Journal of Affective Disorders 121 (2010) 1–9

Contents lists available at ScienceDirect

Journal of Affective Disorders

journal homepage: www.elsevier.com/locate/jad

Special review article

Qui non proficit, deficit: Experimental models for 'integrative' research of affective disorders

Justin L. LaPorte [a], Rupert J. Egan [a], Peter C. Hart [a,b], Carisa L. Bergner [a], Jonathan M. Cachat [b], Peter R. Canavello [b], Allan V. Kalueff [b,*]

[a] Department of Physiology and Biophysics, Georgetown University Medical School, 3900 Reservoir Road, Washington, DC 20057, USA
[b] Department of Pharmacology, Tulane University Medical School, 1430 Tulane Ave., New Orleans, LA 70112, USA

ARTICLE INFO

Article history:
Received 26 June 2008
Received in revised form 24 March 2009
Accepted 7 April 2009
Available online 9 May 2009

Keywords:
Affective disorders
Translational research
Experimental models
Gene × environment × behavior interactions

ABSTRACT

Experimental models are an important tool for the study of biological mechanisms of psychiatric disorders. Although encouraging progress has been made in biological psychiatry of affective disorders, there remain numerous methodological, conceptual, and translational challenges in this field. Mounting clinical data support the view that psychiatric disorders as spectra, rather than as discrete or isolated illnesses. This requires new theories as well as new animal paradigms for "integrative" modeling of psychiatric disorders and their spectra. Here we discuss recent "integrative" experimental models and concepts that promise to advance translational research of affective disorders.

Contents

1. Introduction

Affective disorders are among the most common brain illnesses. This makes them a top priority for biomedical research (Craddock and Forty, 2006; Craddock and Jones, 1999; Veen et al., 2008). Understanding the neural mechanisms of such disorders (Fig. 1A) is an important goal in biological psychiatry (Harrison and Critchley, 2007). A valuable tool for this goal are animal models, commonly used due to their genetic homology with humans, and low cost, time, and space requirements (Crawley, 1999; Sousa et al., 2006). Representing an ethically-sound substitute for human subjects, animal models foster translational biopsychiatry research, given the

* Corresponding author. Department of Pharmacology, Room 3731, Tulane University Medical School, 1430 Tulane Ave. New Orleans, LA 70112, USA. Tel.: +1 504 988 3354.
E-mail address: avkalueff@gmail.com (A.V. Kalueff).

0165-0327/$ – see front matter © 2009 Elsevier B.V. All rights reserved.
doi:10.1016/j.jad.2009.04.010

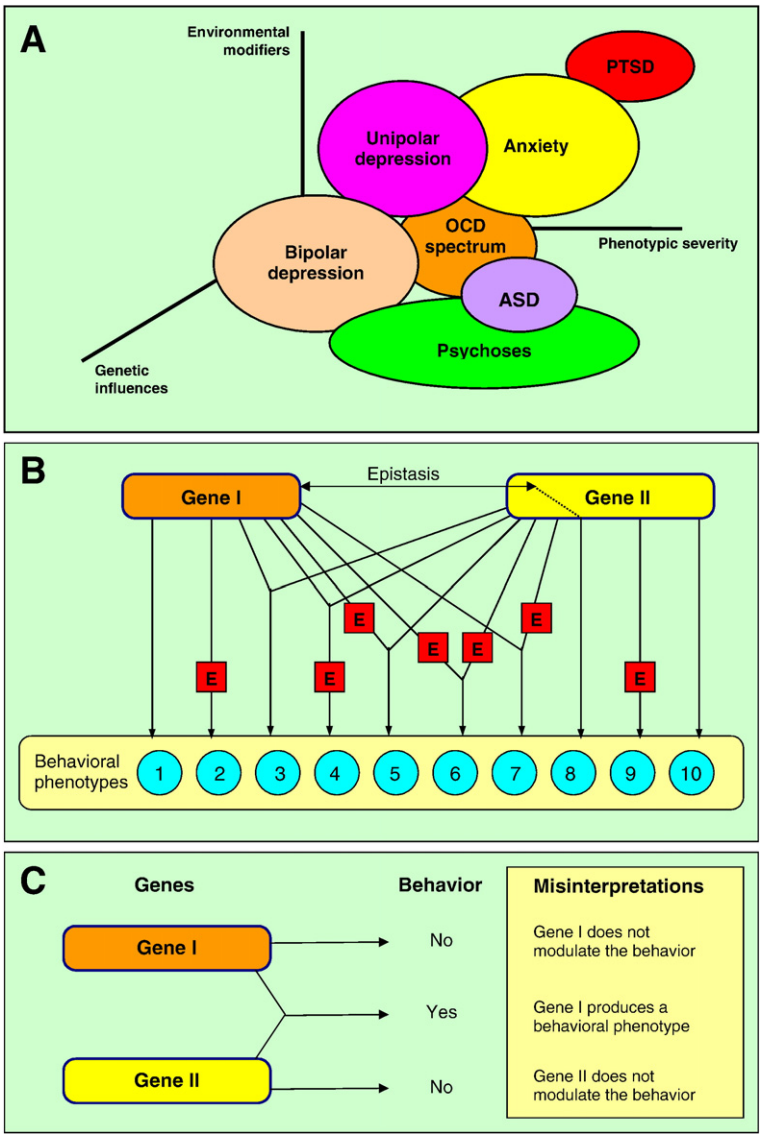

Fig. 1. The emerging complexity of gene × gene × environment × behavior interactions: A — Visual 3D representation of the continuum nature of psychiatric disorders. This figure is based on the dimensional model approach which takes into account not only specific symptomology but accounts for the severity of phenotypes as well as the factors (genes, environment) which influence the development of each symptom. Each trait has its own point on the diagram making a more comprehensive diagnosis possible. PTSD — post-traumatic stress disorder, OCD — obsessive–compulsive disorders, ASD — autism spectrum disorders. B — Simplified example of how only two interacting genes I and II may result in multiple, potentially distinct behavioral phenotypes. Mechanisms include gene's direct effects on behavior (phenotypes 1, 10), the genes' joint effects (phenotype 3), their epistatic interactions (phenotype 8), the genes' interaction with environmental factors E (phenotypes 2, 4, 6, 9), or a combination of a gene's direct effects on behavior with another gene's × E interactions (phenotypes 5, 7). Note that the real nature of most psychiatric disorders is even more complex and polygenic. Further, while not represented here, environmental influences can affect phenotype independently as well. C — Epistatic interactions between two genes (I and II) may mask single-gene effects on behavioral phenotype, and lead to misinterpretation of behavioral data.

ease of their genetic, pharmacological and other experimental manipulations (Crabbe and Morris, 2004; Kalueff et al., 2007d; Kas et al., 2007, 2003; Nestler et al., 2002).

Behavioral models are traditionally used in basic research on affective disorders, including anxiety (Ohl et al., 2001), post-traumatic stress disorder (PTSD) (Siegmund and Wotjak, 2007), 2006) and depression (Cryan and Holmes, 2005). Genetically modified, inbred or selectively bred animals are also employed to model brain disorders, and explore the role of gene–environment (G × E) interactions in their pathogenesis (Crabbe et al., 1999; Crawley et al., 2007; Einat, 2007; Gingrich et al., 2003; Meerlo et al., 2001; Valdar et al., 2006).

Despite the marked progress in basic and clinical research of affective disorders, there are many emerging challenges, including methodological, conceptual and translational impediments (Kalueff et al., 2008b, 2007d; Nestler et al., 2002; Tecott and Nestler, 2004). Here we outline some ways to overcome these difficulties, and discuss innovative models and conceptual frameworks that create more accurate analogues to affective disorders. Researchers may then better tackle the situation

aptly summarized by the Latin proverb "Qui non proficit, deficit" in the title of this paper. Its exact meaning, "He who does not advance, loses ground", embodies the stakes that face the field of biological psychiatry today.

2. Methodological, conceptual, and translational challenges

Methodological considerations represent a well-recognized challenge in biopsychiatry research (Table 1). Factors that contribute to behavioral phenotypes have a high degree of complexity, and are a product of G×E×B (behavior) interactions (Caspi and Moffitt, 2006; Caspi et al., 2003; Rutter et al., 2006). For example, the simplified situation in Fig. 1B shows how interactions between only two genes and environment (see details in the legend) may result in at least 10 different phenotypes. Likewise, epistatic interactions are very common in biological psychiatry (Murphy et al., 2003), and may lead to conflicting behavioral data (Fig. 1C). Another common problem is the risk of misinterpretation due to lack of diagnostic accuracy and the high variation, complexity and comorbidity of clinical phenotypes (Kato, 2007; Skuse, 2006, 2007; Veen et al., 2008), also see Fig. 2A. Unveiling the epigenetic influences in the pathogenesis of mood/affective disorders is yet another challenge, since functional genes can be governed by a complex set of regulations beyond the genome, that researchers are just beginning to understand (Abdolmaleky et al., 2005; Mill and Petronis, 2007; Shelton, 2007; Tsankova et al., 2007). Some other methodological challenges in the field are summarized in Table 1.

Conceptual challenges can often represent even bigger problems. Consider, for example, trans-generational non-genomic inheritance, which may not only operate through epigenetic mechanisms (e.g., DNA methylation, histone acetylation), but also through broader mechanisms related to parental physiology or behavior (Champagne and Meaney, 2001; Gluckman et al., 2007). Though there is a significant body of research on the environmental and genetic effects on behavior, there has been

Table 1
Some methodological, conceptual and translational problems in biological psychiatry, and potential research strategies for overcoming these challenges.

Challenges	Potential solutions	References
Methodological		
Need to link behaviors to neural circuits	Identify specific biological markers (e.g. c-fos expression) of behavioral endpoints; use additional experimental techniques (e.g. fMRI) to isolate circuits and match them with corresponding behaviors	Bruening et al. (2006); Grossberg and Seidman (2006)
Lack of diagnostic accuracy, risks of misinterpretation	Identification and testing of endophenotypes for disorders; reevaluate validity of current diagnostic criteria	Strain and Diefenbacher (2008)
Need more gene–phenotype correlational studies	Incorporate supplementary correlational measures elements into the existing projects	Dick et al. (2000); Mhyre et al. (2005)
Modeling specific animal behaviors with unclear psychiatric classification	Apply new concepts and models of "continuum" natured disorders (see text for details)	Frazer and Morilak (2005)
Difficulty to model purely human phenotypes, role of metacognition	Focus on domains that are relevant to animals; identify new endophenotypes of the disorder	Jablensky (2004)
Modeling stress-related phenomena such as psychosomatic disorders	Use animal genetic and experimental models relevant to psychosomatic research	Crnic (1996); Geerse et al. (2006)
Conceptual		
Very few new experimental models	Experiment outside the usual repertoire of models (think outside the box)	Kalueff et al. (2007d)
Need multi- (vs. single-) domain models	Model separate domains in tandem and their dynamics	Kalueff et al. (2008b)
Need new conceptualization of disorders	Integrate basic research with other aspects of the field (clinical, theory of mind, etc.)	Harrison and Critchley (2007)
Need full appreciation of continuous nature of disorders	Validate models whose phenotypes mimic continuous disorders (spectra)	Sufka et al. (2006)
Need distinction between state vs. trait disorders (e.g. chronic vs. acute anxiety)	Dissection of the differences in temporal onset, and neurobiological substrates; use models of pathogenetic anxiety vs. normal emotional reactivity	Ohl (2005); Ohl et al. (2008)
Need enhanced modeling of pathogenetic transitions	Develop new models that demonstrate disorders in their pathogenetic entirety (e.g. transitions from anxiety to depression)	Warnick et al., 2009; Warnick et al. (2006), also see Fig. 2B
Gap between pharmacological vs. genetic inactivation	Dissect between developmental vs. adulthood effects of drugs and mutations; use inducible knockout models, and pre-, neo- or post-natal drug treatments	Ansorge et al. (2004); Zhao et al. (2006)
Importance of non-genomic inheritance in behavioral phenotypes	Dissect genetic vs. epigenetic factors (breeding, cross-fostering)	Champagne and Meaney (2001); Gluckman et al. (2007)
Role of in peripheral mechanisms that affect behavior (e.g., metabolic syndrome)	Focus on center vs. periphery (e.g., tissue-specific knockouts, targeted drug and/or gene delivery)	Skilton et al. (2007); Toker et al. (2007)
Models of drug×environment interactions	Use models relevant to environmental modifiers (e.g. social support) of drug responses	Majercsik and Haller (2004)
Translational		
Need for cross-species genetics	Use additional different species as model objects; focus on common genetic mechanisms of disorders in humans and animals	Clapcote et al. (2007); Kas et al. (2007)
Need for identification of new candidate genes	Concentrate on cross-species mapping of genes and relation to disorders; implement linkage and/or quantitative trait loci studies on disorder-relevant animal models; use genetically altered mice to dissect gene variants responsible for behaviors	Kas et al. (2007); Valdar et al. (2006)
Need for integration of disciplines	Pursue interdisciplinary collaborations (e.g., psychiatry, psychology, and genetics); expose research to a broader collegial audience	Harrison and Critchley (2007)

fMRI — functional magnetic resonance imaging.

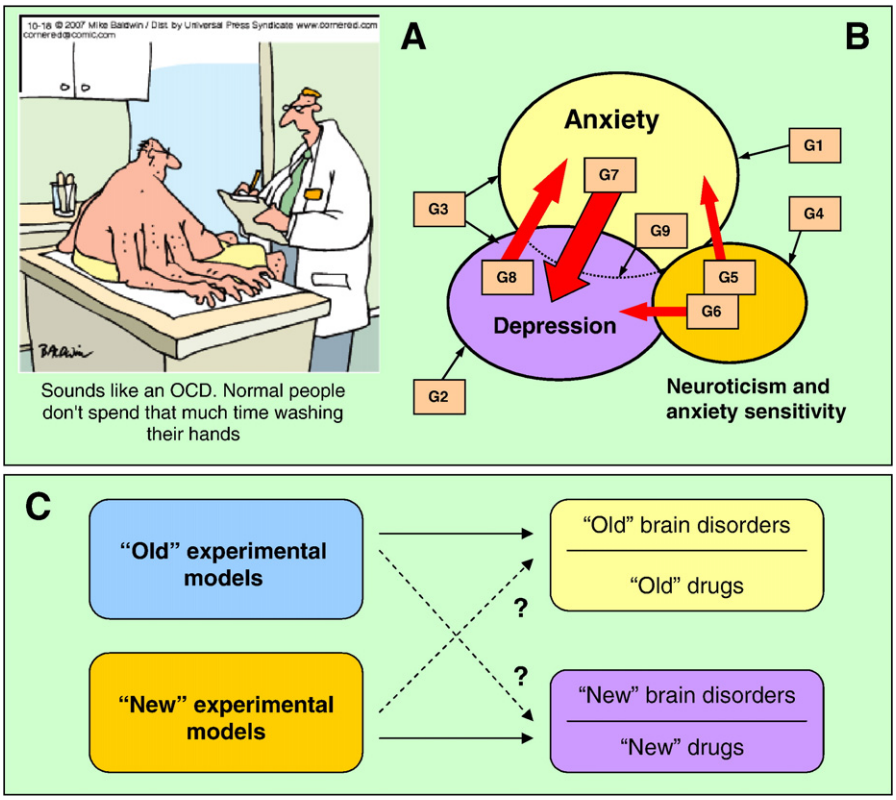

Fig. 2. The complexity of translational psychiatric research: A — There is considerable difficulty in diagnosing patients with complex psychiatric disorders, and a high risk of misinterpretation. In a hypothetical 6-armed patient (cartoon: M. Baldwin, with permission), washing hands clearly takes more time than in a normal 2-armed person. Although this does not automatically qualify for an obsessive–compulsive disorder (OCD), a mechanistic application of clinical diagnostic criteria and misinterpretation of behaviors may lead to this patient being incorrectly diagnosed with OCD. The second point here is relevant to the animal experimentation field, where researchers often focus on robustly affected behavioral measures (e.g., excessive rodent grooming that resembles OCD-like phenotype (Welch et al., 2007). In fact, such phenotypes may have other causes (e.g., hyperactivity, increased pain, itching) beyond OCD. In any case, unlike the patient in this cartoon, animals cannot be asked why they spend more time grooming. Thus, it is difficult to create a valid animal model of a brain disorder, for many of the same reasons that hinder correct behavioral interpretation and/or clinical diagnoses. B — Example of potentially complex genetics of anxiety and depression. Different groups of genes may regulate anxiety (G1), depression (G2), both disorders (G3), anxiety sensitivity and neuroticism — personality traits that are associated with both disorders (G4), the pathogenetic link between anxiety sensitivity/neuroticism and anxiety (G5) or depression (G6), transition from anxiety to depression (G7) or from depression to anxiety (G8; red arrows), as well as genetic determinants of comorbidity of anxiety and depression (G9; also see Fig. 3). C — The utility of new experimental models in biological psychiatry. Traditional well-validated "old" models may (or may not) be able to identify new classes of drugs or target newly-appreciated brain phenomena. This is why principally new models may be needed for developing new drugs and investigating newly recognized types and subtypes of brain disorders.

less emphasis on the disambiguation of the two contributing factors. This poses questions concerning the heritability of psychiatric illness. To what extent is the phenotypic phenomenon observed in the offspring a product of genetic predisposition, familial environment and rearing, or the interactions between them? Although some of these interactions are known, determining the degree of influence will be crucial for the ability to model, prevent, and treat brain disorders (see Table 1 for potential solutions to these and some other challenges).

Another challenge is the growing understanding of the role of peripheral factors in psychiatric pathogenesis. For example, consider metabolic syndrome, a systemic dysregulation characterized by obesity, elevated triglycerides/glucose and lowered high-density lipoproteins (Laclaustra et al., 2007). Because this syndrome is frequently associated with depression, it is highly relevant to mental health research, and requires valid animal models to mimic this pathogenesis (Skilton et al., 2007; Toker et al., 2007). Likewise, serotonin syndrome (SS) occurs with an excess of brain serotonin, and includes both mental (agitation, anxiety, confusion) and "peripheral" (fever, muscle rigidity, midriasis) symptoms (Gillman, 2005). Since genetic polymorphisms affect how the patient reacts to, or catabolizes, serotonergic drugs, the existing animal genetic and pharmacological models of SS (Kalueff et al., 2008) offer the possibility to integrate central and peripheral systems in the pathogenesis of this syndrome.

From a conceptual point of view, biological psychiatry has largely been preoccupied with studying individual disorders, in hopes to better dissect behavioral and genetic correlates (Craddock and Forty, 2006). Similarly, for years the key requirement for animal models was their "specificity", leading to the fact that many traditional well-validated animal paradigms are single-domain models (Kalueff et al., 2007a,b,c,d). However, it is now becoming increasingly understood that human brain disorders have a spectrum nature, and do not occur in isolation (Akiskal, 2003; Benazzi, 2004; Lara et al., 2006). For example, a comprehensive analysis of mood, behavioral and personality disorders (Lara et al., 2006) shows that these disorders can all be

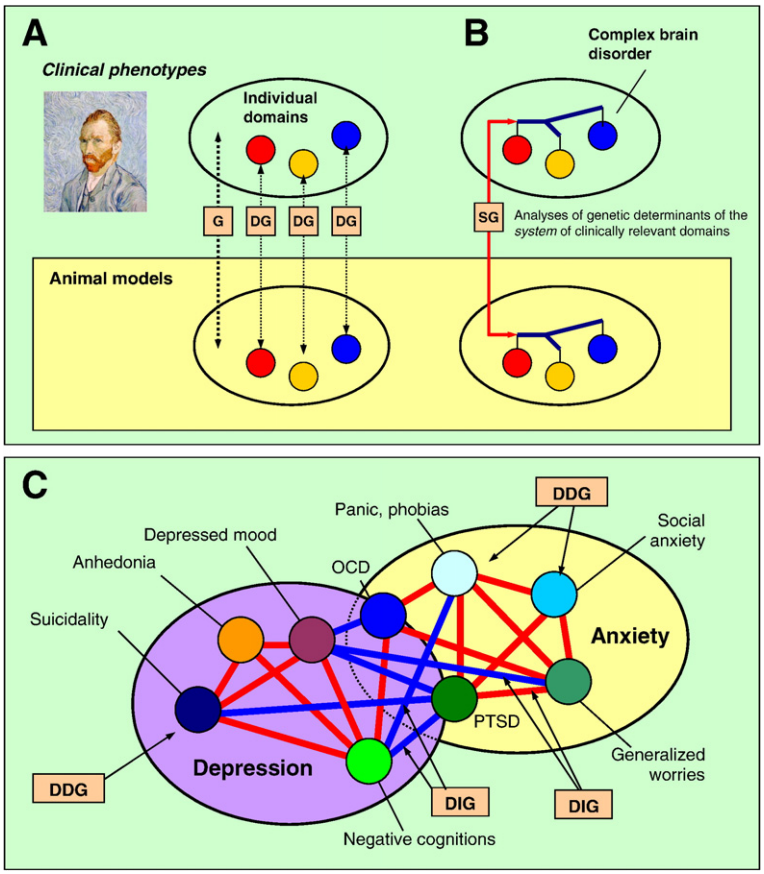

Fig. 3. A brief summary of different concepts used in psychiatric research and their application to psychiatric genetics: A — Traditional approaches to cross-species translational research in men (e.g. Van Gogh, self-portrait) and mice (e.g. photo: vitamin D receptor knockout mouse (Minasyan et al., 2007)) include modeling a brain disorder/syndrome, its domains and their respective genetics across species in the search for genetic determinants of the disorder ("disorder" genes, G) or individual domains/endophenotypes ("domain" genes, DG). B — Domain interplay-oriented approach (Kalueff et al., 2008a) links several domains into a system (based on their overlap/interplay) for subsequent modeling of this system (and its genetics) across species. SG — the genes responsible for overlap and interplay between the domains. C — Further complexity of domain genetics of affective disorders, based on the domain-interplay concept (also see Fig. 2B). This diagram shows how several domains (clinical endophenotypes; marked with small circles) can be linked pathogenetically both within individual disorders (e.g. anxiety, depression; links are indicated by red lines) and across different disorders (blue lines). Respectively, genetic determinants of such disorders may include sets of disorder-specific "domain" genes (DDG) as well as genes not affecting the domains but responsible for the interplay between them ("domain-interplay" genes, DIG) either within or between the two disorders. PTSD — post-traumatic stress disorder. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

interconnected into an overlapping system based on specific traits such as fear and anger. Likewise, a clear overlap between addiction and bipolar depression (Fig. 1A; (Maremmani et al., 2008, 2006), depression and schizophrenia (Kato, 2007), or anxiety and depression (Kalueff and Nutt, 2007; Moffitt et al., 2007), suggests that more emphasis should be put on integrative psychiatry to diagnose and treat these dual disorders. Collectively, this questions the efficacy of testing single domains in animal models, and suggests that the complexity of human phenotypes should be applied to the field of animal modeling (Kalueff et al., 2007d; Kas et al., 2007; Kas and Van Ree, 2004). Thus, multi-domain animal models may allow for a more clinically relevant examination of the disorders, and a better portrayal of the pathogenetic mechanisms in patients (Frazer and Morilak, 2005). While maintaining research within a single domain precludes this advance, multi-domain models offer a larger scope of the pathogenetic networks and may establish more solid genetic, behavioral and neurochemical links between the disorders (Kalueff et al., 2008a,b).

As already mentioned, clinical psychiatric disorders are extremely complex, and researchers may inadvertently lose valuable information by oversimplifying their investigations for ease of interpretation. Thus, while dissecting domains of a disorder can be vital to its elucidation (Kas et al., 2007; Kas and Van Ree, 2004; Owen et al., 2007), an effort toward modeling the more complex and interactive elements of a disorder could prove to be a valuable supplement for such research. Several concepts have been traditionally used in phenotyping of psychiatric disorders (Fig. 3A, B). The G×B approach focuses on the genetic contributions to the behavior of the animal or patient (Hamer, 2002). The G×E approach studies how the genetic effects may be modified by the environment (Caspi and Moffitt, 2006; Caspi et al., 2005; Rutter et al., 2006). The endophenotype concept deconstructs a complex psychiatric disorder into sets of identifiable heritable simpler traits — cognitive, anatomical, morphological, neurophysiological, neurochemical, or endocrinological features — that provide researchers with clues regarding the phenotype/gene

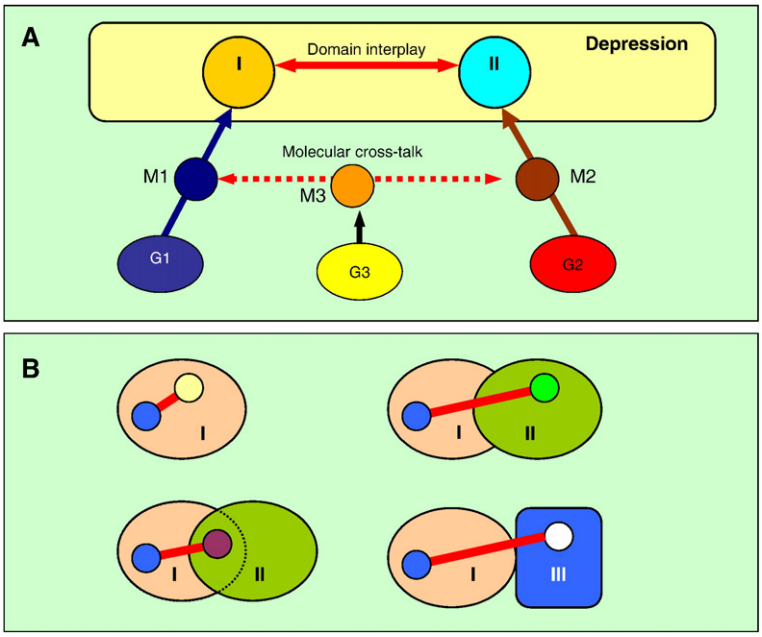

Fig. 4. Possible mechanisms and experimental models to study domain interplay of affective disorders: A — Potential genetic mechanisms for domain interplay. Consider, for example, two domains (I and II) of depression. While it is possible that each domain is controlled by a specific set of genes (G1, G2, encoding molecules M1 and M2), there is another possibility, predicted by the domain-interplay concept. Pathogenic mechanisms of the two domains may also be affected by "third-party" genes (G3) not directly associated with either domain, but encoding molecule M3 that triggers molecular interactions between M1 and M2. This new cross-talk (red broken line) may underlie, at the molecular level, the interplay between the two domains (red solid line), thus affecting the resulting clinical phenotype without directly influencing either domain *per se*. B — Different types of "integrative" animal models of affective disorders. Targeting the simplified system of two domains (marked with small circles), such models may (clock-wise) focus on: domains within the same affective disorder I; domains belonging to two different affective disorders I and II; a combination of one disorder I-specific domain and one "comorbid" domain (common for both disorders); or domains belonging to two different disorders, one of which is affective (I), and another is non-affective (e.g., metabolic syndrome, obesity, epilepsy; III).

connection in the disorder (Cannon and Keller, 2006; Gottesman and Gould, 2003; Gould and Einat, 2007; Walters and Owen, 2007). Finally, the cross-species approach compares similar behavioral traits in different species, thereby creating a stable set of phenotypical characteristics that can be applied to clinical research (Kas et al., 2007).

Although these traditional approaches are useful, other translational strategies may address the emerging complexity and overlap of psychiatric disorders. For example, disorders such as depression and anxiety are frequently comorbid in clinical psychiatry, lie along the same disorder continuum, and share some genes and neurobiological mechanisms (Kalueff and Nutt, 2007); Figs. 1A, 2B, and 3C. Therefore, in order to maximize validity and accuracy of the animal models, researchers may need not only to mimic anxiety and depression phenotypes, but also target the interplay between them and/or their various domains (see further).

3. From modeling individual affective disorders to targeting their integrative pathogenesis

One such approach is the domain-interplay concept (Kalueff et al., 2008a), which advocates the testing of numerous domains and their interplay simultaneously as a dynamic system, rather than simply deconstructing disorders into individual domains (see Figs. 3 and 4A for details). Briefly, this concept suggests going beyond the endophenotype concept, since the study of the dynamic nature of domain systems may shed more light on comorbidity, continuum, and pathogenetic trajectory aspects of psychiatric disorders. Furthermore, animal studies will also be more relevant as a model of psychiatric disorders if the researchers focus on the dynamic system, rather than a particular disorder or its domains.

How can this be implemented practically? A good example of domain interplay-driven basic research on affective disorders includes modeling the anxiety–depression continuum in birds (Feltenstein and Sufka, 2005; Sufka et al., 2006). In this model, the chick distress vocalizations were measured and disambiguated into two distinct phases: the "anxiety" phase (characterized by high stress vocalization immediately after removal from conspecifics) and the "depression" phase (characterized by a low rate of vocalizations 15–20 min after isolation). Anxiolytic drugs were effective in decreasing the distress vocalizations in the anxiety-like phase but not in the depression phase. In contrast, the antidepressant drugs increased vocalizations in the depression-like (but not in the anxiety-like) phase, thus demonstrating how two affective domains and their transitions can be modeled in animals using minimal time (Warnick et al., 2009). The pathogenic anxiety–depression trajectory can also be modeled using the chronic social-defeat stress in rodents (Avgustinovich et al., 2005). In this model, male mice were placed in a confrontational environment for 20 days, leading to observable symptoms of a gradual transition from anxiety (10 days) to depression (20 days), as measured by various tests for anxiety and depression.

Table 2
Summary of some potential models of OCD-related behaviors and their utility to target additional psychiatric or neurological domains.

OCD-related behaviors and models	References	Other relevant domains
Drug-induced behaviors		
Meta-chlorophenylpiperazine and other chemicals (rodents)	Korff and Harvey (2006)	Drug toxicity, anxiety
Behavioral perseverations		
Compulsive head dipping (rodents)	Hoshino et al. (2004)	Anxiety, hyperactivity
Meandering/turning phenotype (rodents)	Kalueff et al. (2007c)	Anxiety, hyperactivity
Compulsive chewing (KO mice)	Chou-Green et al. (2003)	Rett, Tourette
Marble burying (rodents)	Kalueff et al. (2006a,b); Londei et al. (1998)	Anxiety, hyperactivity
Wheel running (aromatase KO mice)	Hill et al. (2007)	Hyperactivity
Spontaneous alternation in Y maze	Korff and Harvey (2006)	Anxiety, memory
Compulsive holeboard checking (rodents)	Korff and Harvey (2006)	Anxiety, hyperactivity
Other stereotypies		
Spontaneous grooming (KO mice)	Hill et al. (2007)	Depression, anxiety
Repetitive stress-evoked grooming behavior (rodents)	Kalueff et al. (2007a)	Depression
Genetic models of grooming (KO mice)	Graybiel and Saka (2002); Welch et al. (2007)	Self-destruction
Barbering (fur-plucking rodents)		Aggression
Self-barbering (rodents)	Garner et al. (2004)	Trichotillomania
Food restriction-evoked hyperactivity (rodents)	Korff and Harvey (2006)	Eating disorders
Reward		
Compulsive drug intake (rodents)	Korff and Harvey (2006)	Drug abuse

KO — knockout mice.

Aggression is a common symptom of bipolar disorder in the clinic, and can be modeled in rodents in the resident–intruder test. These behaviors are sensitive to the action of mood stabilizers (such as lithium) which produce no changes in non-aggressive social interactions. In this way, the assessment of aggressive behaviors can be integrated into the battery of mania tests, relevant to bipolar pathogenesis (Einat, 2007). Likewise, the novelty-induced neophagia test measuring decreased feeding behavior in animals after exposure to a novel stimulus (Dulawa and Hen, 2005), has high "integrative" value for investigating both anxiety and the sensitivity to antidepressant drugs (see (Einat, 2006; Kalueff et al., 2008b) and Table 2 for other examples of integrative multi-domain models).

In addition to behavioral paradigms, there are also interesting "integrative" genetic animal models. For example, Disc1 mutant mice display depression and schizophrenia-like symptoms (Clapcote et al., 2007), confirming some common genetic determinants of the two disorders, and showing how an integrated genetic model can be used to make "linkages" between frequently overlapping psychiatric disorders. Serotonin transporter (SERT) knockout mice and rats have been extensively studied for their affective phenotypes, abnormal coping and fear responses, SS-like behaviors, and atypical brain morphology (Holmes et al., 2003; Homberg et al., 2007; Kalueff et al., 2007b; Wellman et al., 2007). 5-HT1A receptor knockout mice have altered fear-mediating circuitry and increased fear responses (Gross et al., 2000; Klemenhagen et al., 2006), whereas the 5-HT2C receptor mutants show increased compulsive chewing and head-dipping behavior (Chou-Green et al., 2003), relevant to obsessive–compulsive disorder (OCD; see other models of OCD and their relevance to different brain disorders in Table 2).

Double mutant mice represent another interesting group of genetic animal models (Murphy et al., 2003). For example, SERT × BDNF (brain-derived neurotrophic factor) knockout mice show robust emotionality behavior, memory deficits and metabolic problems/obesity (Ren-Patterson et al., 2006; Ren-Patterson et al., 2005). However, the importance of such models (in light of the present paper) is not in the variety of targeted "affective" domains, but rather in the fact that several domains are affected simultaneously, in a way that strikingly resembles a clinically relevant picture of how brain disorders overlap.

From a clinical standpoint, the entire classification system for human brain disorders is set to undergo a drastic change from its current state. Researchers must be prepared to adopt and utilize a newly defined classification system based on examining systems on a dimensional level rather than a set labeling system. Synergistic adoption of this integrative approach by both clinical practitioners and behavioral researchers will allow for better communication, and foster the development of innovative and progressive ways to tackle the complex issues related to the study and treatment of brain disorders.

4. Concluding remarks

As psychiatric disorders are among the fastest growing diseases diagnosed, traditional studies on G x E x B interactions of individual disorders or their specific domains (Fig. 3A) will benefit from a better focus on genes and other factors that determine the domain interplay and "continuum" nature of brain pathogenesis. The emerging complexities of psychiatric phenomena (Figs. 1–3) emphasize the need for genetic and experimental animal models that will better feature complex clinical phenotypes, to parallel clinical data (Frazer and Morilak, 2005; Kalueff et al., 2008c).

Our contention is that the integration of these concepts is a necessary step toward accurately describing the multiple and interrelated factors that contribute to the complex nature of human brain pathogenesis. We recognize that development of new models and concepts represents an essential development in the field of translational biopsychiatry research. Increasing awareness of the integrative nature of human affective disorders (Fig. 1) requires different types of "integrative" animal models to mimic these clinically relevant aspects (Fig. 4B). As already mentioned, actively modeling a *system* of disorders (or domains) can offer a wealth of biological information that has been unexplored previously. This paper has only briefly summarized the developing utility of "integrative" animal models, and discussed how the new domain-oriented concepts may foster translational research.

Indeed, researchers should strive to continually advance the field, and be ready to adopt more comprehensive and systematic approaches to studying brain pathogenesis. It is only through these avenues of investigation can we gain a better perspective on affective disorders, and "*proficit*" their new treatments and preventions.

Role of funding source

The research support for this study came from Georgetown University and NARSAD, a non-profit charity that supports biomedical mental health research.

The research support was used entirely for the scientific purposes of this MS. GU and NARSAD had no further role in the study design, data analysis, interpretation of the data, writing the MS, and in the decision to submit the paper for publication.

Conflict of interest

No conflict declared.

Acknowledgements

This study was supported by the NARSAD YI Award (to AVK) and by Georgetown University Stress and Physiology Research Center (SPaRC).

References

Abdolmaleky, H.M., Thiagalingam, S., Wilcox, M., 2005. Genetics and epigenetics in major psychiatric disorders: dilemmas, achievements, applications, and future scope. Am. J. Pharmacogenomics 5, 149–160.

Akiskal, H.S., 2003. Validating 'hard' and 'soft' phenotypes within the bipolar spectrum: continuity or discontinuity? J. Affect. Disord. 73, 1–5.

Ansorge, M.S., Zhou, M., Lira, A., Hen, R., Gingrich, J.A., 2004. Early-life blockade of the 5-HT transporter alters emotional behavior in adult mice. Science 306, 879–881.

Avgustinovich, D.F., Kovalenko, I.L., Kudryavtseva, N.N., 2005. A model of anxious depression: persistence of behavioral pathology. Neurosci. Behav. Physiol. 35, 917–924.

Benazzi, F., 2004. Is depressive mixed state a transition between depression and hypomania? Eur. Arch. Psychiatry Clin. Neurosci. 254, 69–75.

Bruening, S., Oh, E., Hetzenauer, A., Escobar-Alvarez, S., Westphalen, R.I., Hemmings Jr., H.C., Singewald, N., Shippenberg, T., Toth, M., 2006. The anxiety-like phenotype of 5-HT receptor null mice is associated with genetic background-specific perturbations in the prefrontal cortex GABA–glutamate system. J. Neurochem. 99, 892–899.

Cannon, T.D., Keller, M.C., 2006. Endophenotypes in the genetic analyses of mental disorders. Annu. Rev. Clin. Psychol. 2, 267–290.

Caspi, A., Moffitt, T.E., 2006. Gene–environment interactions in psychiatry: joining forces with neuroscience. Nat. Rev. 7, 583–590.

Caspi, A., Sugden, K., Moffitt, T.E., Taylor, A., Craig, I.W., Harrington, H., McClay, J., Mill, J., Martin, J., Braithwaite, A., Poulton, R., 2003. Influence of life stress on depression: moderation by a polymorphism in the 5-HTT gene. Science 301, 386–389.

Caspi, A., Moffitt, T.E., Cannon, M., McClay, J., Murray, R., Harrington, H., Taylor, A., Arseneault, L., Williams, B., Braithwaite, A., Poulton, R., Craig, I.W., 2005. Moderation of the effect of adolescent-onset cannabis use on adult psychosis by a functional polymorphism in the catechol-O-methyltransferase gene: longitudinal evidence of a gene×environment interaction. Biol. Psychiatry 57, 1117–1127.

Champagne, F., Meaney, M.J., 2001. Like mother, like daughter: evidence for non-genomic transmission of parental behavior and stress responsivity. Prog. Brain Res. 133, 287–302.

Chou-Green, J.M., Holscher, T.D., Dallman, M.F., Akana, S.F., 2003. Compulsive behavior in the 5-HT2C receptor knockout mouse. Physiol. Behav. 78, 641–649.

Clapcote, S.J., Lipina, T.V., Millar, J.K., Mackie, S., Christie, S., Ogawa, F., Lerch, J.P., Trimble, K., Uchiyama, M., Sakuraba, Y., Kaneda, H., Shiroishi, T., Houslay, M.D., Henkelman, R.M., Sled, J.G., Gondo, Y., Porteous, D.J., Roder, J.C., 2007. Behavioral phenotypes of Disc1 missense mutations in mice. Neuron 54, 387–402.

Crabbe, J.C., Morris, R.G., 2004. Festina lente: late-night thoughts on high-throughput screening of mouse behavior. Nat. Neurosci. 7, 1175–1179.

Crabbe, J.C., Wahlsten, D., Dudek, B.C., 1999. Genetics of mouse behavior: interactions with laboratory environment. Science 284, 1670–1672.

Craddock, N., Forty, L., 2006. Genetics of affective (mood) disorders. Eur. J. Hum. Genet. 14, 660–668.

Craddock, N., Jones, I., 1999. Genetics of bipolar disorder. J. Med. Genet. 36, 585–594.

Crawley, J.N., 1999. Behavioral phenotyping of transgenic and knockout mice: experimental design and evaluation of general health, sensory functions, motor abilities, and specific behavioral tests. Brain Res. 835, 18–26.

Crawley, J.N., Chen, T., Puri, A., Washburn, R., Sullivan, T.L., Hill, J.M., Young, N.B., Nadler, J.J., Moy, S.S., Young, L.J., Caldwell, H.K., Young, W.S., 2007. Social approach behaviors in oxytocin knockout mice: comparison of two independent lines tested in different laboratory environments. Neuropeptides 41, 145–163.

Crnic, L.S., 1996. Transgenic and null mutant animals for psychosomatic research. Psychosom. Med. 58, 622–632.

Cryan, J.F., Holmes, A., 2005. The ascent of mouse: advances in modelling human depression and anxiety. Nat. Rev. Drug Discov. 4, 775–790.

Dick, D.M., Johnson, J.K., Viken, R.J., Rose, R.J., 2000. Testing between-family associations in within-family comparisons. Psychol. Sci. 11, 409–413.

Dulawa, S.C., Hen, R., 2005. Recent advances in animal models of chronic antidepressant effects: the novelty-induced hypophagia test. Neurosci. Biobehav. Rev. 29, 771–783.

Einat, H., 2006. Modelling facets of mania—new directions related to the notion of endophenotypes. J. Psychopharmacol. 20, 714–722.

Einat, H., 2007. Different behaviors and different strains: potential new ways to model bipolar disorder. Neurosci. Biobehav. Rev. 31, 850–857.

Feltenstein, M.W., Sufka, K.J., 2005. Screening antidepressants in the chick separation-stress paradigm. Psychopharmacology (Berl.) 181, 153–159.

Frazer, A., Morilak, D.A., 2005. What should animal models of depression model? Neurosci. Biobehav. Rev. 29, 515–523.

Garner, J.P., Weisker, S.M., Dufour, B., Mench, J.A., 2004. Barbering (fur and whisker trimming) by laboratory mice as a model of human trichotillomania and obsessive–compulsive spectrum disorders. Comp. Med. 54, 216–224.

Geerse, G.J., van Gurp, L.C., Wiegant, V.M., Stam, R., 2006. Individual reactivity to the open-field predicts the expression of stress-induced behavioural and somatic pain sensitisation. Behav. Brain Res. 174, 112–118.

Gillman, P.K., 2005. The serotonin syndrome. N. Engl. J. Med. 352, 2454–2456 (author reply 2454–2456).

Gingrich, J.A., Ansorge, M.S., Merker, R., Weisstaub, N., Zhou, M., 2003. New lessons from knockout mice: the role of serotonin during development and its possible contribution to the origins of neuropsychiatric disorders. CNS Spectr. 8, 572–577.

Gluckman, P.D., Hanson, M.A., Beedle, A.S., 2007. Non-genomic transgenerational inheritance of disease risk. Bioessays 29, 145–154.

Gottesman, I.I., Gould, T.D., 2003. The endophenotype concept in psychiatry: etymology and strategic intentions. Am. J. Psychiatry 160, 636–645.

Gould, T.D., Einat, H., 2007. Animal models of bipolar disorder and mood stabilizer efficacy: a critical need for improvement. Neurosci. Biobehav. Rev. 31, 825–831.

Graybiel, A.M., Saka, E., 2002. A genetic basis for obsessive grooming. Neuron 33, 1–2.

Gross, C., Santarelli, L., Brunner, D., Zhuang, X., Hen, R., 2000. Altered fear circuits in 5-HT(1A) receptor KO mice. Biol. Psychiatry 48, 1157–1163.

Grossberg, S., Seidman, D., 2006. Neural dynamics of autistic behaviors: cognitive, emotional, and timing substrates. Psychol. Rev. 113, 483–525.

Hamer, D., 2002. Genetics. Rethinking behavior genetics. Science 298, 71–72.

Harrison, N.A., Critchley, H.D., 2007. Affective neuroscience and psychiatry. Br. J. Psychiatry 191, 192–194.

Hill, R.A., McInnes, K.J., Gong, E.C., Jones, M.E., Simpson, E.R., Boon, W.C., 2007. Estrogen deficient male mice develop compulsive behavior. Biol. Psychiatry 61, 359–366.

Holmes, A., Murphy, D.L., Crawley, J.N., 2003. Abnormal behavioral phenotypes of serotonin transporter knockout mice: parallels with human anxiety and depression. Biol. Psychiatry 54, 953–959.

Homberg, J.R., Olivier, J.D., Smits, B.M., Mul, J.D., Mudde, J., Verheul, M., Nieuwenhuizen, O.F., Cools, A.R., Ronken, E., Cremers, T., Schoffelmeer, A.N., Ellenbroek, B.A., Cuppen, E., 2007. Characterization of the serotonin transporter knockout rat: a selective change in the functioning of the serotonergic system. Neuroscience 146, 1662–1676.

Hoshino, K., Uga, D.A., de Paula, H.M., 2004. The compulsive-like aspect of the head dipping emission in rats with chronic electrolytic lesion in the area of the median raphe nucleus. Braz. J. Med. Biol. Res. 37, 245–250.

Jablensky, A., 2004. Resolving schizophrenia's CATCH22. Nat. Genet. 36, 674–675.

Kalueff, A.V., Nutt, D.J., 2007. Role of GABA in anxiety and depression. Depress. Anxiety 24, 495–517.

Kalueff, A.V., Gallagher, P.S., Murphy, D.L., 2006a. Are serotonin transporter knockout mice 'depressed'?: hypoactivity but no anhedonia. Neuroreport 17, 1347–1351.

Kalueff, A.V., Minasyan, A., Keisala, T., Shah, Z.H., Tuohimaa, P., 2006b. Hair barbering in mice: implications for neurobehavioural research. Behav. Processes 71, 8–15.
Kalueff, A., Aldridge, J.W., Laporte, J.L.H., Murphy, D., Tuohimaa, P., 2007a. Analyzing grooming microstructure in neurobehavioral experiments. Nat. Protocols 11, 1–8.
Kalueff, A.V., Fox, M.A., Gallagher, P.S., Murphy, D.L., 2007b. Hypolocomotion, anxiety and serotonin syndrome-like behavior contribute to the complex phenotype of serotonin transporter knockout mice. Genes. Brain. Behav. 6, 389–400.
Kalueff, A.V., Jensen, C.L., Murphy, D.L., 2007c. Locomotory patterns, spatiotemporal organization of exploration and spatial memory in serotonin transporter knockout mice. Brain Res. 1169, 87–97.
Kalueff, A.V., Wheaton, M., Murphy, D.L., 2007d. What's wrong with my mouse model? Advances and strategies in animal modeling of anxiety and depression. Behav. Brain Res. 179, 1–18.
Kalueff, A., Ren-Patterson, R., LaPorte, J.L., Murphy, D., 2008a. Domain interplay concept in animal models of neuropsychiatric disorders: a new strategy for high-throughput neurophenotyping research. Behav. Brain Res. 188, 243–249.
Kalueff, A.V., Laporte, J.L., Murphy, D.L., Sufka, K., 2008b. Hybridizing behavioral models: a possible solution to some problems in neurophenotyping research? Prog. Neuro-psychopharmacol. Biol. Psychiatry 32, 1172–1178.
Kalueff, A.V., Ren-Patterson, R.F., LaPorte, J.L., Murphy, D.L., 2008c. Domain interplay concept in animal models of neuropsychiatric disorders: a new strategy for high-throughput neurophenotyping research. Behav. Brain Res. 188, 243–249.
Kalueff, A.V., Laporte, J.L., Murphy, D.L., 2008. Pespectives on genetic animal models of serotonin toxicity. Neurochem. Int. 52, 649–658.
Kas, M.J., Van Ree, J.M., 2004. Dissecting complex behaviours in the post-genomic era. Trends Neurosci. 27, 366–369.
Kas, M.J., Van Elburg, A.A., Van Engeland, H., Adan, R.A., 2003. Refinement of behavioural traits in animals for the genetic dissection of eating disorders. Eur. J. Pharmacol. 480, 13–20.
Kas, M.J., Fernandes, C., Schalkwyk, L.C., Collier, D.A., 2007. Genetics of behavioural domains across the neuropsychiatric spectrum; of mice and men. Mol. Psychiatry 12, 324–330.
Kato, T., 2007. Molecular genetics of bipolar disorder and depression. Psychiatry Clin. neurosci. 61, 3–19.
Klemenhagen, K.C., Gordon, J.A., David, D.J., Hen, R., Gross, C.T., 2006. Increased fear response to contextual cues in mice lacking the 5-HT1A receptor. Neuropsychopharmacology 31, 101–111.
Korff, S., Harvey, B.H., 2006. Animal models of obsessive–compulsive disorder: rationale to understanding psychobiology and pharmacology. Psychiatr. Clin. North Am. 29, 371–390.
Laclaustra, M., Corella, D., Ordovas, J.M., 2007. Metabolic syndrome pathophysiology: the role of adipose tissue. Nutr. Metab. Cardiovasc. Dis. 17, 125–139.
Lara, D.R., Pinto, O., Akiskal, K., Akiskal, H.S., 2006. Toward an integrative model of the spectrum of mood, behavioral and personality disorders based on fear and anger traits: I. Clinical implications. J. Affect. Disord. 94, 67–87.
Londei, T., Valentini, A.M., Leone, V.G., 1998. Investigative burying by laboratory mice may involve non-functional, compulsive, behaviour. Behav. Brain Res. 94, 249–254.
Majercsik, E., Haller, J., 2004. Interactions between anxiety, social support, health status and buspirone efficacy in elderly patients. Prog. Neuro-psychopharmacol. Biol. Psychiatry 28, 1161–1169.
Maremmani, I., Perugi, G., Pacini, M., Akiskal, H.S., 2006. Toward a unitary perspective on the bipolar spectrum and substance abuse: opiate addiction as a paradigm. J. Affect. Disord. 93, 1–12.
Maremmani, I., Pacini, M., Perugi, G., Deltito, J., Akiskal, H., 2008. Cocaine abuse and the bipolar spectrum in 1090 heroin addicts: clinical observations and a proposed pathophysiologic model. J. Affect. Disord. 106, 55–61.
Meerlo, P., Easton, A., Bergmann, B.M., Turek, F.W., 2001. Restraint increases prolactin and REM sleep in C57BL/6J mice but not in BALB/cJ mice. Am. J. Physiol. 281, R846–854.
Mhyre, T.R., Chesler, E.J., Thiruchelvam, M., Lungu, C., Cory-Slechta, D.A., Fry, J.D., Richfield, E.K., 2005. Heritability, correlations and in silico mapping of locomotor behavior and neurochemistry in inbred strains of mice. Genes. Brain. Behav. 4, 209–228.
Mill, J., Petronis, A., 2007. Molecular studies of major depressive disorder: the epigenetic perspective. Mol. Psychiatry 12, 799–814.
Minasyan, A., Keisala, T., Lou, Y.R., Kalueff, A.V., Tuohimaa, P., 2007. Neophobia, sensory and cognitive functions, and hedonic responses in vitamin D receptor mutant mice. J. Steroid Biochem. Mol. Biol. 104, 274–280.
Moffitt, T.E., Harrington, H., Caspi, A., Kim-Cohen, J., Goldberg, D., Gregory, A.M., Poulton, R., 2007. Depression and generalized anxiety disorder: cumulative and sequential comorbidity in a birth cohort followed prospectively to age 32 years. Arch. Gen. Psychiatry 64, 651–660.
Murphy, D.L., Uhl, G.R., Holmes, A., Ren-Patterson, R., Hall, F.S., Sora, I., Detera-Wadleigh, S., Lesch, K.P., 2003. Experimental gene interaction studies with SERT mutant mice as models for human polygenic and epistatic traits and disorders. Genes. Brain. Behav. 2, 350–364.
Nestler, E.J., Gould, E., Manji, H., Buncan, M., Duman, R.S., Greshenfeld, H.K., Hen, R., Koester, S., Lederhendler, I., Meaney, M., Robbins, T., Winsky, L., Zalcman, S., 2002. Preclinical models: status of basic research in depression. Biol. Psychiatry 52, 503–528.
Ohl, F., 2005. Animal models of anxiety. Handb. Exp. Pharmacol. 35–69.
Ohl, F., Sillaber, I., Binder, E., Keck, M.E., Holsboer, F., 2001. Differential analysis of behavior and diazepam-induced alterations in C57BL/6N and BALB/c mice using the modified hole board test. J. Psychiatr. Res. 35, 147–154.
Ohl, F., Arndt, S.S., van der Staay, F.J., 2008. Pathological anxiety in animals. Vet. J. 175, 18–26.
Owen, M.J., Craddock, N., Jablensky, A., 2007. The genetic deconstruction of psychosis. Schizophr. Bull. 33, 905–911.
Ren-Patterson, R.F., Cochran, L.W., Holmes, A., Sherrill, S., Huang, S.J., Tolliver, T., Lesch, K.P., Lu, B., Murphy, D.L., 2005. Loss of brain-derived neurotrophic factor gene allele exacerbates brain monoamine deficiencies and increases stress abnormalities of serotonin transporter knockout mice. J. Neurosci. Res. 79, 756–771.
Ren-Patterson, R.F., Cochran, L.W., Holmes, A., Lesch, K.P., Lu, B., Murphy, D.L., 2006. Gender-dependent modulation of brain monoamines and anxiety-like behaviors in mice with genetic serotonin transporter and BDNF deficiencies. Cell. Mol. Neurobiol. 26, 755–780.
Rutter, M., Moffitt, T.E., Caspi, A., 2006. Gene–environment interplay and psychopathology: multiple varieties but real effects. J. Child Psychol. Psychiatry Allied Discipl. 47, 226–261.
Shelton, R.C., 2007. The molecular neurobiology of depression. Psychiatr. Clin. North Am. 30, 1–11.
Siegmund, A., Wotjak, C.T., 2007. A mouse model of posttraumatic stress disorder that distinguishes between conditioned and sensitised fear. J. Psychiatr. Res. 41, 848–860.
Skilton, M.R., Moulin, P., Terra, J.L., Bonnet, F., 2007. Associations between anxiety, depression, and the metabolic syndrome. Biol. Psychiatry 62, 1251–1257.
Skuse, D., 2006. Genetic influences on the neural basis of social cognition. Philos. Trans. R. Soc. Lond. 361, 2129–2141.
Skuse, D.H., 2007. Rethinking the nature of genetic vulnerability to autistic spectrum disorders. Trends Genet. 23, 387–395.
Sousa, N., Almeida, O.F., Wotjak, C.T., 2006. A hitchhiker's guide to behavioral analysis in laboratory rodents. Genes. Brain. Behav. 5 (Suppl. 2), 5–24.
Strain, J.J., Diefenbacher, A., 2008. The adjustment disorders: the conundrums of the diagnoses. Compr. Psychiatry 49, 121–130.
Sufka, K.J., Feltenstein, M.W., Warnick, J.E., Acevedo, E.O., Webb, H.E., Cartwright, C.M., 2006. Modeling the anxiety–depression continuum hypothesis in domestic fowl chicks. Behav. Pharmacol. 17, 681–689.
Tecott, L.H., Nestler, E.J., 2004. Neurobehavioral assessment in the information age. Nat. Neurosci. 7, 462–466.
Toker, S., Shirom, A., Melamed, S., 2007. Depression and the Metabolic Syndrome: Gender-Dependent Associations. Depress Anxiety.
Tsankova, N., Renthal, W., Kumar, A., Nestler, E.J., 2007. Epigenetic regulation in psychiatric disorders. Nat. Rev. 8, 355–367.
Valdar, W., Solberg, L.C., Gauguier, D., Cookson, W.O., Rawlins, J.N., Mott, R., Flint, J., 2006. Genetic and environmental effects on complex traits in mice. Genetics 174, 959–984.
Veen, G., van Vliet, I.M., de Rijk, R.H., Zitman, F.G., 2008. Need for alternative ways of phenotyping of mood, anxiety, and somatoform disorders in biological research. Prog. Brain Res. 167, 277–280.
Walters, J.T., Owen, M.J., 2007. Endophenotypes in psychiatric genetics. Mol. Psychiatry 12, 886–890.
Warnick, J.E., Wicks, R.T., Sufka, K.J., 2006. Modeling anxiety-like states: pharmacological characterization of the chick separation stress paradigm. Behav. Pharmacol. 17, 581–587.
Warnick, J.E., Huang, C.-J., Acevedo, E.O., Sufka, K., 2009. Modeling the anxiety–depression continuum in chicks. J. Psychopharmacol. 23, 143–156.
Welch, J.M., Lu, J., Rodriguiz, R.M., Trotta, N.C., Peca, J., Ding, J.D., Feliciano, C., Chen, M., Adams, J.P., Luo, J., Dudek, S.M., Weinberg, R.J., Calakos, N., Wetsel, W.C., Feng, G., 2007. Cortico-striatal synaptic defects and OCD-like behaviours in Sapap3-mutant mice. Nature 448, 894–900.
Wellman, C.L., Izquierdo, A., Garrett, J.E., Martin, K.P., Carroll, J., Millstein, R., Lesch, K.P., Murphy, D.L., Holmes, A., 2007. Impaired stress-coping and fear extinction and abnormal corticolimbic morphology in serotonin transporter knock-out mice. J. Neurosci. 27, 684–691.
Zhao, Z.Q., Scott, M., Chiechio, S., Wang, J.S., Renner, K.J., Gereau, R.W.t., Johnson, R.L., Deneris, E.S., Chen, Z.F., 2006. Lmx1b is required for maintenance of central serotonergic neurons and mice lacking central serotonergic system exhibit normal locomotor activity. J. Neurosci. 26, 12781–12788.