

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

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Before assigning full etiologic validity to a psychopathologic 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

Table 1. Illustrative Widely Used Neuropsychologic Measures Comparing ADHD (Combined Type) to Controls: Group Differences and Percent Impaired in 3 Samples

Measure	Sample	Effect Size (d)			% ADHD Beyond Control 90th Percentile
		d	η^2	p	
SSRT	MI (all)	.88	.133	<.001	51
	CO	.79	.101	<.001	45
RT Variability	MI	.75	.123	<.001	48
	CO	.77	.125	<.001	44
Stroop CW	MI	.50	.045	<.05	25
	CO	.84	.132	<.001	44
	MGH	.62	.09	<.001	25
CPT	MI	.91	.11	<.001	37
	CO	.54	.053	<.001	35
	MGH	.17	.01	.11	16
Trailmaking	MI	.35	.033	<.05	27
	CO	.35	.031	<.01	24

Sex covaried in Michigan analysis. ADHD, attention-deficit/hyperactivity disorder; CO, Colorado; CPT, Continuous Performance Task commission errors; MGH, Massachusetts General Hospital; MI, Michigan; RT, reaction time; SSRT, stop signal reaction time; Trailmaking = Trails B time; η^2 , partial eta-squared (Cohen 1988), a measure of proportion of variance explained by a factor.

Michigan data (Nigg et al 2004) ascertained through multistage community recruitment and screening procedure using parent and teacher ratings, culminating in a structured diagnostic interview to confirm diagnoses. The Colorado sample (Willcutt et al in press, b) is a subset of participants from the Colorado Learning Disabilities Research Center twin study (DeFries et al 1997). A school-based screening procedure is used to identify twin pairs in which at least one twin meets symptom criteria for DSM-IV ADHD, and full DSM-IV diagnostic criteria are used to confirm diagnosis. One twin from each pair was randomly selected for these analyses. The Boston-MGH sample (Biederman et al 1997) consisted of children consecutively referred to a pediatric psychopharmacology clinic ($n = 405$). Children were comprehensively evaluated with structured diagnostic interviews. Children in each sample also completed other measures, but none provide any substantially different result than what we illustrate with selected measures here. Data on ADHD inattentive and hyperactive-impulsive subtypes omitted (results for those groups were never better than for ADHD-C). Sample breakdowns. Boston MGH: 231 control subjects (109 boys, 122 girls), 145 ADHD-C (59 boys, 86 girls); Michigan: 62 control subjects (37 boys, 25 girls), 79 ADHD-C (61 boys, 18 girls); Colorado: 307 control subjects (137 boys, 170 girls), 63 ADHD-C (45 boys, 18 girls).

diagnose ADHD, there is little need clinically for neuropsychologic measures. The real nosologic question is, how many of these children may reasonably be viewed as having a neuropsychologic deficit along the lines often theorized? These data, which are typical in the literature, suggest that any reasonable cutoff will leave many children with ADHD as “unaffected” or else classify an inordinate number of control children as “affected.” Thus the positive predictive power of the deficits continues to improve with more severe cutoffs, but the negative predictive power gets steadily worse.

Why These Distributional Properties May Be Important

We noted substantial overlap in the distribution of neuropsychologic scores for children with ADHD-C and healthy control children. Low to moderate effect sizes and overlapping distributions suggest that the executive deficits measured by these tasks do not contribute causally to ADHD in all cases. Moreover, ADHD is also characterized by group differences in sensitivity to delay (Sonuga-Barke 2003), slower and more variable response speed (Sergeant et al 2003), weaknesses in temporal discrimina-

tion of stimuli of short duration (Toplak et al 2003) and time estimation/reproduction of longer temporal intervals (Barkley et al 2001), and deficits in motor control (Nigg et al 1998). Although some of these deficits may be secondary to a hypothesized primary deficit (Barkley 1997; Sergeant et al 1999) the cognitive etiology of ADHD is probably multifactorial.

At least two types of multifactorial models could explain this state of affairs. First (tending to be accepted implicitly in research designs) is that all cases of ADHD are caused by similar internal mechanisms that involve dysfunction in each of these different domains. The range of variation when the mechanisms malfunction overlaps with the normal range of variation because of the additive and interactive effects of multiple developmental processes. Under this scenario, the small effect of each pathophysiologic process and their moderation by other, unspecified processes pose a daunting challenge to etiologic research.

Second, and less often discussed, is the possibility that samples of children with a given ADHD subtype as defined by DSM-IV represent two (or more) populations of affected children. Under this scenario, if we take one of the more effective tests (e.g., the stopping test) as a marker of dysfunction and use a 90th percentile cutoff, then between 35% and 50% of the children designated as ADHD-C have a neurologic dysfunction that is detected on a given executive function test, and that leads to abnormal performance and to behavioral impairment (Table 1). The remaining 50% to 70% of children diagnosed with ADHD-C would have some other etiology, which may often be a different neuropsychologic dysfunction or even a different executive dysfunction (indeed, lumping all executive measures together fails to take into account potentially important differences in the degree of their relation to ADHD, as illustrated in Table 1). Some of these other children may have problems in motivation or another neurocognitive domain, and in perhaps a minority of cases the problem reflects a problem in adaptation or context (e.g., response to family distress or peer problems; Johnston and Mash 2001).

Table 2. Illustration of Overlapping Distributions of Impairment Based on Percentage of Individuals in Each Group “Impaired” (>90th Percentile) on a Minimum Number of Measures Across Three Samples

Group	Number of Tasks Failed (%)					
	0	≥1	≥2	≥3	≥4	≥5
Control MI	58	42	18	11	5	2
Control CO	56	44	19	9	3	1
Control MGH	44	56	27	6	1	0
Mean	53	47	22	9	4	1
ADHD MI	27	73	53	30	21	12
ADHD CO	19	81	55	36	18	13
ADHD MGH	18	82	50	28	14	4
Mean	21	79	53	31	18	10

ADHD, attention-deficit/hyperactivity disorder; CO, Colorado; MGH, Massachusetts General Hospital; MI, Michigan. Tasks used varied some what across samples. For Colorado, the tasks used were Continuous Performance Task (CPT) commission and omission errors, Stroop naming, Stroop interference, Trails B, WISC Coding, Verbal Working Memory, Wisconsin Card Sorting Task (WCST) perseverative errors, and Stop Signal RT. For MGH, the tasks used were Coding, Stroop Naming, Stroop Interference, California Verbal Learning Test (CVLT) total, wide range assessment of memory and learning (WRAML) total, WCST perseverative errors, Rey Osterreith organization score, CPT commission errors, CPT omission errors, letter cancellation errors (diagnoses based on DSM-IV proxies, Biederman et al 1997). For Michigan, the tasks used were Stroop Naming, Stroop Interference, Trails B, Tower of London, Stop Signal Reaction Time, response variability, response speed.

Note that ADHD studies often have considered exophenotypic heterogeneity at the behavioral level. For example, studies now more regularly consider whether children with ADHD show distinct cognitive profiles if they have a comorbid presentation (e.g., CD or learning disability [LD]; Willcutt et al 2005), or a particular DSM-IV subtype (Nigg et al 2002). Likewise, a few studies looked at a subgroup from multiplex families (in which more than one member has ADHD; Seidman et al 1995) and at gender differences (Nigg et al 2002). Yet these studies do not explicitly address etiologic heterogeneity, even though they imply it.

We have suggested that only some children with ADHD-C have a deficit in a particular executive function that could contribute to their disorder. The implication is that some other causal pathway leads to the remaining cases. What might that pathway be? Is there any other evidence to support the possibility of at least a second causal pathway? We briefly note 5 types of evidence that are suggestive of multiple causal pathways.

Familial Validation of Executive Dysfunction Subgroup

Nigg and coworkers (2004) divided their sample of children with ADHD into those with and without neuropsychologic impairment (by the 90th percentile rule) then looked at neuropsychologic performance in relatives. They repeated this for several tasks. A heterogeneity model would predict that the relatives of children with ADHD without neuropsychologic impairment would not differ from relatives of control children, but that both groups would do better than relatives of children with ADHD with neuropsychologic impairment. Most of their results supported the heterogeneity model. For stop signal reaction time (SSRT) and response variability, for example, the relatives of “impaired” ADHD children indeed performed worse than the relatives of nonimpaired ADHD and healthy control children ($p < .01$), whereas the latter two did not differ. Crosbie and Schachar (2001) reported a similar finding.

Real-World Impairment and Executive Dysfunction Subtypes

Biederman et al (2004) operationalized executive dysfunction as performance $\geq 1.5 \pm SD$ below the mean of the control group ($n = 257$ ADHD boys and girls; $n = 222$ control participants). Thirty-three percent of ADHD subjects met this operational criteria for executive function deficits compared with 12% of control participants. Compared with ADHD alone, children with ADHD and executive function deficits had an increased risk for grade retention and a decrease in academic achievement, even after controlling for socioeconomic status, LDs, and IQ. No differences were noted in social functioning or psychiatric comorbidity.

Executive Function as a Partially Separable Pathway from Delay Aversion

Solanto and et al (2001) reported that measures of delay aversion and inhibitory deficit (SSRT), although not correlated with each other (suggesting two distinct processes), were both moderately associated with ADHD in a group of school-age children (effect sizes were $d = .91$ for the delay aversion task and $d = .69$ for SSRT). The two tasks independently predicted ADHD status when included in the same regression model. Using our standard 90th percentile cutoff, we revisited those data. Forty-six percent of children with ADHD demonstrated deficits in inhibitory control, and 39% had deficits in delay aversion. Furthermore, whereas 23% had both inhibitory deficits and delay aversion, 15% had delay aversion only, and 23% had “pure” inhibitory

deficits. Interestingly, 39% did not meet these cutoffs on either scale. Likewise, Sonuga-Barke and coworkers (2003) found a significant association between ADHD and a composite measure of executive dysfunction in preschool-age children. Some 44% of children who met a threshold for clinically significant levels of ADHD symptoms also showed executive deficits above our 90th percentile cutoff, and 56% of the ADHD-range children displayed “impaired” delay aversion. Simultaneous analyses of both domains revealed that 29% of ADHD-range children displayed both delay aversion and executive dysfunction, 27% delay aversion only, 15% executive dysfunction only, and 29% neither problem.

Executive Function and Marital Conflict as Partially Independent Pathways

Using the same logic with a different set of pathways in the Michigan sample, Nigg and colleagues (unpublished) assessed child perception of marital conflict (a known contributor to child disruptive behaviors; Grych and Fincham 1990), along with SSRT as an executive measure. These two risk factors correlated only at $r = .03$ (*ns*), and in a simultaneous multiple regression to predict number of parent and teacher symptoms of ADHD exhibited by the child, both content of marital conflict ($\beta = .34$, $p < .001$) and SSRT ($\beta = .29$, $p < .001$) contributed uniquely. Of the children with ADHD-C, 42% had impaired stop inhibition, and 62% had extreme marital conflict, including 30% showing both impaired inhibitory control and extreme marital conflict (13% only inhibitory dyscontrol, 32% only marital conflict) and 25% showing neither.

Genetic Subtypes and Regulatory Neuropsychologic Deficit

Swanson and colleagues (2000) divided children with ADHD-C from the Multimodel Treatment Study of ADHD study into those with and without the long-repeat allele of the dopamine D4 receptor gene. They then compared these two groups to the healthy control children on a composite reaction time index averaged across multiple cognitive tasks. The group with the long-repeat (risk) allele had normal neuropsychologic performance, whereas the ADHD group without that allele had impaired or slow reaction time performance.

Summary

Still other efforts to evaluate neurocognitive subtypes could be cited (Clarke et al 2001). None provide conclusive evidence of the existence of multiple etiologic pathways in ADHD just yet. But taken together these types of data suggest that the possibility warrants serious examination. Indeed, the idea of multiple developmental pathways to ADHD has been articulated and developed in several recent theory papers (Berger and Posner 2000; Nigg et al 2004a, 2004b; Sonuga-Barke 2002); however, the implications of this possibility for resolving the puzzle of ADHD causality have not been incorporated into the field’s research agenda. These implications are potentially profound for both clinical practice and research methodology.

Implications for Clinical Practice

The thesis that a subgroup of children with ADHD has executive deficits suggests reexamination of the assumptions that underpin current clinical practice. Formal adoption of such a subtype definition is premature because it has not yet been fully validated; however, it might prove productive for research purposes that would eventually help clinical practice.

Important work that could be based on such provisional subtyping and could help evaluate whether it has clinical value

would include several elements. First would be to assess whether distinguishing between those cases of ADHD with and without executive dysfunction confers clinical significance, such as worse outcomes (as in Biederman et al 2004). In that case, the presence of “comorbid executive” ADHD might indicate the need for adjunctive therapies targeted at comorbid executive deficits, but these might be supplementary to core therapies and not replace them. Some formalization of this state of affairs might still be useful but would alter practice only incrementally.

The strongest case for the eventual inclusion of a new subtype would be if it could be demonstrated that, for at least a subgroup of children, the disorder is caused by executive dysfunction, and because of this, it is fundamentally different from ADHD associated with other nonexecutive processes. In other words, the presence of executive deficits changes the quality of the condition or the risk of a certain negative outcome, rather than just increasing its complexity. This position would certainly be in keeping with current models of the pathophysiology of ADHD in which executive dysfunction is regarded as directly mediating the link between putative risks (both genetic and environmental) and the emergence of disorder. If this ontologic distinction were echoed at the clinical level, with different treatment profiles for executive and nonexecutive forms, an executive dysfunction subtype may be of critical utility and its inclusion in diagnostic systems justified. Sonuga-Barke (2002, 2003) provides more discussion of potentially distinct treatment requirements for executive and nonexecutive forms of ADHD.

Implications for Research Methodology

The field might consider establishing criteria for an executive dysfunction subtype of ADHD-C. More narrowly and specifically, this might be a subtype with a response inhibition deficit, which would allow for study of additional heterogeneity within executive functions overall (e.g., versus children with working memory problems). More broadly and speculatively, researchers could begin to think about studying children with ADHD who appear to be cognitively healthy versus those with any of a range of neuropsychologic relevant deficits, such as response inhibition and working memory in the executive domain, or arousal (e.g., signal detection) or activation in the state regulation domain. Establishing such an etiologic subtype is premature for clinical purposes, yet it would be a substantial advance if such a subtype could be described and validated in the research literature. That advance might in turn sharpen clinical practice. Conducting the studies that would evaluate this possibility mandates an adequate conceptual framework for doing so. Once a conceptual basis for partitioning heterogeneity is established (e.g., Sonuga-Barke 2002), neuropsychologic testing may become a more valuable and viable element in assessment and potentially in treatment planning to address their particular dysfunctions.

We suggest that it is essential for the field to determine whether a multiple-etiology pathway can be specified based on neurocognitive grounds. If it can, there is real promise of identifying a subgroup or subgroups of affected children who have true neurocognitive dysfunction in one or more domains, such as executive functioning. Work on imaging, genetics, and etiologic determinants of this dysfunction could begin to move forward. In the meantime, efforts to identify the cause of the problems in children with normal executive function also could move forward. This approach provides a concrete way to go beyond DSM-IV in defining relevant groups for study and holds promise for shifting to an etiologically informed nosology in time.

The formal nosologic validity in the syndrome of ADHD would be advanced as well. Eventually, the field could more definitively identify within-child executive response inhibition dysfunction in some children, within-child motivational or arousal problems in other cases, and no-dysfunction in still other cases, analogous to the state of affairs with early-onset versus adolescent limited CD (Richters and Cicchetti 1993). Of course, even further parsing may eventually be possible with regard to types of executive function. Also apparent is that we do not know, for example, whether temporal information processing problems may cut across motivational, reinforcement, or executive domains. Thus, work on multiple theoretical perspectives in the same data sets is essential; however, once even one key subgroup was validated, subsequent versions of the DSM could then begin to be based on etiologic factors in diagnosis, not merely on behavioral descriptors.

On the other hand, if this state of affairs is not clarified, then etiologic studies in ADHD likely will continue to yield small and difficult-to-replicate effects, if causal effects in fact are muted by the presence of multiple distinct subgroups with different etiologies within samples defined by DSM-IV. How might this imagined progress materialize, or its promise be evaluated? To properly evaluate this possibility, researchers might consider the following steps.

1. *Report results for individuals.* For any measures that reveal a significant difference between groups with and without ADHD, studies should routinely report the proportion of individuals in each group with significant impairment on the measure. This result could be in the form of the percentage of children with ADHD exceeding a reasonable clinical cutoff on a measure or group of measures. Alternatively, sensitivity and specificity of measures could be reported, although in either case it is important that the cutoff used be specified (thus, simply reporting discriminant function results without a specific cutoff does not suffice). Along the same lines, researchers reporting neurocognitive analyses might routinely report score ranges as well as the mean and variance of their control and ADHD samples. This idea invokes in general the need for more person-centered (rather than variable-centered) research in ADHD samples.
2. *Collect representative normative data.* Normative research is needed to know how likely it is that a child who has no psychiatric problems will exhibit an “abnormal” score on 1) any given neurocognitive test and 2) on *any of a set* of neurocognitive tests. Obviously, such normative data would be a great contribution to clinical assessment. Less obviously, yet more immediately, it would enable empirically supportable groupings of children on the basis of endophenotypes for etiologic analysis.
3. *Define and test neuropsychologic subtypes.* Greater emphasis can be given in research designs to statistical approaches that enable identification of types, while relying on neuropsychologic measures rather than merely symptom measures. The validity of these subtypes can then be examined by testing whether the subtypes are associated with differences in external correlates, etiology, or treatment response. Based on available data regarding the consistency and magnitude of the difference between groups with and without ADHD (e.g., Nigg, this issue; Sonuga-Barke, this issue; Willcutt et al, this issue), we suggest that researchers, and the DSM-V committees, consider defining neurocogni-

tive subtypes based on exploratory or experimental domains by choosing among the most well-researched measures to date. A (nonexhaustive) list of examples would include measures such as those discussed in the published meta-analyses cited and the measures discussed here.

Conclusion

Neuropsychologic theories of ADHD etiology have become the norm in the past 20 years, following up on a nearly century-long tradition. Those theories have become increasingly sophisticated in the past 10 years with advances in the cognitive and neural sciences (Barkley 1997; Sergeant et al 1999). Although each theory is presented as accounting for all of the cases of the syndrome, we doubt that any theorist of ADHD believes all children in this category share the same common pathway to their problems. However, that accepted fact of heterogeneity is rarely formally acknowledged or addressed in empirical reports. This review argues that it is quite plausible to work from a model that assumes neuropsychologic impairments (in this case, in executive functioning, but one could make the same argument for other neuropsychologic domains) characterize only a portion of children with ADHD. As an illustration, we estimated that 35% to 50% of cases of ADHD-C have response inhibition deficits (one aspect of executive functioning). Researchers may wish to explore comparable data for other types of executive functions as well as other neurocognitive functions. Further study to determine if this dys-executive subset can be reliably classified, and to then examine other indices of the external validity of such a subtype, represents a promising and important next step in the field that leading investigators and norm setters, perhaps including the DSM-V revision committee and granting agencies, would do well to recognize and incorporate.

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