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Neuroimaging: Technologies at the Interface of Genes, Brain and Behavior

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Synopsis

Neuroimaging technologies, because of their unique ability to capture the structural and functional integrity of distributed neural circuitries within individuals, provide a powerful approach to explore the genetic basis of individual differences in complex behaviors and vulnerability to neuropsychiatric illness. Functional magnetic resonance imaging (MRI) studies especially have established important physiological links between genetic polymorphisms and robust differences in information processing within distinct brain regions and circuits that have been linked to the manifestation of various disease states such as Alzheimer's disease, schizophrenia and depression. Importantly, many of these biological relationships have been revealed in relatively small samples of subjects and in the absence of observable differences at the level of behavior, underscoring the power of a direct assay of brain anatomy and physiology in exploring the functional impact of genetic variation. Through the continued integration of genes, brain and behavior, neuroimaging technologies represent a critical tool in ongoing efforts to understand the neurobiology of normal and pathological behavioral states. Multidisciplinary research capitalizing on such neuroimaging-based integration will contribute to the identification of predictive markers and biological pathways for neuropsychiatric disease vulnerability as well as the generation of novel targets for therapeutic intervention.

CONCEPTUAL BASIS AND OVERVIEW

Genes have unparalleled potential impact on all levels of biology. In the context of disease states, particularly behavioral disorders, genes represent the cornerstone of mechanisms that, either directly or in concert with environmental events, ultimately result in disease. Moreover, genes offer the potential to identify at-risk individuals and biological pathways for the development of new treatments. While most human behaviors cannot be explained by genes alone, and certainly much variance in aspects of brain structure and function will not be genetically determined directly, it is anticipated that variations in genetic sequence impacting function will contribute an appreciable amount of variance to these 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 [1]. In the case of psychiatric illness, genes appear to be the only consistent risk factors that have been identified across populations, and the majority of susceptibility for major psychiatric disorders is accounted for by inheritance [2].

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Traditionally, the impact of genetic polymorphisms on human behavior has been directly examined using clinical evaluation, personality questionnaires, and neuropsychological batteries. Genetic epidemiological investigations have directly examined the relationship between specific genetic polymorphisms and behaviors and have reported equivocal results. 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 that often require in excess of several hundred subjects to identify even small gene effects. 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 the brain. Thus, examining the effects of genes on the brain represents a critical step in understanding their ultimate contribution to variability in behavior.

Since genes are directly involved in the development and function of brain regions subserving specific cognitive and emotional processes, functional polymorphisms in genes may be strongly related to the function of these specific neural systems and in turn, mediate their involvement in behavioral outcomes. This is the underlying assumption of our investigations examining the relation between genes and neural systems, what we initially called, “imaging genomics” [3]. More recently we have described this approach as “imaging genetics” [4], because it is typically utilized to explore variation in specific genes and not the genome broadly. The potential for marked differences at the neurobiological level underscores the need for a direct assay of brain function. Accordingly, imaging genetics within the context of a “candidate gene association approach” provides an ideal opportunity to further our understanding of biological mechanisms potentially contributing to individual differences in behavior and personality. Moreover, imaging genetics provides a unique tool with which to explore and evaluate the functional impact of brain-relevant genetic polymorphisms with the potential to understand their impact on behavior. Of course, the relevance of the findings of imaging genetics studies for disease vulnerability will only be made once the variants under study are further associated with disease risk directly or if their impact on brain function is manifest, or even exaggerated, in the diseases of interest.

Neuroimaging techniques, especially those that are noninvasive like MRI, electroencephalography (EEG), and magnetoencephalography (MEG), typically require no more than a few minutes of subject participation to acquire substantial data sets reflecting the acquisition of many hundreds of repeated measures of brain structure or function within a single subject. The efficiency of these techniques allows 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 the brain with power and sensitivity places neuroimaging at the forefront of available tools for the *in vivo* study of functional genetic variation.

IMAGING GENETICS: BASIC PRINCIPLES

1. Selection of Candidate Genes

The protocol for imaging genetics typically involves first identifying a meaningful variation in the DNA sequence within a candidate gene. For the variant to be meaningful it should impact function at the molecular or cellular level (i.e., be a functional variant) and the distribution of such effects at the level of brain systems should be predictable. Short of well-defined functional polymorphisms, candidate genes with identified single nucleotide polymorphisms (SNPs) or other allele variants in coding or promoter regions with likely functional implications (e.g., nonconservative amino acid substitution or missense mutation in a promoter consensus

sequence) involving circumscribed neuroanatomical systems would be attractive substrates. In fact, recent imaging genetics studies have taken the lead in exploring the functionality of candidate variants by first describing their *in vivo* effects at the level of brain systems [5].

Consistent with the goal of genetic association studies to identify variation impacting individual differences in behavior and related risk for disease in the general population, candidate polymorphisms in imaging genetics studies should also be relatively common. That is, the relative frequency of the less common or minor allele should be greater than 5%. In light of the considerable costs of neuroimaging in comparison with behavioral studies and the related sample size limitations, the minor allele frequency of candidate polymorphisms in imaging genetics studies should ideally be greater than 30%. In such cases, the relative contributions of all potential genotypes (i.e., homozygotes for both major and minor alleles and heterozygotes) to brain function can be examined using imaging genetics.

2. Control for Non-Genetic Factors

The contribution of single genes to the structural and functional integrity of brain systems, while putatively more substantial than that to emergent behavioral phenomena, is still presumably small. Furthermore, typically large effects of age, sex and IQ, as well as environmental factors such as illness, trauma, or substance abuse, on phenotypic variance can easily obscure these small potential gene effects. Since association studies in imaging genetics are susceptible to population stratification artifacts (i.e., differing ancestral genetic backgrounds for specific candidate genotypes), as in any case-control association study, ethnic matching within genotype groups and genomic control is also potentially critical [6]. Thus, the identification and contribution of genetic variation to specific phenotypes should be limited to studies in which other potential contributing and confounding factors are carefully matched across genotype groups. If the imaging protocol involves performance of a task, as is typical in functional MRI (fMRI), the groups should also be matched for level of performance, or at least any variability in performance should be considered in the analysis and interpretation of the imaging data. This is because task performance and the fMRI blood oxygenation level dependent (BOLD) signal are tightly linked, and systematic differences in performance between genotype groups could either obscure or masquerade for a true gene effect.

3. Task Selection

There has been a tremendous proliferation of functional neuroimaging studies accompanied by behavioral tasks designed specifically for this experimental setting. Many of these are modified versions of classic behavioral and neuropsychological tests (e.g., the Wisconsin Card Sorting Task) designed to tap neural systems critical to particular behaviors. More recent paradigms have emerged that focus on interactions of specific behaviors and disease states as these questions have become newly accessible with noninvasive imaging (e.g., the emotion Stroop and obsessive-compulsive disorder).

Because of the relatively small effects of single genes, even after controllng for non-genetic and other confounding variables, imaging tasks must maximize sensitivity and inferential value. As the interpretation of potential gene effects depends on the validity of the information processing paradigm, it is best to select well-characterized paradigms that are effective at engaging circumscribed brain regions and systems, produce robust signals in every individual, and show variance across individuals. In short, imaging genetics studies are typically not the appropriate venue to design and test new functional tasks, and to do so might undermine their tremendous potential.

IMAGING GENETICS: APPLICATIONS OF THE PRINCIPLES

The following sections provide introductory examples of how imaging genetics can lead to insights about the biological mechanisms underlying individual differences in complex behavioral traits. In many cases, the genetically driven variability in behavior represents an intermediate phenotype conferring risk for neuropsychiatric disease in the context of specific environmental influences. Exemplars include episodic memory, executive function, temperamental anxiety, and their respective neural underpinnings, namely the hippocampus, prefrontal cortex and amygdala. In each group of studies, neuroimaging was employed to identify the effects of genetic polymorphisms -- often resulting in molecular and cellular alterations, as well as those associated with specific behaviors and/or disease states -- on discrete neural circuitries supporting the associated behavioral and clinical phenomena. In addition, each study incorporated the basic principles of imaging genetics described above, such as the implementation of rigorous controls for non-genetic factors such as age, sex, population stratification and performance on the experimental task. All of the studies also capitalized on existing functional paradigms designed to explore physiological aspects of distinct neural systems.

1. Common Polymorphisms Impacting the Hippocampus and Episodic Memory

BDNF—Brain-derived neurotrophic factor (BDNF) is well known to play a role in neuronal survival, differentiation, and synaptic plasticity. BDNF is highly expressed in the hippocampus, a brain region critical for episodic memory. A common SNP in the human BDNF gene, a valine (Val) to methionine (Met) substitution at codon 66 (Val66Met), is associated with abnormal intracellular trafficking and regulated secretion of pro-BDNF, which is the precursor to functional BDNF [7]. Thus, the BDNF Met66 allele may impact learning and memory supported by the actions of BDNF on local neuronal plasticity and synaptic reorganization. Consistent with the molecular effects of the Met66 allele, studies have documented relatively impaired episodic memory in human subjects carrying the Met66 allele [7]. Converging evidence from several neuroimaging studies using different modalities further suggests that the Met66 effects on memory are mediated in part by its impact on hippocampal structure and function. Magnetic resonance spectroscopy has revealed Met66 allele-associated reductions in hippocampal n-acetyl aspartate, an intraneuronal metabolite closely correlated with glutamate neurotransmission and neuronal integrity [7]. Based on these findings, fMRI was used to study the effects of the BDNF Val66Met on hippocampal activation in healthy volunteers performing a simple declarative memory task. Consistent with the behavioral and NAA findings, Met66 allele carriers showed reduced hippocampal activation during encoding and retrieval stages of episodic memory [8]. A subsequent study found that Met66 allele carriers also exhibited a 12 – 15% reduction in hippocampal volume [9]. These collective neuroimaging studies demonstrate a remarkable consistency in the effects of the BDNF Met66 allele on hippocampal structure and function, thereby providing a detailed account of the underlying mechanisms contributing to the effects of the polymorphism on learning and memory.

APOE—Apolipoprotein E (APOE) is essential for multiple brain functions including neuronal growth and repair, neuroprotection and inflammation. A common allelic variant of the human APOE gene has been associated with late-onset familial Alzheimer's disease [10]. Specifically, the APOE ε4 allele has a dose-dependent effect on risk and age of onset for the disease [11]. Positron emission tomography (PET) studies have reported deficits in resting cortical glucose metabolism in cognitively normal middle-aged subjects with the APOE ε4 allele [12,13]. In the first application of fMRI in imaging genetics, subjects carrying the APOE ε4 allele exhibited significantly greater activation in memory-related brain regions, such as the prefrontal cortex and hippocampus, during a challenging memory task in comparison to those homozygous for the APOE ε3 allele, which is not associated with increased risk for

Alzheimer's disease. In contrast to the strikingly different pattern of brain activation between the two groups, all subjects were cognitively intact and performed the memory task equally well. Such relatively increased neural activity in those with the at-risk allele was interpreted as reflecting possible compensatory phenomena through the recruitment of additional cognitive resources in the face of greater task difficulty and demand. Interestingly, the magnitude of task-related brain activity was significantly correlated with subsequent memory decline. These data suggest that changes in brain information processing during declarative memory are associated with the biological effects of APOE ε4 even if compensation is made at the level of observable behavior, and that such memory-related effects may provide a useful tool for predicting the course of cognitive decline.

KIBRA—A recent study found that a genomic locus encoding the newly discovered brain protein, KIBRA, is significantly associated with normal variability in memory performance [14]. More specifically, a common thymine (T) to cytosine (C) substitution within intron 9 of the human KIBRA gene is significantly associated with differential memory performance. Carriers of the KIBRA T allele exhibit greater free recall of words after both short and long delay periods as well as better memory scores in tests of episodic memory. Importantly, molecular and cellular studies have revealed that the KIBRA is highly expressed in brain regions involved in memory (e.g., hippocampus). In addition, the polymorphism exists in a region that may be critical in allowing KIBRA to interact with other systems to regulate synaptic plasticity such as that associated with learning and memory. Based on these findings, fMRI was used to explore the impact of the KIBRA T allele on memory-related brain activity. During retrieval of paired-associates, non-carriers of the T allele showed significantly increased brain activation compared to T allele carriers in the hippocampus as well as the medial frontal gyrus and parietal cortex. As memory performance did not differ between these groups, the data suggest that non-carriers of the T allele need relatively greater activation in these memory-related brain regions to reach the same level of retrieval performance as T allele carriers. Thus, the potential impact of the KIBRA T allele on synaptic plasticity may manifest as more efficient processing of information in memory-related neural circuits and subsequently superior memory ability.

2. Common Polymorphisms Impacting the Prefrontal Cortex and Executive Function

COMT—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 [15]. 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 [16]. 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 [17]. In fact, this polymorphism has been linked to impairments in executive function and working memory in Val158 carriers [18], suggesting that genetically driven alterations in COMT enzymatic activity and subsequently in synaptic prefrontal dopamine concentrations may lead to diminished prefrontal function. FMRI has revealed that the load of the high-activity Val158 allele consistently predicts a relatively exaggerated prefrontal response during the performance of a well-characterized working memory test [18]. These imaging genetics findings have been interpreted to reflect an inefficient and thus exaggerated response, perhaps in an 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 Val158 allele. Because schizophrenia involves abnormal prefrontal function, the COMT Val158, especially in the context of environmental

triggers such as drug abuse [19], may reflect an important genetic mechanism contributing to this aspect of the disease.

GRM3—The metabotropic glutamate receptor 3 (GRM3), one of a class of receptors modulating synaptic levels of the excitatory neurotransmitter glutamate, is a promising schizophrenia susceptibility candidate gene. A common GRM3 haplotype was strongly associated with schizophrenia and within this haplotype, the A allele of SNP 4 in intron 2 was slightly overtransmitted to probands, and has been associated with poorer performance on several cognitive tests of prefrontal and hippocampal function in both volunteers and patients. The effects of this SNP on neurobiological traits related to risk for schizophrenia and glutamate neurotransmission were recently examined using imaging genetics [20]. FMRI showed relatively deleterious activation patterns in both the prefrontal cortex and hippocampus in control subjects homozygous for the SNP4 A allele. The authors also provided molecular data suggesting the SNP4 A allele alters prefrontal mRNA and protein levels of GRM3 as well as glutamate transporter, which is regulated by GMR3. Collectively, their data suggest that genetic variation in GMR3 affecting glutamate neurotransmission impacts prefrontal and hippocampal physiology and, in turn, related cognitive and mnemonic processes, which may be impaired in schizophrenia.

DISC1—As its name implies, Disrupted-in-schizophrenia 1 (DISC1), which is predominantly expressed within the hippocampus, is another schizophrenia susceptibility candidate gene. Recently, a three-SNP haplotype of DISC1 was associated with schizophrenia in a family-based sample [21]. A common non-synonymous SNP resulting in a serine (Ser) to cytosine (Cys) substitution at codon 704 (Ser704Cys) within this haplotype was specifically associated with schizophrenia. In addition to overtransmission in schizophrenia, the Ser704 allele was associated with altered hippocampal structure and function in healthy subjects, including reduced hippocampal gray matter volume and altered engagement of the hippocampus during several cognitive tasks assayed with fMRI [21]. These convergent data suggest that allelic variation within DISC1, either at Ser704Cys or haplotypes monitored by it, increases the risk for schizophrenia and that the mechanism of this effect involves structural and functional alterations of the hippocampus.

3) Common Polymorphisms Impacting the Amygdala and Temperamental Anxiety

5-HTT—Individual differences in serotonin (5-HT) function have been repeatedly and consistently associated with variability in affect and temperament in mouse, monkey and man [22,23]. Moreover, 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 is easily 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 that 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* [24]. While this *in vitro* effect was initially confirmed using *in vivo* single photon emission computed tomography (SPECT) [25], recent PET studies offering more specific radiotracers and improved spatial resolution have failed to find altered 5-HTT levels associated with the 5-HTTLPR [26,27]. Rather, effects of the 5-HTTLPR have been documented in other 5-HT subsystems, most notably the 5-HT_{1A} receptor [28,29], and such downstream effects may be critical in mediating the neural and behavioral effects of the 5-HTTLPR [30,31].

At the behavioral level, possession of either one or two copies of the S allele has been associated with increased levels of temperamental anxiety [32–34], conditioned fear responses [35], and the development of depression [24], especially in the context of environmental stress [36,37]. FMRI 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, to threat-related facial expressions was significantly exaggerated in S allele carriers [38]. 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 [39–44] and patients with mood disorders [45,46]. In addition, the 5-HTTLPR S allele has been further linked with reduced grey matter volumes in and functional coupling between the amygdala and medial prefrontal cortex [47]. 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.

MAO-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 was associated with relatively exaggerated amygdala reactivity and diminished prefrontal regulation of the amygdala [48]. 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 [49], the imaging genetics data provide important insight regarding the neurobiological and behavioral effects of 5-HT.

TPH-2—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 [5]. Specifically, the T allele of the relatively frequent G(-844)T polymorphism was associated with relatively exaggerated amygdala reactivity. This report provides further insight into the biological significance of TPH2 in the human central nervous system and offers 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 [50]), 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.

SUMMARY AND FUTURE DIRECTIONS

The results of these studies underscore the power of *in vivo* neuroimaging technologies and provide compelling evidence that the application of imaging genetics, in light of the basic principles outlined above, promises a unique opportunity to explore and evaluate the functional impact of brain-relevant genetic polymorphisms. In turn, these efforts will contribute to the identification of biological mechanisms and pathways that mediate individual differences in complex behaviors and vulnerability to disease. While current imaging genetics studies highlight a powerful new approach to the study of genes, brain, and behavior, the true potential of this approach will only be realized by aggressively expanding the scope and scale of the experimental protocols.

Although single gene effects on brain function can be readily documented in small samples (< 20), the contributions of multiple genes acting in response to variable environmental pressures is ultimately necessary for the development of truly predictive markers that account for the majority of variance in any given phenotype, such as stress resiliency. For example, the interactive effect of the BDNF Val66Met and 5-HTTLPR polymorphisms on corticolimbic circuitry has been examined recently in an imaging genetics sample of over 100 subjects [51]. 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 [52,53]. Surprisingly, the BDNF Met66 allele, which is associated with abnormally-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.

Combining existing neuroimaging modalities is another important future direction for imaging genetics. Implementation of multimodal strategies is critical for identifying intermediate mechanisms mediating the effects of genetic polymorphisms on neural circuit function and related behaviors. The potential of multimodal neuroimaging was recently demonstrated in a study employing both PET and fMRI to identify the impact of 5-HT_{1A} autoreceptor regulation of 5-HT release on amygdala reactivity [30]. In the study, adult volunteers underwent ^{11}C-WAY 100635 PET to determine 5-HT_{1A} autoreceptor binding potential, an *in vivo* index of receptor density. On the same day, all subjects also underwent fMRI to determine the functional reactivity of the amygdala. Remarkably, the density of 5-HT_{1A} autoreceptors accounted for 30 – 44% of the variability in amygdala reactivity. Downstream effects on 5-HT_{1A} autoreceptors, notably reduced receptor density, have been hypothesized to mediate neural and behavioral changes associated with the 5-HTTLPR S allele [28]. Thus, these findings suggest that 5-HT_{1A} autoreceptor regulation of corticolimbic circuitry represents a key molecular mechanism mediating the effects of the 5-HTTLPR.

Ultimately, we anticipate that such mechanistic understanding will allow for the early identification of individuals at greater risk for behavioral problems that can have long-term health-related implications. Continued imaging genetics research at the interface of genes, brain, and behavior holds great promise for further explicating the neurobiological mechanisms through which risk of psychiatric disease emerges in the context of environmental adversity [31,54]. Such knowledge will, in turn, facilitate the development of therapeutic interventions,

tailored to individual neurobiologies, which will be more effective in combating the enormous personal and public health burden associated with common psychiatric disorders.

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