Refining psychiatric genetics: from ‘mouse psychiatry’ to understanding complex human disorders

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Investigating the pathogenesis of psychiatric disorders is a complicated and rigorous task for psychiatric geneticists, as the disorders often involve combinations of genetic, behavioral, personality, and environmental factors. To nurture further progress in this field, a new set of conceptual tools is needed in addition to the currently accepted approaches. Concepts that consider cross-species trait genetics and the interplay between the domains of disorders, as well as the full spectrum of potential symptoms and their place along the pathogenetic continuum, are particularly important to address these needs. Here, we outline recent concepts and approaches that can help refine the field and enable more precise dissection of the genetic mechanisms contributing to psychiatric disorders. Behavioral Pharmacology

The complexity of psychiatric disorders: already too complex?

Although the genetic factors play a key role in psychiatric disorders, research in this field is still facing many methodological and conceptual difficulties (LaSalle et al., 2005; Geschwind and Levitt, 2007; Skuse, 2007; Abrahams and Geschwind, 2008). Although some disorders, such as autism, display high heritability (Abrahams and Geschwind, 2008), others (e.g. depression) show more complex gene × experience × personality interactions (Persico and Bourgeron, 2006; Kas et al., 2007). In part, the genetics of psychiatric disorders is difficult to study because they are often polygenic, non-Mendelian, and have developmental trajectories (Cannon and Keller, 2006; Biederman et al., 2007; Grados and Wilcox, 2007; Low and Hardy, 2007). Different genes may contribute to similar traits, whereas the same genetic contributions may result in highly variable phenotypes (Geschwind and Levitt, 2007; Skuse, 2007).

Research in psychiatric genetics is also complicated by the lack of clear and/or uniform diagnostic criteria (Low and Hardy, 2007; Abrahams and Geschwind, 2008) and because of the multidomain, heterogeneous nature of psychiatric disorders (Hasler et al., 2006; Ropers, 2007). Finally, there is also a growing understanding that psychiatric disorders do not represent isolated groups of symptoms, but rather have an interrelated ‘spectrum’ nature (Shavitt et al., 2006; Geschwind and Levitt, 2007; Low and Hardy, 2007) (Fig. 1a).

As psychiatric disorders frequently overlap and co-occur (Kas et al., 2007; Low and Hardy, 2007; Uher and McGuffin, 2008), there is a growing recognition of their shared pathogenetic factors (Akiskal, 2003; Lara et al., 2006; Kalueff et al., 2008). This coincides with the understanding that some disorders, such as anxiety, depression, autism, obsessive-compulsive disorder (OCD), and schizophrenia not only have some common symptoms, but also show overlapping genetic mechanisms (Kaufman et al., 2006; Shavitt et al., 2006; Kalueff and Nutt, 2007; Kas et al., 2007). For example, genes of the γ-aminobutyric acid (GABA) system have been linked to autism, anxiety, and depression (Persico and Bourgeron, 2006; Geschwind and Levitt, 2007; Kalueff and Nutt, 2007), underlying their pathogenetic and clinical overlap. The brain-derived neurotrophic factor (BDNF) gene has been implicated in anxiety, depression, cognitive deficits, and schizophrenia (Kaufman et al., 2006; Kas et al., 2007). Likewise, the serotonin transporter (SERT) gene has been associated with anxiety, OCD, depression, and autism (Devlin et al., 2005; Hu et al., 2006; Grados and Wilcox, 2007; Kalueff et al., 2007b; Moy and Nadler, 2008), also interacting with the BDNF gene (Kaufman et al., 2006) (Fig. 1b).

Animal models represent a valuable tool for developing new concepts, testing neurobiological hypotheses, and finding candidate genes for human psychiatric disorders (Low and Hardy, 2007; Moy and Nadler, 2008). Therefore, researchers from the ‘mouse psychiatry’ field can help refine psychiatric genetics by paralleling their
findings to clinical data (Kas and Van Ree, 2004). For example, animal and human data show that common genetic determinants, including GABAergic (Kalueff and Nutt, 2007), BDNF, and SERT (Murphy et al., 2003; Ren-Patterson et al., 2005) genes, play a role in anxiety-like and depression-like states. Collectively, this suggests that refocusing from individual diseases to a more integral continuum with common genetic and environmental...
determinants will foster translational research in this field (Gould and Gottesman, 2006; Kas et al., 2007; Kalueff et al., 2008).

**Currently accepted approaches**

During the last decades, psychiatric genetics has progressed because of several fundamental concepts, briefly summarized in Fig. 2. The gene(s)-behavior approach focuses on the interaction between the genetic factors (which may involve one or numerous genes) and the experience and behavior of the subject (Hamer, 2002; Kas and Van Ree, 2004). Despite the recent breakthroughs in human genetics, however, it has proven difficult to directly link genotypes with distinct behaviors and to isolate candidate genes that contribute to specific behaviors in afflicted individuals (Hamer, 2002; Mackay and Anholt, 2007). Part of this difficulty stems from the polygenic nature of psychiatric disorders, and from the tendency of earlier researchers to focus on exploring a linear relationship between genes and behavior (Kas and Van Ree, 2004; Grados and Wilcox, 2007; Skuse, 2007). Therefore, a better understanding of the complicated nature of genetic and epigenetic contributors to behavior is needed.

The gene × environment (G × E) interaction approach reconciles the nature versus nurture dichotomy (Caspi and Moffitt, 2006; Mackay and Anholt, 2007), and brings a new understanding that genes and environmental factors interact in interdependent ways (Rutter et al., 2006; Canli and Lesch, 2007). One example comes from clinical studies on the susceptibility to developing depression in relation to SERT polymorphisms and stressful life events. This research shows that individuals with ‘less active’ alleles were more likely to develop depression than those with the greater-expressing ‘long’ alleles only when confronted with several stressful life events (Caspi et al., 2003; Caspi and Moffitt, 2006). Furthermore, G × E interactions are being extensively modeled in animals (Tucci et al., 2006; Valdar et al., 2006), confirming the generality of this approach in psychiatric genetics.

The epigenetics concept recognizes the important role of the regulation of genomic functions through DNA and chromatin reorganizations (without changes in the genome) in both gene × behavior and G × E interactions (Tsankova et al., 2007). These reorganizations have been implicated in several psychiatric disorders such as autism, Angelman, Prader–Willi, and some other syndromes (Canli and Lesch, 2007; Mill and Petronis, 2007; Yasui et al., 2007). Abnormal DNA methylation has been linked to more complex psychiatric disorders such as schizophrenia, addiction, and depression (Tsankova et al., 2007; Malaspina et al., 2008). Errors in epigenetic processes, such as parental imprinting, can also have serious effects on the offspring (Perrin et al., 2007). The epigenetics concept has attracted wide recognition, and is currently a key in reinterpreting psychiatric genetics by bringing added complexity to this field (Colvis et al., 2005; Tsankova et al., 2007).

The endophenotype concept deconstructs complex psychiatric diseases into endophenotypes—objective,
quantifiable, and inheritable traits that serve as biological markers of a disorder (Gould and Gottesman, 2006; Hasler et al., 2006) (Table 1). Part of its rationale was the recognition that different genes may not affect all aspects of a disordered brain similarly, leading to discrete endophenotypes (Hasler et al., 2006). Therefore, researchers could focus instead on endophenotypic domains more specifically, to discover novel genes/alleles or elucidate pathogenetic mechanisms (Meyer-Lindenteg and Weinberger, 2006; Flint and Munafo, 2007). Although the genetics of an endophenotype is, however, presumed to be simpler than that of clinical disorders (Gould and Gottesman, 2006), some data suggest that it may be rather complex as well (Flint and Munafo, 2007). Another difficulty with this approach is its reliance on testing selected domains, which limits its relevance to genetic psychiatry, especially given the frequent overlap and comorbidity of some disorders. Finally, a possible endophenotype could fulfill the criteria of an intermediate phenotype without lying along the pathway to the disease. Such ‘epiphenomenal’ relationships (Walters and Owen, 2007) could significantly complicate interpretation of endophenotypic data and their translation into pathways of human disorders.

Recent concepts in psychiatric genetics
Several recent developments have emerged in the field, meriting further discussion. Largely based on the notion that behaviors and their genetic underpinnings are evolutionarily conserved across different species because of common survival mechanisms, the cross-species trait genetics concept (Kas et al., 2007) models neuropsychiatric domains across species with similar endophenotypes (Fig. 2). It has been suggested that shared genotype–phenotype relationships exist between animals and humans, based on conserved genes functions and analogous phenotypes. For example, cognitive domains (set-shifting, impulsivity, motivation, and memory) can all be examined across species, based on the important role that cognitive dysfunction plays in psychiatric disorders. Likewise, activity domain can be assessed in relation to eating disorders (anorexia) and/or hyperactivity, whereas social interaction is relevant to schizophrenia, OCD, or autism (Kas et al., 2007). This concept has brought more accurate genotype/phenotype relationships to neuro-behavioral research, resulting in enhanced modeling of psychiatric disorders. A problem, however, arises, in that some genes and behaviors do not correlate across species (Ropers, 2007). Moreover, as this and other concepts mainly focus on individual domains and endophenotypes, they may not completely tackle clinical and genetic heterogeneity of psychiatric disorders, their comorbidity, and overlap.

To address such challenges, another approach has recently been suggested, termed the domain interplay concept (Kalueff et al., 2008). This concept is based on assessing the interaction between distinct behavioral domains or endophenotypes, and examining the genetics of their ‘interplay’ in addition to the genetics of ‘domains’ (see a detailed illustration of this concept in Figs 2 and 3). Briefly, often a human disorder A leads to disorder B, co-occurs with it, and increases its risks or worsens pathogenesis and treatment outcomes. In these cases, researchers need to search specifically for those models

Table 1 Glossary of terms

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<th>Term</th>
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<tr>
<td>Susceptibility genes</td>
<td>Genes that affect the causes of a certain psychiatric disorder. They have been found for some disorders including autism, anxiety, and schizophrenia</td>
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<td>Candidate genes</td>
<td>Candidate genes are the genes suspected to play a role in the pathogenesis (based on quantitative trait loci, linkage, association or family studies, genomics analyses, or genetic animal models) but not conclusively identified as contributing to the cause of the disorder (for review, see Ropers, 2007)</td>
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<td>Genetic polymorphism</td>
<td>The situation when two or more versions of a gene exist in the same population. To be considered as a polymorphism, each discrete allele must occur at a rate that cannot be accounted for by mutation alone (an allelic frequency rate of ≥ 1% is used for this determination). Polymorphisms of some brain genes are particularly strongly implicated in psychiatric disorders. In addition, several different polymorphisms of the same gene may have combined effects on the expression of specific psychiatric disorders.</td>
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<td>Serotonin transporter gene</td>
<td>One of the most studied genes in psychiatric genetics. It codes for a protein that reuptakes serotonin from the synaptic cleft, plays a role in many psychiatric disorders (depression, anxiety, autism, OCD), and represents a target for multiple serotoninergic antidepressants. SERT gene has a short ‘s’ allele, which is the less active, and a long ‘l’ allele, which is more active. The ‘s’ allele carriers are more vulnerable to stress, and are less sensitive to antidepressant therapy, compared to ‘l’ allele carriers. Genetically modified animals with reduced or increased SERT function show numerous behavioral phenotypes in affective domains similar to humans with SERT genetic polymorphisms (Holmes et al., 2003).</td>
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<td>Endophenotypes</td>
<td>Objective, quantifiable, and inheritable biological (anatomical, developmental, electrophysiological, metabolic, sensory, or psychological/cognitive) markers of a disorder (Gould and Gottesman, 2006) are present regardless of whether a specific disorder is active, and can be found in nonaffected relatives of the patient at a higher rate than the general population (Cannon and Keller, 2006). The term is analogous to the ‘intermediate phenotype’, often used to describe a quantitative trait that is between the genes and the disorder (Kas et al., 2007; Walters and Owen, 2007).</td>
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<td>Genetic animal models</td>
<td>Inbred or selectively bred strains, as well as genetically altered (mutant or transgenic) animals, that are used to mimic psychiatric disorders based on their genetic traits. These models are available in an ever-increasing range of phenotypes and offer a wealth of information for researchers investigating candidate genes as well as the molecular mechanisms and circuits of brain pathogenesis.</td>
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OCD, obsessive-compulsive disorder; SERT, serotonin transporter.
where an A-like phenotype will exacerbate or increase the probability of B-like domains (Kaluff et al., 2008). Negative interplay between different domains (i.e., when domain C precludes or minimizes risks of domain D) requiring models that will reflect this phenomenon (e.g., mutant mice with C-like behavior that are less prone to display D-like behaviors) may also be observed. The key aspect of this concept is that it does not consider mental illness as a mechanistic combination of disordered domains, but rather links these domains together, integrating them within a common pathogenetic process that constitutes this particular disorder (for a detailed review, see Kaluff et al., 2008).

Importantly, advocating innovative modeling of numerous interlinked domains and their interplay, this approach can be combined with other concepts (Fig. 2), allowing researchers to target the recently appreciated characteristics of psychiatric disorders more effectively. For example, investigations of depression and anxiety can now focus on models that have the ability to display both anxiety and depression simultaneously, or the transformation of one disorder into another (Fig. 3a). One of the goals of translational research is to create an animal model with a wider range of phenotypical characteristics instead of focusing on a specific set that is associated with only one disorder. Therefore, models demonstrating how one

Refining psychiatric genetics based on domain-oriented approaches. (a) This panel shows how the endophenotype approach (Gould and Gottesman, 2006) can be complemented with ‘domain interplay’ genetics. (b) An example of two overlapping and comorbid psychiatric disorders (anxiety and depression) from (a), and several groups of candidate genes potentially involved in their pathogenesis. In addition to genetic determinants for specific domains or endophenotypes (anxiety or depression genes), there may also be genes responsible for several domains simultaneously – ‘comorbidity’ genes (Kaluff and Nutt, 2007), or for personality traits related to both disorders – e.g., anxiety sensitivity or neuroticism genes (Lesch et al., 1996; Hunnerkopf et al., 2007; Stein et al., 2008). Likewise, there may also be genetic determinants of domain interplay per se, playing a role in the transitions from one disorder to another. Understanding that these disorder subtypes are clinically different and also likely to have different genetic and environmental determinants, may help further improve our understanding of their pathogenesis. (c) A simplified explanation of why current ‘cohort’ approaches may yield fewer positive findings. In this model example, a psychiatric disorder A is caused by genes I and II, determining two endophenotypes/domains 1 and 2, respectively. The width of arrows in this diagram indicates the strength of effects of the respective genes on a resulting phenotype, which represents a spectrum between these two domains. When a cohort is formed for genetic analyses, one typical approach is to exclude extreme phenotypes, so a more ‘typical’ clinical phenotype is represented for analyses. Such smoothing of cohorts also has a probabilistic reason, as patients with mixed/milder forms of the disorder will be easier to find. The search for genetic markers in patients of such cohorts, however, will most likely reveal weak effects and associations (because stronger phenotypes and stronger genetic associations are underrepresented in such studies). Another common approach is to select the most disabling phenotype, based on clinical relevance and overall robustness. This will lead to overrepresentation of a particular domain (e.g., domain 2) in cohorts, resulting in false negatives for genes contributing to other disordered domains. In contrast, forming cohorts based on domain-oriented approaches may enable a more accurate dissection of genetic contributors to disorder A.
domain increases the chances of the other domain occurring, can accurately target not only the traditional domains (Kas and Van Ree, 2004; Kas et al., 2007), but also other important clinical features, such as the comorbidity, ‘spectrum’ nature, or the transitions from one disorder to another (e.g. Fig. 3b for review, see Kalouff et al., 2008).

Offering several additional conceptual advantages, this strategy can foster further translational research and experimentation in the field of psychiatric genetics. For example, this approach can help prevent the misinterpretation of animal and human phenotypes by (i) assessing several domains as a system and (ii) focusing on the clinically relevant ‘interplay’ characteristics of the disorder pathogenesis, comorbidity, and risk factors. In addition, the concept also offers the potential to model the entire pathogenic process, giving insights into progressing neurological substrates in disordered brain functions (e.g. depression–anxiety transitions in Fig. 3b). A potential limitation of this approach, of course, is the correct selection of clinically relevant domains for linking them into a meaningful system that is relevant to disorder pathogenesis (Kalouff et al., 2008).

Other ways to refine psychiatric genetics
An important step for improving research is optimizing communication between psychiatrists (who evaluate cohorts of patients) and geneticists, who genotype these cohorts, but often may not know all the nuances of the clinical phenotypes (such the exact composition of disordered domains and/or their severity). In some cases, milder or less typical forms of disorders are under-represented in such cohorts (Skuse, 2007) despite the fact that they may represent important disorder subtypes, and that an understanding of their genetics may lead to key paradigm shifts in the field (Fig. 3c).

Notably, most psychiatric disorders are not single-domain maladies, but have several affected domains (Devlin et al., 2005). For example, autism is characterized by social deficits and behavioral perseverations; schizophrenia by psychotic symptoms and altered cognitive processing; posttraumatic stress disorder by anxiety and strong negative cognitions. Thus, using currently accepted diagnostic criteria, patients with strong social deficits and mild perseverations may be diagnosed as ‘autistic’, as will patients who have strong behavioral perseverations and mild social deficits. Clearly, these two forms of autism most likely have different neural substrates and genetic underpinnings. Categorized together by psychiatrists as an ‘autistic cohort’, however, they might be routinely assessed by geneticists for potential genetic markers. Without having detailed clinical data, this research can ultimately result in confusing or inconclusive data (Fig. 3c), making interpretation of the results and subsequent therapies very complicated.

One example illustrates this notion particularly well. The SERT gene has long been implicated in autism (Devlin et al., 2005), although the exact mechanisms of its role are still unknown. Carriers of the long (l) SERT allele are prone to OCD-like behavioral symptoms (Hu et al., 2006), and therefore might be at higher risk for autism (Devlin et al., 2005). In contrast, carriers of the short (s) SERT allele are at higher risk of depression and anxiety (including social anxiety) (Devlin et al., 2005; Grados and Wilcox, 2007). Therefore, they too are likely to show association with autism, but now in the social deficit domain. Collectively, this may explain a large number of conflicting reports that will confuse the literature, even for a single gene and a highly heritable disorder (Devlin et al., 2005; Hu et al., 2006; Grados and Wilcox, 2007).

In contrast, by including both domains within a conceptual system, they can be targeted differently (e.g. ‘social deficit + perseverations’ vs. ‘perseverations + social deficit’ subtypes) even under the general classification of autism (Frazier et al., 2008). Clearly, other factors may further complicate such studies. For example, mental retardation correlates with autism severity. It, however, represents another, most likely separate (developmental) domain that may confound studies focusing specifically on genetic vulnerability to autism (Skuse, 2007). Thus, in addition to improving experimental design for psychiatric genetics studies (Payton, 2006; Uher and McGuffin, 2008), a better dissection of different domains of a particular disorder will enable a more precise understanding of its genetic mechanisms.

From individual disorders to pathogenetic spectra: thinking outside the box
Rethinking psychiatric disorders is also needed to understand the genetic factors ‘outside’ an individual illness and its subtypes. As such disorders frequently co-occur and may trigger each other (Kas et al., 2007; Low and Hardy, 2007; Uher and McGuffin, 2008), further research should address those aspects of their pathogenesis. For example, consider two different clinical cases shown in Fig. 3b. Although anxiety and depression are highly comorbid, a progression from anxiety to depression, and vice versa, has long been known in the literature (Moffitt et al., 2007). The ‘directional trajectory’ of pathogenesis (i.e. depression→anxiety vs. anxiety→depression) may be a key factor in determining the correct mode of treatment for the disorder, as the two trajectories may have different pathogenetic mechanisms and genetic vulnerabilities. Although this dynamic aspect of pathogenesis is largely ignored by current genetic ‘cohort’ approaches described above, it clearly deserves further attention and consideration.

Psychiatrists may also recognize symptoms of more than one disorder in an individual patient. They may, however,
fail to address the continuum aspect of pathogenesis, and more likely could focus on the more debilitating/severe of any two disorders. In this way, current categorizations of disorders may be inadequate. For example, a patient may be diagnosed with ‘depression with an anxiety component’, whereas in reality the patient’s symptoms have only recently developed into a primarily depression-like disorder after a longer-term anxiety disorder was present. The treatment of such cases will clearly benefit from domain-oriented approaches, uncovering the two specific directions of pathogenesis and of their potentially differential genetics (Fig. 3b).

Likewise, experimental models that hone in on systems of such domains may accelerate progress in clinical neuroscience by offering valid analogs that more directly correspond to clinical data. For example, animal models of anxiety and depression show a substantial overlap in these two domains, resembling clinical comorbidity (Kalueff and Nutt, 2007) or even mimicking the transition from anxiety-like to depression-like states (Angustinovich et al., 2005; Sufka et al., 2006). Thus, further focus on specific genetic aspects of such models may be particularly promising and clinically relevant.

Concluding remarks

In summary, neuropsychiatric disorders display a significant commonality of symptoms and pathogenetic mechanisms, accompanied by shared genetic determinants that contribute to overlapping endophenotypes and complex genotype × genotype × environment interactions. Diverging from the traditional approach (which views psychiatric disorders as largely discrete and unrelated), this strategy can help prevent an overly simplistic way to conceptualize mental illness.

The knowledge that psychiatric disorders share common genes, symptoms, and pathogenetic mechanisms emphasizes the need for genetic animal models that target common (integrative) mechanisms of brain pathogenesis (Kalueff et al., 2007c). Translational research, based on recently developed cross-species and domain-oriented concepts discussed here (Figs 2 and 3), may provide important insights into the spectrum nature of psychiatric disorders.

Finally, the recognition of a greater genetic complexity of different disordered domains (Fig. 3) is becoming another important development in the field. It may stimulate constructive debate regarding the way that psychiatric diseases and their genetics are conceptualized and dissected. At the same time, the inability to address today these paradigm shifts in both clinical and experimental studies may affect future psychiatric genetics research by creating obstacles to a more full understanding of the genetic underpinnings of brain pathology.

Acknowledgements

This study is supported by the Intramural Research Program of the National Institute of Mental Health (NIMH/NIH, USA) and NARSAD YI Award (to A.V.K).

References


