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Identification of Neurogenetic Pathways of Risk for Psychopathology

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Abstract

Imaging genetics has been a highly effective and increasingly applied strategy for identifying the impact of genetic polymorphisms on individual differences in neural circuitry supporting complex behaviors. The application of imaging genetics towards further elucidating neural circuitry associated with the pathophysiology of psychiatric illness is of particular interest given its potential to guide the development and improvement of current therapeutic methods. The identification of genetic variants that contribute to or predict the disruption of specific neural pathways associated with psychopathology may also serve as useful markers of risk demarcating individuals with elevated susceptibility for psychiatric illness and affording early or even preemptive treatment strategies. In the continued development of this technique, recent multimodal neuroimaging strategies and studies examining the effects of multiple genes in concert within large subject populations have shown promise in the development of a more complete understanding of the interrelationships between genes, brain function, behavior and associated risk for psychopathology.

Keywords

psychopathology; neurogenetic pathways

INTRODUCTION

Advances in our knowledge about molecular, cellular and circuit mechanisms in brain associated with specific cognitive and emotional behavioral processes have improved our understanding of psychopathology. The ultimate goal of such knowledge is the development of more effective therapeutic methods and, when possible, the prevention of disease. In the context of psychiatric disease states, the role of genetic variation represents a cornerstone that can either directly or in concert with environmental factors facilitate disease onset. Moreover,

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the identification of genetic variations associated with disease development can be used to identify at-risk individuals and biological pathways contributing to disease. While most human behaviors cannot be explained by genes alone, and much of the variance in brain structure and function will not be directly genetically determined, we anticipate that variations in genetic sequence impacting function will contribute an appreciable amount of variance to the resultant complex biological and behavioral phenomena. This conclusion is implicit in the results of studies of twins that have revealed heritabilities ranging from 40% to 70% for various aspects of cognition, temperament, and personality [Plomin et al., 1994]. Although uncertainties abound (e.g., the definition of a 'gene' is still under revision [Mattick, 2004; Richards, 2006]), the integration of human genetics and neuroscience is leading to major advances in our understanding of the biology of human mental health and disease.

Traditionally, the impact of genetic polymorphisms on human behavior has been directly examined using clinical evaluations, personality questionnaires and neuropsychological batteries. Genetic epidemiological investigations have directly examined the relationship between specific genetic polymorphisms and behaviors and have reported equivocal results [Malhotra and Goldman, 1999]. This is not surprising for at least two reasons. First, there is considerable individual variability in dimensions of observable behavior as well as subjectivity in the assessment of behavior necessitating very large samples, often exceeding several hundred subjects, to identify even small gene effects [Glatt and Freimer, 2002]. Moreover, it is apparent that there are etiological subgroups within any given disease that obscure effects at the broader group level. Second and perhaps most importantly, the effects of genes are not expressed directly at the level of behavior. As discussed in detail below, gene effects on behavior are mediated by their molecular and cellular effects on information processing in brain. Thus, examining gene effects on brain represents a critical step in understanding their ultimate contribution to variability in behavior and related risk for psychiatric disease.

Human neuroimaging (e.g., fMRI, EEG/MEG, PET), because of its capacity to assay detailed brain structure and function within individuals, has unique potential as a tool for characterizing functional genetics in neural circuitry. This is the underlying assumption of our investigations examining the relation between genes and neural systems, what we describe as "imaging genetics" [Hariri et al., 2006]. Imaging genetics provides a unique tool with which to explore and evaluate the functional impact of brain-relevant genetic polymorphisms and identify neural pathways through which these variants contribute to the emergence of variability in behavior and disease risk. Moreover, most commonly employed neuroimaging techniques allow for the ability to investigate the specificity of gene effects by examining their influence on multiple functional systems (e.g., prefrontal, striatal, limbic) in a single subject in one experimental session. This capacity to rapidly assay differences in brain structure and information processing with enhanced power and sensitivity places neuroimaging at the forefront of available tools for the in vivo study of functional genetic variation.

SELECTED IMAGING GENETICS FINDINGS (Table I)

Serotonin Transporter

Abnormal 5-HT neurotransmission has been implicated in the pathophysiology of mood and anxiety disorders, and 5-HT substrates are a key target of drugs used to treat these disorders. A common polymorphism in the promoter region (5-HTTLPR) of the serotonin transporter (5-HTT) gene has been the most studied of genetic variants impacting 5-HT neurotransmission. Such interest is in part mediated by the critical role of the 5-HTT in regulating 5-HT signaling at both pre- and postsynaptic receptors (via active clearance of released 5-HT from the synapse) as well as the widespread use of antidepressant drugs which selectively block this reuptake mechanism. In comparison to the 5-HTTLPR long (L) allele, the short (S) allele has been associated with reductions in 5-HTT expression and 5-HT reuptake in vitro [Lesch et al.,

1996]. Though recent PET studies using specific radiotracers and improved spatial resolution have failed to find altered 5-HTT levels associated with the 5-HTTLPR [Shioe et al., 2003; Parsey et al., 2006], the effects of the 5-HTTLPR have been documented in other 5-HT subsystems, most notably the 5-HT_{1A} receptor [David et al., 2005; Lee et al., 2005], and such downstream effects may be critical in mediating the neural and behavioral effects of the 5-HTTLPR [Fisher et al., 2006; Hariri and Holmes, 2006].

At the behavioral level, possession of either one or two copies of the S allele has been associated with increased levels of temperamental anxiety [Schinka et al., 2004; Sen et al., 2004; Munafo et al., 2005], conditioned fear responses [Garpenstrand et al., 2001] and development of depression [Lesch et al., 1996], especially in the context of environmental stress [Caspi et al., 2003; Kendler et al., 2005]. Functional MRI studies have provided a unique understanding of how the 5-HTTLPR may impact temperamental anxiety and risk for depression. In a landmark study, fMRI revealed that the reactivity of the amygdala, a brain region critical in mediating emotional arousal, was significantly exaggerated in S allele carriers in response to threat-related facial expressions [Hariri et al., 2002]. Since this original study, there have been multiple replications of the association between the S allele and relatively increased amygdala reactivity in both healthy volunteers [Heinz et al., 2004, 2006; Canli et al., 2005b, 2006; Hariri et al., 2005; Brown and Hariri 2006] and patients with mood disorders [Furmark et al., 2004; Domschke et al., 2006]. In addition, the 5-HTTLPR S allele has been further linked with reduced gray matter volumes in and functional coupling between the amygdala and medial prefrontal cortex [Pezawas et al., 2005]. As the magnitude of amygdala reactivity (as well as its functional coupling with medial prefrontal cortex) is associated with temperamental anxiety, these imaging genetics findings suggest that the 5-HTTLPR S allele may be associated with increased risk for depression upon exposure to environmental stressors because of its mediation of exaggerated corticolimbic reactivity to potential threat.

Monoamine Oxidase A

5-HT neurotransmission is also regulated through intracellular degradation via the metabolic enzyme, monoamine oxidase A (*MAO-A*). A common genetic polymorphism in the *MAO-A* gene, resulting in a relatively low-activity enzyme, has been associated with increased risk for violent or antisocial behavior. A recent fMRI study reported that the low-activity MAO-A allele is associated with relatively exaggerated amygdala reactivity and diminished prefrontal regulation of the amygdala [Meyer-Lindenberg et al., 2006]. The magnitude of functional coupling between these regions predicted levels of temperamental anxiety, suggesting that the genetic association between the MAO-A low-activity variant and abnormal behavior may be mediated through this circuit. Interestingly, both the 5-HTTLPR S and MAO-A low-activity alleles presumably result in relatively increased 5-HT signaling and exaggerated amygdala reactivity. As the directionality of these effects are consistent with animal studies documenting anxiogenic effects of 5-HT [Maier and Watkins, 2005], the imaging genetics data provide important insight regarding the neurobiological and behavioral effects of 5-HT.

Tryptophan Hydroxylase

Recent imaging genetics studies examining the impact of variation in 5-HT subsystems highlight the potential reciprocal nature by which functional imaging and molecular genetics approaches can be mutually informative in advancing our understanding of the biological mechanism of behavior. Tryptophan hydroxylase-2 (TPH2) is the rate-limiting enzyme in the synthesis of neuronal 5-HT and thus plays a key role in regulating 5-HT neurotransmission. A recent study found that a SNP in the regulatory region of the human TPH2 gene affects amygdala function [Brown et al., 2005]. Specifically, the T allele of the relatively frequent G (−844)T SNP was associated with exaggerated amygdala reactivity. This report provides further insight into the biological significance of TPH2 in the human central nervous system

and provides a critical next step in our understanding of the importance of this newly identified second tryptophan hydroxylase isoform for human brain function. Moreover, it marks an important advance in the application of functional neuroimaging to the study of genes, brain and behavior. In contrast to previous studies of genetic effects on brain function, where the molecular and cellular effects of the candidate variants had been previously demonstrated (e.g., 5-HTTLPR, *MAO-A*, *COMT* & *BDNF*), these fMRI data provide the first evidence for potential functionality of a novel candidate polymorphism. In this way, the initial identification of a systems-level effect of a specific polymorphism provides impetus for the subsequent characterization of its functional effects at the molecular and cellular level. Building on this initial imaging genetics finding (and a subsequent replication [Canli et al., 2005a]), a recent molecular study has demonstrated that the G(−844)T is in strong linkage with another promoter SNP that impacts transcriptional regulation of TPH2 and may affect enzyme availability and 5-HT biosynthesis. Such scientific reciprocity between imaging and molecular genetics illustrates how the contributions of abnormalities in candidate neural systems to complex behaviors and emergent phenomena, possibly including psychiatric illnesses, can be understood from the perspective of their neurobiological origins.

Catechol-*O*-Methyltransferase

Because dopamine transporters are virtually absent at cortical synapses, dopamine regulation in the prefrontal cortex is uniquely coupled to inactivation mechanisms in postsynaptic neurons and glia [Sesack et al., 1998]. Catechol-*O*-methyltransferase (*COMT*), a methylation enzyme that converts released dopamine to inactive 3-methoxytyramine, is believed to play an important role in the inactivation of prefrontal dopamine [Weinshilboum et al., 1999]. A common polymorphism (Val158Met) in the *COMT* gene affects enzyme activity, with the thermolabile Met allele having one-fourth the activity of the thermostable Val allele. Thus, the COMT Val158Met polymorphism may impact dopamine regulated prefrontal cortical activity during executive and working memory tasks that tax this functional circuitry and are affected by variations in dopamine signaling [Goldman-Rakic, 1996]. In fact, this polymorphism has been linked to impairments in executive function and working memory in Val158 carriers [Egan et al., 2001], suggesting that genetically driven alterations in COMT enzymatic activity and subsequent synaptic prefrontal dopamine concentrations may lead to diminished prefrontal function. Functional MRI has revealed that the load of the high-activity Val158Met allele consistently predicts a relatively exaggerated prefrontal response during the performance of a well-characterized working memory test [Egan et al., 2001]. These imaging genetics findings have been interpreted to reflect an inefficient and thus exaggerated response, perhaps in effort to maintain task performance or as a reflection of diminished prefrontal signal to noise resulting from decreased concentrations of prefrontal dopamine associated with the high-activity Val158Met allele.

In contrast, the COMT 158Met allele has been associated with increased anxiety and emotional dysregulation. In a recent study [Drabant et al., 2006], we found that the 158Met allele was associated with a dose-dependent increase in hippocampal and ventrolateral PFC activation in response to threatening facial expressions. In Met/Met homozygotes, limbic and prefrontal regions also showed increased functional coupling. Moreover, in these same subjects, the magnitude of amygdala-orbitofrontal coupling was inversely correlated with novelty seeking, an index of temperamental inflexibility. These results indicate that heritable variation in dopamine neurotransmission associated with the 158Met allele of the *COMT* polymorphism results in heightened reactivity and connectivity in corticolimbic circuits. This may reflect a genetic predisposition for inflexible processing of affective stimuli, a mechanism possibly accounting for aspects of arousal and behavioral control that contribute to emotional dysregulation previously reported in met/met individuals.

Dopamine Transporter, Dopamine D2 and D4 Receptors

Dopamine neurotransmission via mesolimbic projections to ventral striatum is believed to play a critical role in modulating reward-related behavior including reward seeking. Dysfunction in dopamine signaling is thought to be associated with altered reward seeking behaviors including addiction. Key components of this circuitry include the dopamine transporter (DAT) which acts as the primary reuptake mechanism for dopamine, the post-synaptic inhibitory D2 and D4 receptors and the inhibitory somatodendritic D2 autoreceptor. A recent study examined the degree to which genetic polymorphisms in these genes predicted variation in brain function during a positive and negative feedback task associated with monetary reward [Forbes et al., 2007]. Functional genetic polymorphisms within each of these genes independently predicted significant variation in ventral striatum response to the task. For each of these polymorphisms the allele associated with relatively increased dopamine release and availability within ventral striatum predicted relatively greater ventral striatal reactivity. Remarkably, this effect seems to be specific to ventral striatal dopamine release as a polymorphism associated with greater prefrontal dopamine release was not associated with ventral striatal reactivity.

DEVELOPMENTAL CONSIDERATIONS

As the field of genetics has transitioned to examining interactions with environmental influences, changes in gene expression across the lifespan can no longer be ignored. Therefore, examining the links between genetic polymorphisms and alterations in brain function should be examined in younger populations. Adolescence is a period of increased vulnerability for mood and anxiety disorders, with a significant rise in prevalence of these conditions in the general population. This is considered a time of rapid transformation, involving changes in social, physical, cognitive, and emotional development. Not only are environmental challenges present during this time, but also structural imaging studies have shown that cortical development continues into early adulthood [Gogtay et al., 2004]. Investigation of alterations in corticolimbic reactivity as a function of genetic variation in adolescence may help identify the varying mechanisms by which genetics, environment, and development interact to affect neurobiological pathways that contribute to increased susceptibility to affective disorders. Of additional interest will be to understand how functional genetic variation interacts with experience-dependent epigenetic regulation of gene expression (e.g., histone acetylation or DNA methylation) to further bias behaviorally relevant neurobiological processes during critical developmental windows [Szyf et al., 2007; Tsankova et al., 2007] (Table I).

A number of considerations in understanding younger populations have been demonstrated within the relatively young field of developmental neuroimaging that require further investigation. For example, previous data has shown that there are developmental shifts during childhood and adolescence in the response specificity of the amygdala to facial expressions that may be relevant for the emergence of affective disorders [Thomas et al., 2001]. Furthermore, age-related changes in serotonin transporter density have also been observed [van Dyck et al., 2000], although not in all studies [Hesse et al., 2003]. Associations similar to those of adult populations have been found with the 5-HTTLPR and depression in adolescent populations, with significant genotype-environmental risk interaction as well as sex differences [Eley et al., 2004], but replication of such studies in additional child and adolescent populations is necessary. A recent study has reported differences in functional connectivity and gray matter volume in limbic regions as a function of an interaction between the 5-HTTLPR and life stress [Canli et al., 2006]; however, similar studies in younger subjects are needed to understand the dynamic interplay between genes and environment that may differ across the lifespan.

FUTURE DIRECTIONS

We have described a number of studies wherein specific genetic polymorphisms with identified functional relevance have been associated with modulation of brain function. We believe the broad spectrum of neural circuitry these studies have targeted and the positive identification of relationships between functionally relevant genetic polymorphisms and brain function across these neural systems underscores the effectiveness of imaging genetics. Studies exploring the degree to which genetic variation predicts functional coupling between interconnected brain areas further suggest this technique is capable of assessing the effects of genetic variation on the engagement of neural networks, not just individual brain regions.

More complex applications of imaging genetics may prove even more effective at revealing behaviorally and clinically meaningful biological mechanisms. For example, multimodal neuro-imaging represents a promising research technique for linking molecular mechanisms that drive variation in brain function. A recent multimodal neuro-imaging study using both PET and fMRI exemplifies this capability. A critical regulator of 5-HT neurotransmission is an inhibitory feedback mechanism mediated by the somatodendritic 5-HT_{1A} autoreceptor. The 5-HT_{1A} autoreceptor is expressed on a population of serotonergic neurons projecting from the brainstem raphe to cortical and limbic target regions. Via inhibitory feedback 5-HT_{1A} autoreceptor activation contributes to diminished neuronal activity and reduced 5-HT release at post-synaptic targets. A population of healthy adults underwent both an fMRI session to assess amygdala reactivity and a PET imaging session to assess 5-HT_{1A} autoreceptor binding potential with the radioligand [^{11}C]-WAY100635 [Fisher et al., 2006]. Remarkably, 30–44% of the variation in amygdala reactivity was predicted by variation in 5-HT_{1A} autoreceptor availability. This relationship suggests a specific molecular mechanism by which regulation of 5-HT release at downstream targets can impact amygdala reactivity. Interestingly, the 5-HTTLPR is associated with reduced 5-HT_{1A} autoreceptor availability [David et al., 2005]. Thus, the collective results of these studies potentially illuminate how multimodal neuroimaging coupled with molecular genetics can establish specific and detailed links between common genetic variation, modulation of molecular signaling cascades, brain function and related behaviors.

It is increasingly clear that a complex interaction of multiple genetic and environmental factors contribute to psychiatric disease etiology, severity and responsiveness to treatment. In looking towards the future, imaging genetics studies taking advantage of larger sample populations and accounting for relevant environmental factors may prove useful in further elucidating how genes modulate brain function. For example, the interactive effect of the *BDNF* Val66Met and 5-HTTLPR on corticolimbic circuitry has been examined recently in an imaging genetics sample of over 100 subjects [unpublished data]. An epistatic mechanism between these molecules is suggested by pharmacological and animal models linking 5-HTT and *BDNF* in cell signaling related to stress-mediated neuroplasticity [Luellen et al., 2006; Ren-Patterson et al., 2006]. Surprisingly, the BDNF Met66 allele, which is associated with abnormal regulated BDNF release and reduced hippocampal activity, appears to block the effects of the 5-HTTLPR S allele on reduced amygdala volume. Presumably, the reduced responsivity of the Met66 allele protects against the exaggerated 5-HT signaling associated with the 5-HTTLPR S allele. Such studies provide an example of the biologic epistasis that likely underlies the pathogenesis of a complex disease in human brain.

Although the findings of these studies are not yet readily translated to the clinical practice of psychiatry today, they do provide examples of how the integration of advances in molecular genetics and neuroimaging can lead to the eventual application of these technologies in the diagnosis and treatment of psychiatric illness. Individualized treatment strategies based on targeted neurogenetic pathways will very likely contribute to more effective and tolerated

intervention platforms. Even more compelling is the potential of these approaches to establish predictive genetic and neurobiological markers of disease risk that will guide strategies for active prevention.

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TABLE I

Summary of Polymorphisms Impacting Behaviorally Relevant Brain Function

Gene	Protein	Polymorphisms	Functional effects
Corticolimbic circuitry for emotional arousal, threat reactivity and stress sensitivity			
SLC6A4 (17q11.1)	5-HT transporter/facilitates active 5-HT reuptake	5-HTTLPR short and long alleles	S allele—reduced promoter activity and gene expression; increased amygdala reactivity; decreased functional coupling between amygdala and PFC
MAOA (Xp11.3)	Preferentially catalyzes the oxidative deamination of 5-HT	High (3.5- and 4-repeat) and low (2-, 3-, 5-repeat) activity alleles	2, 3, and 5-repeat alleles—reduced enzyme activity; increased amygdala reactivity; decreased functional coupling between amygdala and medial PFC
TPH2 (12q21.1)	Rate limiting enzyme in neuronal 5-HT synthesis	G(−844)T	−844T allele—increased amygdala reactivity
COMT (22q11.21)	Metabolic degradation of synaptic dopamine	Val158Met	Met158 allele—decreased enzyme activity; increased functional coupling between amygdala and PFC
Mesolimbic circuitry for reward sensitivity and impulsivity			
SLC6A3 (5p15.3)	DA transporter/facilitates active DA reuptake	DAT1 9- and 10-repeat alleles	9-repeat allele—reduced DAT expression; increased ventral striatum reactivity
DRD2 (11q.23)	Inhibitory pre- and post-synaptic receptor	DRD2 −141C Ins/Del	−141C Del—reduced DRD2 function; increased ventral striatal reactivity
DRD4 (11p15.5)	Inhibitory post-synaptic receptor	DRD4 7- and non-7 repeat alleles	7-repeat allele—reduced DRD4 function; increased ventral striatal reactivity