Review

Biological Psychiatry

From Psychiatric Disorders to Animal Models: A Bidirectional and Dimensional Approach

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ABSTRACT

Psychiatric genetics research is bidirectional in nature, with human and animal studies becoming more closely integrated as techniques for genetic manipulations allow for more subtle exploration of disease phenotypes. This synergy highlights the importance of considering the way in which we approach the genotype-phenotype relationship. In particular, the nosologic divide of psychiatric illness, although clinically relevant, is not directly translatable in animal models. For instance, mice will never fully recapitulate the broad criteria for many psychiatric disorders; additionally, mice will never have guilty ruminations, suicidal thoughts, or rapid speech. Instead, animal models have been and continue to provide a means to explore dimensions of psychiatric disorders to identify neural circuits and mechanisms underlying disease-relevant phenotypes. The genetic investigation of psychiatric illness can yield the greatest insights if efforts continue to identify and use biologically valid phenotypes across species. This review discusses the progress to date and the future efforts that will enhance translation between human and animal studies, including the identification of intermediate phenotypes that can be studied across species and the importance of refined modeling of human disease–associated genetic variation in mice and other animal models.

Keywords: Amygdala, Anxiety, BDNF, Dentate Gyrus, Intermediate Phenotype, Pattern Separation, Serotonin

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Understanding of behavioral disorders has benefited from the reciprocal nature of genetic research in humans and animal models. Animal models remain an important tool for studying the functional role of human mutations, and basic animal research has driven studies of candidate genetic variation in humans. Within the realm of behavioral disorders, numerous examples of the reciprocity between human and animal research already exist, but as discussed later in this review, a refinement of the way we approach disease-related phenotypes, combined with more subtle genetic techniques, would help strengthen this translational interplay.

One area of research that began in animal models and has since garnered substantial interest in human research has been the role of the so-called social neuropeptides, oxytocin and vasopressin, and their potential role in human social behaviors (1). Initial work in animal models revealed a conserved role for these peptides in the modulation of social behavior (2). Mice with null mutations in the genes encoding either oxytocin or the V1a vasopressin receptor subtype lack the ability to remember a previously encountered conspecific, a memory deficit that is specific for social cues (3,4). In addition, oxytocin and vasopressin play a critical role in the formation and maintenance of pair bonds in monogamous prairie voles (5). In mice, which are not monogamous, oxytocin is also required for social reward (6). Given that many psychiatric conditions and behavioral disorders include strong social components, such as the profound social deficits observed in autism and schizophrenia, these animal studies have spurred research on the function and potential contribution of these genes and their receptors in humans (7). Specifically, genetic variation within the loci that encode these neuropeptides and their receptors has been tied to differences in diverse, socially relevant traits and nominally to autism (8). Much of the work on oxytocin suggests that it may be involved in complex social abilities in humans (9); intranasal oxytocin increases trust, in particular contexts, and heightens a subject's ability to infer emotional states of others accurately (10–12). In addition, two single nucleotide polymorphisms (SNPs) in the oxytocin receptor gene (rs53576A and rs2254298A) have emerged as genetic candidates for social deficits in humans, including decreased maternal sensitivity and empathy (13,14). In work that parallels findings in prairie voles, a variant of the human vasopressin receptor gene, *AVPR1A*, has been associated with differences in human pair bonding, with variant RS3-334 associated with decreased relationship quality (15).

The converse also occurs. Animal models have been especially relevant for validating and exploring highly penetrant, rare genetic mutations identified via family pedigrees or population studies. Sequencing of exons in serotoninergic and dopaminergic genes in highly impulsive individuals in a Finnish founder population revealed a mutation that introduces a stop codon in the serotonin 2B receptor gene (16). A critical piece of evidence supporting the functional contribution of this mutation came from serotonin 2B knockout mice, which also display increased impulsive behaviors (16). Equally informative, if not more so, are the occasions when a knockout mouse fails to recapitulate human disease phenotypes. For instance,

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Lesch-Nyhan syndrome is a rare X-linked developmental disorder resulting from mutations in the hypoxanthine phosphoribosyltransferase gene (*HPRT*), which leads to a buildup of uric acid and results in neurologic phenotypes including uncontrolled writhing, repetitive movements, and self-injurious behaviors. However, knockout of the mouse *Hprt* gene does not result in the profound phenotypes observed in humans (17,18). Instead, comparative genetic studies revealed that the phenotypic disparity between mice and humans is likely due to phosphoribosyltransferase domain containing 1 gene (*PRTFDC1*), a paralog of *HPRT* that is a functional gene in humans but an inactivated pseudogene in mice (19). BAC transgenic mice with a functional human copy of *PRTFDC1* and mutant *Hprt* demonstrated increased aggression and amphetamine-induced stereotypies, reminiscent of the symptoms of Lesch-Nyhan syndrome. This finding suggests that *PRTFDC1* is an important genetic modifier of *HPRT* deficiency and provides important implications for unraveling the molecular etiology of Lesch-Nyhan syndrome (20).

There is a clear mutualistic relationship between these research disciplines. However, despite this relationship, the experiments pursued by clinical researchers working with human subjects and basic researchers working with animal models are often not directly translatable for both conceptual and technical reasons. For instance, experiments on the role of social neuropeptides in monogamy and social recognition in rodent models relate broadly but nonspecifically to their potential role in empathy, maternal attentiveness, and autism in humans. It is difficult to hypothesize a shared mechanism or clinically relevant intervention from these dual lines of research. In addition, knockout mice are technically poor models for understanding the potentially complex effects of common genetic variants. This review focuses on improving conceptual translatability by studying the same intermediate phenotypes in both humans and animals and highlights transgenic strategies in animal models that more directly model human genetic variation, improving their clinical relevance.

IMPROVING TRANSLATABILITY THROUGH INTERMEDIATE PHENOTYPES

It has largely been acknowledged by the research community that there is limited biological validity underlying the current classification of psychiatric illness. Based on *DSM* guidelines, opposite symptoms can characterize the same disorder, whereas many other symptoms are shared across disorders. Both fatigue or decreased energy and increased agitation or restlessness are considered symptoms of depression (21), whereas altered sleep patterns, mood dysregulation, and cognitive changes transcend diagnostic categories. Underscoring the idea that nosologically distinct disorders have mutual biological underpinnings, a large-scale genetic study found that five disorders—schizophrenia, bipolar disorder, autism, depression, and attention-deficit disorder—share common genetic risk factors (22). This finding parallels what is known about the genetics of autoimmune disorders where a handful of genetic variants have been implicated in multiple disorders (23,24).

Given these facts, numerous approaches have been proposed for studying the biological underpinnings of psychiatric disorders in a way that accommodates potentially shared biological mechanisms and the diversity of symptoms observed in psychiatric illness. Among the earliest of these approaches, in 1967, Gottesman and Shields (25) introduced to psychiatry the term "endophenotype," from the Greek "endos," meaning interior, which they adopted from a report on evolutionary biology. The original definition of an endophenotype required meeting several criteria, including having sufficient heritability, showing increased expression in unaffected relatives of probands, cosegregating with a disorder in a family, being stable over time, and having good psychometric properties (26). This "bottom-up" approach for studying the neural basis of psychiatric illness has become nearly synonymous with breaking down psychological disorders and processes into biological mechanisms.

More recently, there has also been a "top-down" push by some psychiatrists to adopt a dimensional approach to diagnostic criteria, which was proposed but ultimately not adopted in *DSM-5* (27). This approach acknowledges the symptom overlap of many disorders and proposes that the overlapping syndromes are the product of shared risk factors that drive abnormalities in behavioral spectra, such as motivation and reward anticipation. This concept of dimensions mirrors the logic underlying the National Institute of Mental Health Research Domain Criteria initiative, which posits that mental illness would be best understood as disorders of brain structure and function that implicate specific domains of cognition, emotion, and behavior (27,28). Current research at the National Institute of Mental Health is focused on identifying new dimensions, such as pattern separation and social recognition (see later), suitable for research on the genetic and biological basis of psychiatric illness.

In addition to these bottom-up and top-down approaches, more recent debates have suggested the use of a third, potentially unifying term, "intermediate phenotype," which we will use throughout this review. This term has many advantages. Analogous to its use in other areas of complex genetics, it implies that a trait is in a predictable path from gene to disease. Intermediate phenotypes are not restricted by the stringent criteria used to define endophenotypes. Finally, the intermediate phenotypes we discuss in this review include both biological and behavioral phenotypes, bridging a potential conceptual divide between endophenotype and dimensional approaches. Because many of these phenotypes exist in both animal models and humans, there is a substantially enhanced opportunity for translation by focusing on intermediate phenotypes rather than disease categories.

Impaired Pattern Separation and Dentate Gyrus Function: Examples of Behavioral and Neural Intermediate Phenotypes

Both human and animal studies support the fact that a region of the hippocampus, the dentate gyrus (DG), is essential for pattern separation during memory encoding. Pattern separation is a process by which similar experiences or events are transformed into discrete, nonoverlapping representations (29,30) and represents a behavioral intermediate phenotype.

Experimental evidence for a role of the DG in pattern separation first came from lesion studies in rodents showing that ablation of the DG impaired discrimination of two spatial locations based on distal environmental cues (31). More recent studies relying on genetic approaches specifically to manipulate DG functions have yielded similar results (32), and multitetrode recordings have shown that subtle morphing of a rat's environment is sufficient to elicit remapping of firing rates of place cells in the DG, suggesting that small changes in spatial input can produce highly divergent output (29). Collectively, these studies suggest that the DG is required to minimize interference between overlapping spatial or contextual information. Neurocognitive testing and functional magnetic resonance imaging studies in humans have also suggested a role for the DG in pattern separation (33,34); high-resolution functional magnetic resonance imaging studies detected specific changes in activity in the DG/CA3 circuit during a pattern separation task. Function of the DG represents a neural intermediate phenotype.

According to the theory (35), impaired pattern separation is the consequence of DG malfunction and leads to excessive generalization, causing an organism to group multiple contexts or items together even if they are dissimilar. Such a maladaptive response may contribute to the generalization of previously encountered aversive events to new "innocuous" experiences as seen in individuals with panic disorder and posttraumatic stress disorder (36–38). For example, for someone who developed posttraumatic stress disorder as a result of the terrorist attacks of 9/11, the sight of a plane flying over New York City may trigger flashbacks and panic. Impaired pattern separation has also been reported in aging and in individuals with mild cognitive impairment. Deficits in pattern separation and function of the DG may represent important intermediate phenotypes for these different disorders and contribute to some of their associated impairments. We have shown that increasing adult hippocampal neurogenesis in animal models improves pattern separation (39), and we hypothesize that increasing human hippocampal neurogenesis may improve impairments related to pattern separation in individuals with mild cognitive impairment or anxiety disorders.

Impaired pattern separation is an example where translation works from animals to humans. A brain region was identified in rodents that mediates pattern separation (the DG); this triggered human investigations aimed at identifying patients with pattern separation deficits and dysfunction of the DG (33). These patients become candidates for pharmacologic interventions aimed at improving pattern separation, such as compounds that stimulate DG neurogenesis (40).

GENETICS OF INTERMEDIATE PHENOTYPES

The rate-limiting factor in identifying gene variants related to disease is often the effect size of the risk allele on phenotypic variance. Because genes do not encode psychiatric phenomena, but instead encode gene products that influence the circuits underlying a behavior, genetic variation should have enhanced penetrance at the level of quantitative intermediate phenotypes, such as circuit function or discrete behavioral traits. The genetic architecture of such phenotypes is hypothesized to be simplified compared with the disease itself. Both biologic and behavioral intermediate phenotypes support these assumptions.

At a biological level, the field of imaging genetics has demonstrated that so-called psychiatric risk alleles are more closely tied to variance on a brain systems level compared with clinical diagnoses (41). For instance, a polymorphism in the promoter of the serotonin transporter gene promoter (5-HTTLPR) accounts for 10% of variance in amygdala activation (42), whereas its role in predicting behavioral phenotypes, such as neuroticism, depression, or antidepressant response, is at least an order of magnitude lower, likely ranging around 1%–3% (43–48).

Behaviorally, it has also been shown that relatively simple traits display stronger genetic associations than do diseases per se. As previously mentioned, oxytocin and vasopressin are required for normal social recognition in rodents (49). Using social recognition as an intermediate phenotype, a study found that a SNP near the oxytocin receptor (rs237887) was strongly associated with social recognition memory in families with one high-functioning autistic child (50). This SNP accounted for 10% of the variation in test performance but failed to reach significance when associated with autism diagnosis, mirroring the mixed reports of oxytocin/autism associations in the literature. A similar trend was seen for variation in the vasopressin receptor 1a gene. This finding is particularly striking because mice and humans use different modalities (olfactory vs. visual) as a primary means of social recognition, suggesting that the physiologic underpinnings of social recognition have remained evolutionarily conserved across perceptual boundaries and further supporting the use of such intermediate phenotypes as a way to enhance translational analyses.

Despite the potential utility of intermediate phenotypes, most large-scale genetic associations to date have been undertaken based on categorical diagnoses. Most of the associations that have been reported in the literature have been gene/disease associations. These genetic variants become candidates for further study at the level of intermediate phenotype to identify biological mechanisms underlying disease states. However, by investigating the genetics of intermediate phenotypes beyond a priori candidate genes, we may gain insight into genes that are important for disease but have an effect size that is too small to detect in traditional gene/disease association studies. Because intermediate phenotypes are independent of disease diagnoses and may span multiple disorders, they may point to unique pharmacologic targets that could be effective across disorders, in much the same way that selective serotonin reuptake inhibitors (SSRIs) are currently used in different categories of disease. Alternatively, the panoply of intermediate mediates and brain circuits disrupted may be specific to a particular population, and a personalized multidrug approach based on treatment of intermediate phenotypes may be warranted.

The same intermediate phenotype approach should be applied to models of drug responsiveness and their underlying genetic factors. Current therapeutics such as SSRIs have myriad behavioral and biological effects, including decreased immobility in the forced swim test (51), increased hippocampal neurogenesis (52), and reregulation of the hypothalamic-pituitary axis (53,54). It is unclear which of these many effects

are responsible for the antidepressant effects of these medications. An intermediate phenotype approach would consist of studying these effects in isolation; for example, what is the impact of stimulating neurogenesis on behavior? Our work suggests that one of the main effects in baseline conditions is to improve pattern separation and, in some conditions, to decrease anxiety (39). One could use neurogenesis as a screen for novel therapies aimed at specific populations that display a pattern separation deficit. Such a population would have to be characterized based on a combination of behavioral tests (55) and possibly imaging modalities that still need to be developed (56). Identifying the role of genetic variation within drug-responsive intermediate phenotypes would provide an additional level of potential treatment precision and insight into individual differences in drug efficacy.

Utility of Mouse Models to Identify Mechanisms Underlying Intermediate Phenotypes

Consistent with the idea that different disorders may be influenced by shared underlying intermediate phenotypes, brain-derived neurotrophic factor (BDNF) has been widely implicated in a range of psychiatric conditions, including but not limited to major depressive disorder, schizophrenia, addiction, Rett's syndrome, and eating disorders (57). There are broad-ranging roles for BDNF in axon targeting, neuron growth, maturation of synapses, and synaptic plasticity. Also, levels of BDNF are altered by stress exposure and display complex interactions with sex steroids (57). There are multiple potential mechanisms by which this molecule can affect disease-related traits both directly and via interactions with environmental or hormonal modulators.

To date, numerous mouse models have been developed to understand the role of BDNF better in various intermediate phenotypes (57,58). However, the most relevant demonstration of the importance of animal models for studying intermediate phenotypes and their genetic underpinnings comes from a mouse model of a common variant in the *BDNF* gene, Val66Met. In the human population, a common SNP in the *BDNF* coding region is found in 20%–30% of the Caucasian population (59) and leads to a methionine substitution for valine at codon 66 (Val66Met). A meta-analysis confirms that the Met allele is associated with decreased hippocampal volumes (60). Hippocampal volume and function represent intermediate phenotypes that are sensitive to antidepressant treatment (61–64) and have been implicated in many disorders, including major depressive disorder (65,66), posttraumatic stress disorder (67), anxiety disorders (38), and schizophrenia (68).

BDNF Val66Met has been modeled in mice by introducing this mutation into the endogenous mouse *Bdnf* gene, which has proven to be a particularly powerful translational approach. The Met allele in mice leads to a 30% reduction in activity-dependent release of BDNF, although expression levels are not altered (69). In addition, hippocampal volume is decreased in Met-allele mice, and neurons in the DG show decreased dendritic complexity. Behaviorally, Met-allele mice show decreased freezing in contextual fear conditioning, a hippocampal-dependent phenotype, and show increased levels of anxiety. Also, Met-allele, but not Val-allele, mice are insensitive to the anxiolytic effects of SSRIs (69). Parallel experiments also demonstrated that both mice and humans carrying the Met allele showed reductions in extinction learning when a neutral cue was paired with an aversive stimulus, an intermediate phenotype that may be relevant to therapeutic interventions that include an extinction component.

One of the most valuable aspects of this model is that, having been clearly linked to intermediate phenotypes important for psychiatric illness, it enables a mechanistic investigation of these phenotypes in a way that cannot be pursued in humans; this includes invasive assessments of neuronal attributes, gene expression, and neurophysiology. For example, more recent work has demonstrated that the Met66 prodomain is structurally different from its Val66 counterpart and that it is secreted at lower levels from hippocampal neurons in culture (70). It was also shown that Met66 prodomain (but not Val66) modulates neuronal morphology through growth cone retraction, potentially explaining the decreased hippocampal size associated with the Met allele. In addition, humans carrying the Met allele displayed increased amygdala activity and decreased activity in the ventromedial prefrontal cortex during cue presentation, which may indicate better ventromedial prefrontal cortex modulation of amygdala activity in Val/Val individuals (71). Work in *Bdnf* Val66Met mice provides a putative mechanism for this by demonstrating that spike timing–dependent plasticity is absent in the infralimbic–medial prefrontal cortex of Met/Met mice and that Met/Met mice also display reduced *N*-methyl-D-aspartate and gamma-aminobutyric acid receptor–mediated transmission in pyramidal neurons (72). Finally, Met/Met mice also display decreased antidepressant responsiveness at a behavioral level. Potentially underlying this, Met/Met mice fail to increase *Bdnf* levels after treatment with fluoxetine and fail to show fluoxetine-induced enhancements in hippocampal synaptic plasticity (73). *Bdnf* knockout models largely could not have been used to reveal the above-mentioned mechanisms, highlighting the importance of generating a model of the human disease–associated genetic variant itself. The clear translational utility of BDNF and other direct genetic models, such as the 5-HTT Ala56 mouse (74), have revealed a pressing need for additional direct models of genetic variation in mice.

One area where such "humanized" models would provide significant advances and clarification is in the role of serotoninergic variation. Serotoninergic systems have been broadly implicated in diverse psychiatric disorders, and drugs that affect this system, including SSRIs, are the most commonly prescribed pharmacotherapies for many disorders. A variable number tandem repeat in the gene encoding 5-HTT (*5-HTTLPR*) has been extensively implicated in disease-related phenotypes. This polymorphism, which occurs in the regulatory region for 5-HTT, is related to differences in 5-HTT levels in human cell lines (75) and has been associated with both anxiety and depression, although these findings, along with evidence that the short (S) allele may be more environmentally reactive, have been inconsistent in human studies (42,43,45,46,76). However, the largest meta-analysis performed to date reports a significant association between the S allele and depression in individuals exposed to early life traumas (45), highlighting the importance of gene/environment interactions.

Given the variable reports of associations in human studies, imaging studies linking intermediate phenotypes and 5-HTTLPR have been performed based on the assumption that brain activation patterns would be a more reliable readout of genotype effects than complex clinical diagnoses. Magnetic resonance imaging studies investigating the relationship between 5-HTTLPR and amygdala activity have shown that healthy S allele carriers have higher levels of amygdala activity compared with individuals homozygous for the long allele (42). In addition, 5-HTTLPR has been linked to differences in the amygdala–anterior cingulate cortex circuit, with S allele carriers demonstrating reductions of functional coupling (41).

Both primate and mouse models broadly support the involvement of 5-HTT variation in disease-relevant phenotypes. Rhesus macaques have a similar variable number of tandem repeats in their own gene, and a substantial literature suggests that the S allele confers increased stress responsiveness, enhancing alcohol sensitivity (77) and other behavioral anomalies in animals raised in a stressful environment (78). In addition, mice heterozygous for *SLC6A4*, the gene that encodes 5-HTT, which have 5-HTT levels ~50% lower than wild-type mice, have also been proposed as a model for the S allele (79). *SLC6A4* heterozygotes show enhanced vulnerability to psychosocial stress, displaying increased suppression of locomotor activity and social avoidance (80). However, in many instances, the 5-HTT-linked phenotypes studied in humans and in animal models are not identical, and without transparent comparison of intermediate phenotypes across species or a direct model of *5-HTTLPR* in mice, the translation of these findings is confounded.

In addition to variation in the transporter, significant efforts have focused on the inhibitory receptor, serotonin receptor 1A (5-HT1A), which regulates the firing of serotoninergic raphe neurons, affecting serotonin levels at projection sites throughout the brain. Within this system, genetic techniques have been particularly important for parsing the role of 5-HT1A in both anxiety-related and depression-related phenotypes. A complex phenotype is demonstrated by 5-HT1A null mutant mice that includes increased anxiety, increased stress coping, and decreased antidepressant responsiveness (81,82). Mouse models enabling both spatial and temporal control of the 5-HT1A receptor have implicated different receptor populations and developmental phases in these diverse phenotypes. Specifically, postnatal suppression of 5-HT1A levels selectively in the raphe led to increased anxiety without affecting stress reactivity (83). Conversely, adult suppression of raphe receptor levels did not affect anxiety but did increase stress resiliency and antidepressant responsiveness, a finding independently confirmed through the use of small interfering RNAs to decrease adult 5-HT1A levels in the raphe (84,85).

These findings have been proposed as a model for rs6295, a common promoter polymorphism in the human *HTR1A* gene. The G allele of this SNP has been linked to increased risk of suicide, increased incidence of depression, and decreased antidepressant responsiveness (86). This allele fails to bind the transcriptional repressor, Deaf-1, in cell lines derived from raphe neurons, leading to increased transcription (87), and is associated with higher 5-HT1A binding potential in G-allele carriers (88). Future efforts to develop a humanized mouse model of this polymorphism will be integral to identifying its direct and complex effects on both biological and behavioral intermediate phenotypes and their underlying mechanisms.

CONCLUSIONS

As psychiatry and neuroscience converge, intermediate phenotypes, especially combined with novel transgenic techniques, will facilitate translational investigation. These approaches may have particular value for investigating, at a circuit level, the ways in which genes and the environment interact to shape behavioral phenotypes and predisposition to psychiatric illness. However, although the intermediate phenotype approach has face validity at a conceptual level, there are many important questions relevant for the field of psychiatry that can be answered only by scientific and medical advances. Among the most pressing is how treatments designed to alter intermediate phenotypes will be best used to treat psychiatric illness. We may be moving toward a more personalized approach where patients will be first stratified based on a series of intermediate phenotypes and then treated with a cocktail of drugs targeting these specific phenotypes.

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