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Genome-wide scans of genetic variants for psychophysiological endophenotypes: Introduction to this special issue of *Psychophysiology*

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Abstract

This special issue addresses the heritability and molecular genetic basis of 17 putative endophenotypes involving resting EEG power, P300 event-related potential amplitude, electrodermal orienting and habituation, antisaccade eye tracking, and affective modulation of the startle eye blink. These measures were collected from approximately 4,900 twins and parents who provided DNA samples through their participation in the Minnesota Twin Family Study. Included are papers that detail the methodology followed, genome-wide association analyses of single nucleotide polymorphisms and genes, analysis of rare variants in the human exome, and a whole genome sequencing study. Also included are 11 articles by leading experts in psychophysiology and genetics that provide perspective and commentary. A final integrative report summarizes findings and addresses issues raised. This introduction provides an overview of the aims and rationale behind these studies.

Descriptors

Endophenotypes; Molecular genetics; Minnesota Twin Family Study

In this special issue, we present a unique set of findings with important theoretical implications for the value of the endophenotype concept. An endophenotype is a quantitative attribute measured through a laboratory test that taps into the genetic liability for the development of a psychiatric disorder. Here, we provide a series of articles that detail the best-powered set of investigations ever undertaken to investigate the genetic architecture of a broad range of wellmeasured psychophysiological endophenotypes, applying state-of-the-art molecular genetic methods for this purpose.

Why endophenotypes? Because the search for genetic variants related to overt symptoms or diagnoses of psychiatric disorders has proven difficult. Despite technological advances that have revolutionized the degree to which we can probe and map the human genome, and the publication of thousands of papers dedicated to this goal, there have been few replicated findings, and those that exist account for at best a very small amount of variance. As useful as the psychiatric disorder categories in the Diagnostic and Statistical Manual or

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International Classification of Diseases systems may be clinically, there is no reason to suppose that they are well suited to understanding the biological systems pertinent to the etiology of a disorder or the genetic mechanisms responsible for the functioning of these systems.

This concern has led to a quest to identify candidate endophenotypes linked to disorder neurobiology that, because they are more proximal to the effects of genes, have a theoretically greater likelihood of being strongly associated with etiologically relevant genetic variants (e.g., see Hodgkinson et al., [2010], for an example of such a strong effect). Although the concept of the endophenotype was introduced to psychiatry over 40 years ago by Gottesman and Shields (1972), it was only after Gottesman and Gould reintroduced and refined it in 2003 that endophenotypes began to garner much interest. A PubMed search using the term “endophenotype” produced 2,400 publications, with over 2,000 published since 2006. Despite this intense interest, there have been few published genome-wide association studies (GWASs) of putative psychophysiological endophenotypes using SNP (single nucleotide polymorphism) arrays that provide broad coverage of common genetic polymorphisms. Because GWAS is a powerful method for detecting specific genetic influences on polygenic traits, the promise of endophenotypes as tools for facilitating the identification of psychiatrically-relevant molecular genetic variants has not been put to an adequate test.

This special issue of *Psychophysiology* represents an attempt to fill this gap. Beginning in the early 1990s, the Minnesota Center for Twin and Family Research (MCTFR) has recruited families comprising parents and pairs of their child or adolescent offspring and followed the offspring longitudinally through young adulthood. Parents and their children have been assessed in the psychophysiology laboratory using protocols that were selected for their potential as endophenotypes for substance abuse or for disorders that are often comorbid with addiction, such as antisocial personality, schizophrenia, and mood disorders (Iacono, 1985, 1998; Iacono, Lykken, & McGue, 1996). Using data from these participants, we have conducted 17 separate molecular genetic investigations involving measures derived from P300 amplitude, electrodermal activity, startle eye blink, antisaccade error, and electroencephalographic spectral characteristics.

The investigations described here are based on MCTFR families with twin children who both visited our psychophysiology laboratory and provided a DNA sample (N = 4,905 individuals). Participants in the MCTFR constitute a general population sample. Because their selection was not conditional on the types of inclusion and exclusion criteria common to psychiatric case-control studies, molecular genetic investigations can be carried out on all of the endophenotypes without regard to how the results might be affected by the types of disorder screened in or out for study. In addition, the findings can be expected to be broadly applicable to the general population. By carrying out the same set of a priori analyses on all the endophenotypes with all available MCTFR participants, we hoped to reduce effects attributable to reliance on small sample size, selective reporting of results, piecemeal publication, and a need to obtain positive outcomes to justify publication—, factors that are believed to be responsible for many of the failures to replicate molecular genetic as well as

other types of scientific findings (Button et al., 2013; Duncan & Keller, 2011; Duncan, Pollastri, & Smoller, 2014; Ioannidis, 2008, 2011).

The first paper in this special issue provides an overview of the MCTFR as well as a detailed exposition of the genetic methodology employed in each paper. In brief, each paper uses the family data to conduct a biometric analysis of endophenotype heritability—an analysis that is seldom part of molecular genetic studies because they typically are not based on individuals who are related to each other. Using the molecular genetic data, we also calculated SNP heritability, providing an index of the degree to which measured genetic variants on our genotyping array captured the heritability estimated from the biometric model. These analyses were followed by GWAS on each endophenotype, providing an opportunity to determine the degree to which each of over 500,000 SNPs and 17,000 genes was associated with each psychophysiological measure.

These six papers are followed by two additional reports that further explore the genetic basis of the endophenotypes. The first extends the GWAS (which focuses on common genetic variants) by examining the association of each endophenotype with rare variants found in the coding portions of the human genome (exons). The second further extends this work using whole-genome sequencing, a procedure with substantial power to detect private mutations of possibly large effect that might be anywhere in the genome but are present in only a single family or individual. These two papers thus complement the GWAS series by examining the possible etiologic contribution of polymorphisms that are considerably less common.

In sum, our goal was to provide a comprehensive, state-of-the-art, multi-faceted investigation into the utility of the concept of endophenotypes using a unique dataset of twins and parents. By publishing these findings, we provide other scientists opportunities to pursue potential leads in their research, whether such findings are used for studying the genetic basis of psychophysiological measures generally or of endophenotypes and the traits for which they identify genetic risk (e.g., alcoholism, depression, schizophrenia). We expect this special issue to also encourage meta-analysis and the formation of consortia whereby other investigators can join with us (or we with them) to build on our findings. We are adding the data from this special issue to National Institutes of Health (NIH) databases like dbGaP and the sequencing short read archive (SRA), which will make it possible for other investigators to access directly the phenotype and genetic data on which these reports are based. Lastly, participant DNA samples are available to qualified investigators through the NIH-sponsored Rutgers University Cell and DNA Repository.

We wish to thank *Psychophysiology* editor Bob Simons for his support and having the vision to encourage the development of this special issue. We were fortunate to be joined by a distinguished group of scientists who agreed to provide Perspective and Commentary pieces on this set of papers. They along with other referees deserve our thanks for providing critical peer review of these articles and sharing many insights and suggestions that have enhanced the quality of this special issue. Indeed, the enthusiasm with which these scientists tackled their assigned tasks supports our conclusion that, while much remains to be discovered, these potentially foundational papers are well positioned to facilitate future efforts to

uncover the genetic basis of psychophysiological measures and associated psychiatric conditions.

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