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Commentary on “Synergistic Effects of COMT and TPH2 on Social Cognition”:

Epistasis and Complex Neuropsychiatric Phenotypes

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In psychiatry, the phenomena that break on the shores of clinical attention involve disturbances of high-order, intrapsychic, and interpersonal functions. They may manifest dramatically, but arrive via largely unseen currents, biased by the depth contours of each patient’s evolving and interacting biological systems. In this regard, psychiatric genetics’ aim is in large part bathymetric: to understand the submerged molecular topography guiding the development and course of clinical syndromes so that ultimately new treatment targets can be identified. However, inherent in the mapping of genes to psychiatric conditions are two formidable barriers.

First, the symptomatology defining clinical treatment goals reflects the dynamics of superordinate computational systems (e.g., cognitive and emotional) and their interface with social and internal mental life. Such surface, shoreline phenomena are far removed from the genetic floor, which operates at the level of protein production and function. This behavior-gene divide, or “vertical” problem, has driven the influential endophenotype approach, which advocates genetic association studies of illness-linked, heritable, and lasting quantitative traits that are biologically closer to the contributing risk genes than the observed clinical disorder (Gottesman & Gould, 2003).

Second, though variable estimates may exist as to the number and type of causal genetic variants (i.e., the mixture of large-effect/rare variants relative to small-effect/ common variants) in an individual with a heritable psychiatric condition such as, for instance, schizophrenia, it is clear that overall, because the clinical expression of illness is characteristically complex and multivariate, the genetic terrain underlying many psychiatric disorders is likely to be equally so. At the molecular level, this “horizontal” problem includes non-additive interactions among networks of genetic variants (Bateson & Mendel, 1902; Fisher, 1918), which may theoretically obscure meaningful signals in both single candidate gene and standard genome-wide association studies (Moore, 2003). Consequently, as more functional gene variants are discovered and their context biology unraveled, increasing attention to principled investigations of epistatic interactions promises to

elucidate the relevant gene *pathways* important for the phenotype of interest. This is a crucial divergence from single variant approaches not only because it carries the possibility of increasing the predictive value of genetic models, but also because it may clarify which aspects of a gene's function might be most relevant to the phenotypic readout.

In this issue, Lin and colleagues report on associations between a measure of social cognition and variants in *COMT* and *TPH2*. When viewed through the lenses of the “vertical” and “horizontal” problems of psychiatric genetics, their approach raises a number of interesting issues for the evolving field of psychiatric genetics.

With respect to the vertical problem of choosing an effective outcome measure, Lin and colleagues selected the recently developed managing emotions subtest of the Mayer-Salovey-Caruso Emotional Intelligence Test (MSCEIT)—a late addition to the National Institute of Mental Health (NIMH) Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) neuropsychological battery as the sole social cognition assay. This test requires quantification of the efficacy of various hypothetical behavioral interventions on maintaining or restoring one's good mood, and it has yet to be evaluated for full schizophrenia endophenotype criteria (e.g., whether it is heritable, co-segregates with illness within families, or is also disproportionately observed in relatives of affected individuals). Thus, much work remains to determine the likelihood that genes affecting the MSCEIT trait are directly relevant to schizophrenic genetic risk architecture. Looking forward, it is important to ask of the ever-growing list of complex phenotypes being examined through the lens of genetics: If an assay ultimately fails to meet endophenotype criteria, could knowledge of its genetic determinants (assuming it is indeed a genetically driven trait) still be valuable in understanding and treating the illness of interest? In specific cases, the answer may be yes. For instance, the phenotype, though driven by genetic variables orthogonal to those underlying the illness itself, may interact with illness-related phenomena and be linked to an important functional outcome domain. In such a case, understanding the genetic underlay of this phenotype, potentially downstream and incidental to the causative genetic aberration, may still help lead to augmentative, symptom- (rather than illness-) targeted therapeutics.

With regard to the horizontal problem of choosing genetic predictors, Lin and colleagues adopt a neurochemical strategy, hypothesizing serotonergic and dopaminergic mechanisms underlying socio-emotional and cognitive aspects of social cognition, respectively, then selecting known functional variants in each of these systems as the study's independent variables. Taking a step further, the authors query their data for novel gene-gene interaction effects, which, as mentioned above, are expected to play an important role in shaping the fabric of complex neuropsychiatric phenotypes. Assuming that the *TPH2* genotype deviation from Hardy-Weinberg Equilibrium is due to sampling rather than genotyping and that the discovered interaction between *COMT* and *TPH2* are replicable effects, the authors and readers alike are left with a particularly provocative challenge for future work: where is the interaction occurring biologically? *TPH2* regulating serotonin synthesis—and *COMT* regulating catechol methylation—operate relatively distantly from each other, broadly impacting different sets of signaling cascades and different neurotransmitter systems. Further, both noradrenergic-serotonergic and dopaminergic-serotonergic intersections

abound in the brain—for example, consider the robust serotonergic innervation of the basal ganglia (Boureau & Dayan, 2011)—and aside from a recent suggestion that serotonin might be able to inhibit the binding of COMT substrates to COMT in vitro (Tsou et al., 2012), bridging COMT and TPH2 function likely requires several intermediaries and cell types and may, in fact, be mediated at the level of circuits and brain regions. Are there diminishing scientific returns with hypothesizing epistatic interactions between more divergent genes, or rather, does this simply open gates to much needed translational work in the field of psychiatric genetics? Either way, there does not seem to be a reasoned way forward without continued search for meaningful epistasis in neuropsychiatry. With increasing sample sizes, broader molecular hypotheses out of the recent explosion of gene expression network data, and novel multivariate approaches, the field will be able to provide increasing coverage of the genetic interactome as it pertains to psychiatric illness.

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References

- Bateson, W.; Mendel, G. Mendel's principles of heredity: A defence. Cambridge, England: Cambridge University Press; 1902.
- Boureau YL, Dayan P. Opponency revisited: Competition and cooperation between dopamine and serotonin. *Neuropsychopharmacology*. 2011; 36(1):74–97. [PubMed: 20881948]
- Fisher RA. The correlation between relatives on the supposition of Mendelian inheritance. *Transactions of the Royal Society of Edinburgh*. 1918; 52:399–433.
- Gottesman I, Gould TD. The endophenotype concept in psychiatry: Etymology and strategic intentions. *American Journal of Psychiatry*. 2003; 160(4):636–645. [PubMed: 12668349]
- Moore JH. The ubiquitous nature of epistasis in determining susceptibility to common human diseases. *Human Heredity*. 2003; 56(1-3):73–82. [PubMed: 14614241]
- Tsao D, Wieskopf JS, Rashid N, Sorge RE, Redler RL, Segall SK, et al. Serotonin-induced hypersensitivity via inhibition of catechol O-methyltransferase activity. *Molecular Pain*. 2012; 8:25.10.1186/1744-8069-8-25 [PubMed: 22500608]