Review

Biological Psychiatry

Imaging Genetics and Genomics in Psychiatry: A Critical Review of Progress and Potential

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ABSTRACT

Imaging genetics and genomics research has begun to provide insight into the molecular and genetic architecture of neural phenotypes and the neural mechanisms through which genetic risk for psychopathology may emerge. As it approaches its third decade, imaging genetics is confronted by many challenges, including the proliferation of studies using small sample sizes and diverse designs, limited replication, problems with harmonization of neural phenotypes for meta-analysis, unclear mechanisms, and evidence that effect sizes may be more modest than originally posited, with increasing evidence of polygenicity. These concerns have encouraged the field to grow in many new directions, including the development of consortia and large-scale data collection projects and the use of novel methods (e.g., polygenic approaches, machine learning) that enhance the quality of imaging genetic studies but also introduce new challenges. We critically review progress in imaging genetics and offer suggestions and highlight potential pitfalls of novel approaches. Ultimately, the strength of imaging genetics and genomics lies in their translational and integrative potential with other research approaches (e.g., nonhuman animal models, psychiatric genetics, pharmacologic challenge) to elucidate brain-based pathways that give rise to the vast individual differences in behavior as well as risk for psychopathology.

Keywords: Candidate, Genetics, Genomics, Imaging, MRI, Neurogenetics, Polygenic

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By linking genetic and epigenetic variation to brain structure, function, connectivity, and chemistry via neuroimaging measures (1), imaging genetics and genomics can inform the neural mechanisms through which genetic and molecular differences impact cognition, emotion, and behavior in health and disease. Since being pioneered nearly 20 years ago by candidate gene studies of receptor ligand binding (2–6) (Supplement), imaging genetics has incorporated a host of allied neuroimaging techniques, most frequently structural magnetic resonance imaging (MRI) and functional MRI (fMRI), and has been integrated with traditional psychiatric genetics (7–9) and nonhuman animal models (10–13). More recently, this approach has been extended to epigenetics (14,15), and, as imaging genomics, to discovery-based (16,17) and polygenic (18,19) approaches.

Accompanying an exponential increase in publications, imaging genetics and genomics have also been confronted by several qualitative concerns, including the proliferation of studies with small sample sizes, limited replication, unclear mechanisms relating genes to brain and brain to behavior, and evidence that effect sizes may be smaller than originally thought and perhaps no larger than effects for traditional psychiatric diagnoses (9,20). Such concerns and the desire to find new genes and pathways via genomic approaches have led to the formation of consortia and large-scale projects to increase sample size (21–26) as well as the adoption of methodological and technological innovations in genetics (e.g., genome-wide association studies [GWASs], epigenetics), neuroimaging (e.g., multimodal positron emission tomography, fMRI), and psychiatric genomics (e.g., polygenic risk scores, linkage disequilibrium score regression) (9,14,18,27–30), all of which enhance the quality of imaging genetic studies and each of which is also subject to new potential pitfalls.

In this article, we critically review the current state of imaging genetics and genomics, highlighting unique strengths, considerations, and limitations of distinct approaches, while considering their utility for psychiatry going forward. We suggest that some criteria to evaluate the usefulness of intermediate phenotypes according to an endophenotype conceptualization are retrograde and counterproductive when applied to imaging genetics in some instances. We argue that single variant analyses remain informative in the context of a polygenic architecture that underlies most imaging phenotypes. Furthermore, we discuss the lack of replication in imaging genetics and what has been learned, and not learned, from meta-analytic efforts. Next, we review the use of candidate and discovery-based polygenic methods that aim to better characterize the complex polygenic architecture of imaging phenotypes and consider pitfalls that these techniques may face and how they may be minimized. We highlight

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Table 1. Converging Evidence: Example of *FAAH* rs324420 Genotype (C/A; C385A)

Source of Evidence	Findings	Benefits	Limitations
In Vitro Function	A allele homozygosity is associated with less FAAH cellular expression in T lymphocytes and transfected cells owing to post-translation mechanism preceding folding (145).	Controlled functional characterization and isolation of step at which allelic variation impacts function.	Unclear if similar function is observed in vivo among an interactive system.
In Vivo Function	A allele carriers had lower [^{11}C]CURB PET binding (FAAH binding) (146).	In vivo functional characterization.	Often small samples, unclear links to behavior and other relevant phenotypes (e.g., brain function, structure).
Nonhuman Animal Manipulation	Knock-in mouse model: A allele is associated with forebrain FAAH protein expression, hydrolytic activity, and elevated anandamide. A allele is associated with increased projections from infralimbic to basolateral amygdala and enhanced fear extinction and reduced anxiety (13).	Controlled manipulation of system using a variety of means (e.g., pharmacologic, genetic).	Unclear whether translates to humans and related conditions. Questionable phenotypic convergence across species for some phenotypes.
Human Manipulation (Pharmacologic Challenge)	Human: THC administration is associated with reduced anxiety and threat-related amygdala reactivity (147).	Manipulation of a specific system allowing causal inferences to be drawn. For some substances, limitations on who can be exposed for human studies.	Temporary and chronic manipulation unclear translation to genetic risk. Uncertain whether artificial manipulations create other systematic changes.
Imaging Genetics and Genomics	A allele is associated with decreased threat-related amygdala reactivity and increased amygdala habituation (148).	Provides a tractable and clinically. relevant phenotype. Offers system-level insight.	Molecular mechanisms of association unclear.
Psychiatric/ Behavioral Association (Candidate or GWAS)	A allele is associated with enhanced fear extinction and reduced anxiety and stress sensitivity (10).	Provides clinical relevance.	Unclear biological mechanisms.
Treatment	FAAH inhibition improves anxiety in rodent models (149). Most common self-reported reason for using cannabis is anxiety reduction. THC administration reduces anxiety in clinical populations (150).	Evaluation of applicable therapeutic potential.	Dependent on other evidence, ability and safety to manipulate target. Lack of regional specificity in humans.

The endocannabinoid system has been linked to stress recovery, anxiety, and substance use across a host of models. FAAH is an enzymatic regulator of endocannabinoid signaling. Within the endocannabinoid system, it primarily degrades the endocannabinoid ligand anandamide.

FAAH, fatty acid amide hydrolase; GWAS, genome-wide association study; PET, positron emission tomography; THC, Δ^9-tetrahydrocannabinol.

the potential of molecular genomic methods to verify and mechanize relationships between the dynamic genome and neural phenotypes. Finally, we consider how imaging genetics and genomics hold their greatest potential not in isolation but as methods that can be used alongside other techniques (e.g., pharmacologic challenge), levels of analysis (e.g., the transcriptome, psychiatric genetics), and nonhuman animal research (e.g., genetic models) in the search for mechanistic consilience (Table 1). With further integration with molecular genetics, basic neuroscience, and psychiatric genetics and the accumulation of not only large but also longitudinal samples, imaging genetics and genomics will be able to more adequately model and test the complex interplay between genes, brain, body, environment, and behavior and expand these pathways (Figure 1). It is hoped that such mechanistic characterization will ultimately improve the nosology, treatment, and prevention of mental illness.

IS THE ENDOPHENOTYPE CONCEPTUALIZATION OF INTERMEDIATE PHENOTYPES USEFUL?

Theoretically, intermediate phenotypes, such as imaging phenotypes, lie along a mechanistic pathway through which genetic variation and/or environmental experiences contribute to clinical phenotypes (Figure 1A) (31). We refer here to the traditional pathway from the static genome to neural intermediate phenotypes and behavior, although modern genetics regularly challenges such unidirectionality (Figure 1B). Within the theoretical discussion of intermediate phenotypes, the greatest attention has often focused on the endophenotype conceptualization, which stipulates that endophenotypes are associated with psychiatric disease and are heritable, among other considerations (32).

The requirement of disease association presupposes the research value of psychiatric nosology. This is problematic because many, if not all, psychiatric diagnoses are heterogeneous amalgamations of symptoms, with the same diagnosis having distinct putative etiologies, as is becoming more clear following the Research Domain Criteria project (33,34). Such diagnostic heterogeneity may dilute and even obliterate intermediate phenotype–disease association. For example, although anhedonia is a cardinal symptom of depression, it is not among the most common symptoms (35). As such, anhedonia-related neural circuitry may not be identified or may be minimized in a general patient/control subject study (36,37). Indeed, some reports have associated depression with blunted reward-related activity in the ventral striatum (38,39), whereas others have not (40). Or consider that despite the polygenic nature of psychosis (41), some patients presenting with psychosis have a genetic variation in Huntingtin (42) or velocardiofacial syndrome (43). Thus, it is possible that distinct etiologies associated with unique presentations could be lost