Attention-Deficit/Hyperactivity Disorder Endophenotypes

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Attention-deficit/hyperactivity disorder (ADHD) is a highly heritable disorder with a multifactorial pattern of inheritance. For complex conditions such as this, biologically based phenotypes that lie in the pathway from genes to behavior may provide a more powerful target for molecular genetic studies than the disorder as a whole. Although their use in ADHD is relatively new, such "endophenotypes" have aided the clarification of the etiology and pathophysiology of several other conditions in medicine and psychiatry. In this article, we review existing data on potential endophenotypes for ADHD, emphasizing neuropsychological deficits because assessment tools are cost effective and relatively easy to implement. Neuropsychological impairments, as well as measures from neuroimaging and electrophysiological paradigms, show correlations with ADHD and evidence of heritability, but the familial or genetic overlap between these constructs and ADHD remains unclear. We conclude that these endophenotypes will not be a quick fix for the field but offer potential if careful consideration is given to issues of heterogeneity, measurement and statistical power.

Key Words: ADHD, endophenotype, genetic, neuropsychology, executive functions

Behavioral genetic studies leave no doubt that genes play a significant role in the development of attention-deficit/hyperactivity disorder (ADHD). Heritability estimates from twin studies are consistently high, ranging from .6 to .9 (e.g., Hudziak et al 1998; Rhee et al 1999; Sherman et al 1997). Yet, molecular genetic studies of ADHD have yielded conflicting results. Candidate gene studies show an inconsistent pattern of replication (Faraone et al 2005), and the three research groups that have conducted genome scans of ADHD thus far have identified largely nonoverlapping chromosomal regions as potentially harboring susceptibility genes (Arcos-Burgos et al 2004; Bakker et al 2003; Fisher et al 2002; Ogdie et al 2002). Such inconsistencies, although often found in complex phenotypes in which multiple genetic and nongenetic factors are acting in concert, present challenges to understanding the genetic architecture of ADHD.

Two reasons behind inconsistencies in molecular genetic studies of complex conditions are low statistical power to detect genes of small effect and heterogeneity (Faraone et al 1999) and research suggests that these characteristics are true of ADHD. In a recent meta-analysis, candidate genes from the catecholamine and serotonin systems that were significantly associated with ADHD showed pooled odds ratios ranging from 1.2 to 1.5 (Faraone et al 2005). Suarez et al (1994) have also shown how low power to find genes of small magnitude could lead to an inconsistent pattern of replication across genome scans. Both twin and family studies raise the further possibility of genetic heterogeneity in ADHD (Faraone, unpublished data; Rasmussen et al 2002; Todd et al 2001). Although subgroups have not been definitively parsed, promising delineations might occur via comorbidity (e.g., with conduct and bipolar disorders [Doyle and Faraone 2002; Faraone et al 1998]), persistence of ADHD into adolescence (Faraone et al 2000), empirically derived latent classes (Todd 2000), and, in population but not clinical samples, DSM-IV subtypes (Faraone 2002). Molecular genetic studies have begun to explore sources of heterogeneity (McCracken et al 2000; Rowe et al 1998; Waldman et al 1998), but results have not been definitive because large samples are needed for subgroup analyses.

To address these challenges, there is growing interest in using endophenotypes in molecular genetic studies. The term "endophenotype" has been used in various ways. Most definitions refer to a phenotype more proximal to the biological etiology of a clinical disorder than its signs and symptoms and influenced by one or more of the same susceptibility genes as the condition (e.g., Almasy and Blangero 2001; Gottesman and Gould 2003; Skuse 2001). The power of these biologically based phenotypes is based on several assumptions, most important of which is that the endophenotype is less genetically complex than the disorder it underlies. This reduced complexity is due both to the endophenotype's relative proximity to gene products in the chain of events leading from gene to behavior and to its potential to target one of likely several pathophysiological deficits that combine to create the overall condition. Because the endophenotype is influenced by fewer genetic (and environmental) risk factors than the disorder as a whole, its use would result, theoretically, in greater statistical power to detect the effects of the individual genes. Additionally, endophenotypes can also be used to help elaborate on or revise the suspected pathophysiological basis of the condition (Freedman et al 1999; Gottesman and Gould 2003), including heterogenous processes, via subsequent expression studies.

Although there is no definitive pathophysiological model of ADHD, evidence for frontostriatal impairment in ADHD comes from the success of stimulant medications as well as animal models of hyperactivity that implicate dopamine pathways consistent with these regions (e.g., Gainetdinov et al 1999; Rubinstein et al 1997). Additionally, behavioral similarities exist between adult patients with frontal lesions and children with ADHD (Mattes 1980). Dysfunction in frontostriatal pathways has also been demonstrated by neuroimaging studies (e.g., Seidman et al 2005), electrophysiological studies (Chabot and Serfontein

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1996), and studies of neuropsychological tests that are presumed to tap frontal systems (Willcutt et al 2005).

This article reviews evidence for the utility of measures from these domains as endophenotypes for ADHD. We emphasize neuropsychological measures because of their low cost and ease of implementation relative to neuroimaging and psychophysiology paradigms but also briefly review studies that used these latter methods. We start by describing criteria for an endophenotype, then assess the extent to which candidate endophenotypes for ADHD meet these criteria, and finally offer recommendations for future studies.

Endophenotypes: Criteria

Proposed criteria for useful endophenotypes in psychiatry (e.g., Almasy and Blangero 2001; Gottesman and Gould 2003; Leboyer et al 1998; Skuse 2001) vary somewhat but share several key elements. Specifically, researchers suggest that useful endophenotypes should 1) co-occur with the condition of interest; however, because an endophenotype may be useful for understanding heterogenous conditions, it need not be universal within the disorder; 2) be measured by tools with good psychometric properties, including reliability; 3) show evidence of heritability; and 4) show familial–genetic overlap with the disorder in question. The issue of familial overlap is important because, without such evidence, we could find genes for a biologically based phenotype, but they may not be genes for the disorder of interest. Because an endophenotype is conceptualized as an expression of the genetic liability for a disorder, it should appear in individuals who carry genes for a condition but do not express the disorder itself, that is, the unaffected relatives of diagnosed individuals. Deficits found in affected but not unaffected relatives raises the possibility that impairments are a result of the disorder itself or of unique environmental factors. The presence of an endophenotype in unaffected relatives may further augment the statistical power of molecular genetic studies because of their increased prevalence in families compared with the disease entity.

In this article, we focus on association with ADHD, heritability, and familial overlap of candidate deficits from neuropsychology to assess their suitability as ADHD endophenotypes. We then briefly summarize these criteria as they relate to neuroimaging and psychophysiological measures. We address measurement issues in our discussion of strategies to move the field forward. For more in-depth discussion of measurement issues related to neuropsychological endophenotypes for ADHD, including sensitivity, construct and discriminant validity, and developmental factors, we refer the reader to Doyle et al (in press-b).

Neuropsychological Endophenotypes for ADHD

Association with ADHD—Executive Functions

A large literature indicates that individuals with ADHD exhibit relatively poor performance on neuropsychological tests of "executive" functions, presumed to assess the integrity of frontal systems, particularly the prefrontal cortex (Pennington and Ozonoff 1996; Seidman 2004; Sergeant et al 2002). Executive functions (EFs) have been variably defined but are largely agreed to include working memory, response inhibition, set shifting, abstraction, planning, organization, fluency, and aspects of attention (Lyon and Krasnegor 1996).

To date, inhibitory control, particularly the ability to withhold a pre-potent response, has been the most widely discussed core deficit in ADHD (Barkley 1997), and numerous studies support relatively poor performance on neuropsychological measures of inhibition in ADHD (Nigg 2001; Schachar et al 1995). Pennington and colleagues (1996) have argued that intact working memory (i.e., the ability to hold and manipulate information held in temporary storage) is essential to successful inhibitory control, and Castellanos and Tannock (2002) suggest that visual spatial working memory is of particular interest as an endophenotype from a neuroscience perspective based on data from human and animal studies. Although other components of EF have received less theoretical attention, in a recent meta-analysis (Willcutt et al 2005) comparable effect sizes (Cohen's d .43–.69) were found in ADHD versus non-ADHD samples on measures of inhibition, working memory, planning, organization, and set shifting as well as measures of processing speed, inattention, and impulsivity. Thus, EF deficits broadly conceived are associated with ADHD. Such deficits are also robust to statistical correction for comorbid psychiatric or learning disorders (Willcutt et al 2005).

Despite consistently finding differences between ADHD and control groups, researchers have recently begun to attend to the heterogeneity of these impairments within ADHD. For example, Nigg et al (2005) found that only 35%–50% of combined-type ADHD subjects at different research sites showed deficits on commonly studied measures of inhibition, interference control, and processing speed/set shifting. Studies have also suggested that various EF measures show poor negative predictive power for ADHD because a substantial portion of ADHD cases fail to show impaired performance (e.g., Doyle et al 2000; Hinshaw et al 2002). Combining across measures does not considerably alter the number of individuals who show impairments (Doyle et al 2000; Nigg et al 2005). Thus, despite their strong association with the disorder, EF deficits are not found universally in ADHD.

Association with ADHD—Other Neuropsychological Constructs

Other neuropsychological mechanisms such as impairments in state regulation and delay aversion are interesting candidate endophenotypes to consider in conjunction with EF deficits because their association with ADHD is supported empirically and because they may relate to the neuropsychological heterogeneity within ADHD samples. Because of space constraints, we refer the readers to recent reviews of theoretical models that encompass these constructs (Sergeant 2005; Sonuga-Barke 2005) for more detailed explications. Briefly, one of the main contributions of Sergeant and colleagues' cognitive energetic model of ADHD (Sergeant 2000) is their hypothesis that impairments on tasks requiring effortful control of attention and executive processes could be due, at least in part, to deficiencies in activation, arousal, and effort that control the allocation of cognitive resources rather than impaired cognitive resources per se. One potential index of such state regulation difficulties is variability of reaction time (RT), a measure of the consistency of a response after presentation of a stimulus. As reviewed by Castellanos and Tannock (2002), RT variability is one of the most replicated deficits in ADHD. Yet like EF deficits, RT variability does not appear to be universal within ADHD samples (Nigg et al 2005).

Delay aversion is a construct grounded in an animal model of altered reinforcement and extinction processes. Such processes are hypothesized to relate to dysfunction in the meso-limbic-cortical branch of the dopamine system (Johansen et al 2002; Sagvolden et al 1998). Based on their animal model, Sagvolden and colleagues posited that goal-directed behavior in ADHD youth requires frequent, potent reinforcers proximal to the