Causal Heterogeneity in Attention-Deficit/Hyperactivity Disorder: Do We Need Neuropsychologically Impaired Subtypes?

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Before assigning full etiologic validity to a psycopathologic disorder, disease theory suggests that a causal dysfunction in a mechanism within the affect individuals must be identified. Existing theories on attention-deficit/hyperactivity disorder (ADHD) suggest such dysfunctions in cognitive, neuropsychological, or motivational processes in the child. To date, researchers have tested these theories by comparing groups with DSM-defined ADHD to children without ADHD. Using executive functioning as an illustration of an issue that exists across all such theories, this article describes substantial overlaps in the group performance data. Thus only a subgroup may have executive deficits. Noted are other supportive data suggesting multiple pathways to ADHD. The article explores implications and recommends that future theory and research give more consideration to the probability that only a subset of behaviorally defined children will have a deficit in a given neurocognitive mechanism believed to contribute to the disorder. Creation of a provisional set of criteria in DSM-V for defining an "executive deficit type" could stimulate research to validate the first etiologic subtype of ADHD and spur the development of more sophisticated causal models, which in the longer term may give clinicians ways to target and tailor treatments.

Key Words: ADHD, neuropsychology, executive functions, heterogeneity, DSM-V

Attention-deficit/hyperactivity disorder (ADHD) is defined by behaviors that are judged "often present" based on parent and teacher report, interview, or direct observation (American Psychiatric Association 1994). Identifying within-child causal mechanisms for this behavioral syndrome is a core objective in the field because disease theory suggests that for a disorder to be considered fully valid as a disease construct, it must 1) be psychometrically valid and lead to impairment (well-established for ADHD; Lahey and Willcutt 2002) and 2) evidence a scientifically identifiable (factual) dysfunction of a psychologic or biological mechanism within the individual (Wakefield 1992). Despite real limitations to Wakefield's (1992) harmful dysfunction concept, it has heuristic value as a basis for evaluating nosology. For example, Richters and Cicchetti (1993) argued that in the case of conduct disorder (CD), only the subgroup with childhood onset or persistent CD (Moffitt 1993) has an internal dysfunction that would justify a "disorder" designation by Wakefield's (1992) criteria.

The past decade has, accordingly, seen a resurgence and refinement of theories of within-child causal mechanism for ADHD, emphasizing neural pathways and neuropsychologic processes that may be dysfunctional (Barkley 1997; Berger and Posner 2000; Castellanos and Tannock 2002; Nigg 2001; Sagvolden et al, in press; Sergeant et al 1999). These theories represent a blend of classic neuropsychology and contemporary and classic cognitive science, address emotion and motivation as well as cognition, and increasingly address presumed neural instantiation of the relevant mechanisms. For simplicity, this article refers to all as "neuropsychologic" functions. Note that the issue here is not whether impulsivity involves the brain, because all behavior does under the materialist assumption of science. The issue, rather, is whether a neural or neuropsychologic level of analyses—or a particular neuropsychologic pathway—is the most useful level for understanding why this disorder develops or is the most important determinant of the syndrome's expression (Turkheimer 1998).

These neuropsychologic theories differ in important ways. Barkley (1997) provides a sophisticated account of the development of executive functions and regulatory control involving a range of interrelated abilities subserved by regions of prefrontal cortex and associated connections in thalamus and basal ganglia (also see Pennington and Ozonoff 1996; Schachar et al 1993). Sergeant and colleagues (1999) detail a state regulation or energetic conception of ADHD, which emphasizes physiologic and performance data, including event rate dependence of some performance deficits (van der Meere 2002). Such data suggest low cortical arousal in relation to a right-lateralized noradrenergic neural system, low "activation" (a process of ongoing response readiness subserved by left lateralized dopaminergic networks), or effort (closely related to motivation). Sagvolden and colleagues (in press) emphasized reinforcement–response abnormalities involving disrupted dopaminergic functions and secondary failure of learning, conditioning, and appetitive systems that motivate behavior. Yet in each theory the dysfunctions emphasized are believed to be part of a causal developmental pathway giving rise to the ADHD syndrome. We will emphasize executive functions as a primary illustrative theory herein because it is arguably the most well researched of these models and perhaps the closest to being ready for the next level of validation; however, similar arguments to those we advance herein will likely hold true as well for the other neuropsychological theories. Therefore, the intent here is not to build support for or against a particular neuropsychologic model, but to illustrate the likelihood that any such model will only partially account for the phenomenon of ADHD.

We turn, then, to executive functions as our illustrative domain. Substantial evidence supports the involvement of neural

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structures relevant to executive functions in ADHD, including well-replicated group deficits on relevant tests (Barkley 2002; Nigg 2001; Pennington and Ozonoff 1996; Schachar et al 1993) and early appearing and persistent reduced volume in key neural structures (Swanson and Castellanos 2002). Moreover, although many neuropsychologic correlates of ADHD also correlate with "near neighbor" diagnoses such as conduct or learning disorders, the ADHD group effects on key executive measures appear to be independent of these comorbid conditions (Nigg et al 1998; Rucklidge and Tannock 2002; Seidman et al 2001; Willcutt et al 2005). Whether the reverse is true (executive deficits in conduct disorder with subthreshold ADHD symptoms covaried, for example) has rarely been tested or demonstrated (but see Seguin et al 1999 for a positive finding here). A further complexity concerns whether the profile of executive component function weaknesses is the same in different disorders (Pennington and Ozonoff 1996), or even in different children with ADHD. Nonetheless, the evidence on balance is that executive function problems (e.g., in response suppression, visual working memory, and possibly set shifting) are involved in ADHD and are viable candidate core dysfunctions. These lines of work thus represent important progress in clarifying neuropsychologic dysfunction in ADHD. Although much work is still required to assess the causal status of executive dysfunction within these models (Nigg et al 2004a), such converging evidence has appeared to put the field well on the way to identifying a core deficit in ADHD and therefore better validating the condition as a mental disorder by Wakefield's (1992) criteria; however, the effort to fully map this pathway—or any other pathway—is likely to proceed slowly without recognition of etiologic heterogeneity in research designs.

The Assumption of Etiologic Homogeneity and Its Impact on Research

The implicit assumption of causal homogeneity and the associated empirical search for simple single deficits has shaped the research agenda in much of the field. The modal research report compares a group of children with ADHD or one of its subtypes (now defined by DSM-IV) with a group of children who do not meet criteria for ADHD. Based on whether they see a statistically significant group difference, researchers judge that a given theory of ADHD dysfunction is or is not supported.

Clearly it is problematic to draw conclusions about a theory from a single study. One issue is sampling variation and generalizability. Any one negative or positive finding might be due to sampling distribution and type I or type II error. Replication and meta-analyses are needed. Meta-analyses indicate that children with ADHD as a group exhibit abnormal performance on a range of executive and as well as nonexecutive measures (Nigg, this issue; Willcutt et al, this issue) with effect sizes ranging from $d = .6–.9$ for many executive tasks to $d = 1.3$ for a small number of studies of delay aversion. The same effect size range also is observed in structural neuroimaging studies (Swanson and Castellanos 2002).

Yet interpreting these moderate associations as evidence of a single core deficit in all children with ADHD is problematic for another reason. In the meta-analyses just noted, the modest effect size magnitudes that are typical for executive functions (e.g., $d = .6–.8$) suggest substantial distributional overlap between ADHD and non-ADHD samples. Moreover, samples of children with ADHD invariably exhibit greater sample variance (not to be confused with within-child variability) in their scores than do control samples. In clinical measurement, that excess sample variance is on the "poor performance" end of the distribution. Thus, 1) the ADHD and control performance distributions overlap to a substantial degree in all studies, and 2) some children with ADHD perform in the normal range. Consistent with that picture, efforts to evaluate the clinical predictive power of executive function tests in relation to ADHD tend to show that these tests have worthwhile sensitivity but poor specificity (Barkley et al 1992; Doyle et al 2000; Grodzinsky and Barkley 1999; Hinshaw et al 2002; Willcutt et al, in press). In other words, individuals with a "bad score" are likely to have ADHD, but only a minority of children with ADHD exhibit a deficit on any specific test. Therefore, the absence of a specific neurocognitive weakness cannot be used to rule out ADHD (Grodzinsky and Barkley 1999). Such clinical results would be expected with substantial distributional overlap, unequal sample variances, and the ADHD sample tail on the "bad" end of the distribution. In short, group effects reported in the literature are apparently carried by a subset of the children with ADHD.

Empirical Evidence for Overlapping Distributions: Illustration from Three Sites

Table 1 illustrates that this type of finding is typical across a range of executive function and related tests and across sampling locations. The table shows data from three active research centers with expertise in ADHD on a handful of widely studied neuropsychologic measures (additional measures were available at all sites and yielded similar results). These research centers provided a total of 887 children (51% boys), including 600 control participants (47% boys) and 287 ADHD combined type (ADHD-C; 57% boys). Each data set is described in the literature (see brief description and sample population numbers in the table footnote). They represent samples ascertained through community- and clinic-based recruitment strategies, and thus between them, they are typical of most studies of ADHD.

The between-group comparisons were generally quite significant and well replicated (Table 1). The effect sizes listed are fairly typical (recall the meta-analyses just noted). Table 1 then further reports a statistic that is rarely reported in the literature. How many children with ADHD-C performed in an "abnormal" or "impaired" range on the given test? Here we arbitrarily selected the 90th percentile as the cutoff for impairment (the story would be essentially the same with a 95th percentile or other cutoff). That is, as can be seen in Table 1, generally no more than half of the children with ADHD-C can be reasonably classified as "impaired," even by this relatively liberal criterion, on any given measure.

One might reason that children with ADHD fail on multiple tasks, and that the picture might be different were that considered. To check this possibility, we recorded the number of children in control and ADHD groups in each sample who "failed" (at the 90th percentile criterion) 1 or more, 2 or more, 3 or more, 4 or more, and 5 or more tasks on the broad and varying batteries administered at these 3 research centers. Even though the centers varied in the tasks used and in the number of tasks available to be "counted" (see Table 2), results were consistent across all three samples. Table 2 illustrates the substantial overlap that remained in the distributions of "impairment" between control subjects and children with ADHD. The pooled data indicate that batteries of neuropsychologic measures yield relatively weak sensitivity/specificity indices for clinical purposes when we rely on DSM-IV. However, if one relies on DSM-IV to