstract

The lack of appropriate animal models is a major limitation in research of bipolar disorder (BPD) as at this time there are very few models for this devastating disease. Whereas limited attempts were made to develop comprehensive models for BPD, the new notion of endophenotypes encourages us to explore the possibility of developing separate models for separate facets of the disorder. Since more models are available for depression, there is a dire need for models for mania that will be relatively easy and simple to induce and test and will therefore be practical for purposes of screening possible new drugs or mutant mice that are developed based on novel molecular theories. Such models may already be tentatively available as they were developed in the context of other disorders, but there is a need to validate them for mania.

The present paper proposes such models for most of the facets of mania including: increased energy, activity or restlessness; extreme irritability; reduced sleep; provocative, intrusive or aggressive behavior; increased sexual drive; abuse of drugs; distractibility, reduced ability to concentrate; and unrealistic beliefs in one's abilities and powers resulting in poor judgment.

Validating these models may demand a major research effort but it may be worthy as validated models for the different facets of mania could then be used efficiently and may also be utilized to construct a standard battery of tests that can serve to explore the various components of manic-like behavior in rodents.

Key words: Bipolar disorder, Mania, Animal models, Endophenotypes, Facets of disease, Validity, Test battery.

Introduction

Defining the need

The first conclusion of a 2002 workgroup under the auspices of the National Institute of Mental Health (NIMH) strategic planning initiative for mood disorders research was that “the field **desperately needs better animal models** of depression and mania.” The workgroup summary further explains that the lack of appropriate animal models “is one of the major limitations in the ability of the field to **translate findings** in genetics and molecular and cell biology to the clinic” and that “without such improved models of human disease, it is impossible to know whether particular molecular and cellular findings in animals are isolated epiphenomena or relevant to the clinical situation” (Nestler et al., 2002).

Animal models are essential for translational research, bringing novel molecular and biochemical findings into the realm of a behaving organism. However, modeling psychiatric disorders is a difficult task because (a) we do not know the biological bases of the disorders and (b) much of the clinical diagnosis is based on psychiatric interview (rather than biomarkers) and we can't converse with our animals. Modeling affective disorders includes an additional level of complexity since we accept that animals have emotions (the behavioral outcome of affect in humans) but we do not know that they have affect. On top of these difficulties, modeling bipolar disorder (BPD) stands out in its complexity because of the oscillating nature of the disease (Kofman and Belmaker, 1991; Einat et al., 2000; Nestler et al., 2002; Einat et al., 2003).

At this time, practical animal models for the entire scope of BPD are in fact non-existent and the common practice is to use separate models for depression- and mania-like behaviors. This was considered a major flaw of such models but new thoughts about the nature of BPD may suggest that separate models for facets of the disease may in fact be very helpful for drug development as well as for research of the basic pathophysiology of BPD. Specifically, in recent years there is a significant support for the notion that BPD (as other psychiatric disorders) is a heterogeneous disease that may contain a cluster of symptoms that can be reduced and dissected into component parts (endophenotypes) at both behavioral and genetic levels (Lenox et al., 2002). This new notion of endophenotypes of disease should impact the field of animal models in two ways: 1) modeling facets of the disease and 2) attending to individual differences in animals as a way to probe the genetic basis of specific behavioral components.

The intention of the present paper is to examine the first aspect, exploring possible tentative models for the different facets of the disorder. Whereas attending to individual variability is also an extremely important aspect of modeling endophenotypes, it is dependent on first developing appropriate models for the facets of bipolar disorder which should therefore be our first goal. Additionally, simple models for the separate components of the disorder, which can be induced quickly and tested in an efficient manner, may be an extremely important set of tools for screening of either drugs or mutant animals. Such tools are critical at this time as the available models lag behind the efficiency of drug discovery and mutagenesis processes (Tecott and Nestler, 2004).

Bipolar disorder includes both depression and mania symptoms but modeling depression had been dealt with more heavily, probably because of the higher prevalence of major depression in the population compared with BPD that resulted in significant

investment by major pharmaceutical companies in the attempts to develop better, more specific drugs for depression. These efforts can support the research in BPD since models developed for major depression can also be used to model depressive episodes of BPD. However, no major attempts have been done to develop new models or test batteries that will represent the manic episodes or the oscillatory nature of BPD.

The development of new models for mania is an important task but is a time consuming process. I believe that as a practical possibility we can try and explore existing models and tests that are used in other contexts. Such tests, if validated for mania, can be utilized to develop a battery of relatively simple alternatives to test new antimanic drugs or mutant mice. In order to explore such possible models we have to investigate the different components (signs and symptoms) of manic episodes and search for similar phenomena in laboratory animals (preferably rodents) that are easy to induce and easy to measure.

Basics of modeling

Animal models have to be induced, tested and validated. The induction phase is where a manipulation is used that results in a change to the normal animal in a way that somehow reflects a diseased state whereas the accompanying test is geared to demonstrate the change and differentiate in a quantitative measurable way the “healthy” versus the “sick” animals (Szechtman and Eilam, 2005). Induction of models is usually done in one of three ways: pharmacological, environmental/behavioral or genetic.

- Pharmacological – by administering drugs to animals that affect their behavior.
- Behavioral/environmental – by changing the environment of the animal in a way that will influence its behavior.
- Genetic – either by inbreeding for specific traits or, in the last decade by directly manipulating genes.

A variety of tests were developed to examine the behavioral changes that are relevant to the modeled disease, some specific tests will be discussed later.

Validity of models is usually evaluated on three axes: face validity, predictive validity and construct validity (Willner, 1991; Einat et al., 2003).

- Face validity reflects the resemblance in behavior between the model animal and the afflicted person.
- Predictive validity reveals the effects of drugs: the improvement in the animal condition after treatment with drugs that improve the human disease (and the lack of effects of other drugs that are not effective for the treatment of the human disease).
- Construct validity relates to a possible biological mechanism that is involved in the disease and in the model. Unfortunately we do not know the underlying pathophysiology of mania so construct validity can only be hypothetical.

Modeling facets of mania

The most frequently used models for mania emphasize one facet of the disorder – hyperactivity. The reason for that is probably simplicity as hyperactivity can be easily induced (using psychostimulants is the common way) and easily measured (using a

variety of automated equipment such as activity monitors or videotracking systems). However, it is clear that hyperactivity by itself does not represent mania as not every hyperactive individual is manic (for example, ADHD is another disorder that induced hyperactivity) and not every manic patient must be hyperactive. It is clear that attempts to model mania must include other components of the disorder:

Manic signs and symptoms that are used in clinical diagnosis include (modified from NIMH disorders site at <http://www.nimh.nih.gov/publicat/bipolar.cfm#bp1>).

- Increased energy, activity or restlessness
- Excessively “high”, overly good, euphoric mood
- Extreme irritability
- Racing thoughts and talking very fast, jumping from one idea to the other
- Distractibility, reduced ability to concentrate
- Reduced sleep
- Unrealistic beliefs in one’s abilities and powers
- Poor judgment
- Spending sprees
- A lasting period of behavior that is different than usual
- Increased sexual drive
- Abuse of drugs, particularly cocaine, alcohol and sleeping medications
- Provocative, intrusive or aggressive behavior
- Denial that anything is wrong.

On its face, not all of these signs and symptoms can be modeled in animals. Although some of us, behavioral scientists who had been working with rodents for years, sometimes feel that we can communicate with our animals, this is not a scientific claim and therefore any sign or symptom that is based solely on the patients’ verbalization of their feelings or mood can not be modeled. As such symptoms such as euphoric mood, racing thoughts, unrealistic beliefs in one’s powers, spending sprees and denial cannot be tested in animals.

Yet, many facets of the disease are clearly behavioral (or can be extrapolated to behavior) and therefore can be objectively measured and consequently modeled. These components include:

- Increased energy, activity or restlessness.
- Extreme irritability.
- Reduced sleep.
- Provocative, intrusive or aggressive behavior.
- Increased sexual drive.
- Abuse of drugs (measures of drug response and measures of hedonistic, pleasure seeking behavior).
- Distractibility, reduced ability to concentrate (measures of distractibility and switching).
- Unrealistic beliefs in one’s abilities and powers and poor judgment (measures of risk-taking behavior).

Facets of mania that may be impossible to model in rodents include: excessively “high”, overly good, euphoric mood; denial that anything is wrong; racing thoughts and

talking very fast, jumping from one idea to the other; spending sprees and a lasting period of behavior that is different than usual.

A good battery of models for mania should include as many as possible of the components of mania and a number of ways to induce each of these components therefore offering the researcher a wide arsenal of possibilities to attempt and translate any novel molecular or biochemical finding into the behavioral arena.

Pharmacological induction of models may be the quickest way and therefore the most appropriate for a test battery, followed by behavioral/environmental induction (when the procedure is relatively simple) and by genetic induction either by breeding or by targeted mutations which is the most time-consuming. However, pharmacological induction has its own disadvantages as the target of the drug is known and may be unrelated to the disorder therefore limiting a-priori the model for both drug screening and for any research related to the etiology or pathology of the disease. For example, reserpine-induced hypoactivity is a commonly used model for the screening of antidepressant drugs e.g. (Einat et al., 1999) but we know that reserpine depletes all monoamines whereas there is no depletion of monoamines in depressed patients (Willner, 1984). Environmental/behavioral induction may be a better choice if the procedure is quick enough and especially when the environmental manipulation is similar to events that may trigger the disease in patients. For example, exposure to inescapable predator odor can be quickly induced and is a traumatic event for a rodent that results in long lasting anxiety that can be easily tested and may model components of PTSD (Cohen et al., 2003). Genetic manipulations models were developed using selective breeding in rats and more recently, using targeted mutations in mice. For example, the Flinders Sensitive Line of rats demonstrate a number of depression-like behaviors that are responsive to antidepressants and can be helpful in screening new antidepressant drugs and in the study of the psychopathology of depression (Osterlund et al., 1999; Einat et al., 2002). Targeted mutations in mice may be the source of even better models as they permit not only screening but actual study of the possible etiology of the disease. Moreover, with novel theories about the disorder, the ability to develop new strains with specific mutations enables us to try and generate hypothesis driven models (O'Brien et al., 2004). However, the genetic approach to modeling is the most time consuming and labor intensive and while it may be the best approach to further our understanding of the disorder, may not be the best choice in an attempt to develop a screening tests battery.

The present paper suggests ways to induce and test many of the above components of mania based on a variety of existing models a few of which were already validated for screening of mood stabilizers whereas others have strong face validity but should be now validated for predictability (predictive validity) relating to mania and to its treatment.

Increased energy, activity or restlessness

As described above, the hyperactivity component of mania is the most frequently used model for the disorder. Pharmacological induction of hyperactivity, usually with psychostimulants is easy to generate and easy to test, it's quite reliable and was validated for the prototypic mood stabilizers lithium (Smith, 1981; Lerer et al., 1984) and valproate (Kuruvillea and Uretsky, 1981; Post and Weiss, 1989; Shaldubina et al., 2002). Whereas

amphetamine is the drug of choice for inducing the model, other psychostimulants have also been used successfully (Shaldubina et al., 2002).

Environmental/behavioral methods are also used to induce hyperactivity in the context of modeling mania but most are more time consuming. For example, Gessa and his colleagues (Gessa et al., 1995) demonstrate that sleep deprivation results in a brief period of hyperactivity that is responsive to lithium treatment (therefore validating the procedure for the screen of novel antimanic drugs) and their model gains further validity from data showing that sleep deprivation precipitates manic attacks in BPD patients. However the sleep deprivation procedure is long and laborious compared with the pharmacologically-induced model; it results in only a brief period of arousal, and therefore may not be the preferable choice as part of a test battery.

Genetic manipulations also offer some possibilities with rat and mice lines that are innately hyperactive (Adriani et al., 2003; Ralph-Williams et al., 2003). As discussed above, the genetically manipulated animals may be an excellent choice for research into the underlying mechanisms of the disease but may not be the most efficient way for high throughput test batteries.

Hyperactivity can be easily measured by a variety of automated tools the most common of which are either automated activity monitors (Shaldivin et al., 2001) or videotracking systems (Einat et al., 2003).

Extreme irritability

Irritability can be defined as extreme reactions to relatively minute stimuli. In rodents, irritability was previously measured as vocal reactions to a touch, jumping reactions to touch (Blasig et al., 1973; Wei, 1973; Rasmussen et al., 1990) and attempts to struggle while being restrained (Himmelsbach et al., 1935). All these are relatively easy to measure.

A variety of drugs can induce irritability in rodents including PCPA (Dalhouse, 1976), PCA (Humphries et al., 1980; Humphries et al., 1981), trimethyltin (Hagan et al., 1988), imidazole (Ferrari et al., 1989) and others. However, the most frequently described extreme irritable behavior in rodents is during periods of psychoactive drugs withdrawal, especially for opiate drugs (Himmelsbach et al., 1935; Blasig et al., 1973; Wei, 1973; Rasmussen et al., 1990). Among other symptoms of withdrawal, vocal response and jumping in response to minute tactile stimuli are widely described in the literature. Opiate withdrawal is relatively simple to induce and therefore can be easily used as part of a test battery.

Interestingly, an excellent method that was developed in the 1930's to evaluate withdrawal syndrome also points us to a way to induce irritability without drugs therefore establishing an environmental/behavioral avenue of induction. In a study by Himmelsbach and his colleagues (Himmelsbach et al., 1935) they demonstrate that by restraining a rat in a supine position the amount of struggle of the animal represents its irritability and drug withdrawal state. Moreover, from their data it is clear that control animals also show similar struggling behavior during the first sessions of the test but, unlike the drug-withdrawn animals, the struggling in control rats tolerates across sessions. Hence, it is possible that the irritability-like behavior during the first sessions can be used as a quick and simple way to model irritability in mania.

Some genetically modified animals also demonstrate extreme irritability. For example, BDNF knockout heterogenous mice are hyperresponsive to a variety of stimuli (Morozov et al., 2001) and since BDNF may be strongly related to depression (Manji and Duman, 2001) and to bipolar disorder (Einat et al., 2003), such mice, when available, may be useful for both drug screening and study into the basic pathology of the disorder.

Reduced sleep

Psychostimulants have long been known to reduce sleep (Berridge and Stalnaker, 2002) and can easily be used to model this facet of mania. Similar effects were demonstrated with monoamine oxidase inhibitors such as clorgyline (Popova et al., 2000), with GABAA drugs such as muscimol (Sato et al., 2003) or picrotoxin (Langebartels et al., 2001) or with prostaglandin inhibition (Hayaishi, 1999).

A number of lines of genetically altered mice also show reduced sleep, for example mice with null mutation for the alpha1 or beta2 subunits of the GABAA receptor show markedly reduced sleep (Blednov et al., 2003) and MAO-A knockouts were less sensitive to the sleep induction effects of alcohol compared to WT controls (Popova et al., 2000).

Provocative, intrusive or aggressive behavior

Aggressive behaviors are relatively easy to test and measure in rodents in a variety of social interaction situations (Blanchard et al., 2003) the most common of is probably the resident-intruder test (Miczek and O'Donnell, 1978; Holmes et al., 2002). Many manipulations are known to increase aggression in rodents.

Pharmacological manipulations such as administration of PCPA (Sheard, 1973), clonidine (Nikulina and Klimek, 1993), testosterone (Frye et al., 2002) or corticosterone (Mikics et al., 2004) were demonstrated to increase aggressive behaviors in rodents.

Environmental/behavioral manipulations were reported to increase aggression including first and foremost isolation (Miczek and O'Donnell, 1978) but also a variety of acute stressors such as foot-shock that was shown to increase fighting in male rats (Ulrich and Craine, 1964) and mice (Legrand and Fielder, 1973). Additionally, deprivation from a known reinforcer was reported to increase aggression and rats used to having sweet solution bottles in their home cages reacted with aggression in the social interaction test when these bottles were removed (Belozertseva et al., 2004). A new model reflecting aggression that was recently introduced is a competition for food model where dominance and submissiveness are defined (Malatynska and Knapp, 2005). It is an interesting model that already has initial pharmacological validation and certainly deserves attention and further investigation.

A variety of mutant mice were reported to have increased aggressive tendencies (Miczek et al., 2001).

Increased sexual drive

Sexual activity in rodents had been heavily studied in a variety of contexts including depression (D'Aquila et al., 1994; Ferreira-Nuno et al., 2002). Nevertheless, most studies examine manipulations that decrease sexual behavior. One study however reports that neonatal treatment with mifepristone (RU 486) significantly increases sexual activity in adult male mice to about double the numbers of intermissions and ejaculations

(Csaba and Karabelyos, 2001). Interestingly, the same study reports that tamoxifen abolishes the increased sexual activity and since initial evidence suggest that tamoxifen may also have antimanic properties (Bebchuk et al., 2000; Chen et al., 2000; Einat et al., 2004), these results may add a tentative component of predictive validity to this behavior as a model for the sexuality facet of mania. Many folk herbal medicine and plant extracts are used as sex stimulants and at least some were tested in animals and were demonstrated to increase sexuality. For example, red sage (*Salvia haematodes*) was shown to increase the frequency of mounts and intromissions in rats (Islam et al., 1991).

Limbic seizures (induced by lithium-pilocarpine) were noted to increase sexual behavior (Persinger, 1994) and so were lesions in the hypothalamus (Dorner et al., 1969) or in the posterior part of the lateral amygdala (Chateau and Aron, 1988). Environmental manipulations such as exposure to estrous female induce sexual behavior however this is a natural response and it is not clear how it can be used to model hypersexuality. Yet, it is noteworthy that male rodents (as other animals) that are exposed to estrous female develop a pattern of behavior that may include other facets of mania (Kavaliers et al., 2001).

Response to drugs and hedonistic behavior

A common method to evaluate hedonistic properties in rodents is by testing responses to reinforcers such as sweet solution (Willner et al., 1987). However, most work done in that methodology was directed at modeling depression and therefore was centered on manipulation that result in anhedonia in animals (Willner et al., 1987; Ferreira-Nuno et al., 2002). Some studies however, mostly done in the context of drug abuse research, did explore manipulations that result in increase hedonistic behaviors in rodents. Some examples include: benzodiazepine administration which was demonstrated to increase alcohol consumption (Soderpalm and Hansen, 1998) or the well documented effects of cannabinoids to increase the pleasure of eating (Harrold and Williams, 2003).

Interestingly, isolation rearing in rats was reported to increase hedonistic traits as measured by elevated consumption of both alcohol and sucrose solution (Hall et al., 1998). Genetic manipulations can also result in differential hedonic traits as different mice lines show different preference for the consumption of both alcohol and sweet solutions (Bachmanov et al., 1996) and rat lines bred for alcohol preference demonstrate other hedonistic-like preferences such as higher preference for sweet solution compared with controls (Kampov-Polevoy et al., 1999).

Distractibility, reduced ability to concentrate.

Distractibility can be measured in rodents in a variety of learning tasks. After animals have learned a task that results in reinforcement, it is possible to distract them and to measure the level of distraction. For example, Agmo and colleagues (Agmo et al., 1997) trained animals to reach sweet solution in a maze and measured the distractibility effect of adding an additional arm to the maze. That same study demonstrates that amphetamine can increase distractibility therefore offering an easy and quick way to induce a model for this facet of mania. Furthermore, under specific schedule, valproic acid appears to block the amphetamine-induced distractibility (therefore demonstrating possible predicative validity).

Reduced ability to concentrate can also be tested in other learning paradigms although the interpretation as it is related to rodents may be more complicated. For example, quinpirole was demonstrated to have long-lasting effects on the ability of animals to learn a modified task in the Morris water maze (Einat and Szechtman, 1993) and whereas the behavioral change can be attributed to quinpirole-induced compulsive-like behavior (Szechtman et al., 2001) it can equally be interpreted as related to reduced ability to concentrate.

Unrealistic beliefs in one's abilities and powers and Poor judgment

Whereas we have no insights into rodents' beliefs it is possible to examine the behavioral consequences of omnipotent ideation and poor judgment which are increase in risk taking. Risk taking behaviors can be induced in a variety of ways and tested in many established tests for anxiety (risk taking behavior may represent the mirror image of anxiety in many tests).

Psychostimulants can induce increases in risk-taking behavior as demonstrated by reduced anxiety-like measures such as increased time spent in the center of an open field or increased crossing into the brightly lit area of a black/white box (Einat et al., 2003). Behavioral and environmental manipulations can also induce risk-taking behavior. For example, an exposure of male mice to an estrous female odor reduces their fear from a predator (Kavaliers et al., 2001) and brief stress to mice (applied in different modalities) reduces the latency to emerge from shelter onto a large open field (Quartermain et al., 1996).

Genetic manipulations can result in "risk taking" mice. For example, the 5HT_{3A} knockout mice were demonstrated to be less anxious (and therefore higher risk takers) than WT controls in a number of tests for anxiety (Kelley et al., 2003).

Summary

The need for additional models for mania is clear (Einat et al., 2000; Einat et al., 2003; Einat, 2004; Tecott and Nestler, 2004) and the new notion of endophenotypes of disease (Lenox et al., 2002; Gottesman and Gould, 2003) encourages attempts to separately model the different facets of this devastating disorder (Einat, 2004). The efficient screening of new drugs and new mutant animals, developed based on molecular findings related to BPD is highly dependent on our ability to offer new animal models that can be easily induced and tested (Tecott and Nestler, 2004).

As described above, most of the facets of mania can be modeled in rodents including increased energy, activity or restlessness; extreme irritability; reduced sleep; provocative, intrusive or aggressive behavior; increased sexual drive; abuse of drugs; distractibility, reduced ability to concentrate; and unrealistic beliefs in one's abilities and powers resulting in poor judgment. Models developed in other contexts may be appropriate for use also for these facets of mania as long as they can be validated (Einat, 2004). The summary of some such tentative models is presented in table 1.

Many of these models are relatively simple and quick to induce and provide clear testing methods and unambiguous quantitative measures that can be easily utilized by the non-behavioral scientist. Additionally, it is noteworthy that some of the models may include more than one facet of the disease. For example, psychostimulants

administration results in hyperactivity, reduced sleep, increased distractibility and poor judgment (risk taking behavior); isolation may induce aggression and increased response to psychoactive drugs and acute stress was demonstrated to induce aggression as well as poor judgment (risk taking behavior). Moreover, a variety of mutant mice (sometimes nicknamed “popcorn mice” because of their extreme behavioral phenotype) were reported to be hyperactive, irritable and aggressive (Morozov et al., 2001). Careful approach is needed regarding the induction of more than one model with one manipulation because the above examples are extracts from different reports and the application of the manipulation was not equal across studies (different doses and schedules of drugs, different applications of stress etc.). Yet, it may be worthwhile to explore whether one, relatively simple manipulation can induce a number of behavioral changes that reflect different components of mania and that can be validated as model for all these behavioral changes. Some examples of such manipulations that affect more than one facet of mania are shown in Table 2. Other manipulations may also have multi-facet effects but these were not explored before as most of the described studies were not conducted in the context of bipolar disorder.

Considering the general lack of appropriate models of bipolar disorder it is tempting to start utilizing some of the above mentioned models immediately however, it is important to note some challenges:

- The new concept of endophenotypes of disease supports the development of separate models for the separate facets of the disorder but considering that bipolar disorder is never just one behavioral change, models that include a number of mania-like behaviors may still be the preferred ones.
- The representation of a continuous, chronic disease by a behavioral change that resembles at best a single manic episode may not be ideal and although models of this kind are helpful in the process of understanding the disorder and developing new drugs one must keep in mind that these are models and not a full representation of the disease. Whereas this issue is mostly clear to behavioral and modeling scientists it may be important to emphasize it to scientists from other areas that are planning to utilize animal models in their research.
- Pharmacological models are usually the easier to induce but as mentioned above, may also be the ones with the most limitations.
- Validation in the context of bipolar disorder is necessary before any attempts to use a model that was developed in a different context.

The validation process of these models must include a component of predictive validity that is that the behavioral abnormality induced in the model will be normalized after chronic treatment with prototypic mood stabilizers such as lithium or valproate but not by other, non-antimanic drugs (Willner, 1986; Einat and Belmaker, 2001; Einat et al., 2003). The validation process of any model can be a long and laborious process but considering the dire need for models it may be of extreme importance and should receive immediate attention from researchers in the field as well as from funding agencies. Models that will be validated properly can then be used quickly and efficiently and may be utilized individually or to construct a standard battery of tests that can be used to explore the various components of manic-like behavior in rodents.

Table 1: Some examples of tentative models for the different facets of mania.

Behavioral facet	Induction	Testing and Validation
Increased energy and activity	Pharmacological: psychostimulants Environmental/behavioral: sleep deprivation. Genetic: innately hyperactive mice lines.	Testing: a variety of automated tools testing activity levels in different environments. Validation: lithium as well as anticonvulsant mood stabilizers decrease psychostimulant-induced hyperactivity; lithium reduces sleep-deprivation induced hyperactivity.
Irritability	Pharmacological: PCPA; PCA; trimethyltin; imidazole; withdrawal from psychoactive drugs. Environmental/behavioral: supine restrain. Genetic: BDNF knockout mice.	Testing: vocal and physical reactions to minute stimuli; struggle.
Reduced sleep	Pharmacological: psychostimulants, MAO inhibitors; GABBA drugs. Genetic: GABBA targeted mutations; MAO inhibitors knockouts.	Testing: measures of sleep.
Aggression	Pharmacological: PCPA; clonidine; testosterone; corticosterone. Environmental/behavioral: isolation; acute stressors; deprivation; food competition. Genetic: a variety of mutations.	Testing: social interaction; resident-intruder; success gaining food.
Increased sexual drive	Pharmacological: neonatal treatment with RU 486; folk herbal medicine such as <i>Salvia haematodes</i> . Other manipulations: lithium-pilocarpine induced limbic seizures; lesions to hypothalamus or to posterior lateral amygdala.	Testing: sexual behavior. Validation: tamoxifen inhibits neonatal RU 486-induced hypersexuality.
Response to drugs and hedonistic behavior	Pharmacological: benzodiazepines; cannabinoids. Environmental/behavioral: isolation rearing. Genetic: different mouse lines have different preference intensity for drugs and for other reinforcement. Alcohol preferring rats show other hedonistic-like behaviors.	Testing: response to drugs – operant paradigms; conditioned place preference; sensitization. Hedonistic behavior – preference for reinforcement.
Distractibility and reduced concentration.	Pharmacological: psychostimulants.	Testing: learning tasks. Validation: valproate reported to reduce amphetamine-induced distractibility.
Poor judgment (risk-taking)	Pharmacological: psychostimulants. Environmental/behavioral: exposure to estrous female odor; brief stress. Genetic: 5HT _{3A} knockout mice are less anxious (risk takers) compared with WT controls.	Testing: a mirror image of most tests for anxiety-like behavior.

Table 2: Examples of manipulations that affect more than one facet of mania-like behavior

Manipulation	Behavioral change
Psychostimulant administration	Increased activity
	Reduced sleep
	Distractibility (reduced concentration)
	Risk taking
PCPA administration	Irritability
	Aggression
Sleep deprivation	Increased activity
	irritability
	Aggression
Restrain	Irritability
	Risk taking

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