The glue of (ab)normal mental life: Networks of interacting thoughts, feelings and behaviors
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Appendix C

Where are the genes?

Abstract

This commentary was written in response to a target article by Johnson, Penke and Spinath (2011, published in the same issue of the European Journal of Personality) in which the missing heritability problem was discussed from many different angles. In this commentary, we present another reason for the apparent discrepancy between heritability estimates and gene-hunting results in psychopathological research (i.e., the missing heritability problem): if syndromes are networks of causally related symptoms in which both symptoms and relations between them are driven by different sets of genetic polymorphisms, then gene hunting based on a phenotypic sumscore might be ill-advised because it will only capture genetic variance that is shared among those symptoms and their relations.

Depressed parents predispose their children to become depressed as well. This phenomenon is not so much attributable to a depressogenic environment (inadvertently created by the parents) as it is due to the fact that major depression is a moderately heritable syndrome, with heritability estimates ranging between 37% and 60% (Boomsma et al., 2002; Kendler, Gatz, Gardner, & Pedersen, 2006; P. F. Sullivan, Neale, & Kendler, 2000). Combined with the high heritability of other mental disorders (Boomsma et al., 2002), it is surprising that despite many efforts, the genetic culprits have not been identified (see e.g., Sklar, 2002). For psychological traits in general, identified genetic polymorphisms typically account for less than 2% of the genetic variance (Levinson, 2006; Mitchell & Porteus, 2009).

The apparent discrepancy between high heritability and the inability to identify the responsible genetic polymorphisms has been termed the missing heritability problem and is pervasive in the realm of psychopathology (Manolio et al., 2009). In the same issue, Johnson et al. propose various plausible mechanisms that contribute to the missing heritability problem, ranging from methodological factors that might result in inflated heritability estimates to problems with the specific research strategies employed in gene hunting. Pertaining to the latter, in this commentary, we elaborate on a potential problem on which Johnson et al. did not reflect: what if the way we define a syndrome in current gene-hunting efforts is incorrect?

In psychopathological research, the most commonly used proxy for a phenotype is

the typical operationalization of a syndrome, that is, a sumscore (i.e., the total number of symptoms of a disorder present) that can be further dichotomized, using, for example, criteria as specified by the Diagnostic and Statistical Manual of Mental Disorders Fourth Edition (DSM-IV), to reflect the presence/absence of a particular disorder. In its most rudimentary form, genetic association studies identify genes or genetic variants as predisposing to a mental disorder if they predict the dependent variable in the design, that is, the (dichotomized) sumscore (van der Sluis, Kan, & Dolan, 2010). So far, this strategy has not been very successful at identifying the important genetic polymorphisms in the onset of mental disorders. In our view, this may be partly due to the fact that one of its most important assumptions—that a sumscore forms a valid representation of a syndrome—is fundamentally flawed.

Current approaches to gene hunting rely on the assumption that the relation between a phenotype, for example, major depression—and its observable attributes—for example, the A criterion in DSM-IV is one of measurement: a psychological phenomenon causes its observable attributes (e.g., extraversion causes party-going behavior: McCrae & Costa, 2008, p. 288). One of the far-reaching consequences of such a common cause view is that correlations among the observed attributes themselves are deemed spurious; they only exist because they share a common cause: mental rotation skills and verbal intelligence are only correlated because they share a common cause, namely general intelligence. In terms of searching for genes that are implicated in the onset of a syndrome, this view translates into the following chain of events: genes, via a host of hypothesized endophenotypes, result in a syndrome and that syndrome, because of a measurement relationship, causes a set of observable symptoms. But as we have argued elsewhere (Cramer et al., 2010), relations between symptoms might not only be non-spurious in nature but might also the very essence of what constitutes a syndrome (similar arguments have been made for general intelligence: van der Maas et al., 2006). For example, consider the correlation between two symptoms of major depression: insomnia and fatigue. Under the assumption of a common cause, the correlation between these two symptoms is spurious; it only arises because insomnia and fatigue share a common cause, major depression. It is, however, more likely to assume that this correlation exists because there is a real, straightforward causal relation between these two symptoms: if you do not sleep, you will become tired. Similar arguments can be made for a host of other psychological phenomena—for example, consider feeling comfortable around people and party-going behavior: do we need an overarching ‘extraversion’ trait to explain why these observed behaviors tend to covary?—and as such, it is premature to dismiss direct relations between observed attributes as being mere spurious by-products of an overarching construct. What does this mean for gene hunting efforts?

If constructs are indeed networks of causally related observables, individual differences are most likely to arise as differences in the strength of those relations: when Alice suffers from depressed mood, she fairly easily develops suicidal thoughts (i.e., strong relation between the observable symptoms ‘depressed mood’ and ‘suicidal ideation’), whereas Bob does not ever contemplate suicide while feeling depressed (i.e., relatively weak relation). Furthermore, it is likely that the strength of such relations stands at least partly under genetic control. Now, it is not likely that each relation is influenced by the same set of genes for the sheer number of relations \((k^2 - k)\) in a network containing \(k\) observables/symptoms) in any given network greatly diminishes this possibility and the relations probably differ in terms of the endophenotypes (and thus genes) involved (e.g., the more physiological homeostatic processes that are likely to govern relations between sleep and fatigue versus the more cognitive processes that are probably invoked in the relation between depressed mood and suicidal thoughts).

Hence, when trying to relate genetic polymorphisms to a sumscore, one only cap-
tures the genetic variance that is shared among those individual symptoms (including their relations); the different genetic polymorphisms that are responsible for individual differences in the strength of the relations between those symptoms are completely left unaccounted for. As such, the network approach may explain at least partly why current approaches cannot find the genetic culprits of mental disorders. By properly modeling their etiology, we increase our power to detect risk variants. It is, after all, the relations between symptoms that glue them together into a syndrome.