Published in final edited form as:

Neurosci Biobehav Rev. 2007 ; 31(6): 825–831.

Animal Models of Bipolar Disorder and Mood Stabilizer Efficacy:

a Critical Need for Improvement

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Abstract

The limited number of suitable animal models of bipolar disorder available for in-depth behavioral, biochemical, histological, and pharmacological analysis is a rate limiting step in the process of understanding the relevant neurobiology of the disorder, as well as the development of novel medications. In the search for new models, both new and old approaches hold promise for future discoveries. Clinical studies regarding the underlying genetics and pathophysiology of bipolar disorder are providing important clues. In particular, the identification of susceptibility genes for bipolar disorder will help to define specific neurobiological processes, and associated behaviors, that are unquestionably involved in the pathways connecting genes and distal symptoms. These endophenotypes will hold great value in further enhancing the validity of animal models and will strongly complement symptom-based models and models of medication efficacy. Regardless of the path taken by different researchers to develop better models, we believe that this area of work requires additional attention not only from researchers but also from funding agencies.

Keywords

Manic-depressive illness; animal model; depression; antidepressants; lithium; valproic acid; antipsychotics; rat; mouse

Bipolar disorder is a common disease affecting between 1 and 4% of the world's population, depending upon whether a narrow or broad definition is used (Box I). The course of the disease is characterized by mood episodes - mania, depression, and combination mixed episodes - which are separated by periods of euthymia (normal mood). However, this episodic nature, with intervening periods of recovery, often disguises a more severe impact. Bipolar disorder is pervasive, with effects on many aspects of life, including physical health, and it is commonly comorbid with other psychiatric diseases. The mortality of bipolar disorder arises not only from a rate of suicide approaching 15%, but additionally from the existence of significant medical and psychiatric comorbidities, often limited social and economic functioning, and poor inter-episode recovery (see (Goodwin and Jamison, 1990; Woods, 2000; Michaud et al., 2001; Calabrese et al., 2003; Evans et al., 2005; Kupfer, 2005; Valtonen et al., 2005)).

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both authors contributed equally to this editorial and the associated special issue of *Neuroscience and Biobehavioral Reviews*.

The cumulative effect of recurring bouts of depression and mania leads to an increased rate of marital and family breakdown, unemployment, impaired career progress and consequent financial difficulties (Woods, 2000; Kleinman et al., 2003). This morbidity associated with bipolar disorder is increasingly being recognized; for example, using 1998 figures, it was estimated that in the United States alone, lifetime costs of persons with bipolar disorder would be 24 billion U.S. dollars (Begley et al., 2001). The average cost for a single manic episode was estimated at \$11,720 and a total of \$624,785 per individual for chronic treatment (Begley et al., 2001). Further, the World Health Organization, which ranks diseases not solely based upon fatal outcomes, but additionally upon non-fatal outcomes in a measurement referred to as a disability-adjusted life-years (DALY), found that, worldwide in 1999, bipolar disorder ranked 20th among all disease categories (Michaud et al., 2001). DALYs associated with bipolar disorder are higher in developed countries such as the United States, and are predicted to increase in the severity of impact in future years.

Despite the high prevalence and severity of bipolar disorder, remarkably little has been ascertained for certain regarding the underlying neurobiology of the disorder, or the means by which effective medications (for example, lithium, valproate, carbamazepine, lamotrigine, and antipsychotics) exert their therapeutic actions. This makes the task of developing animal models extremely difficult, and there appear to be few “low-hanging fruits”. However, the task is critical - without an understanding of the above issues, and without the development of models to test hypotheses, truly novel treatments for bipolar disorder will remain elusive, with discoveries more likely to be serendipitous than planned. Indeed, all existing medications were either discovered via serendipity, or were the result of testing medications previously approved for other indications (namely, antipsychotics and anticonvulsants) (Gould et al., 2004).

It is well established that the development of fully validated and appropriate animal models is a task of major importance for all of psychiatry. However, there is no greater need than for bipolar disorder (Nestler et al., 2002; Gould and Manji, 2004; Einat, 2006b; Einat, 2006a; Cryan and Slaterry, 2007). The limited number of suitable models for in-depth behavioral, biochemical, histological, and pharmacological analysis, has greatly hindered progress in understanding the relevant neurobiology of, and in developing novel medications for, bipolar disorder. Thus, the paucity of appropriate animal models is a rate-limiting step in the process of investigating the neurobiology of bipolar disorder and for the development of a future generation of mood stabilizing medications.

Bipolar disorder is problematic to model in animals for a number of reasons (Box II). First, there is a general problem in modeling diseases where there are no established biomarkers for the disease state or the effects of treatment. Furthermore, the general concept of an animal model for a disease of human ‘affect’ is always problematic, as one cannot simply assume that animals have ‘affect’. Specifically for bipolar disorder, the cyclic nature of the disease creates an additional level of complexity. A limited number of investigators have attempted to generate a cycling model where animals alternate between manic-like and depression-like states. One model of this type was suggested by Antelman and his colleagues and was based on oscillations in the responses of rats to intermittent cocaine injections (Antelman et al., 1998; Caggiula et al., 1998; Antelman et al., 2000). Although there is merit to this model, it also has significant problems. Most work describing the consequences of intermittent psychostimulant administration emphasizes a process of sensitization rather than oscillatory responses (e.g. (Robinson and Becker, 1986; Stewart and Badiani, 1993)). Psychostimulant-induced behaviors, and associated biochemical changes, that may be related to bipolar disorder show sensitization in behavioral responses including hyperactivity (Post, 1980), stereotypy (Einat and Szechtman, 1995), increased hedonia (Papp et al., 1993), or increased sexual behavior (Fiorino and Phillips, 1999). However, oscillations have been shown only in very limited measures (e.g. hypoalgesia) that appear to be poorly related to bipolar disorder symptoms or any suggested bipolar disorder

endophenotypes. This shortcoming, as well as the time frame required to generate the model, has limited its utility and use by the scientific community. Another model that includes both measures of manic- and depressive-like behavior is based on the behavior of individual rats in dominant and submissive relationships. The performance of these individual animals may correspond to human manic-like and depressed-like behaviors, and are responsive to antimanic and antidepressant medications respectively (Malatynska and Knapp, 2005; Malatynska et al., 2008). Post and colleagues have also developed a model based on the phenomenon of kindling that they propose as relevant to bipolar disorder pathophysiology and the mechanism of action of anticonvulsants used for treatment (Post, 2007). The kindling model predicts temporal variation in the function of neural circuits and associated episodes, evolution and cyclicity (Post, 2007). This model was instrumental in the pioneering early use of anticonvulsant mood stabilizers, especially carbamazepine (Post et al., 1982). Noting the difficulty in developing comprehensive models, attempts have been made to classify existing animal behavioral tests and models into a number of general areas including a focus on particular *symptoms*, *bipolar endophenotypes and pathophysiology*, and *response to existing medications*. However, all these approaches are limited given that the basic behavioral biology of symptoms is often poorly understood, we have few well-validated endophenotypes for bipolar disorder, and we currently know very little for certain about underlying susceptibility genes, the underlying neurobiology, or about the mechanism of action of existing medications. New ideas can be used to develop hypothesis-driven models that are based on manipulations of systems considered related to the disease or to its treatment (construct validity, rather than face validity, based models). Although this is an important effort, no model has yet evolved to the extent that it is comprehensive enough to be used in the context of studying the disorder or treatments outside the scope of the specific molecule or pathway that was initially manipulated. It is nevertheless possible that such developments will occur in the near future, although it is unlikely that a defect in a single specific molecule or pathway is responsible for the disorder or for the beneficial effects of all existing treatments.

Symptom-based models

Symptom-based models are attempts to represent observable signs and symptoms of bipolar disorder. These models almost invariably are behavior-based (rather than alternative measures of neurobiological function or neurochemical assays). Symptom-based models of bipolar disorder often attempt to represent aspects of either the depressive or the manic phase of the illness. Thus, the models in question generally have face validity toward the psychiatric symptoms observed in bipolar disorder. Symptoms of mania that can be modeled in animals include increased activity, irritability, reduced need for sleep (or other changes in sleep patterns), aggressive behavior, sexual drive, distractibility, and risk-taking behavior, all of which are commonly observed in human mania (Einat, 2006a). Models of the depressive phase of bipolar disorder commonly make use of models previously validated in the context of depression research. Models are available for symptoms such as anhedonia, changes in sleep patterns, fatigue, poor hygiene, and changes in appetite or weight (Cryan and Holmes, 2005). The symptom-based modeling approach can take additional forms, such as modeling of particular symptoms of the disease in different strains of mice. This approach can serve to explore the biological and genetic basis of differences between strains as previously done in the context of behaviors and their related disorders (Einat, 2007).

Endophenotypes and pathophysiology

Endophenotypes are quantifiable components of neurobiological function, distinct from psychiatric symptoms. They can be neurophysiological, biochemical, endocrine, neuroanatomical, cognitive, or neuropsychological. Heritability and stability (state-independence) are important components of any useful clinical endophenotype (Gottesman

and Gould, 2003). Importantly, they characterize an approach that reduces the complexity of symptoms and multifaceted behaviors, resulting in units of analysis that are more amenable to being modeled in animals (Gould and Gottesman, 2006). The complexity of the pathways from genes to psychiatric symptoms is increasingly appreciated and it is often difficult to discern whether tested animal behaviors are truly analogous to human behaviors. Consequently, animal models that study the relevance of changes on the levels of proteins, circuits and synapses, and brain function, without regard to modeling of symptoms, may have tremendous utility.

Evolving theories suggest that endophenotypes for bipolar disorder, based upon genetic and biological contributions, include attention deficits, circadian rhythm instability, abnormal modulation of motivation and reward, brain structural changes, and increased sensitivity to stress and stimulant medications (Lenox et al., 2002; Glahn et al., 2004; Hasler et al., 2006; McClung, 2007). Some of these are more amenable to modeling in animals than others. For example, a polymorphism in the putative bipolar disorder susceptibility gene, brain derived neurotrophic factor (BDNF), has been linked to anatomic variations in the hippocampus and prefrontal cortex (Pezawas et al., 2004), as well as to hippocampal and prefrontal cortex cognitive performance (Egan et al., 2003; Hariri et al., 2003; Rybakowski et al., 2005) in humans. Significant preclinical support for the involvement of BDNF in both learning and memory and neuronal growth/plasticity has been gathered (Egan et al., 2003; Lu, 2003). Limbic-hypothalamo-pituitary-adrenocortical pathway malfunction, and dysregulation of reward pathway function, are other putative endophenotype for bipolar disorder, and extensive animal models to study these pathway, are already in existence (Seong et al., 2002; Gould et al., 2003; Hasler et al., 2004; Akil, 2005; Roybal et al., 2007). Ultimately, the endophenotypes most valuable for affective disorders may be specific structural, functional, and neuropsychological deficits, which at face value have poor correlation with overt symptom-based models (Lenox et al., 2002; Glahn et al., 2004; Hasler et al., 2004; McDonald et al., 2004; Gould and Gottesman, 2006).

Pathophysiological models are closely related to endophenotypes, and are based upon clinical genetic association studies, postmortem brain analysis and in vivo neuroimaging, or upon putative mechanisms of drug action. For example, mitochondrial dysfunction has been suggested as an underlying cause of bipolar disorder, with evidence from all the above areas (Kato et al., 2007). A mouse has been created that has expression of mutant polymerase γ (POLG), a mitochondrial gene implicated in bipolar disorder (Kasahara et al., 2006). These mice have an altered diurnal activity rhythm and periodic activity changes associated with the estrous cycle; phenotypes that were worsened by a tricyclic antidepressant (amitriptyline), but improved by the mood stabilizer lithium (Kasahara et al., 2006; Kato et al., 2007). Ion dysfunction is another pathophysiology-based hypothesis that has been successfully translated to rodents (El-Mallakh et al., 1995; Herman et al., 2007). Recent findings have also implicated a number of intracellular pathways and molecules in the etiology of BPD and in the therapeutic effects of mood stabilizers. One of these new hypotheses is related to mechanisms of cellular resilience and neuroplasticity (Manji et al., 2003).

Response to existing medications

Understanding the mechanism of action of current medications, and developing new medications, is a major goal of bipolar disorder research. A number of models have been developed that show sensitivity to available drugs. Models of the mechanism of actions of bipolar disorder drugs, such as lithium (O'Brien et al., 2004; Belmaker and Bersudsky, 2007; O'Donnell and Gould, 2007; Rowe et al., 2007) or the anticonvulsants (Bourin and Corina, 2007; Post, 2007), have considerable value. A number antidepressant-sensitive models are proving viable, both in developing new treatments for bipolar depression as well as helping to

define the mechanism of actions of drugs such as lithium and lamotrigine (Bourin and Corina, 2007; O'Donnell and Gould, 2007).

Novel hypotheses regarding drug action can derive from the study of effects of medications. For example, data suggests that neuroprotective effects of some mood stabilizing medications (in particular lithium and valproate) may be critical to the therapeutic effects of these compounds (Manji et al., 1999; Chuang, 2004). However, one valid criticism of developing models based upon the behavioral effects of existing medications is the issue of pharmacological isomorphism. By definition, novel medications will not act on precisely the same pathways as existing medications. Therefore, models developed to be sensitive to existing medication categories may not help discover medications with truly novel mechanisms of action. Therefore, testing the effects of drugs in models originally developed based upon symptoms, pathophysiology, and endophenotypes may be particularly valuable in developing truly novel medications.

Conclusions

The approaches mentioned above are all valid mechanisms to develop appropriate models of bipolar disorder. Of course, many approaches do not fall into neat categories, and as the field progresses, inflexibility will likely hinder success. For example, risk-taking is an overt symptom of bipolar mania but may have clearly definable neurobiological underpinnings suggestive of a valid endophenotype (Young et al., 2007). Anhedonia, which is a symptom of the depressed phase of bipolar disorder, may also have concise neurobiological underpinnings that, if quantifiable, will be valuable as endophenotypes (Cryan and Slattery, 2007).

While new models need to be developed, their development will be predicated, in part, on advances in our clinical understanding of susceptibility genes, as well as on the validation of how genes relate to clinical endophenotypes (Le-Niculescu et al., 2007). Novel approaches to manipulate the mouse genome, and to modulate brain circuits and cellular signaling pathways, will be required (Morozov et al., 2003; Einat and Manji, 2006). The preceding brief discussion sets the stage for this special issue of *Neuroscience and Biobehavioral Reviews* devoted to the topic of Animal Models of Bipolar Disorder and Mood Stabilizer Efficacy. We hope that this special journal issue will stimulate more intense interest and collaborative studies relating to animal models of bipolar disorder and help to forward the development of better models that are imperative for the progress of translational research. The current tendency of funding agencies often is to support work on models primarily when the aims are associated with a specific mechanistic hypothesis or the development of a single new medication. However, the development of improved animal models, regardless of their immediate relationship with a specific mechanism or drug, are a critical step in the understanding of bipolar disorder. It is our hope that increased emphasis on this important task, emerging with this special issue, will influence decision makers associated with funding agencies to include bipolar disorder model development as a critical area that requires additional support.

Box 1 Classification and clinical description of bipolar disorder

Bipolar Disorder is classified (per the American Psychiatric Association's Diagnostic and Statistical Manual IV; DSM-IV) into bipolar I or II, based on clinical presentation. Under DSM-IV criteria, bipolar I disorder is defined by a history of one or more manic episodes, whereas bipolar II is defined by a history of one or more hypomanic episodes and at least one depressive episode. Over the course of a lifetime, bipolar disorder type I affects at least 1% of the world's population when DSM-IV criteria are applied. Bipolar disorder type II (DSM-IV defined) affects 1 to 3.5%, as defined by DSM-IV, and up to 11% when utilizing

less strict “spectrum” criteria that overlap with DSM-IV defined depression (Angst et al., 2003; Merikangas et al., 2007).

Patients with bipolar disorder typically alternate between episodes of depression and episodes of mania. The depressive phases are generally indistinguishable for those seen in unipolar depression and consist of anhedonia (decreased ability to experience pleasure), feelings of guilt, worthlessness, and helplessness, decreased energy, difficulty concentrating, changes in appetite and weight, and thoughts of death or suicide. The manic phases are characterized by a heightened mood, a hyperaroused state, racing thoughts, increased speed and volume of speech, quicker thought, brisker physical and mental activity levels, inflated self esteem, grandiosity, increased energy (with a corresponding decreased need for sleep), irritability, impaired judgment, heightened sexuality, and sometimes frank psychotic symptoms including hallucinations and delusions.

In hypomania, a less severe form of mania, the changes noted for the description of mania above are generally present at more moderate levels and do not result in hospitalization. Bipolar disorder commonly first appears in young adulthood, though early and late onset is not uncommon (Young, 2005; Youngstrom et al., 2005). The differentiation between bipolar disorder type I and II is based on clinical presentation, and not neurobiology, epidemiology, genetics, or response to medications.

Box II Modeling bipolar disorder in animals presents multiple difficulties

In humans, the disease is cyclic

There is believed to be tremendous clinical heterogeneity

There is limited knowledge about the underlying pathophysiology

Despite heritability estimates of 80%, there is limited (albeit improving) knowledge regarding the underlying susceptibility genes

There are a limited number of well validated clinical endophenotypes

There is limited knowledge about how existing mood stabilizing medications exert their therapeutic actions

References

- Akil H. Stressed and depressed. *Nat Med* 2005;11:116–118. [PubMed: 15692589]
- Angst J, Gamma A, Benazzi F, Ajdacic V, Eich D, Rossler W. Diagnostic issues in bipolar disorder. *Eur Neuropsychopharmacol* 2003;13(Suppl 2):S43–50. [PubMed: 12957719]
- Antelman SM, Caggiula AR, Edwards DJ, Gershon S, Kucinski BJ, Kiss S, Kocan D. Long-term oscillation of corticosterone following intermittent cocaine. *J Neural Transm* 2000;107:369–375. [PubMed: 10821445]
- Antelman SM, Caggiula AR, Kucinski BJ, Fowler H, Gershon S, Edwards DJ, Austin MC, Stiller R, Kiss S, Kocan D. The effects of lithium on a potential cycling model of bipolar disorder. *Prog Neuropsychopharmacol Biol Psychiatry* 1998;22:495–510. [PubMed: 9612846]
- Begley CE, Annegers JF, Swann AC, Lewis C, Coan S, Schnapp WB, Bryant-Comstock L. The lifetime cost of bipolar disorder in the US: an estimate for new cases in 1998. *Pharmacoeconomics* 2001;19:483–495. [PubMed: 11465308]
- Belmaker RH, Bersudsky YL. Lithium-pilocarpine seizures as a model for lithium action in mania. *Neurosci Biobehav Rev* 2007 doi:
- Bourin M, Corina P. The role of mood stabilizers in the treatment of depressive facets of bipolar disorders. *Neurosci Biobehav Rev* 2007 doi:10.1016/j.neubiorev.2007.03.001

- Caggiula AR, Antelman SM, Kucinski BJ, Fowler H, Edwards DJ, Austin MC, Gershon S, Stiller R. Oscillatory-sensitization model of repeated drug exposure: cocaine's effects on shock-induced hypoalgesia. *Prog Neuropsychopharmacol Biol Psychiatry* 1998;22:511–521. [PubMed: 9612847]
- Calabrese JR, Hirschfeld RM, Reed M, Davies MA, Frye MA, Keck PE, Lewis L, McElroy SL, McNulty JP, Wagner KD. Impact of bipolar disorder on a U.S. community sample. *J Clin Psychiatry* 2003;64:425–432. [PubMed: 12716245]
- Chuang DM. Neuroprotective and neurotrophic actions of the mood stabilizer lithium: can it be used to treat neurodegenerative diseases? *Crit Rev Neurobiol* 2004;16:83–90. [PubMed: 15581403]
- Cryan JF, Holmes A. The ascent of mouse: advances in modelling human depression and anxiety. *Nat Rev Drug Discov* 2005;4:775–790. [PubMed: 16138108]
- Cryan JF, Slattery DA. Animal models of mood disorders: recent developments. *Curr Opin Psychiatry* 2007;20:1–7. [PubMed: 17143074]
- Egan MF, Kojima M, Callicott JH, Goldberg TE, Kolachana BS, Bertolino A, Zaitsev E, Gold B, Goldman D, Dean M, Lu B, Weinberger DR. The BDNF val66met polymorphism affects activity-dependent secretion of BDNF and human memory and hippocampal function. *Cell* 2003;112:257–269. [PubMed: 12553913]
- Einat H. Establishment of a Battery of Simple Models for Facets of Bipolar Disorder: A Practical Approach to Achieve Increased Validity, Better Screening and Possible Insights into Endophenotypes of Disease. *Behav Genet*. 2006a
- Einat H. Modelling facets of mania - new directions related to the notion of endophenotypes. *J Psychopharmacol*. 2006b
- Einat H. Different behaviors and different strains: potential new ways to model bipolar disorder. *Neurosci Biobehav Rev* 2007 doi:10.1016/j.neubiorev.2006.12.001
- Einat H, Manji HK. Cellular plasticity cascades: genes-to-behavior pathways in animal models of bipolar disorder. *Biol Psychiatry* 2006;59:1160–1171. [PubMed: 16457783]
- Einat H, Szechtman H. Perseveration without hyperlocomotion in a spontaneous alternation task in rats sensitized to the dopamine agonist quinpirole. *Physiol Behav* 1995;57:55–59. [PubMed: 7878126]
- El-Mallakh RS, Harrison LT, Li R, Changaris DG, Levy RS. An animal model for mania: preliminary results. *Prog Neuropsychopharmacol Biol Psychiatry* 1995;19:955–962. [PubMed: 8539431]
- Evans DL, Charney DS, Lewis L, Golden RN, Gorman JM, Krishnan KR, Nemeroff CB, Bremner JD, Carney RM, Coyne JC, DeLong MR, Frasure-Smith N, Glassman AH, Gold PW, Grant I, Gwyther L, Ironson G, Johnson RL, Kanner AM, Katon WJ, Kaufmann PG, Keefe FJ, Ketter T, Laughren TP, Leserman J, Lyketsos CG, McDonald WM, McEwen BS, Miller AH, Musselman D, O'Connor C, Petitto JM, Pollock BG, Robinson RG, Roose SP, Rowland J, Sheline Y, Sheps DS, Simon G, Spiegel D, Stunkard A, Sunderland T, Tibbits P Jr, Valvo WJ. Mood disorders in the medically ill: scientific review and recommendations. *Biol Psychiatry* 2005;58:175–189. [PubMed: 16084838]
- Fiorino DF, Phillips AG. Facilitation of sexual behavior in male rats following d-amphetamine-induced behavioral sensitization. *Psychopharmacology (Berl)* 1999;142:200–208. [PubMed: 10102773]
- Glahn DC, Bearden CE, Niendam TA, Escamilla MA. The feasibility of neuropsychological endophenotypes in the search for genes associated with bipolar affective disorder. *Bipolar Disord* 2004;6:171–182. [PubMed: 15117396]
- Goodwin, FK.; Jamison, KR. *Manic-Depressive Illness*. Oxford University Press; New York: 1990.
- Gottesman II, Gould TD. The endophenotype concept in psychiatry: etymology and strategic intentions. *Am J Psychiatry* 2003;160:636–645. [PubMed: 12668349]
- Gould TD, Gottesman II. Psychiatric endophenotypes and the development of valid animal models. *Genes Brain Behav* 2006;5:113–119. [PubMed: 16507002]
- Gould, TD.; Gray, NA.; Manji, HK. The cellular neurobiology of severe mood and anxiety disorders: implications for the development of novel therapeutics, in *Molecular Neurobiology for the Clinician*. Charney, DS., editor. American Psychiatric Press, Inc.; Washington: 2003. p. 123-227.
- Gould TD, Manji HK. The molecular medicine revolution and psychiatry: bridging the gap between basic neuroscience research and clinical psychiatry. *J Clin Psychiatry* 2004;65:598–604. [PubMed: 15163244]

- Gould TD, Quiroz JA, Singh J, Zarate CA, Manji HK. Emerging experimental therapeutics for bipolar disorder: insights from the molecular and cellular actions of current mood stabilizers. *Mol Psychiatry* 2004;9:734–755. [PubMed: 15136794]
- Hariri AR, Goldberg TE, Mattay VS, Kolachana BS, Callicott JH, Egan MF, Weinberger DR. Brain-derived neurotrophic factor val66met polymorphism affects human memory-related hippocampal activity and predicts memory performance. *J Neurosci* 2003;23:6690–6694. [PubMed: 12890761]
- Hasler G, Drevets WC, Gould TD, Gottesman, Manji HK. Toward Constructing an Endophenotype Strategy for Bipolar Disorders. *Biol Psychiatry* 2006;60:93–105. [PubMed: 16406007]
- Hasler G, Drevets WC, Manji HK, Charney DS. Discovering endophenotypes for major depression. *Neuropsychopharmacology* 2004;29:1765–1781. [PubMed: 15213704]
- Herman LH, Gould TD, Tel-Malkah R. Mimicking human bipolar ion dysregulation models mania in rats. *Neurosci Biobehav Rev* 2007 doi:
- Kasahara T, Kubota M, Miyauchi T, Noda Y, Mouri A, Nabeshima T, Kato T. Mice with neuron-specific accumulation of mitochondrial DNA mutations show mood disorder-like phenotypes. *Mol Psychiatry* 2006;11:577–593. [PubMed: 16619054]
- Kato T, Kubota M, Kasahara T. Animal models of bipolar disorder. *Neurosci Biobehav Rev* 2007 doi:10.1016/j.neubiorev.2007.03.003
- Kleinman L, Lowin A, Flood E, Gandhi G, Edgell E, Revicki D. Costs of bipolar disorder. *Pharmacoeconomics* 2003;21:601–622. [PubMed: 12807364]
- Kupfer DJ. The increasing medical burden in bipolar disorder. *Jama* 2005;293:2528–2530. [PubMed: 15914754]
- Le-
Niculescu HM, Farland MJ, Mamidipalli S, Ogden CA, Kuczenski R, Kurian SM, Salomon D, R Tsuang MT, Numberger JJ Jr. Niculescu AB 3rd. Convergent functional genomics of bipolar disorder: from animal model pharmacogenomics to human genetics and biomarkers. *Neurosci Biobehav Rev* 2007 doi:
- Lenox RH, Gould TD, Manji HK. Endophenotypes in bipolar disorder. *Am J Med Genet* 2002;114:391–406. [PubMed: 11992561]
- Lu B. BDNF and activity-dependent synaptic modulation. *Learn Mem* 2003;10:86–98. [PubMed: 12663747]
- Malatynska E, Knapp RJ. Dominant-submissive behavior as models of mania and depression. *Neurosci Biobehav Rev* 2005;29:715–737. [PubMed: 15876455]
- Malatynska EP, Pinhasov A, Creighton CJ, Crooke JJ, Reitz AB, Brenneisen DE, Lubomirski MS. Assessing activity onset time and efficacy for clinically effective antidepressant and antimanic drugs in animal models based on dominant-submissive relationships. *Neurosci Biobehav Rev* 2008 doi:
- Manji HK, Moore GJ, Chen G. Lithium at 50: have the neuroprotective effects of this unique cation been overlooked? *Biol Psychiatry* 1999;46:929–940. [PubMed: 10509176]
- Manji HK, Quiroz JA, Sporn J, Payne JL, Denicoff K, N AG, Zarate CA Jr. Charney DS. Enhancing neuronal plasticity and cellular resilience to develop novel, improved therapeutics for difficult-to-treat depression. *Biol Psychiatry* 2003;53:707–742. [PubMed: 12706957]
- McClung CA. Circadian genes, rhythms and the biology of mood disorders. *Pharmacol Ther* 2007;114:222–232. [PubMed: 17395264]
- McDonald C, Bullmore ET, Sham PC, Chitnis X, Wickham H, Bramon E, Murray RM. Association of genetic risks for schizophrenia and bipolar disorder with specific and generic brain structural endophenotypes. *Arch Gen Psychiatry* 2004;61:974–984. [PubMed: 15466670]
- Merikangas KR, Akiskal HS, Angst J, Greenberg PE, D HM, Petukhova M, Kessler RC. Lifetime and 12-month prevalence of bipolar spectrum disorder in the national comorbidity survey replication. *Arch Gen Psychiatry* 2007;64:543–552. [PubMed: 17485606]
- Michaud CM, Murray CJ, Bloom BR. Burden of disease--implications for future research. *Jama* 2001;285:535–539. [PubMed: 11176854]
- Morozov A, Kellendonk C, Simpson E, Tronche F. Using conditional mutagenesis to study the brain. *Biol Psychiatry* 2003;54:1125–1133. [PubMed: 14643079]
- Nestler EJ, Gould E, Manji HK, Buncan M, Duman RS, Greshenfeld HK, Hen R, Koester S, Lederhendler I, Meaney M, Robbins T, Winsky L, Zalcman S. Preclinical models: status of basic research in depression. *Biol Psychiatry* 2002;52:503–528. [PubMed: 12361666]

- O'Brien WT, Harper AD, Jove F, Woodgett JR, Maretto S, Piccolo S, Klein PS. Glycogen synthase kinase-3 β haploinsufficiency mimics the behavioral and molecular effects of lithium. *J Neurosci* 2004;24:6791–6798. [PubMed: 15282284]
- O'Donnell KCGould TD The behavioral actions of lithium in rodent models: leads to develop novel therapeutics. *Neurosci Biobehav Rev* 2007 doi:
- Papp M, Willner P, Muscat R. Behavioural sensitization to a dopamine agonist is associated with reversal of stress-induced anhedonia. *Psychopharmacology (Berl)* 1993;110:159–164. [PubMed: 7870877]
- Pezawas L, Verchinski BA, Mattay VS, Callicott JH, Kolachana BS, Straub RE, Egan MF, Meyer-Lindenberg A, Weinberger DR. The brain-derived neurotrophic factor val66met polymorphism and variation in human cortical morphology. *J Neurosci* 2004;24:10099–10102. [PubMed: 15537879]
- Post RM. Intermittent versus continuous stimulation: effect of time interval on the development of sensitization or tolerance. *Life Sci* 1980;26:1275–1282. [PubMed: 6991841]
- Post RM Kindling and sensitization as models for affective episode recurrence, cyclicity, and tolerance phenomena. *Neurosci Biobehav Rev* 2007 doi:
- Post RM, Uhde TW, Putnam FW, Ballenger JC, Berrettini WH. Kindling and carbamazepine in affective illness. *J Nerv Ment Dis* 1982;170:717–731. [PubMed: 6754868]
- Robinson TE, Becker JB. Enduring changes in brain and behavior produced by chronic amphetamine administration: a review and evaluation of animal models of amphetamine psychosis. *Brain Res* 1986;396:157–198. [PubMed: 3527341]
- Rowe MK Wiest C Chuang DM GSK-3 is a viable potential target for therapeutic intervention in bipolar disorder. *Neurosci Biobehav Rev* 2007 doi:
- Roybal K, Theobald D, Graham A, Dinieri JA, Russo SJ, Krishnan V, Chakravarty S, Peevey J, Oehrlein N, Birnbaum S, Vitaterna MH, Orsulak P, Takahashi JS, Nestler EJ, Carlezon WA Jr. McClung CA. From the Cover: Mania-like behavior induced by disruption of CLOCK. *Proc Natl Acad Sci U S A* 2007;104:6406–6411. [PubMed: 17379666]
- Rybakowski JK, Borkowska A, Skibinska M, Hauser J. Illness-specific association of val66met BDNF polymorphism with performance on Wisconsin Card Sorting Test in bipolar mood disorder. *Mol Psychiatry*. 2005
- Seong E, Seasholtz AF, Burmeister M. Mouse models for psychiatric disorders. *Trends Genet* 2002;18:643–650. [PubMed: 12446150]
- Stewart JJ, Badiani AA. Tolerance and sensitization to the behavioral effects of drugs. *Behav Pharmacol* 1993;4:289–312. [PubMed: 11224198]
- Valtonen H, Suominen K, Mantere O, Leppamaki S, Arvilommi P, Isometsa ET. Suicidal ideation and attempts in bipolar I and II disorders. *J Clin Psychiatry* 2005;66:1456–1462. [PubMed: 16420084]
- Woods SW. The economic burden of bipolar disease. *J Clin Psychiatry* 2000;61(Suppl 13):38–41. [PubMed: 11153811]
- Young JW Minassian AP Paulus MP Geyer MA Perry WA reverse-translational approach to bipolar disorder: rodent and human studies in the behavioral pattern monitor. *Neurosci Biobehav Rev* 2007 doi:
- Young RC. Bipolar disorder in older persons: perspectives and new findings. *Am J Geriatr Psychiatry* 2005;13:265–267. [PubMed: 15845751]
- Youngstrom EA, Findling RL, Youngstrom JK, Calabrese JR. Toward an evidence-based assessment of pediatric bipolar disorder. *J Clin Child Adolesc Psychol* 2005;34:433–448. [PubMed: 16026213]