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COMMENTARY

Genetics, neuroscience, and psychopathology: Clothing the emperor

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Abstract

This ground-breaking series of articles reports findings from genome-wide analyses of endophenotypic indicators of psychopathology including electrocortical activity/reactivity, electrodermal and startle blink responses, and neurocognitive task performance. Findings challenge the long-held notion that endophenotypes more clearly reflect the impact of specific genes than referent clinical phenotypes. Implications for the concept of endophenotypes and biological psychopathology research more broadly are discussed.

Descriptors: Endophenotypes, Psychophysiology, Neuroscience, Genetics, Genome, Twins

"Those among us who are unwilling to expose their ideas to the hazard of refutation do not take part in the scientific game."

—Popper (1959)

"School yourself to severe gradualness in the accumulation of knowledge . . . [R]emember that science demands from a man all his life. If you had two lives that would be not enough for you."

—Pavlov (1936)

The current series of papers represents, without question, a landmark statement on genetics, neuroscience, and psychopathology. The publication of these papers in collective form makes the central take-home message all the more powerful. I comment briefly on the articles' substantive content and then discuss the implications of this work for the endophenotype concept and for biological research on mental disorders.

What is the core message of this set of articles? In short, that neurophysiological endophenotypes for mental disorders (i.e., brain or brain-related indicators presumed to index underlying genetic liability; Gottesman & Gould, 2003) do not exhibit a clearer genetic architecture or more strongly reflect the impact of specific genes than disorder phenotypes themselves—despite showing appreciable biometric (twin estimated) and genetic (genome-wide complex trait analysis estimated) heritabilities in most cases. In-depth genomic analyses of an array of well-established biobehavioral endophenotypes employing a range of quantitative approaches and varying thresholds for significance revealed only a small handful of robust effects, whether the authors examined common or rare variants. Most dependent variables showed either zero or only one single nucleotide polymorphism (SNP) or gene effect across all analyses; the only exceptions were antisaccade task errors (one significant imputed SNP and three significant genes), delta-power electroencephalogram (EEG; two significant genes), aversive startle potentiation (two significant genes), and pleasant startle inhibition (two significant genes). The compelling take-home message is that heritable brain or brain-based indicators of liability for mental disorders are, like the disorders themselves, highly polygenic—with single genes contributing only weakly to observed-score variance (cf. Bush & Moore, 2012).

These results deserve to be taken seriously for several reasons. They are based on data from a highly reputable multiwave study conducted by leading investigative experts. The sample size, although modest for a genome-wide association study, is unprecedented for a genomic analysis of endophenotypes derived from a single sample—and while questions can be raised about the power to detect effects per se, there can be little doubt about the small magnitude of any existing effects. The procedures for collection of data and quantification of dependent variables were exceptionally rigorous, and the data were analyzed in a range of ways using state-of-the-art techniques. And of further note, the lead investigator on this work, William Iacono, has devoted much of his career to the study of biological indicators of psychopathology, with particular emphasis on neurophysiological endophenotypes. The reported findings can therefore be viewed as the dispassionate statement of a scholar who has invested greatly in this topic and cares deeply about it.

Taken seriously, these results have important implications for the concept of endophenotypes and for biologically oriented research on psychopathology more broadly. Regarding endophenotypes, findings from this special series cast doubt on the notion of heritable liability indicators as a "royal road" to understanding the genetics of mental disorders. They indicate that the genetic basis of heritable neurophysiological and neurobehavioral indicators of clinical phenotypes such as major depression, alcoholism, and schizophrenia is no less complex than that of the clinical phenotypes themselves. The strong implication is that approaches other than genomic analysis of endophenotypes are needed to advance understanding of the genetics of psychopathology. It

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seems worthwhile, for example, to focus near-term effort on establishing effective models for the genetics of simpler physical phenotypes such as height (Chatterjee et al., 2013) that can serve as referents for genetic models of clinical or neurophysiological phenotypes. Research on physiological variables more proximal to the action of specific genes (e.g., pharmacologic phenotypes; Stark et al., 2010), and closely affiliated behaviors, is also likely to be worthwhile. As an example, multilevel investigation of receptor genes distinctly associated with nicotine dependence (Greenbaum & Lerer, 2009) could potentially serve as the basis for a pharmacogenetic model of smoking addictions.

With regard to research on biological psychopathology more broadly, findings from the current series of articles raise important questions about current reporting and publishing practices in the field. In particular, one is faced with the question of how to think about the largely null results that emerged even from markedly less conservative, familywise-corrected tests for SNPs or genes previously identified as candidates for targeted endophenotypes, or for mental disorder phenotypes more broadly. The troubling implication is that published findings from many, perhaps most, smaller-*N*, molecular genetic studies are untrustworthy. If this is true, it makes sense to put some effort into finding out why. The reason is that whatever forces operated to create and sustain a distorted image of reality in this instance—including factors such as data mining, positive publication bias, editorial triaging, and insistence on "innovation over incrementation"—may well be at play in other sectors of the discipline (Ioannidis, 2008, 2011).

To address these issues, it may be necessary to establish new paradigms for biological psychopathology research and revised policies for publication. The current featured work, including plans the authors have for publicly archiving the data from this investigative series, offers a glimpse of what a new paradigm could look like. Extending from the neurophysiological and genomic data reported in this series of studies to incorporate clinical-diagnostic, trait-dispositional, and behavioral measures available for this large participant sample (Iacono, Carlson, Taylor, Elkins, & McGue, 1999), and drawing on the multiwave longitudinal aspect of the research design, one can envision the beginnings of a multidomain, longitudinal variable network for delineating predictive relations among measures from differing assessment domains in participants across successive periods of the lifespan. Once established, a data network of this kind could be progressively expanded by bridging to other large-*N* datasets through common linking variables (Kern, Hampson, Goldberg, & Friedman, 2014; Patrick, 2014)—including genomic, psychological, behavioral, and/or physiological data—and use of statistical imputation.

In sum, the current work is illuminating and provocative. It illustrates how true advances in the field can be made—that is, by subjecting key theoretical questions to stringent empirical tests, with a readiness to accept that cherished long-held ideas might be proven false. It also points the way forward to new avenues for psychopathology research. Against the constant thrum of fast-break publications on topics deemed to be of maximum probable "impact," funded on grounds of maximal perceived "innovation" and "significance," this meticulous set of down-to-earth papers serves as a vivid reminder of the centrality of skepticism, rigor, and integrity to scientific progress.

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