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

Supplemental Information

The Origins of Imaging Genetics

Guided by convergent evidence from *in vitro*, psychiatric, and behavioral candidate gene studies (e.g., **Table 1**), imaging genetics began in 1998 before the draft of the human genome was complete. Characterizing the replication challenge that is inherent to the field, the first two imaging genetics studies (1, 2) reached opposing conclusions on whether the missense ankyrin repeat and kinase domain containing 1 (*ANKK1)* C/T single nucleotide polymorphism (SNP), rs1800497 (also known as Taq1A, previously assigned to *DRD2*[1]), is associated with *in vivo* dopamine receptor type 2 (D2R) availability and density. Pohjalainen and colleagues (1) found that the T allele of rs1800497 is associated with *reduced* dopamine type 2/3 receptor availability in the striatum among 54 healthy volunteers. Contrastingly, Laruelle and colleagues (2) found no difference in binding according to rs1800497 genotype in a sample of healthy controls (n=47) and patients with schizophrenia (n=23); however, a consistent unreported trending association is observed in controls. A meta-analysis of *in vivo* and postmortem studies supports the association between the T allele and reduced D2R availability among healthy individuals (3). The mechanism underlying these functional associations remains controversial; it is plausible that they may emerge as a result of interactions between *ANKK1* and *DRD2* or linkage disequilibrium patterns with nearby SNPs within *DRD2*, or otherwise unknown interactions. Nonetheless,

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[1] Notably, this SNP was initially mistakenly believed to be within the dopamine receptor type gene (*DRD2*) but actually resides downstream of *DRD2* within *ANKK1*, which codes for a protein kinase involved in signal transduction.

evidence suggests that this SNP may be associated with psychiatric phenotypes (4, 5) potentially as a result of these functional associations; (but see also (6)) and lack of GWAS significance (7).

These initial imaging genetic findings were followed in 1998 and 2000 by ligand binding studies by Heinz and colleagues in humans and rhesus monkeys that associated SPECT imaging of [I-123]β-CIT binding to polymorphisms within the serotonin transporter (*SLC6A4)* and dopamine transporter (*SLC6A3)* genes (8-11). Alongside *in vitro* studies, these initial imaging genetics studies have been highly influential, inspiring a wealth of research examining associations between these genotypes and individual differences in structural and functional neural phenotypes as well as psychiatric disorders and variability in behavior (e.g., (12)). Thus, from its ligand-based beginnings, imaging genetics has produced findings that converge with data from multiple other modalities providing potential mechanistic pathways through which genetic variation in some of the most well-studied candidate loci may impact psychiatrically relevant behavior and risk. For further historical review please see (13).

Imaging genetics did not become widespread until it employed functional magnetic resonance imaging (fMRI) to examine associations between functional polymorphisms in the apolipoprotein E (*APOE*), catechol-O-methyltransferase (*COMT*) and serotonin transporter (*SLC6A4*) and neural activation during memory and emotion tasks (14, 15). These studies paved the way for the broader adoption of imaging genetics in the context of functional and structural MRI due to its lower cost, wide availability and lack of ionizing radiation exposure. Further, the larger sample sizes that can be obtained using MRI have led to the development of massive datasets through data sharing and large scale studies (16-21). In addition to encouraging new ways of characterizing brain function and structure such as examining interactions within and between large scale brain networks, these large datasets allow for the application of analytic

techniques such as GWAS (22), gene x gene interaction (23), gene x environment interaction (24), and pathway analysis (25) that may link both genes and behavioral phenotypes to brain function in new and interesting ways. This extension to MRI has enabled the rapid expansion of the field and helped popularize the intermediate phenotype approach in psychiatry by helping contextualize gene – behavior relationships through the mediating effects of brain (**Figure 1A**) (26), which has subsequently been refined in the form of the research domain criteria (RDoC) for psychiatric disease (27).

Gene x Environment Interaction

Given large effects of the environment, and in particular childhood maltreatment and poverty, on the expression of psychopathology, a complete etiologic understanding requires the incorporation of environmental factors (28). The interplay between genotype and environmental factors (including adversity and advantage) may occur due to selective environmental exposure due to genotype (i.e., gene-environment correlation) or due to their interaction (i.e., gene x environment interaction, GxE). Inspired by GxE observations in traditional psychiatric genetics that have been profoundly influential (29) but have also grown increasingly contentious (30), imaging genetics has begun to interrogate GxE using single variant and polygenic approaches. For example, studies have linked a functional variant in FKBP5 that has been associated with stress-related psychopathology and disease, to threat-related amygdala responsiveness in the context of prior childhood maltreatment (31, 32). That this association occurs in the context of adversity occurring early in life is consistent with observations in clinical and molecular epigenetic research (33). In another recent example, within 3 independent samples, polygenic risk for schizophrenia was negatively associated with cortical thickness only among male

participants who used cannabis (34). While these findings are intuitively appealing and provide

ample mechanistic speculation for psychopathology risk, it is important to highlight that GxE

research within an imaging genetics framework is confronted by a host of unique challenges

including assessment of the environment in resource intensive studies, the need to appropriately

model covariates, as well as power limitations introduced by interactive terms; a more complete

discussion of these unique challenges is presented in (24).

Supplemental References

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