

Attention-Deficit/Hyperactivity Disorder Endophenotypes

Alysa E. Doyle, Erik G. Willcutt, Larry J. Seidman, Joseph Biederman, Virginie-Anne Chouinard, Julie Silva, and Stephen V. Faraone

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

From the Department of Psychiatry, Harvard Medical School (AED, LJS, JB) Boston, Massachusetts; Pediatric Psychopharmacology Unit, Massachusetts General Hospital (AED, LJS, JB, VAC, JS), Boston, Massachusetts; University of Colorado, Boulder, Colorado (EGW); Massachusetts Mental Health Center (LJS), Boston, Massachusetts; and SUNY Upstate Medical University (SVF), Syracuse, New York.

Address reprint requests to Alysa E. Doyle, Ph.D., Massachusetts General Hospital, YAW 6900, 55 Fruit Street, Boston, MA 02114; E-mail: doylea@helix.mgh.harvard.edu.

Received July 27, 2004; revised March 9, 2005; accepted March 9, 2005.

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 heterogeneous 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

behavior being reinforced. If such reinforcers are lacking or distal, inattention and motor impulsivity occur. Consistent with this model, Sonuga-Barke and colleagues have shown that children with ADHD exhibit aversion to delay. That is, they show preferences for immediate but smaller rewards compared with delayed larger rewards, particularly when the immediate reward reduces the length of a task (e.g., (Sonuga-Barke et al 1996). Solanto et al (2001) found that measures of inhibitory control and delay aversion were not highly correlated in ADHD subjects; however, the two measures together identified the majority of ADHD cases in a discriminant function analysis. Based on these data, which were replicated in preschoolers (Sonuga-Barke et al 2003), Sonuga-Barke (2003) has proposed a dual-pathway model of ADHD involving both EF and delay aversion. Although further data are needed to determine whether the predictions of this model are borne out, this theory marks an important contribution to the field as the first formal model of neuropsychological heterogeneity in ADHD.

Association with ADHD—Summary

Although no single neuropsychological deficit has emerged as a necessary and sufficient cause of ADHD, those related to EFs, state regulation (especially RT variability), and delay aversion show replicated association with ADHD and thus fulfill criterion 1 for an ADHD endophenotype. Although we have discussed these three neuropsychological constructs separately in line with their individual theoretical literatures, some researchers may argue that state regulation and the ability to withstand delay are aspects of executive processes. Further work is needed to map the relationship between these constructs and the heterogeneity of these impairments within ADHD samples.

Heritability

For neuropsychological measures to be useful endophenotypes for ADHD, they should show evidence of heritability. A significant literature suggests that general cognitive functioning (IQ) is highly heritable (Plomin 1999); however, data on the heritability of specific neuropsychological functions are limited. Table 1 shows twin studies that have examined constructs that are relevant to ADHD. For ease of explication, the table is divided according to measures of attention, EFs, and other functions; however, it should be noted that many of these measures are multifactorial in nature and are thus supported by multiple cognitive functions. In these samples, heritabilities range from zero to 88%, with the majority of studies showing at least some genetic influence. These data provide preliminary evidence that measures of attention and EF show genetic influence. Yet many studies are characterized by small sample sizes, and only a limited number of measures have been examined.

Although larger samples are needed to estimate more accurately the heritability of relevant neuropsychological measures, current data suggest that these measures may have lower heritability than ADHD. These lower heritability estimates may partially reflect measurement issues. For example, one possibility is that these lower estimates are due to error variance or low reliability. Furthermore, measures that are not normally distributed may not be amenable to quantitative genetic analyses, even after data transformation procedures. Yet even if such measures are less heritable than ADHD, they may be more useful for finding genes than the disorder itself if a smaller number of genes contribute to individual differences on the EF measure than contribute to the overall ADHD diagnosis (because the magni-

tude of effect for a single gene depends on the number of genes involved; Faraone et al 2000; Risch 1990a).

To date, few studies have investigated the relationship of individual genes with performance on neuropsychological measures. Studies have suggested an association between the catechol-O-methyltransferase (COMT) val allele and perseverative errors (Egan et al 2001; Joober et al 2002; Malhotra et al 2002), and other studies suggest a role in aspects of attention of the dopamine 4 receptor gene (DRD4; Auerbach et al 2001; Fossella et al 2002) and a region of the monoamine oxidase A gene related to transcription induction (MAOA-LPR; Fossella et al 2002). Thus far, however, none of these studies has documented a gene contributing more than 5% of the variance to test performance. Additionally, studies (Auerbach et al 2001; Fossella et al 2002) also provide evidence that multiple genes are likely to be contributing to these measures. Thus, these data raise the possibility that at least some neuropsychological measures may themselves be complex phenotypes.

Overlap with ADHD

Family Studies. Table 2 illustrates family studies that have assessed neuropsychological deficits in relatives of ADHD youth. Two studies failed to find such deficits in parents of ADHD probands (Asarnow et al 2002; Murphy and Barkley 1996). Studies that have distinguished between affected and unaffected relatives of ADHD probands suggest subtle deficits in unaffected relatives and greater deficits in relatives who themselves have ADHD (Doyle et al, in press-a; Nigg et al 2004; Seidman et al 2000; Slaats-Willemse et al 2003), with a lack of consistency in the specific deficits found to be impaired in unaffected relatives. Nonetheless, although findings are not definitive, the fact that several studies find some evidence of deficits in unaffected relatives provides support for partial familial overlap of ADHD and neuropsychological weaknesses, for example, on measures of inhibition and processing speed.

Adoption Studies. Two adoption studies of ADHD have examined neuropsychological performance. In one, biological parents of ADHD children performed more poorly on measures of visual attention and reaction time than did adoptive relatives of ADHD children (Alberty-Corush et al 1986), but no differences between biological and adoptive parents were found on an impulsivity measure. In the second (Nigg et al 1997), biological parents of ADHD boys showed hemispheric asymmetry on a visuospatial orienting task compared with the adoptive parents of ADHD boys and parents of control boys. Together these studies suggest impairments on measures of visual attention may be part of the genetic susceptibility to ADHD.

Twin Studies. Twin designs can provide estimates of bivariate heritability (h^2g), a statistic ranging from 0 to 1.0 that indicates the extent to which variability in one trait is attributable to the same genetic influences that impact another trait. To date, two twin studies have used objective neuropsychological measures to assess bivariate heritability with ADHD. Kuntsi et al (2001) examined the bivariate heritability of extreme hyperactivity and measures of working memory, delay aversion, and reaction time. Bivariate heritability was not estimated for a measure of response inhibition because it did not differ between the hyperactive group and controls in initial phenotypic analyses. A composite measure of tasks that best discriminated groups with and without hyperactivity was also examined; the composite included measures of reaction time, omission errors, delay aversion task, and verbal IQ. Results showed statistically significant genetic overlap between extreme hyperactivity and RT variability ($h^2g = .64$) and

Table 1. Twin Studies of Neuropsychological Measures Relevant to ADHD

Study	N (Pairs:MZ/DZ)	Measure	Function	Twin Intraclass Correlations		Heritability (h ²)
				rMZ	rDZ	
A. Measures of Attention						
Goodman and Stevenson 1989	102/111	E scan	Visual attention/scanning	.54	.33	.42 ^a
Bartfai et al 1991	10 (MZA)/10 (MZT)/DZT	SPAN	Selective attention	.53	-.06	.71 ^b
Myles-Worsley and Coon 1997	59/33	SPAN accuracy	Selective attention	.19	.31	Models not fit to data
		SSAT baseline accuracy	Average identification accuracy	.44	.01	Did not differ significantly from zero
		SSAT P/N ratio	Selective attention	.51	.20	.41 ^b
Fan et al 2001	26 / 26	DS-CPT d'	Target discrimination/vigilance	.26	.08	.28 ^b Did not differ significantly from zero
		DS-CPT beta	Decision criteria	.37	-.14	Models not fit to data
		ANT Alerting	Maintenance of alert state (vigilance)	.47	.38	.18 ^b
Holmes et al 2002	20 / 20	ANT Orienting	Visual orienting (selective attention)	.10	.40	.00 ^b
		CPT-IP matches	Vigilance	-.18	.53	Heritability not calculated
B. Measures of Executive Functions						
Goodman and Stevenson, 1989	102/111	Wechsler FFD Index	Working memory (includes measures of vigilance & processing speed)	.60	.44	.32 ^a
Pennington et al 1995	20/30	WCST perseverative errors	Perseveration	.49	.21	.56 ^a
		WCST total errors	Impulsivity/ abstract problem solving	.60	.16	.88 ^a
Fan et al 2001	26/26	ANT Conflict	Executive control of attention	.73	.28	.72 ^b
Holmes et al 2002	20/20	MFFT number correct	Impulse control (includes aspects of attention)	.79	-.42	Heritability not calculated; authors conclude MFFT number correct may be genetically influenced
		MFFT number incorrect	Impulse control	.73	-.08	
		CPT-IP false alarms	Impulse control	-.10	.38	
Campana et al 1996	15/9	WCST Categories	Abstract problem-solving/ set-shifting	.02	-.06	Heritabilities based on intrapair correlations did not differ significantly from zero
		WCST Perseverative Errors	Perseveration	.17	-.01	
Ando et al 2001	143/93	WCST Total Errors	Impulsivity/ abstract problem solving /set-shifting	.33	-.03	
			Revision of spatial and verbal working memory span tasks and developed by Shah and Miyake (1996)	Verbal working memory	.44	.23
			Spatial working memory	.50	.22	.49 ^b

Table 1. Continued

Study	N (Pairs:MZ/ DZ)	Measure	Function	Twin Intraclass Correlations		Heritability (h ²)
				rMZ	rDZ	
Swan and Cannelli 2002	80/78	Stroop Color–Word Interference	Interference control (includes processing speed)	.55	.14	.50 ^b
		Trails B	Set shifting (includes processing speed)	.42	.30	.50 ^b
C. Measures of Processing Speed and Other Functions						
Holmes et al 2002	20/20	MFFT mean RT	Processing speed	.80	.31	Heritability not calculated
Swan and Cannelli 2002	80/78	Wechsler Digit Symbol	Processing Speed (includes attention and fine motor skills)	.73	.19	.68 ^b
		Controlled Oral Word Association	Verbal Fluency	.51	.41	.34 ^b

ANT, Attention Network Task; CPT, Continuous Performance Test; DS, Degraded stimulus; DZT, Dizygotic twins reared together; E scan, scattered letters test (subject crosses out the letter E); FFD, Freedom From Distractibility Index; MFFT, Matching Familiar Figures Test; MZA, Monozygotic twins reared apart; MZ, Monozygotic twins reared together; SPAN, Span of Apprehension Test; SSAT, Spontaneous Selective Attention Task; WCST, Wisconsin Card Sorting Test;

^aBased on intraclass correlation.

^bBased on biometrical model fitting.

the composite score ($h^2g = .80$). Bivariate heritability estimates were relatively high for commission errors ($h^2g = .60$); however, these were not statistically significant due to the small sample size. Delay aversion did not show any evidence of genetic overlap with hyperactivity ($h^2g = -.06$).

The second study examined a larger sample of twins selected for DSM-IV ADHD (Chhabildas et al, unpublished data). The battery included measures of response inhibition, working memory, vigilance, set shifting, and processing speed. Estimates of bivariate heritability were somewhat lower than those obtained by Kuntsi and Stevenson ($h^2g = .20-.38$) but were significant for all variables with the exception of set shifting. Higher bivariate heritabilities were obtained for inattentive symptoms than for hyperactive–impulsive symptoms. Similar to Kuntsi et al, the highest bivariate heritability was obtained for a composite score that included measures of processing speed, vigilance, working memory, and response inhibition.

Candidate Gene Studies of Neuropsychological Deficits in ADHD Samples

The small number of molecular genetic studies of ADHD and neuropsychological measures are generally inconclusive. Although three studies find an association between DRD4 and test performance, only one study (Langley et al 2004) found this association to be with the 7-repeat allele that is typically associated with increased risk for ADHD. The other two studies (Manor et al 2002; Swanson et al 2000) suggest that the short alleles of DRD4 were associated with slow, variable, and impulsive responses on computerized attention tests, raising the possibility that both high and low levels of synaptic dopamine could be associated with neurocognitive deficits (Fossella et al 2002). Although one study found an association between the dopamine 5 receptor gene (DRD5) and performance on a CPT (Manor et al 2004), additional studies did not find associations between COMT and a battery of measures tapping attention, reaction time,

response inhibition, and working memory (Mills et al 2004) or a gene from the glutamate system (GRIN2A) and inhibitory control and verbal short term and working memory (Adams et al 2004); however, the association between these latter genes and the ADHD diagnosis overall remains unclear.

Summary of Neuropsychological Literature

Considered together, family, twin, and adoption studies suggest that impairments on neuropsychological measures related to EF as well as processing speed, visual attention, and response variability may be associated with the genetic liability to ADHD. Family and twin studies also suggest that familial–genetic overlap is most robust for scores based on multiple neurocognitive measures. Yet the low magnitude of bivariate heritability and the relatively small effect size of deficits in unaffected relatives also indicate that either a significant proportion of the genetic influences on ADHD differ from the genetic influences on these measures or else that some factor is limiting the detection of the extent of the shared genetic influences. Such a factor could be measurement issues, underlying neurocognitive heterogeneity of ADHD, or a combination of these. We return to these latter issues in the context of recommendations for future studies.

Neuroimaging and Electrophysiological Endophenotypes for ADHD

Neuroimaging

Association with ADHD. Both structural and functional neuroimaging studies have documented abnormalities in frontal-subcortical circuits that regulate attention, inhibition, and intentional motor behavior in ADHD samples (Seidman et al 2005); however, the majority of studies with implications for endophenotype research involve structural neuroimaging. Volumetric differences have been found repeatedly in the dorsolateral prefrontal cortex, the dorsal anterior cingulate cortex, the cau-

Table 2. Family Studies of Attention-Deficit/Hyperactivity Disorder (ADHD) and Neuropsychologic Measures

Study	Diagnostic System	Relatives	N	Measures	Measures Impaired in Relatives	Neuropsychologic Function(s) Implicated by Impairments in Unaffected Relatives (or Correction by Relative ADHD Status)
Murphy and Barkley 1996	DSM-III-R	Parents	Probands w/ severe ADHD = 25; probands w/ mild ADHD = 25; control subjects = 25	WCST, CPT, Verbal Selective Reminding Test, Digit Span	None (did not distinguish between affected and unaffected)	N/A
Asarnow et al 2002	DSM-III-R	Parents	ADHD probands = 190; control probands = 115	DS-CPT, Trails B, SPAN	None (did not distinguish between affected and unaffected)	N/A
Seidman et al 2000	DSM-III-R	Siblings of boys	Affected sibs of ADHD probands = 40; unaffected sibs of ADHD probands = 116; Control subjects = 118	Stroop, WCST, ROCF WRAML, CVLT, Auditory CPT, LC	Affected relatives: Overall battery, Stroop Word, Color and Color-Word subtests, WCST Perseverative Errors, WRAML list learning Unaffected relatives: WRAML list learning (overall battery fell short of significance, $p = .06$)	Verbal learning (general EFs, based on near-significance of overall battery)
Slaats-Willemse et al 2003	DSM-IV	Siblings from multiplex families	Affected sibs of ADHD probands = 25; unaffected sibs of ADHD probands = 25; Control subjects = 48	Stroop Go-NoGo and SAT from Amsterdam Neuropsychologic Battery	Affected relatives: Go-NoGo, SAT accidental responses, Stroop Interference Unaffected relatives: No significant differences vs. control subjects, but linear effect across affected, unaffected, and control groups on	Impulsivity/response inhibition all tests
Nigg et al 2004	DSM-IV	Parents and siblings	ADHD—combined type = 165; ADHD—inattentive type = 80; control subjects = 141	SS Task, Trails B, Tower of London, Stroop	Before correction for relative ADHD: SSRT in mothers of female probands, Trails B in relatives of children with ADHD-C, variability of basic RT in mothers; After correction for relative ADHD: SSRT in mothers of female probands, Trails B in relatives of children with ADHD-C,	Response inhibition and set shifting/processing speed in specific subgroups
Doyle et al, in press	DSM-IV (and DSM-III-R)	Parents and siblings of girls	Affected relatives of ADHD probands = 106; unaffected relatives of ADHD probands = 189; controls subjects = 243	Wechsler Digit Span, Oral Arithmetic, Digit Symbol/Coding; Stroop, WCST, ROCF WRAML, CVLT, Auditory CPT, WRAT-R Reading and Math	Affected relatives: Overall battery, ^a Stroop Word, ^a Color, ^a Color Word, ^a Wechsler Oral Arithmetic, ^a WRAT-R Reading ^a and Math ^a Unaffected relatives: Overall battery, ^a Stroop Color Word, ^a Stroop Interference, WRAT-R Math Analyses limited to multiplex families yielded deficits in unaffected relatives as above, as well as on Stroop Color, Wechsler Oral Arithmetic)	Interference control (and/or processing speed/naming), mathematics skills; other aspects of EF (e.g., working memory)

CPT, Continuous Performance Test; CVLT, California Verbal Learning Test; DS, Degraded Stimulus; EF, executive functions; LC, Letter Cancellation; SPAN, Span of Apprehension test; ROCF, Rey-Osterreith Complex Figure; WCST, Wisconsin Card Sorting Test; WRAML, Wide Range Assessment of Memory and Learning. SAT, Sustained.

^aSignificant for DSM-III-R diagnoses as well.

date nucleus, the putamen, and the globus pallidus (Castellanos and Tannock 2002; Ernst et al 1994; Faraone and Biederman 1998; Giedd et al 2001; Seidman and Valera 2002; Zametkin et al 1990). Yet recent studies suggest more widespread abnormalities that include cortical regions and the cerebellum (Berquin et al 1998; Castellanos et al 2002; Mostofsky et al 1998, 2002). In one large study (Castellanos and Tannock 2002), after controlling for total cerebral volume, only the difference for cerebellar volume remained significant. Similar to neuropsychological studies, imaging studies of ADHD also show significant variability (Seidman et al 2005). One possibility is that this variability is due to low statistical power because the majority of structural neuroimaging studies have included groups smaller than 20 individuals. Given their sample sizes, most studies have not had the ability to address issues related to heterogeneous subgroups within ADHD.

Heritability. Although few in number, twin studies using structural neuroimaging paradigms suggest that the volume of relevant brain regions is under significant genetic control. As in neuropsychological studies, however, specific estimates of heritability should be interpreted cautiously because of limited sample sizes. In a small sample of twins, Pennington and colleagues (2000) found heritabilities of .56–.97 for subcortical and cortical volumes, left and right neocortex, and total cerebral volume. Regions of particular interest to ADHD researchers have also shown high levels of heritability. For example, two studies reported heritabilities of .5–.9 for frontal regions (Carnelli et al 2002; Thompson et al 2001). In a multivariate twin design, Posthuma et al (2000) found that 88% of the variation of cerebellar volume was found to be due to genetic factors after the effects of age, gender, height, and intracranial space were parsed out.

Family-Genetic Overlap with ADHD. To date, only one study has assessed the familial overlap between ADHD and structural magnetic resonance imaging (MRI) measurements. Durston et al (2004) examined 30 ADHD youth, their 30 unaffected siblings, and 30 matched control subjects. Results showed reduced volumes in both the ADHD group and their unaffected siblings in right prefrontal gray matter and left occipital gray and white matter. Intracranial volume was reduced in ADHD youth, with a statistical trend toward reductions in unaffected siblings. Reductions in other cortical areas were observed; however, these did not reach statistical significance. Of interest was the fact that right cerebellar volume was reduced almost 5% in ADHD subjects versus control subjects, with no statistical difference between unaffected relatives and control subjects for this region. This finding was interpreted as suggesting that cerebellar reductions were associated with disease status rather than with the familial vulnerability to ADHD. Yet the effect size between unaffected relatives and control subjects was .26, suggesting that with a larger sample size, reduced volume of this region may also be implicated in the familial liability to ADHD.

Electrophysiology

Association with ADHD. A substantial literature has documented an association between ADHD and electrophysiological measures of brain functions. Electroencephalographic (EEG) measures, which assess the wavelike background electrical activity in the brain, suggest that ADHD subjects exhibit greater slow-wave (delta and, particularly, theta) activity as well as reduced alpha and beta waves, compared with control subjects (Barry et al 2003a). These results suggest hypoarousal in areas including frontal regions.

Event-related potentials (ERPs) measure changes in brain electrical activity in response to specific stimuli. Barry, Johnstone, and Clarke's (2003b) review of this literature suggests ADHD versus control differences across a variety of ERP paradigms. Particularly robust is the finding in children aged 12 years and younger of reduced amplitude of the posterior P3 wave, thought to peak between 300 and 500 msec after presentation of a stimulus, in response to an auditory oddball task that taps aspects of attention and working memory. Reduced P3 amplitude is also evident in the visual attention mode and with regard to anomalous processing (a reduced frontal N2 peak) after stimuli that evoke inhibitory processes.

Variability of electrophysiological findings is also evident across ADHD samples. Although more work is needed to explore whether such differences can be accounted for by small sample sizes and methodological differences across laboratories, reviews highlight different possibilities for delineating true heterogeneity (e.g., with regard to DSM-IV subtypes [Barry et al 2003a] or across subtypes based on groupings from cluster analyses involving different patterns of hypo- and hyperarousal [Clarke et al 2002]).

Heritability. A conceptual and meta-analytic review of twin studies of electrophysiological measures indicates that genetic factors contribute significantly to both EEG and ERP measures (van Beijsterveldt and van Baal 2002), with heritability of EEG alpha power and alpha peak frequency estimated to be .8 and ERP P3 amplitude and latency .6 and .5, respectively. Large interstudy discrepancies were also noted and attributed to small sample sizes and methodological differences. Other EEG and ERP parameters show evidence of genetic influence but have only been examined in a limited number of studies.

Family-Genetic Overlap with ADHD. To date, no studies have addressed the familial overlap of ADHD and electrophysiological measures. Meta-analytic findings, however, have documented reduced P3 amplitude in men with a family history of alcoholism compared with control subjects, particularly on visual tasks (Polich et al 1994), and Carlson et al (2002) found that in twins discordant for alcoholism, both affected and unaffected co-twins had reduced P3 amplitudes compared with nonalcoholic control twins. Iacono and colleagues (2002) have shown that this familial relationship is not specific to alcoholism. In their study, paternal antisocial personality disorder, in addition to alcohol abuse and dependence, was associated with reduced P3 amplitudes on a visual oddball test, and a similar but nonsignificant effect size for reduced P3 amplitude was found for sons of fathers with other substance abuse and dependence. These and other data (for a review, see Iacono et al 2003), such as the link between P3 amplitude reductions and a range of externalizing disorders including ADHD, the frequent comorbidity of externalizing and alcohol/substance use disorders, and evidence for shared genetic liability between externalizing disorders themselves have led Iacono, Malone, and McGue (2003) to hypothesize a genetically influenced latent trait of behavioral disinhibition that underlies a range of externalizing disorders and that can be indexed by reduced P3 amplitude. This hypothesis is interesting in light of family studies of ADHD suggesting cosegregation of ADHD and antisocial and bipolar disorders as well as higher relative risks associated with these comorbidities in ADHD families. Therefore, although research is needed in ADHD samples, these results highlight the potential utility of reduced P3 amplitude as an endophenotype for ADHD.

Summary: Neuroimaging and Electrophysiology Measures

Data from neuroimaging and electrophysiology paradigms suggest anomalies in individuals with ADHD when compared with control subjects. Patterns of MZ versus DZ correlations suggest that significant portions of variation in volumetric measures of the brain as well as in both EEG and ERP measures are due to genetic factors, suggesting that these measures meet one important criterion for a potential ADHD endophenotype. Yet further data are needed to determine the familial genetic overlap of measures from these paradigms with ADHD. Additionally, given the phenotypic, genetic, and likely neuropsychological heterogeneity in ADHD, the heterogeneity that has been observed in the neuroimaging and electrophysiological literatures should be explored further rather than simply attributing these inconsistencies to limited statistical power in studies with small sample sizes.

Discussion and Recommendations for Future Studies

The convergence of data from neuropsychological, neuroimaging, and electrophysiological studies suggest that neural mechanisms are disrupted in the ADHD brain and that these disruptions offer a potential window into the inherited diathesis of ADHD. If a single deficit or characteristic pattern of findings on these measures were identified in ADHD samples, particularly one that was reliable, heritable, and cofamilial, such a deficit would be an obvious candidate for use in molecular genetic studies. However, the literature does not yet yield definitive evidence for a specific endophenotype for ADHD.

Neuropsychological impairments in the construct of EFs broadly conceived, as well as impairments in state regulation and delay aversion, are associated with the ADHD. Such measures also show preliminary evidence of heritability and at least some familial–genetic overlap with ADHD diagnosis. Thus, they offer clear potential for molecular genetic studies. Of particular interest is evidence from family and twin studies suggesting familial–genetic overlap of ADHD and weaknesses in response inhibition, interference control, and processing speed. Yet the variability of deficits across studies, the partial rather than substantial overlap between these and other measures and ADHD in family and twin studies, the generally lower levels of heritability of neuropsychological measures compared with ADHD, and the lack of evidence for individual genes accounting for more than 5% of the variance in different tests all suggest that there is more work to be done to capitalize on the potential advantages of neuropsychological measures as ADHD endophenotypes.

The potential utility of neuroimaging and electrophysiological measures as endophenotypes may be constrained by their expense and the specialized equipment and training required for their implementation. Nonetheless, because such paradigms show association with ADHD and evidence of heritability, and also offer a window into neural pathways, these measures may still prove to be useful targets in molecular genetic studies of ADHD, particularly if they were to show robust familial or genetic overlap with the disorder. Given that only one structural neuroimaging study and no electrophysiological studies to date have examined unaffected ADHD relatives, a comparison of the relative advantage of candidate neuroimaging and electrophysiological versus neuropsychological endophenotypes is premature. Family and twin studies that assess overlap of these measures with ADHD are of interest to the field, particularly those large enough to address questions about heterogeneity.

In the remainder of the paper, we recommend additional strategies to move research in ADHD endophenotypes forward. We emphasize neuropsychological measures due to their ease of administration to large samples relative to neuroimaging and electrophysiological studies and to the fact that many research groups may already have neuropsychological data available.

Further Exploration of Neuropsychological Heterogeneity in ADHD

Examination of neuropsychological heterogeneity may allow targeting of more homogenous endophenotypes, which, in turn, would increase their utility for finding genes. Previously, we have argued for attention to family history, comorbidity, and DSM-IV subtypes and symptom dimensions to assist with endophenotype selection by determining whether qualitative or quantitative differences on these dimensions exist within ADHD samples (Doyle et al, *in press-b*). The benefits of this further cognitive analysis of ADHD would be most easily seen if distinct subtypes exist within ADHD that reflect unique pathophysiological deficits (e.g., as hypothesized by Sonuga-Barke's [2002] dual pathway model). However, such research may not yield definitive answers for endophenotype studies if heterogeneity at the neurocognitive level does not reflect genetic heterogeneity (Faraone and Tsuang 2003; Tsuang and Faraone 1995). For example, it is possible that ADHD could arise from a single, fixed pool of genetic influences, yet appear to be neuropsychologically heterogeneous, because of the influence of measurement issues, development, co-occurring conditions, and the other genetic or environmental influences that affect a specific individual. In an equally plausible model, ADHD cases may arise from various combinations of risk factors from a much larger pool, such that risk factors are potentially but not necessarily overlapping (Faraone and Tsuang 2003; Tsuang and Faraone 1995). Additionally, the same neurobiological deficits could be associated with different genes in different samples (e.g., deficits in different subcortical regions that project to the frontal cortex may produce similar "executive" impairments; Pennington and Ozonoff 1996). This possibility is reasonable because the prefrontal cortex is one of the most widely interconnected regions in the brain (Goldberg and Seidman 1991). Thus, attention to heterogeneity offers important potential for identifying subtypes that would be more strongly associated with candidate endophenotypic constructs; however, further cognitive analysis alone may not clarify the optimal neuropsychological endophenotypes for ADHD.

Direct Assessment of Statistical Power

Empirical strategies, focused on maximizing the power of potential endophenotypes in individual samples, offer further potential either in conjunction with or as an alternative to analysis of neuropsychological heterogeneity. Risch (1990b) has demonstrated that the statistical power of a linkage study increases with the magnitude of risk ratios (i.e., lambdas), which are computed by dividing the affection rate among each relative type by the rate of affection in the population. Low λ values may be due to a variety of factors, such as oligogenic transmission, genetic heterogeneity, phenocopies, and low penetrance. Risch (1990b) has suggested that defining disease status in a manner that increases λ would increase the power of linkage studies. Faraone et al (1995) reviewed λ values from schizophrenia studies and showed their utility in discriminating endophenotypes based on their potential for increasing the statistical power of linkage studies. Egan et al (2001) used this strategy in families of patients with schizophrenia and found relative risk to be

elevated for neuropsychological measures of processing speed, set shifting and verbal learning compared with the relative risk for the diagnosis. For ADHD, the potential value of endophenotypes is seen in the fact that λ values for the transmission of the ADHD diagnosis in family studies are consistently low, ranging from 2 to 3 for the risk to siblings and 2 to 8 for the risk to parents (Faraone et al 2000).

Increasing Statistical Power Through Reduction of Error Variance

An additional way to maximize power is to reduce error variance. Individual studies have demonstrated evidence of test–retest, inter-rater, or internal consistency reliability for neuropsychological (e.g., Kuntsi et al 2001), neuroimaging (e.g., Seidman et al 1999), and electrophysiological measures (e.g., Iacono et al 2002). Yet further attention to the psychometric properties of measurement tools in these domains is needed. For example, with regard to neuropsychological measures, reliability may differ across levels of ability (Pennington et al 1996) or when different algorithms are applied to a given experimental measure (Kuntsi et al 2001; Logan et al 1997). Our recent review (Doyle et al, *in press-b*) highlights other issues that could contribute error to measures of EF, including the limited sensitivity and the multifactorial nature of clinical neuropsychological measures, developmental changes, and state factors, such as sleep disturbances. Experts have advocated greater attention to the psychometric properties of EF measures (e.g., Denckla 1996; Pennington et al 1996), and such investigations are essential for determining whether heterogeneity is real. Measures that show good psychometric properties across the full range of performance, including better than normal, may also be more useful for genetic studies than those with a truncated distribution in which most individuals score perfectly (e.g., commission errors on a continuous performance test). This would allow for quantitative trait analyses and could also capitalize on statistically powerful designs using discordant relative pairs in which one is high and the other low on a quantitative trait (e.g., Dolan and Boomsma 1998; Eaves and Meyer 1994; Risch and Zhang 1995).

Computerized experimental measures borrowed from cognitive neuroscience may offer greater precision of measurement than clinical neuropsychological tasks (Nigg 2001) via assessment of reaction time rather than correct versus incorrect responses or the use of control tasks or constraints on alternative problem solving strategies (MacDonald and Carter 2002). Yet such measures should be used cautiously as they may have limited standardization across labs and minimal normative data. Other methods of reducing error variance in endophenotype studies include aggregating data from multiple sources. Rice and Todorov (1994) recommend the use of longitudinal or repeated measures designs for diagnostic assessment to reduce measurement errors in genetic studies. This strategy could be applied to neuropsychological data. Factor scores or conceptually derived scales that aggregate information from more than one neuropsychological measure of a construct could also reduce error associated with any one test. The literature reviewed here underscores the utility of this strategy because aggregate measures in twin and family studies have shown greater familial overlap with ADHD than individual measures in several studies. Yet the use of aggregated measures should also be undertaken with care, given that one reason to use endophenotypes is to simplify complex phenotypes into component parts (BF Pennington, *personal communication*). Therefore, measures should ideally be aggregated to provide better measures of specific

constructs rather than a summary score for a broad construct. Factor analysis may also provide a means of capturing multiple neurocognitive deficits were they to exist in ADHD, and such a strategy has been useful in the assessment of familial neurocognitive deficits in schizophrenia (Krabbendam et al 2001).

Selection of Measures Showing High Heritability or for Which a Given Gene Contributes a Significant Amount of Variance

Because the literature on the heritability of neuropsychological measures is sparse, twin studies with large samples are needed to better document which measures are most heritable. Such studies may benefit from collaborations across research groups to achieve adequate sample sizes. In the absence of twin data, family studies can be used to test whether a putative endophenotype is familial and to calculate upper limits of heritability. Additionally, studies should further assess the complexity of neuropsychological measures themselves because identification of measures for which specific genes contribute a large amount of variance would assist in the selection of measures for further study.

Statistical Methods for Phenotype Selection

Finally, recent advances in statistical methods may offer empirical strategies for selecting endophenotypes for analyses in molecular genetic studies when a priori specification of specific measures is premature. For example, Lange and colleagues (2003) have developed a strategy to test the association of multiple quantitative phenotypes with a given marker that eliminates the need to adjust for multiple comparisons in a subsequent family-based association test. In the first stage, the association phenotypes and the marker locus is tested using a population-based statistic grounded in generalized estimating equations that model the quantitative phenotypes as a function of genotypes of interest using noninformative families. The phenotype with the strongest genetic component can then be tested for association with the marker. For linkage analyses, Hauser and colleagues (2004) have developed a strategy to identify subsets of families, based on their score on a covariate, that provide the greatest evidence for linkage. Such strategies provide useful methods for endophenotype selection in light of the fact that the multifactorial nature of ADHD may not yield definitive evidence for choosing between multiple candidate measures.

Conclusions

Although evidence for genetic influences on ADHD has been accumulating since the 1960s (Lopez 1965), a great deal of work still lies ahead to understand the mechanisms linking genes to brain dysfunction and the expression of ADHD symptoms. Specification of genetic and environmental risk factors and their associated pathophysiological risk mechanisms will help characterize early predictors of persistence and morbidity that, in turn, will pave the way for more refined treatment and primary prevention strategies for ADHD. Although their use in ADHD is relatively new, endophenotypes have aided the clarification of the etiology and pathophysiology of several other conditions in medicine and psychiatry (e.g., Borecki et al 1990; Freedman et al 2001). The data reviewed here suggest that neuropsychological, neuroimaging, and electrophysiological endophenotypes for ADHD offer potential to move molecular genetics research forward. Such studies will, however, require careful consideration of heterogeneity and measurement to reduce the complexity of the endophenotypes themselves and take advantage of

their potential to target a more homogenous piece of the etiological puzzle of ADHD.

This work was supported in part by Grant Nos. K08-MH-66072 to AED and R21-MH066191 (Networking Grant) to SVF. We thank Joel Nigg, Ph.D., Bruce Pennington, Ph.D., and Irwin Waldman, Ph.D., for their comments on a related draft.

AED is a member of the McNeil Speakers Bureau and has served on the Eli Lilly Cognition Advisory Board. JB receives research support from the following pharmaceutical companies: Shire, Eli Lilly, Pfizer, McNeil, Abbott, Bristol-Myers-Squibb, New River Pharmaceuticals, Cephalon, Janssen, Neurosearch. He is a speaker for the following speaker's bureaus: Shire, Lilly, McNeil, and Cephalon; he is on the advisory board for the following companies: Eli Lilly, Shire, McNeil, Janssen, Novartis, and Cephalon.

Aspects of this work were presented at the conference "Advancing the Neuroscience of ADHD," February 28, 2004, in Boston, Massachusetts. The conference was sponsored by the Society of Biological Psychiatry through an unrestricted educational grant from McNeil Consumer & Specialty Pharmaceuticals.

- Adams J, Crosbie J, Wigg K, Ickowicz A, Pathare T, Roberts W, et al (2004): Glutamate receptor, ionotropic, N-methyl D-aspartate 2A (GRIN2A) gene as a positional candidate for attention-deficit/hyperactivity disorder in the 16p13 region. *Mol Psychiatry* 9:494–499.
- Alberts-Corush J, Firestone P, Goodman JT (1986): Attention and impulsivity characteristics of the biological and adoptive parents of hyperactive and normal control children. *Am J Orthopsychiatry* 56:413–423.
- Almasy L, Blangero J (2001): Endophenotypes as quantitative risk factors for psychiatric disease: Rationale and study design. *Am J Med Genet* 105:42–44.
- Ando J, Ono Y, Wright MJ (2001): Genetic structure of spatial and working memory. *Behav Genet* 31:615–624.
- Arcos-Burgos M, Castellanos FX, Konecki D, Lopera F, Pineda D, Palacio JD, et al (2004): Pedigree disequilibrium test (PDT) replicates association and linkage between DRD4 and ADHD in multigenerational and extended pedigrees from a genetic isolate. *Mol Psychiatry* 9:252–259.
- Asarnow RF, Nuechterlein KH, Subotnik KL, Fogelson DL, Torquato RD, Payne DL, et al (2002): Neurocognitive impairments in nonpsychotic parents of children with schizophrenia and attention-deficit/hyperactivity disorder. *Arch Gen Psychiatry* 59:1053–1060.
- Auerbach JG, Benjamin J, Faroy M, Geller V, Ebstein R (2001): DRD4 related to infant attention and information processing: A developmental link to ADHD? *Psychiatr Genet* 11:31–35.
- Bakker S, van der Meulen E, Buitelaar J, Sandkuijl L, Pauls D, Monsuur A, et al (2003): A whole-genome scan in 164 Dutch sib pairs with attention-deficit/hyperactivity disorder: Suggestive evidence for linkage on chromosomes 7p and 15q. *Am J Hum Genet* 72:1251–1260.
- Barkley RA (1997): ADHD and the nature of self-control. New York: Guilford Press.
- Barry RJ, Clarke AR, Johnstone SJ (2003a): A review of electrophysiology in attention-deficit/hyperactivity disorder: I. *Qualitative and quantitative electroencephalography*. *Clin Neurophysiol* 114:171–183.
- Barry RJ, Johnstone SJ, Clarke AR (2003b): A review of electrophysiology in attention-deficit/hyperactivity disorder: II. *Event-related potentials*. *Clin Neurophysiol* 114:184–198.
- Bartfai A, Pedersen NL, Asarnow RF, Schalling D (1991): Genetic factors for the span of apprehension test: A study of normal twins. *Psychiatry Research* 38:115–124.
- Berquin PC, Giedd JN, Jacobsen LK, Hamburger SD, Krain AL, Rapoport JL, et al (1998): Cerebellum in attention-deficit hyperactivity disorder: A morphometric MRI study. *Neurology* 50:1087–1093.
- Borecki IB, Rao DC, Yaouanq J, Lalouel JM (1990): Serum ferritin as a marker of affection for genetic hemochromatosis. *Hum Hered* 40:159–166.
- Campana A, Macciardi F, Gambini O, Scarone S (1996): The Wisconsin Card Sorting Test (WCST) performance in normal subjects: A twin study. *Neuropsychobiology* 34:14–17.
- Carlson SR, Iacono WG, McGue M (2002): P300 amplitude in adolescent twins discordant and concordant for alcohol use disorders. *Biol Psychol* 61:203–227.
- Carmelli D, Swan GE, DeCarli C, Reed T (2002): Quantitative genetic modeling of regional brain volumes and cognitive performance in older male twins. *Biol Psychol* 61:139–155.
- Castellanos FX, Lee PP, Sharp W, Jeffries NO, Greenstein DK, Clasen LS, et al (2002): Developmental trajectories of brain volume abnormalities in children and adolescents with attention-deficit/hyperactivity disorder. *JAMA* 288:1740–8.
- Castellanos FX, Tannock R (2002): Neuroscience of attention-deficit/hyperactivity disorder: The search for endophenotypes. *Nat Rev Neurosci* 3:617–628.
- Chabot RJ, Serfontein G (1996): Quantitative electroencephalographic profiles of children with attention deficit disorder. *Biol Psychiatry* 40:951–963.
- Clarke A, Barry R, McCarthy R, Selikowitz M, Brown C (2002): EEG evidence for a new conceptualisation of attention deficit hyperactivity disorder. *Clin Neurophysiol* 113:1036–1044.
- Denckla MB (1996): A theory and model of executive function: A neuropsychological perspective. In: Lyon GR, Krasgenor NA, editors. *Attention, Memory and Executive Function*. Baltimore, MD: Paul H. Brooks, 263–277.
- Dolan CV, Boomsma DI (1998): Optimal selection of sib pairs from random samples for linkage analysis of a QTL using the EDAC test. *Behav Genet* 28:197–206.
- Doyle AE, Biederman J, Seidman L, Reske-Nielsen J, Faraone SV (in press-a): Neuropsychological functioning in relatives of girls with and without ADHD. *Psychol Med*.
- Doyle AE, Biederman J, Seidman L, Weber W, Faraone S (2000): Diagnostic efficiency of neuropsychological test scores for discriminating boys with and without attention deficit hyperactivity disorder. *J Consult Clin Psychol* 68:477–488.
- Doyle AE, Faraone S (2002): Familial links between ADHD, conduct disorder and bipolar disorder. *Curr Psychiatry Rep* 4:146–152.
- Doyle AE, Faraone SV, Seidman LJ, Willcutt EG, Nigg JT, Waldman ID, et al (in press-b): Are endophenotypes based on measures of executive functions useful for molecular genetic studies of ADHD. *J Child Psychol Psychiatry*.
- Durston S, Hulshoff H, Schnack HG, Buitelaar JK, Steenhuis MP, Minderaa RB, et al (2004): Magnetic resonance imaging of boys with attention-deficit/hyperactivity disorder and their unaffected siblings. *J Am Acad Child Adolesc Psychiatry* 43:332–340.
- Eaves L, Meyer J (1994): Locating human quantitative trait loci: Guidelines for the selection of sibling pairs for genotyping. *Behav Genet* 24:443–455.
- Egan MF, Goldberg TE, Gscheidle T, Weirich M, Rawlings R, Hyde TM, et al (2001): Relative risk for cognitive impairments in siblings of patients with schizophrenia. *Biol Psychiatry* 50:98–107.
- Ernst M, Liebenauer L, King A, Fitzgerald G, Cohen R, Zametkin A (1994): Reduced brain metabolism in hyperactive girls. *J Am Acad Child Adolesc Psychiatry* 33:858–868.
- Fan J, Wu Y, Fosella JA, Posner MI (2001): Assessing the heritability of attentional networks. *BMC Neurosci* 2:14.
- Faraone S, Kremen W, Lyons M, Pepple J, Seidman L, Tsuang M (1995): Diagnostic accuracy and linkage analysis: How useful are schizophrenia spectrum phenotypes. *Am J Psychiatry* 152:1286–1290.
- Faraone SV (2002): Report from the third international meeting of the Attention-Deficit Hyperactivity Disorder Molecular Genetics Network. *Am J Med Genet* 114:272–276.
- Faraone SV, Biederman J (1998): Neurobiology of attention-deficit hyperactivity disorder. *Biol Psychiatry* 44:951–958.
- Faraone SV, Biederman J, Mennin D, Russell RL (1998): Bipolar and antisocial disorders among relatives of ADHD children: Parsing familial subtypes of illness. *Am J Med Genet* 81:108–116.
- Faraone SV, Biederman J, Monuteaux MC (2000): Toward guidelines for pedigree selection in genetic studies of attention deficit hyperactivity disorder. *Genet Epidemiol* 18:1–16.
- Faraone SV, Perlis RH, Doyle AE, Smoller JW, Goralnick J, Holmgren MA, et al (2005): Molecular genetics of attention-deficit/hyperactivity disorder. *Biol Psychiatry*, 57:1313–1323.
- Faraone SV, Tsuang D, Tsuang MT (1999): Genetics and Mental Disorders: A Guide for Students, Clinicians, and Researchers. New York: Guilford Press.

- Faraone SV, Tsuang MT (2003): Heterogeneity and the genetics of bipolar disorder. *Am J Hum Genet* 123C:1–9.
- Fisher SE, Francks C, McCracken JT, McGough JJ, Marlow AJ, MacPhie IL, et al (2002): A genomewide scan for loci involved in attention-deficit/hyperactivity disorder. *Am J Hum Genet* 70:1183–1196.
- Fossella JA, Sommer T, Fan J, Wu Y, Swanson JM, Pfaff DW (2002): Assessing the molecular genetics of attention networks. *BMC Neurosci* 4:14.
- Freedman R, Adler LE, Leonard S (1999): Alternative phenotypes for the complex genetics of schizophrenia. *Biol Psychiatry* 45:551–558.
- Freedman R, Leonard S, Gault J, Hopkins J, Cloninger C, Kaufmann C, et al (2001): Linkage disequilibrium for schizophrenia at the chromosome 15q13–14 locus of the alpha7-nicotinic acetylcholine receptor subunit gene (CHRNA7). *Am J Med Genet (Neuropsychiatr Genet)* 105:20–22.
- Gainetdinov RR, Wetsel WC, Jones SR, Levin ED, Jaber M, Caron MG (1999): Role of serotonin in the paradoxical calming effect of psychostimulants on hyperactivity. *Science* 283:397–402.
- Giedd J, Blumenthal J, Molloy E, Castellanos F (2001): Brain imaging of attention deficit/hyperactivity disorder. *Ann N Y Acad Sci* 931:33–49.
- Goldberg E, Seidman LJ (1991): Higher cortical functions in normals and in schizophrenia: A selective review. In: Steinhauer SR, Gruzeliar JH, Zubin J, editors. *Handbook of Schizophrenia. Volume 5: Neuropsychology, Psychophysiology and Information Processing*. Amsterdam: Elsevier Science, 553–597.
- Goodman R, Stevenson J (1989): A twin study of hyperactivity: II. The aetiological role of genes, family relationships and perinatal adversity. *J Child Psychol Psychiatry* 30:691–709.
- Gottesman II, Gould TD (2003): The endophenotype concept in psychiatry: Etymology and strategic intentions. *Am J Psychiatry* 160:636–645.
- Hauser ER, Watanabe RM, Duren WL, Bass MP, Langefeld CD, Boehnke M (2004): Ordered subset analysis in genetic linkage mapping of complex traits. *Genet Epidemiol* 27:53–63.
- Hinshaw SP, Carte ET, Sarni N, Treuting JJ, Zupan B (2002): Preadolescent girls with attention-deficit/hyperactivity disorder: II. *Neuropsychological performance in relation to subtypes and individual classification*. *J Consult Clin Psychol* 70:1099–1111.
- Holmes J, Hever T, Hewitt L, Ball C, Taylor E, Rubia K, Thaper A (2002): A pilot twin study of psychological measures of attention deficit hyperactivity disorder. *Behav Genet* 32:389–395.
- Hudziak J, Heath A, Madden P, Reich W, Bucholz K, Slutske W, et al (1998): Latent class and factor analysis of DSM-IV ADHD: A twin study of female adolescents. *J Am Acad Child Adolesc Psychiatry* 37:848–857.
- Iacono WG, Carlson SR, Malone SM, McGue M (2002): P3 event-related potential amplitude and the risk for disinhibitory disorders in adolescent boys. *Arch Gen Psychiatry* 59:750–757.
- Iacono WG, Malone SM, McGue M (2003): Substance use disorders, externalizing psychopathology, and P300 event-related potential amplitude. *Int J Psychophysiol* 48:147–178.
- Johansen E, Aase H, Meyer A, Sagvolden T (2002): Attention-deficit/hyperactivity disorder (ADHD) behaviour explained by dysfunctioning reinforcement and extinction processes. *Behav Brain Res* 130:37–45.
- Joober R, Gauthier J, Lal S, Bloom D, Lalonde P, Rouleau G, et al (2002): Catechol-O-methyltransferase Val-108/158-Met gene variants associated with performance on the Wisconsin Card Sorting Test. *Arch Gen Psychiatry* 59:662–663.
- Krabbandam L, Marcellis M, Delespaul P, Jolles J, van Os J (2001): Single or multiple familial cognitive risk factors in schizophrenia? *Am J Med Genet (Neuropsychiatr Genet)* 105:183–188.
- Kuntsi J, Stevenson J (2001): Psychological mechanisms in hyperactivity: II. The Role of Genetic Factors. *J Child Psychol Psychiatry* 42:211–219.
- Kuntsi J, Stevenson J, Oosterlaan J, Sonuga-Barke E (2001): Test-retest reliability of new delay aversion task and executive function. *Br J Dev Psychol* 19:339–348.
- Lange C, Lyon H, DeMeo D, Raby B, Silverman EK, Weiss ST (2003): A new powerful non-parametric two-stage approach for testing multiple phenotypes in family-based association studies. *Hum Hered* 56:10–17.
- Langley K, Marshall L, van den Bree M, Thomas H, Owen M, O'Donovan M, et al (2004): Association of the dopamine D4 receptor gene 7-repeat allele with neuropsychological test performance of children with ADHD. *Am J Psychiatry* 161:133–138.
- Leboyer M, Bellivier F, Nosten-Bertrand M, Jouvent R, Pauls D, Mallet J (1998): Psychiatric genetics: Search for phenotypes. *Trends Neurosci* 21:102–105.
- Logan GD, Schachar RJ, Tannock R (1997): Impulsivity and inhibitory control. *Psychol Sci* 8:60–64.
- Lopez RE (1965): Hyperactivity in twins. *Can Psychiatr Assoc J* 10:421–426.
- Lyon GR, Krasnegor NA (1996): Attention, Memory, and Executive Function. Baltimore, MD: Paul H. Brookes.
- MacDonald AW III, Carter CS (2002): Cognitive experimental approaches to investigating impaired cognition in schizophrenia: A paradigm shift. *J Clin Neuropsychol* 24:873–882.
- Malhotra AK, Kestler LJ, Mazzanti C, Bates JA, Goldberg T, Goldman D (2002): A functional polymorphism in the COMT gene and performance on a test of prefrontal cognition. *Am J Psychiatry* 159:652–654.
- Manor I, Corbex M, Eisenberg J, Gritsenko I, Bachner-Melman R, Tyano S, et al (2004): Association of the dopamine D5 receptor with attention deficit hyperactivity disorder (ADHD) and scores on a continuous performance test (TOVA). *Am J Med Genet* 127B:73–77.
- Manor I, Tyano S, Eisenberg J, Bachner-Melman R, Kotler M, Ebsstein RP (2002): The short DRD4 repeats confer risk to attention deficit hyperactivity disorder in a family-based design and impair performance on a continuous performance test (TOVA). *Mol Psychiatry* 7:790–794.
- Mattes JA (1980): The role of frontal lobe dysfunction in childhood hyperkinesis. *Compr Psychiatry* 21:358–369.
- McCracken JT, Smalley SL, McGough JJ, Crawford L, Del'Homme M, Cantor RM, et al (2000): Evidence for linkage of a tandem duplication polymorphism upstream of the dopamine D4 receptor gene (DRD4) with attention deficit hyperactivity disorder (ADHD). *Mol Psychiatry* 5:531–536.
- Mills S, Langley K, Van Den Bree M, Street E, Turic D, Owen MJ, et al (2004): No evidence of association between catechol-O-methyltransferase (COMT) Val158Met genotype and performance on neuropsychological tasks in children with ADHD: A case-control study. *BMC Psychiatry* 4:15.
- Mostofsky S, Reiss AL, Lockhart P, Denckla MB (1998): Evaluation of cerebellar size in attention-deficit hyperactivity disorder. *J Child Neurol* 13:434–439.
- Mostofsky S, Cooper K, Kates W, Denckla M, Kaufmann W (2002): Smaller prefrontal and premotor volumes in boys with attention-deficit/hyperactivity disorder. *Biol Psychiatry* 52:785–794.
- Murphy KR, Barkley RA (1996): Parents of children with attention-deficit/hyperactivity disorder: Psychological and attentional impairment. *Am J Orthopsychiatry* 66:93–102.
- Murphy KR, Barkley RA (1996): Parents of children with attention-deficit/hyperactivity disorder: Psychological and attentional impairment. *Am J Orthopsychiatry* 66:93–102.
- Myles-Worsley M, Coon H (1997): Genetic and developmental factors in spontaneous selective attention: A study of normal twins. *Psychiatr Res* 71:163–174.
- Nigg JT (2001): Is ADHD a disinhibitory disorder? *Psychol Bull* 127:571–598.
- Nigg JT, Blaskey L, Stawicki J, Sachek J (2004): Evaluating endophenotype model of ADHD neuropsychological deficit: Results for parents and siblings of children with DSM-IV ADHD combined and inattentive subtypes. *J Abnorm Psychol* 113:614–625.
- Nigg JT, Swanson JM, Hinshaw SP (1997): Covert visual spatial attention in boys with attention deficit hyperactivity disorder: Lateral effects, methylphenidate response and results for parents. *Neuropsychologia* 35:165–176.
- Nigg JT, Willcutt EG, Doyle AE, Sonuga-Barke E (2005): Causal heterogeneity in attention-deficit/hyperactivity disorder: Do we need neuropsychological subtypes? *Biol Psychiatry* 57:1224–1230.
- Ogdie M, Macphie I, Minassian S, Yang M, Fisher S, Francks C, et al (2002): A genomewide scan for attention-deficit/hyperactivity disorder in an extended sample: Suggestive linkage on 17p11. *Am J Hum Genet* 72:1268–1279.
- Pennington BF, Bennetto L, McAleer OK, Roberts RJ, Jr (1996): Executive functions and working memory: Theoretical measurement issues. In: Lyon GR, Krasnegor NA, eds. *Attention, Memory and Executive Function*. Baltimore, MD: Paul H. Brookes Publishing Co, 327–348.
- Pennington BF, Filipek PA, Lefly D, Chhabildas N, Kennedy DN, Simon JH, et al (2000): A twin MRI study of size variations in human brain. *J Cogn Neurosci* 12:223–232.
- Pennington BF, Ozonoff S (1996): Executive functions and developmental psychopathology. *J Child Psychol Psychiatry* 37:51–87.
- Plomin R (1999): Genetics and general cognitive ability. *Nature* 402:C25–29.
- Polich J, Pollock VE, Bloom FE (1994): Meta-analysis of P300 amplitude from males at risk for alcoholism. *Psychol Bull* 115:55–73.

- Posthuma D, de Geus EJ, Neale MC, Hulshoff Pol HE, Baare WEC, Kahn RS, et al (2000): Multivariate genetic analysis of brain structure in an extended twin design. *Behav Genet* 30:311–319.
- Rasmussen E, Neuman R, Heath A, Levy F, Hay D, Todd R (2002): Replication of the latent class structure of attention-deficit/hyperactivity disorder (ADHD) subtypes in a sample of Australian twins. *J Child Psychol Psychiatry* 43:1018–1028.
- Rhee SH, Waldman ID, Hay DA, Levy F (1999): Sex differences in genetic and environmental influences on DSM-III-R attention-deficit/hyperactivity disorder. *J Abnorm Psychol* 108:24–41.
- Rice J, Todorov A (1994): Stability of diagnosis: Application to phenotype definition. *Schizophr Bull* 20:185–190.
- Risch N (1990a): Linkage strategies for genetically complex traits. I. Multilocus models. *Am J Hum Genet* 46:222–228.
- Risch N (1990b): Linkage strategies for genetically complex traits. II. The power of affected relative pairs. *Am J Hum Genet* 46:229–241.
- Risch N, Zhang H (1995): Extreme discordant sib pairs for mapping quantitative trait loci in humans. *Science* 268:1584–1589.
- Rowe DC, Stever C, Giedinghagen LN, Gard JM, Cleveland HH, Terris ST, et al (1998): Dopamine DRD4 receptor polymorphism and attention deficit hyperactivity disorder. *Mol Psychiatry* 3:419–426.
- Rubinstein M, Phillips TJ, Bunzow JR, Falzone TL, Dziewczapolski G, Zhang G, et al (1997): Mice lacking dopamine D4 receptors are supersensitive to ethanol, cocaine, and methamphetamine. *Cell* 90:991–1001.
- Sagvolden T, Aase H, Zeiner P, Berger D (1998): Altered reinforcement mechanisms in attention-deficit/hyperactivity disorder. *Behav Brain Res* 94:61–71.
- Schachar R, Tannock R, Marriott M, Logan G (1995): Deficient inhibitory control in attention deficit hyperactivity disorder. *J Abnorm Child Psychol* 23:411–437.
- Seidman L, Biederman J, Monuteaux M, Weber W, Faraone SV (2000): Neuropsychological functioning in nonreferred siblings of children with attention deficit hyperactivity disorder. *J Abnorm Psychol* 109:252–265.
- Seidman LJ, Doyle A, Fried R, Valera E, Crum K, Matthews L (2004): Neuropsychological function in adults with attention-deficit/hyperactivity disorder. *Psychiatr Clin North Am* 27:261–282.
- Seidman L, Valera E (2002): The ADHD brain. In: Biederman J, editor. *ADHD: Current Understanding of Etiology, Diagnosis, and Neurobiology*. Boston: Veritas Institute for Medical Education, 44.
- Seidman L, Valera E, Makris N (2005): Structural brain imaging of attention-deficit/hyperactivity disorder. *Biol Psychiatry* 57:1263–1272.
- Seidman LJ, Faraone SV, Goldstein JM, Goodman JM, Kremen WS, Toomey R, et al (1999): Thalamic and amygdala-hippocampal volume reductions in first-degree relatives of patients with schizophrenia: An MRI-based morphometric analysis. *Biol Psychiatry* 46:941–954.
- Sergeant J (2000): The cognitive-energetic model: An empirical approach to attention-deficit hyperactivity disorder. *Neurosci Biobehav Rev* 24:7–12.
- Sergeant J (2005): Modeling attention-deficit/hyperactivity disorder: A critical appraisal of the cognitive-energetic model. *Biol Psychiatry* 57:1248–1255.
- Sergeant JA, Geurts H, Oosterlaan J (2002): How specific is a deficit of executive functioning for attention-deficit/hyperactivity disorder? *Behav Brain Res* 130:3–28.
- Sherman D, Iacono W, McGue M (1997): Attention deficit hyperactivity disorder dimensions: A twin study of inattention and impulsivity hyperactivity. *J Am Acad Child Adolesc Psychiatry* 36:745–753.
- Skuse DH (2001): Endophenotypes and child psychiatry. *Br J Psychiatry* 178:395–396.
- Slaats-Willemse D, Swaab-Barneveld H, de Sonneville L, van der Meulen E, Buitelaar J (2003): Deficient response inhibition as a cognitive endophenotype of ADHD. *J Am Acad Child and Adolesc Psychiatry* 42:1242–1248.
- Solanto M, Abikoff H, Sonuga-Barke E, Schachar R, Logan G, Wigal T, et al (2001): The ecological validity of delay aversion and response inhibition as measures of impulsivity in AD/HD: A supplement to the NIMH multimodal treatment study of AD/HD. *J Abnorm Child Psychol* 29:215–228.
- Sonuga-Barke EJ (2002): Psychological heterogeneity in AD/HD—a dual pathway model of behaviour and cognition. *Behav Brain Res* 130:29–36.
- Sonuga-Barke EJ (2003): The dual pathway model of AD/HD: An elaboration of neuro-developmental characteristics. *Neurosci Biobehav Rev* 27:593–604.
- Sonuga-Barke EJ (2005): Casual models of attention-deficit/hyperactivity disorder: From simple single deficits to multiple developmental pathways. *Biol Psychiatry* 57:1231–1238.
- Sonuga-Barke EJ, Dalen L, Remington B (2003): Do executive deficits and delay aversion make independent contributions to preschool attention-deficit/hyperactivity disorder symptoms? *J Am Acad Child Adolesc Psychiatry* 42:1335–1342.
- Sonuga-Barke EJ, Williams E, Hall M, Saxton T (1996): Hyperactivity and delay aversion. III: The effect on cognitive style of imposing delay after errors. *J Child Psychol Psychiatry* 37:189–194.
- Suarez BK, Hampe CL, Van Eerdewegh P (1994): Problems of replicating linkage claims in psychiatry. In: Gershon ES, Cloninger CR, Barrett JE, editors. *Genetic Approaches in Mental Disorders*. Washington, DC: American Psychiatric Press, 23–46.
- Swanson J, Oosterlaan J, Murias M, Schuck S, Flodman P, Spence MA, et al (2000): Attention deficit/hyperactivity disorder children with a 7-repeat allele of the dopamine receptor D4 gene have extreme behavior but normal performance on critical neuropsychological tests of attention. *Proc Natl Acad Sci U S A* 97:4754–4759.
- Thompson PM, Cannon TD, Narr KR, van Erp T, Poutanen V-P, Huttunen M, et al (2001): Genetic influences on brain structure. *Nat Neurosci* 4:1253–1258.
- Todd RD (2000): Genetics of attention deficit/hyperactivity disorder: Are we ready for molecular genetic studies? *Am J Med Genet (Neuropsychiatr Genet)* 96:241–243.
- Todd RD, Neuman RJ, Lobos EA, Jong YJ, Reich W, Heath AC (2001): Lack of association of dopamine D4 receptor gene polymorphisms with ADHD subtypes in a population sample of twins. *Am J Med Genet (Neuropsychiatr Genet)* 105:432–438.
- Tsuang MT, Faraone SV (1995): The case for heterogeneity in the etiology of schizophrenia. *Schizophr Res* 17:161–175.
- van Beijsterveldt CE, van Baal GC (2002): Twin and family studies of the human electroencephalogram: A review and a meta-analysis. *Biol Psychol* 61:111–138.
- Waldman ID, Rowe DC, Abramowitz A, Kozel ST, Mohr JH, Sherman SL, et al (1998): Association and linkage of the dopamine transporter gene and attention-deficit hyperactivity disorder in children: Heterogeneity owing to diagnostic subtype and severity. *Am J Hum Genet* 63:1767–1776.
- Willcutt EG, Doyle AE, Nigg JT, Faraone SV, Pennington BF (2005): Validity of the executive function theory of ADHD: A meta-analytic review. *Biol Psychiatry* 57:1336–1346.
- Zametkin AJ, Nordahl TE, Gross M, King AC, Semple WE, Rumsey J, et al (1990): Cerebral glucose metabolism in adults with hyperactivity of childhood onset. *N Eng J Med* 323:1361–1366.