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Imaging Genetics

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As research in developmental and clinical sciences has progressed in the last decades, there have been many important technological and methodological advances in the increasingly complimentary fields of molecular genetics and neuroimaging. These advances have facilitated fruitful collaboration across once disparate disciplines, with early results shedding new light on the mechanisms giving rise to individual differences in complex behaviors and related psychiatric disorders. At the leading edge of such efforts is imaging genetics, an experimental strategy for the effective integration of molecular genetics and neuroimaging technologies for the study of biological mechanisms mediating individual differences in behavior and related risk for psychiatric disorders. Imaging genetic studies have the potential to provide a more complex and nuanced understanding of the pathways and mechanisms through which the dynamic interplay of genes, brain, and environment shapes variability in behavior. The broader potential of imaging genetics is to inform risk and resiliency; however, it is likely to be realized only through its orchestrated application within longitudinal developmental studies. To date, no imaging genetic studies of development or of childhood psychiatric disorders have yielded published results, although such studies are underway. The results of these studies may have important implications for the diagnosis and treatment of such psychiatric disorders.

WHY STUDY GENES?

Genes have an unparalleled potential impact on all levels of biology. In the context of disease states, particularly behavioral disorders, genes are fundamental to our understanding of the mechanisms involved in the development of disease. Whereas most human behaviors cannot be explained by genes alone, and certainly much of the variance in aspects of brain information processing will not be genetically determined directly, variations in a genetic sequence that have an impact on gene function will contribute a substantial amount of variance to these more complex phenomena. This conclusion is implicit in results garnered from twin studies that have demonstrated heritabilities of 40% to 70% for various aspects of cognition, temperament, and personality.[5] Psychiatric illnesses cluster within families, suggesting a highly heritable component to disease susceptibility.[6-8] Genes, therefore, have the potential to identify underlying mechanisms of variability in behavior and disease risk, particularly in cases of child and adolescent psychiatric disorders, which have been shown to be at least similar to, and in some cases, more heritable than adult disorders.[9-12] Within this context, imaging genetics is a promising technique representing the specific ability to understand the neurobiological

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Similar descriptions of this experimental strategy have appeared in American Journal of Medical Genetics (*Fisher et al., 2008*),[1] Development and Psychopathology (*Viding et al., 2006*),[2] Biological Psychiatry (*Hariri et al., 2006*),[3] *and* British Medical Bulletin (*Hariri and Weinberger, 2003*).[4]

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mechanisms through which genes may have an impact on variability in these emergent phenomena.

The classic approach used in genetic association analyses involves the use of candidate genes. A candidate gene is a gene whose variation is suspected of being directly associated with an observable behavioral or clinical (i.e., disease-related) property of the individual (called a *phenotype*). With this approach, a genetic variant (known as a polymorphism) that potentially has an impact on the function of a behaviorally or clinically relevant biological process is identified, and then, deviations in the frequency of one gene variant (called an *allele*) in populations expressing the phenotype are determined. Ideally, the genetic variation should have an impact on molecular or cellular function of the gene or protein (i.e., be a functional variation), and the target phenotype should be stable, robust, and quantifiable. Within the imaging genetics framework, the target phenotype is usually a physiological response of the brain during specific behavioral processes (e.g., amygdala reactivity when viewing threatening facial expressions).

WHY FUNCTIONAL IMAGING?

Previous investigations of candidate genes have attempted to associate functional polymorphisms directly with a behavior; however, such findings have been weak and inconsistent (e.g., the 5-HTTLPR short allele and negative emotionality).[13] There are considerable interindividual differences in the dimensions of observed behavior, as well as subjectivity in behavioral measures, often requiring daunting sample sizes to detect gene effects.[14] More importantly, gene effects are not expressed directly at the level of behavior but rather are mediated by effects on molecular and cellular cascades biasing information processing in brain circuitries mediating behavioral responses to environmental challenge. Functional neuroimaging, using functional magnetic resonance imaging, EEG, or positron emission tomography, provides an efficient and effective tool with which to explore the impact of brain-relevant genetic polymorphisms by quantifying the activity of specific brain regions in association with particular cognitive and emotional tasks that the research participant is asked to perform during the procedure. These techniques promise to identify neural pathways through which these variants contribute to the emergence of variability in behavior and disease risk (Fig. 1).

BASIC PRINCIPLES

Three basic principles have been articulated for imaging genetics.[4] These are selection of candidate genes, control for nongenotype factors, and selection of appropriate tasks for the subject to perform during functional imaging. Well-defined functional polymorphisms (single-nucleotide polymorphisms or other structural variants) in coding or promoter regions previously linked with specific physiological effects at the cellular level and whose impact has been described in distinct brain regions are an ideal starting point (Table 1). Selecting variants that have known neurobiological consequences (e.g., increases in serotonin [5-HT] signaling) is important because of an emphasis in imaging genetics on specifying mechanisms through which genes have an impact on brain and related behavior. Because potential genetic effects are still relatively small compared with typically large effects of age, sex, and IQ, as well as environmental influences (e.g., illness, injury, substance abuse), controlling for these potential confounds is necessary. Furthermore, because imaging genetic studies focus on a single or relatively few polymorphisms against a background of millions, these studies must carefully control for population stratification, which refers to differences in the genetic background of subjects, reflecting their unique ancestry, against which the relation between a specific genotype and phenotype is tested. Because of small genetic effects, choosing a well-characterized behavioral task for subjects to perform during functional neuroimaging that is

both sensitive and specific to the brain process under investigation is of crucial importance to the success of identifying functional correlates of genetic variation. The ideal tasks for these investigations are thus ones that have been established to engage specific brain systems robustly in all subjects, as well as display variance both across control subjects and between patients and comparison subjects. Moreover, in child and adolescent populations, tasks that are both developmentally appropriate and acceptable for use with the specific psychiatric sample being studied should be chosen. For example, in previous imaging studies, amygdala reactivity to threat-related emotional facial expressions has been assayed using a well-characterized challenge paradigm that robustly engages the amygdala and interconnected corticolimbic structures. Importantly, this task has been shown to effectively engage the amygdala in control subjects[15-19] and to demonstrate altered amygdala function in diverse psychiatric disorders.[20-23] Child and adolescent psychiatric populations should also be characterized using behavioral or questionnaire measures that are able to identify relatively homogenous groups for analysis (i.e., separating out a small homogenous group of children with proactive aggression from within the broader and more heterogeneous group of children with conduct disorder). Whereas such steps increase the likelihood of identifying significant genetic regulation of interindividual variability in brain function and related behaviors, multiple genetic polymorphisms (many of which will be of small effect) acting in concert or opposition in the context of unique environmental challenges will ultimately account for the majority of variance in any given neural or behavioral phenotype.

SEROTONIN AND EMOTIONAL BEHAVIOR

One of the most replicated findings in the field of imaging genetics is the impact of a common polymorphism in the promoter region (5-HTTLPR) of the 5-HT transporter (5-HTT) gene on amygdala reactivity in adults.[24] Abnormal 5-HT neurotransmission has been implicated in the pathophysiology of mood and anxiety disorders and has been a target of pharmacological intervention (e.g., selective serotonin reuptake inhibitors). In comparison to the 5-HTTLPR long (L) allele, the short (S) allele has been associated with alterations conferring relatively increased 5-HT signaling.[25] At the behavioral level, possession of either one or two copies of the S allele has been associated with increased levels of temperamental anxiety,[26-28] conditioned fear responses,[29] and development of depression, particularly in the context of environmental stress.[30,31] Against this background, imaging genetics has been used to reveal that threat-related reactivity of the amygdala, a brain region critical in mediating behavioral and physiological arousal, is significantly increased in S allele carriers in comparison to L allele homozygotes.[18] In addition, the 5-HTTLPR S allele has been further linked with reduced gray matter volume in and functional coupling between the amygdala and medial prefrontal cortex.[32] Because the magnitude of threat-related amygdala reactivity (the response of the amygdala to threat-related signals), as well as its functional coupling with medial prefrontal cortex, is associated with temperamental anxiety, these imaging genetic findings suggest that the 5-HTTLPR S allele may be associated with increased risk for depression upon exposure to environmental stressors because of the polymorphism's influence on the reactivity of this corticolimbic circuitry. However, no studies have yet been published investigating the association between the 5-HTTLPR and functional brain activity in children or adolescents. The imaging genetic research with the 5-HTTLPR highlights the effectiveness of this strategy in illuminating specific mechanisms that may mediate individual variability in behavior and risk for disease. Additional imaging genetic findings are summarized in Table 1.

DEVELOPMENTAL CONSIDERATIONS

As the field of behavioral and psychiatric genetics transitions to examining interactions between genes and environmental influences in shaping behavior and disease risk,[33] consideration of developmental trajectories can no longer be ignored. The functional synergy

between genes and brain likely changes throughout development because both experience and biology influence the expression of genes. This process is studied in the rapidly evolving field known as "epigenetics." For example, these emerging studies on epigenetics[34] suggest that certain exogenous factors including environmental stress can literally turn on or off the expression of genes. Gene expression also varies with endogenous shifts such as hormone fluctuations during puberty. Therefore, existing imaging genetic findings in adult populations may not apply to children and adolescents, and further study in these target populations is required because no studies using imaging genetics in children or adolescent populations have yet been published. Additionally, structural imaging studies have shown that cortical development continues into adulthood.[35] Therefore, examining the links between genetic polymorphisms and alterations in brain function must also be appreciated across development. Because few psychopathologies arise de novo in adulthood without previous warning signs in childhood, longitudinal applications of imaging genetics have the potential to uncover key neurobiological pathways involved in both disease risk and resiliency. For example, as previously described, functional coupling between the amygdala and regulatory circuits in the medial prefrontal cortex are affected by genetically driven variability in 5-HT function and are also important in the pathophysiology of depression. These prefrontal areas, however, exhibit relatively protracted development,[35] and studying genetic effects on the maturation of this coupling during adolescence may help our understanding of the development of depression risk. In turn, such understanding may advance formulation of individually tailored intervention and prevention strategies particularly in high-risk children.

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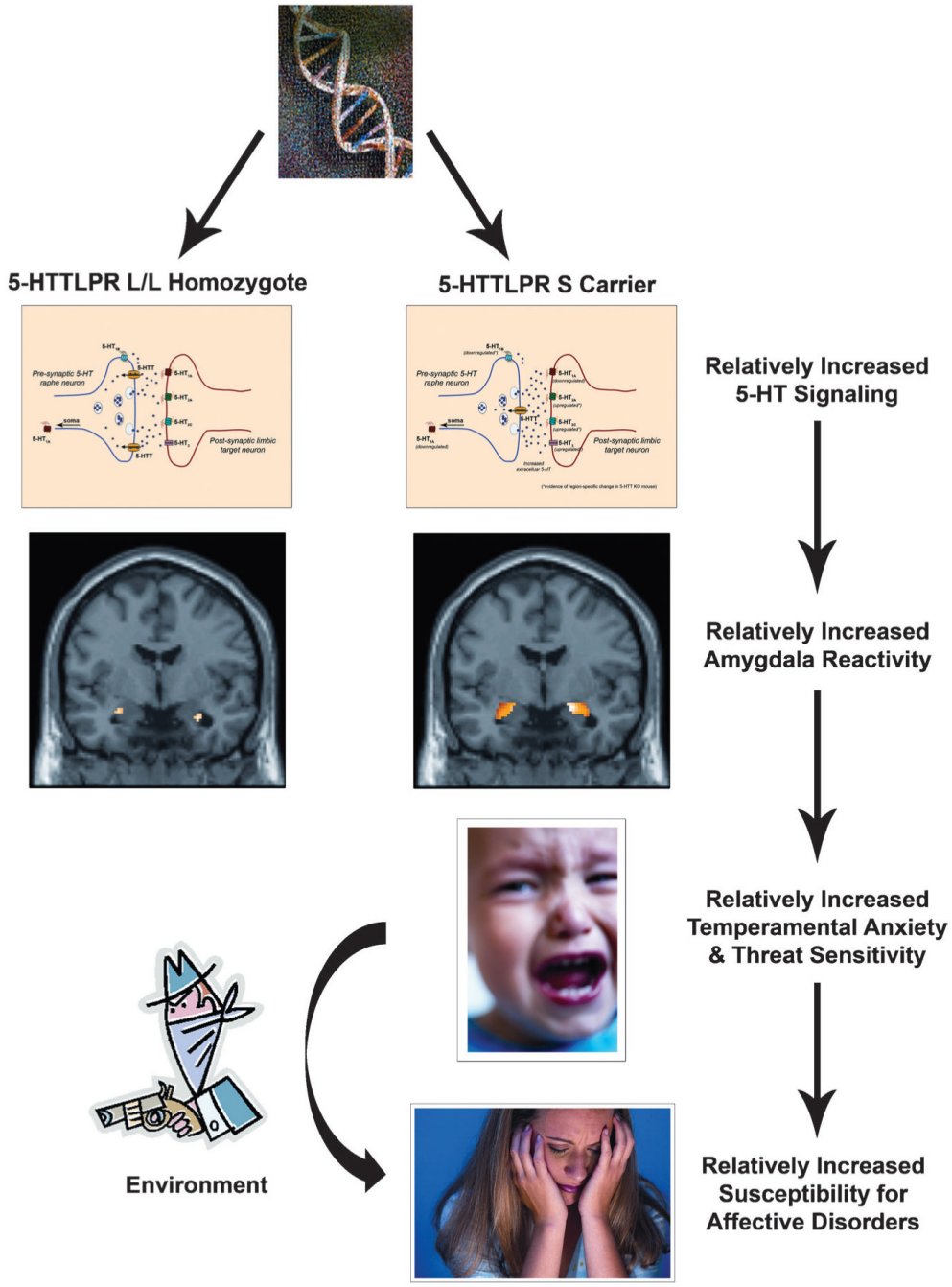

FIG. 1.

Imaging genetics allows for the identification of how common genetic polymorphisms (e.g., 5-HTTLPR) influencing molecular processes (e.g., serotonin signaling) bias neural pathways (e.g., amygdala reactivity) mediating individual differences in complex behavioral processes (e.g., trait anxiety) related to disease risk in response to environmental adversity. (Reprinted from *Trends Cogn Sci*. [10:182–191] Hariri AR, Holmes A. Genetics of emotional regulation: the role of the serotonin transporter in neural function. Copyright 2006, with permission from Elsevier.)

TABLE 1

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—increased 5-HT signaling, 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 (22q11.2)	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 DAT1 expression, increased ventral striatum reactivity
DRD2 (11q.23)	Inhibitory presynaptic and postsynaptic receptor	DRD2 −141C Ins/Del	−141C Del—reduced DRD2 function, increased ventral striatum reactivity
DRD4 (11p15.5)	Inhibitory postsynaptic receptor	DRD4 7- and non-7 repeat alleles	7-repeat allele—reduced DRD4 function, increased ventral striatum reactivity

Note: 5-HT = serotonin; 5-HTTLPR = serotonin-transporter-linked polymorphic region; COMT = catechol-O-methyl transferase; DA = dopamine; DAT1 = dopamine transporter gene 1; Del = deletion; DRD2 = dopamine receptor D2; DRD4 = dopamine receptor D4; MAOA = monoamine oxidase A; Ins = insertion; PFC = prefrontal cortex; SLC6A3 = solute carrier family 6 (neurotransmitter transporter, dopamine), member 3; SLC6A4 = solute carrier family 6 (neurotransmitter transporter, serotonin), member 4; TPH2 = tryptophan hydroxylase 2. (Reprinted with permission of John Wiley &Sons, Inc., from Fisher PM, Muñoz KE, Hariri AR. Identification of neurogenetics pathways of risk for psychopathology, 1–7. *Am J Med Genet C Semin Med Genet*. Vol.148, No. 2, 2008, 147–153. Copyright 2008, John Wiley & Sons, Inc.)