

Testing for Neuropsychological Endophenotypes in Siblings Discordant for Attention-Deficit/Hyperactivity Disorder

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Background: Neurocognitive deficits associated with attention-deficit/hyperactivity disorder (ADHD) might be useful intermediate endophenotypes for determining specific genetic pathways that contribute to ADHD.

Methods: This study administered 17 measures from prominent neuropsychological theories of ADHD (executive function, processing speed, arousal regulation and, motivation/delay aversion) in dizygotic (DZ) twin pairs discordant for ADHD and control twin pairs (ages 8–18 years) to compare performance between twins affected with ADHD ($n = 266$), their unaffected co-twins ($n = 228$), and control children from twin pairs without ADHD or learning difficulties ($n = 332$).

Results: The ADHD subjects show significant impairment on executive function, processing speed, and response variability measures compared with control subjects. Unaffected co-twins of ADHD subjects are significantly impaired on nearly all the same measures as their ADHD siblings, even when subclinical symptoms of ADHD are controlled.

Conclusions: Executive function, processing speed, and response variability deficits might be useful endophenotypes for genetic studies of ADHD.

Key Words: ADHD, endophenotype, executive function, genetics, neuropsychology, processing speed

The Genetics and Neuropsychology of Attention-Deficit/Hyperactivity Disorder

Attention-deficit/hyperactivity disorder (ADHD) is a heterogeneous disorder with a complex, multifactorial etiology (1,2). Twin studies indicate that ADHD is highly heritable, and molecular genetic studies have identified 8–10 candidate genes that might increase susceptibility to ADHD (3,4). However, each of these genes accounts for a relatively small proportion of the total variance in ADHD symptoms, and the majority of the genetic variance in ADHD remains unexplained.

The neuropsychology of ADHD is also multifactorial, with no single deficit that is necessary or sufficient to explain all cases of ADHD (e.g., 5–7). One prominent cognitive theory suggests that ADHD symptoms arise from a general weakness in executive functions (EF) or in a more specific aspect of executive control such as response inhibition or working memory (e.g., 8–11). In addition, groups with ADHD exhibit significant aversion to delay (12), slower and more variable response speed (13–15), and atypical responses to reward or punishment cues in some situations (16–18).

Neuropsychological Endophenotypes for ADHD

Owing to the neuropsychological complexity of ADHD, several authors have suggested that neuropsychological measures might be useful endophenotypes for genetic studies of ADHD (e.g., 19,20). Although there is ongoing debate about the optimal criteria for an endophenotype, virtually all conceptualizations

refer to a phenotype that is more proximal to the genetic etiology of the disorder than its behavioral symptoms and is influenced by at least one of the genes that increase susceptibility to the disorder (e.g., 21–23). Theoretically, the endophenotype might have a simpler etiology than the symptoms of the disorder, because it is closer to the specific gene products in the pathway from genes to expressed symptoms. The endophenotype might then provide increased power to detect the effect of individual genes on a heterogeneous disorder such as ADHD.

Studies of Unaffected Relatives. Because biological siblings share one-half of their segregating genes on average (e.g., 24), unaffected relatives of probands with ADHD are likely to share a subset of the susceptibility genes that lead the proband to express the disorder. The endophenotype should then also be present in the unaffected relatives, albeit potentially reduced in severity. Several studies have measured neuropsychological performance in unaffected relatives to test whether these measures are useful endophenotypes for ADHD.

Seidman *et al.* (20) examined six putative measures of EF in siblings with and without ADHD and found that the neuropsychological profile of siblings without ADHD did not differ significantly from control subjects, except on a single measure of verbal learning. However, it is important to note that the siblings who met criteria for ADHD also differed from control subjects on only two measures, suggesting that the specific measures administered in this study might not consistently differentiate between groups with and without ADHD.

Two studies focused exclusively on response inhibition and found that small samples of unaffected siblings of ADHD probands did not differ from their ADHD siblings on measures of response inhibition (25,26). Nigg *et al.* (23) examined performance of relatives of ADHD probands on measures of a broader range of neuropsychological tasks. Relatives exhibited weaknesses on measures of output speed, set-shifting, response inhibition, and response variability. However, these results are complicated by the fact that response inhibition deficits were only found in relatives of girls with ADHD, and response variability deficits were found in only mothers of probands with

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ADHD. In summary, these previous studies provide some support for neuropsychological measures as endophenotypes for ADHD but suggest that results might differ in male and female subjects.

The Current Study

In this study we administered an extensive battery of neuropsychological measures to dizygotic (DZ) twin pairs discordant for ADHD and control DZ twin pairs in which neither twin has ADHD. Because unaffected siblings are likely to share a subset of the genetic influences and concomitant neuropsychological weaknesses that lead to ADHD symptoms in the affected proband, we hypothesized that the unaffected co-twins would exhibit significant neuropsychological weaknesses in comparison with twins without ADHD on at least a subset of these measures.

Methods and Materials

Participants

Recruitment. Participants completed the measures described in this paper as part of the Colorado Learning Disabilities Research Center (CLDRC) twin study, an ongoing study of the etiology of learning disabilities and ADHD (27,28). Parents of all twins between the ages of 8 and 18 years in local school districts were contacted by letter and invited to participate in the initial screening component of the study. If either of the twins met criteria for any DSM-IV ADHD subtype on the basis of parent or teacher ratings completed during the screening, the twin pair was invited to participate in the remainder of the study. Twins with significant reading difficulties were independently recruited as part of the overall study, but twins with reading difficulties alone were not included in the analyses described here. A subset of the twins who met criteria for ADHD also exhibited significant learning difficulties (32%), consistent with the rate of comorbidity in other samples (e.g., 29). The comparison sample comprised twin pairs from the same school districts in which neither twin met screening criteria for ADHD or significant reading difficulties. Approximately 35% of the families who were contacted agreed to participate in the initial screening procedure, and 95% of the families in the screening sample agreed to participate in the larger study if invited.

Exclusionary Criteria. Potential participants with a documented brain injury, significant hearing or visual impairment, or other rare genetic or environmental etiology (e.g., Fragile X syndrome, Down syndrome, or other sex chromosome anomalies) were excluded from the sample. In addition, three participants were excluded from analyses owing to a Full Scale IQ score below 75.

Diagnostic Measures and Operational Definition of ADHD

ADHD Symptoms. The Disruptive Behavior Rating Scale (DBRS; 30) was used to obtain parent and teacher ratings of the 18 symptoms of DSM-IV ADHD. Items rated as “often” or “very often” were scored as positive symptoms, and items rated as “never or rarely” or “sometimes” were scored as negative symptoms, consistent with previous studies that used similar rating scales (e.g., 31). The algorithm from the DSM-IV field trials for the disruptive behavior disorders was used to combine parent and teacher ratings of ADHD symptoms (32). This procedure codes each symptom as positive if it is endorsed by either the parent or the teacher. Individuals with six or more symptoms of inattention but fewer than six symptoms of hyperactivity-impulsivity were coded as predominantly inattentive type, participants

with six or more symptoms of hyperactivity-impulsivity but fewer than six symptoms of inattention were categorized as predominantly hyperactive/impulsive type, and individuals with six or more symptoms on both dimensions were coded as combined type.

Age of Onset and Functional Impairment Across Settings.

Consistent with DSM-IV criteria, children were categorized as ADHD only if symptoms were present before age 7 and if these symptoms caused significant functional impairment across settings. Because the participants were 8–18 years old at the time of the study, age of onset was defined by parent report only. Both parent and teacher ratings were used to assess impairment across settings. As part of the DBRS, parents and teachers rated the extent to which ADHD symptoms led to difficulties in social interactions, academic performance, and daily activities. Each rater also completed a questionnaire developed for this study that assessed academic functioning (grades, understanding of assignments, completion of homework) and social functioning (number of friends and quality and duration of friendships) as well as a widely-used measure that asks parents and teachers to estimate the proportion of children who like, dislike, or ignore the participant (33). For each measure significant impairment was operationalized as a score below the 10th percentile of the comparison sample, and participants were included in the ADHD group if they exhibited significant impairment in multiple domains.

A total of 304 participants met criteria for DSM-IV ADHD (11.8% of the overall screened sample). Consistent with other community samples (e.g., 34), the majority of participants met criteria for the inattentive type ($n = 192$), and most of the remaining participants met criteria for the combined type ($n = 74$). Results from our sample and others call into question the validity of the hyperactive-impulsive type in school-age children (35) and suggest that this subtype is not consistently associated with the neuropsychological weaknesses that characterize the inattentive and combined types (e.g., 36,37). In light of these results and the small number of individuals with the hyperactive-impulsive type ($n = 38$), these subjects were excluded from analyses.

To examine differences between the inattentive and combined types, initial comparisons were conducted while including in the ADHD groups only those individuals who met criteria for the inattentive type (i.e., comparison group vs. non-ADHD co-twins of inattentive probands vs. inattentive type-only probands), then repeated while including only probands who met criteria for the combined type. Consistent with previous results from this sample and others (28,36,38), the pattern of results was virtually identical for the two subtypes. Therefore, to simplify interpretation both subtype groups were included in a single group with ADHD for the analyses described in this article.

Because twins in a pair are not completely independent observations, one twin was selected at random from each twin pair in which both twins met inclusion criteria for the control or ADHD groups. Results were virtually identical when analyses were repeated in a sample in which the selected twin was replaced by the co-twin that was excluded from the first set of analyses, suggesting that the random selection of one twin from each of these pairs did not inadvertently bias the results. The current analysis included 332 control twins randomly selected from each control DZ twin pair, 228 unaffected DZ co-twins of ADHD probands, and 266 DZ twins with ADHD (inattentive or combined subtype).

Cognitive Measures

Reading Achievement and Intelligence. Full Scale IQ was assessed with the Wechsler Intelligence Scale for Children, Revised (WISC-R; 16 years old and younger; 39) or the Wechsler Adult Intelligence Scale (WAIS; 17 and 18 years old; 40), and reading achievement was assessed with the Peabody Individual Achievement Test (PIAT; 41). To simplify interpretation a reading composite score was created on the basis of a discriminant function analysis of the PIAT Reading Recognition, Reading Comprehension, and Spelling subtests (42).

Neuropsychological Measures. The neuropsychological battery was selected to include measures that have been shown to be most strongly associated with ADHD in previous studies. The battery includes tasks that tap several different domains of EF as well as measures of processing speed, response variability, motivational processes, and delay aversion. Owing to space constraints, an abbreviated description of each task is provided in Table 1. All measures are described in detail in previous reports (15,28,43–58).

Procedures

Testing procedures are described in detail elsewhere (e.g., 28). Briefly, the measures of intelligence, reading achievement, and processing speed were administered in an initial testing session, and the neuropsychological measures were completed during a separate testing session approximately 2 weeks later. All examiners were unaware of the diagnostic status of the child and the results of the testing completed in other sessions. Parents of participants who were taking psychostimulant medication were asked to withhold medication for 24 hours before each session of the study to minimize the influence of this intervention on the results. The procedures implemented in this study were approved internally by the institutional review boards at the University of Colorado, Boulder, and the University of Denver.

Descriptive Characteristics

The mean age, socioeconomic status (SES; Hollingshead, unpublished data), and IQ scores of the probands with ADHD and their unaffected co-twins were significantly below the mean of the comparison group (Table 2). As expected, on the basis of the way the sample was defined, the mean number of ADHD symptoms was also significantly higher for the group with ADHD than for the comparison groups without ADHD. In addition, the siblings of ADHD probands who did not meet criteria for ADHD exhibited significantly more symptoms of ADHD than the control subjects. These results suggest that at least a subset of siblings of children with ADHD exhibit subclinical manifestations of the disorder even though they do not meet full criteria for ADHD.

Data Analyses

Data Adjustments. As expected, correlational analyses revealed that performance on all neuropsychological variables improved as a linear function of age ($p < .01$ for all measures). Therefore, to control for the influence of age on any of the results, an age-adjusted score was created for each measure by regressing the variable onto age and age-squared and saving the residual score. The distribution of each age-adjusted variable was then assessed for outliers before any additional analyses. Outliers were defined as scores that fell more than 3 SDs from the mean of the overall sample and more than .5 SD beyond the next most extreme score. Each outlier was adjusted to a score .5 SD units beyond the next highest score, with multiple outliers rescored to .1 SD apart.

Analyses

An initial multivariate analysis of covariance (ANCOVA) revealed a significant main effect of group on the neuropsychological tasks [$F = 28.5, p < .01$]. Subsequent one-way analyses of variance were then conducted for each individual cognitive measure to specify further the nature of the overall main effect.

Group Differences in Intelligence and Reading Ability. Some researchers argue that FSIQ and symptoms of comorbid disorders should always be statistically controlled to ensure that neuropsychological impairments associated with ADHD cannot be explained more parsimoniously by group differences on these correlated variables (e.g., 59,60). Conversely, ADHD symptoms might directly cause a child to perform poorly on standardized tests of intelligence or reading (e.g., 8). In these cases, it would not be appropriate to control for these variables, because this would remove variance that is associated with ADHD. These issues have not been resolved conclusively, and the optimal approach is likely to vary depending on the specific research question. Therefore, with the exception of the exclusion of participants with FSIQ scores below 75 from all analyses and the exclusion of control participants who met criteria for reading disability (RD), neither IQ nor reading ability were considered in the algorithms used to define the groups. Instead, we directly tested whether group differences in the neuropsychological measures are explained by group differences in intelligence or reading ability.

Controlling for ADHD Symptoms. Although unaffected co-twins do not meet full criteria for ADHD, it is possible that subclinical symptoms might lead to lower neuropsychological scores. Therefore, ADHD symptoms were controlled in a secondary analysis to test whether any deficits in unaffected siblings of the ADHD probands are explained by subclinical elevations of ADHD symptoms. If group differences remain significant, it would suggest that neuropsychological deficits are a pathophysiological risk marker for ADHD rather than simply a symptom correlate.

Results

Table 3 provides the unadjusted means of the groups for each neuropsychological measure. Intraclass sibling correlations were significant for nearly all measures (Table 3), suggesting that familial factors contribute to individual differences on many of these tasks. Probands with ADHD are significantly impaired in comparison with the control twins on all EF, processing speed, and response variability measures but none of the motivation or delay aversion measures. The unaffected co-twins of ADHD probands also performed significantly more poorly than the control group on all EF, processing speed, and response variability measures.

Group Comparisons Controlling ADHD Symptoms

To test whether neuropsychological weaknesses in unaffected co-twins of probands with ADHD were explained by subclinical elevations of ADHD symptoms, a one-way ANCOVA was conducted for each measure with ADHD symptoms as a covariate (Table 3). The non-ADHD siblings of probands with ADHD remained significantly impaired relative to the control group on two of the four processing speed measures and all EF measures except Wisconsin Card Sorting Test (WCST), Time Estimation, and spatial working memory.

Group Comparisons Controlling FSIQ and Reading Ability

When FSIQ and reading ability were controlled, the group with ADHD remained significantly impaired on nearly all mea-

Table 1. Neuropsychological Measures

Measure	Description ^a	Reference
Executive Functions		
Response inhibition		
CPT commission errors	Commission errors on an 18-min CPT that requires the participant to respond whenever a 1 is immediately followed by a 9.	(49)
Stop-signal Task	A computerized task is used to calculate stop-signal reaction time (SSRT), a measure of speed of inhibitory control.	(51)
Vigilance		
CPT omission errors	Omission errors on an 18-min CPT task.	(49)
Interference Control		
Stroop	An interference-control score was operationalized by subtracting the mean Z score on Word and Color naming trials from the Z score on an Interference containing both word and color information.	(48)
Set-shifting		
Wisconsin Card Sorting Test	Sort cards on the basis of one of three possible rules, then switch to a new sorting rule after feedback. The dependent variable is total perseverative errors (sorting to the previous rule after a rule change).	(50)
Trailmaking Test, Part B	Total time to connect a series of circles containing numbers and letters in ascending order, alternating between numbers and letters (i.e., 1, A, 2, B, 3, C, . . .).	(54)
Working Memory		
WISC-R Digit Span	In the 1st half the participant repeats verbatim a series of numbers presented by the examiner. The 2nd half requires the participant to repeat the numbers in reverse order.	(39)
Counting Span	The participant counts aloud the number of yellow dots on a series of cards, then is asked to recall, in order, the number of yellow dots that appeared on each of the cards in the set.	(44)
Sentence Span	The participant provides the last word for a set of simple sentences read by the examiner then reproduces the words that they said in order after each set is completed.	(56)
Spatial Working Memory	The dependent variable was total errors on the spatial working memory subtest of the Cambridge Neuropsychological Test Automated Battery (CANTAB).	(52)
Time Estimation	A light is presented on a computer monitor for 1, 4, 8, 12, or 20 sec, after which the participant attempts to hold down the space bar for the same period of time that the light was illuminated. The primary dependent measure is the mean absolute value of the difference between the time estimated by the participant and the time that the light was actually on.	(43)
Processing Speed		
WISC-R Coding	This subtest requires the participant to rapidly copy symbols associated with specific digits on the basis of a key provided.	(39)
WISC-III Symbol Search	The participant matches a symbol to an identical target that is displayed among several distracter stimuli that share some physical features	(58)
Rapid Automatized Naming	In each of the four trials the participant names as many depictions of objects, colors, numbers, and letters as possible in 15 sec.	(47)
Perceptual Speed Composite	Scores on the Educational Testing Service Identical Pictures test and Colorado Perceptual Speed, two widely-used tests that require speeded visual perception, were combined to create a <i>Perceptual Speed</i> Composite score.	(45,46,55)
Response Variability		
Stop-signal Go trial RT SD	SD of reaction time on the Go trials of the stop-signal task.	(51)
Motivation/Delay Aversion		
The Doors Task	On each trial the participant sees the image of a closed door on the screen and is asked to decide whether they wish to open the door or stop the game and keep the money they have earned. If the participant opens the door they either win or lose \$0.25. Participants win on 9 of the first 10 trials, then the proportion of winning trials declines steadily. The primary dependent measure is the number of trials completed.	(53)
Delay Aversion	The participant chooses between a small reward (\$0.25) after a 2-sec delay and a larger reward (\$0.50) provided after a 30-sec delay. The task includes 20 trials, no matter which reward is selected on each trial.	(57)

CPT, Continuous Performance Test; WISC-R, Wechsler Intelligence Scale for Children—Revised; WISC-III, WISC—Third Revision; RT, reaction time.

^aInhibition, interference, working memory, and set-shifting tasks are described in detail by Willcutt *et al.* (28), processing speed tasks are described by Shanahan *et al.* (15).

asures that were initially significant (Table 3). In contrast, the unaffected co-twins of probands with ADHD remained significantly impaired relative to the control group for stop-signal reaction time (SSRT) and SD of Go trial reaction time only.

Gender

Because some previous studies suggest that girls with ADHD are at stronger familial risk for ADHD and might exhibit

greater neurocognitive weaknesses (e.g., 61,62), a final series of analyses was conducted to test whether non-ADHD co-twins of male and female probands differed on any of the neuropsychological measures. These analyses revealed only one significant gender difference, such that unaffected co-twins of female probands exhibited more impairment on Time Estimation than co-twins of male probands ($p = .03$).

Table 2. Descriptive Characteristics of Twins

	Control Siblings Mean (SD)	Non-ADHD Siblings of ADHD Probands Mean (SD)	ADHD Probands Mean (SD)	<i>F</i> ^a
Demographic Variables				
<i>n</i>	332	228	266	
Gender	160 M, 172 F	84 M, 144 F	190 M, 76 F	
Age	11.9 _a (2.4)	11.1 _b (2.6)	11.2 _b (2.6)	8.3 ^b
Socioeconomic status	3.3 _a (1.0)	3.0 _b (1.2)	2.9 _b (1.2)	4.9 ^b
WISC-R				
Full Scale IQ	113.5 _a (12.5)	106.7 _b (13.6)	101.8 _c (12.7)	66.8 ^b
Verbal IQ	114.5 _a (13.1)	106.7 _b (14.0)	102.3 _c (14.7)	62.8 ^b
Performance IQ	109.7 _a (13.0)	105.4 _b (13.0)	101.1 _c (12.2)	35.5 ^b
Academic Achievement				
Reading ability composite	1.4 _a (1.3)	.6 _b (1.4)	.1 _c (1.5)	76.7 ^b
ADHD Symptoms				
Inattention	.8 _a (1.4)	1.2 _b (1.6)	7.7 _c (1.1)	2329.0 ^b
Hyperactivity-impulsivity	.4 _a (.9)	.9 _b (1.4)	3.6 _c (3.0)	241.7 ^b
Total symptoms	1.2 _a (1.8)	2.1 _b (2.4)	11.3 _c (3.5)	1377.7 ^b

Peabody Individual Achievement Test = Wechsler Intelligence Scale for Children, Revised (WISC-R). Means with different subscripts are significantly different, $p < .01$. ADHD, attention-deficit/hyperactivity disorder.

^a $df = 2, 871$.

^bIndicates significance, $p < .01$.

Discussion

To test the utility of neuropsychological measures as endophenotypes for ADHD, measures of EF, processing speed, response variability, motivational processes, and delay aversion were administered to a large sample of probands with DSM-IV ADHD and their unaffected co-twins. Consistent with previous research, performance of probands with ADHD is significantly impaired compared with control subjects on all EF, processing speed, and response variability measures. The performance of co-twins without ADHD differed significantly from control subjects on nearly all of the same measures even when subclinical ADHD symptoms were controlled, indicating that these weaknesses are not simply a clinical correlate or alternate manifestation of ADHD symptomatology. These results suggest that measures of EF, processing speed, and response variability might be promising endophenotypes for ADHD. In contrast to previous studies (6,17), neither the probands nor their co-twins exhibited significant weaknesses on the measures of delay aversion or other motivational processes.

The SSRT and the SD of Go-trial RT on the stop-signal task remained significantly impaired after controlling for IQ, reading ability, and ADHD symptoms, suggesting that these measures might be tapping a robust endophenotype of ADHD. The finding of slower and more variable response speed in siblings of ADHD probands is consistent with previous results showing that unaffected relatives might have difficulty sustaining sufficient cognitive activation, despite not showing the full behavioral manifestation of ADHD (23). The finding of an SSRT deficit is also consistent with other studies (23,25,26) that have measured SSRT in unaffected relatives. Moreover, Durston *et al.* (63) measured the neuroanatomy of unaffected siblings of ADHD probands and found that the unaffected siblings have reduced right prefrontal gray matter volume relative to control subjects. Right frontal regions have long been reportedly involved in the pathophysiology of ADHD and more recently have been touted as the neural correlate of behavioral response inhibition as measured by SSRT (64). Taken together, these findings suggest that further research into the genetic and neurophysiological influences on

SSRT and overall arousal regulation might augment understanding of the etiology and pathophysiology of ADHD.

Unaffected siblings of female probands and unaffected siblings of male probands showed similar deficits on nearly all tasks. This finding contrasts with a previous study that found SSRT deficits in relatives of girls with ADHD but not relatives of boys with ADHD (23) but is consistent with other studies that did not find gender differences in the neuropsychological correlates of ADHD (20,65). These inconsistent results suggest that additional research with larger samples is needed to clarify questions of gender moderation of neuropsychological effects in probands and unaffected relatives.

Although sibling correlations were significant for nearly all individual neuropsychological measures, correlations were largest for measures of EF, processing speed, and response variability. This pattern of results is consistent with other (unpublished) analyses of the present sample that suggest that weaknesses in EF and response variability are heritable phenotypes that share genetic variance with ADHD (66).

Limitations and Future Directions

This study tested whether measures derived from five prominent cognitive theories of ADHD were useful endophenotypes for ADHD. This required the administration and analysis of an extensive battery of tests, increasing the likelihood that some false positive results could occur by chance. However, the pattern of results is generally robust and consistent across domains, and the unaffected co-twins of probands with ADHD performed significantly worse than control subjects on 16 of 18 measures, far more than would be expected by chance alone.

Twins with reading disability (RD) were also recruited as part of the overall study (28), but twin pairs with RD alone were not included in the analyses described here. Because probands with ADHD and probands with RD were selected independently (i.e., probands with ADHD were selected without regard to their reading status), this recruitment method does not over-select for probands with both ADHD and RD. Nonetheless, it is possible that parents of children with both RD and ADHD might be more likely to agree to participate, because the study focuses on both

Table 3. Sibling Correlations and Neuropsychological Performance of the Groups

Measure	Sibling Correlation ^a	Control Mean (SD)	Non-ADHD Co-Twins of ADHD Probands Mean (SD)	ADHD Probands Mean (SD)	Effect Sizes for Group Comparisons			Significant Group Differences After Covariance ^b		
					Control vs. ADHD	Control vs. Non-ADHD co-Twins	Non-ADHD Co-Twins vs. ADHD	IQ	Reading Ability	ADHD Symptoms
Executive Function										
Response inhibition										
CPT commissions	.07/.09	9.2 (15.5)	20.3 (47.6)	27.4 (44.2)	.55 ^c	.31 ^d	.15 ^c	C>P	C>P	C>S
SSRT	.30 ^c /.47 ^c	285.9 (109.4)	354.5 (144.5)	380.1 (159.7)	.73 ^c	.51 ^e	.22 ^c	C>S,P	C>S,P	C>S
Vigilance										
CPT omissions	.35 ^c /.22 ^c	11.0 (11.6)	15.4 (16.0)	18.3 (15.7)	.53 ^c	.31 ^e	.18 ^e	None	C,S>P	C>S,P
Interference Control										
Stroop	.04/.19 ^c	-.15 (.80)	.03 (.90)	.07 (.79)	.28 ^e	.21 ^d	.05	C>P	C>P	C>S
Set-shifting										
WCST ^f	.20 ^e /.27 ^c	13.3 (9.9)	15.7 (9.3)	20.0 (17.8)	.46 ^c	.25 ^d	.30 ^c	C,S>P	C,S>P	C,S>P
Trailmaking Part B	.21 ^c /.28 ^c	34.1 (19.1)	41.3 (24.8)	52.6 (33.0)	.69 ^c	.33 ^c	.39 ^c	C,S>P	C,S>P	C>S>P
Working Memory										
Digit Span	.31 ^c /.32 ^c	11.2 (2.9)	10.1 (2.9)	9.3 (3.0)	.59 ^c	.32 ^c	.27 ^e	C>P	C>P	C>S,P
Counting Span	.26 ^c /.36 ^c	7.6 (2.4)	6.6 (2.7)	6.1 (2.4)	.61 ^c	.39 ^c	.19 ^e	C>P	C>P	C>S,P
Sentence Span	.23 ^c /.39 ^c	5.9 (2.0)	5.1 (2.3)	4.8 (2.3)	.54 ^c	.36 ^e	.16 ^e	C>P	None	C>S,P
CANTAB errors ^f	.29 ^c /.39 ^c	32.2 (16.1)	39.7 (17.6)	44.7 (18.6)	.72 ^c	.45 ^d	.28 ^c	C>P	C,S>P	C>P
Time Estimation ^{g,h}	.48 ^c /.42 ^e	-.20 (.58)	.12 (.86)	.25 (1.01)	.54 ^c	.42 ^d	.15	None	None	None
Processing Speed										
Coding	.22 ^c /.23 ^c	10.5 (2.8)	9.9 (3.0)	8.0 (3.0)	.86 ^c	.20 ^e	.63 ^c	C,S>P	C,S>P	C>P
Symbol Search ^f	.31 ^c /.22 ^c	12.9 (3.4)	12.1 (3.3)	10.7 (3.4)	.66 ^c	.23 ^d	.43 ^c	C,S>P	C,S>P	C>P
Rapid Naming ^h	.36 ^c /.20 ^c	.06 (1.01)	-.38 (1.0)	-.89 (1.1)	.71 ^c	.24 ^e	.47 ^c	C,S>P	C,S>P	C>S>P
Perceptual Speed ^h	.38 ^c /.29 ^c	-.02 (1.1)	-.36 (1.1)	-1.1 (1.1)	1.0 ^c	.31 ^c	.71 ^c	C,S>P	C,S>P	C>S>P
Response variability										
Go RT SD	.18 ^c /.47 ^c	166.0 (45.6)	196.3 (66.6)	213.9 (76.1)	.76 ^c	.53 ^c	.25 ^c	C>S>P	C>S>P	C>S,P
Motivation/Delay Aversion										
Doors Task ^g	.16 ^d /.24 ^c	61.3 (29.1)	63.8 (29.7)	59.9 (29.5)	.05	.08	.13	None	None	None
Delay Aversion ^g	.20 ^d /.29 ^c	32.7 (5.5)	32.7 (5.5)	31.7 (5.6)	.17	.00	.17	None	None	S>P

C, control twins; S, siblings of ADHD probands without ADHD; P, ADHD probands; SSRT, stop-signal reaction time; None, no group differences when covariate was included in the model; CPT, Continuous Performance Test; WCST, Wisconsin Card Sorting Test; CANTAB, Cambridge Neuropsychological Test Automated Battery; RT, reaction time.

^aIntraclass sibling correlation. Correlations in control pairs are left of the slash, and correlations between pairs with an ADHD proband are right of the slash.

^bAll scores are rescaled so that > indicates that the group(s) on the left of the symbol had better performance.

^cp < .001, significance after covarying age and gender.

^dp < .05, significance after covarying age and gender.

^ep < .01, significance after covarying age and gender.

^fThese six tasks were added later on in the battery and have the following quantities (n): ^fcontrol subjects (n = 236); siblings (n = 136); ADHD probands (n = 156); ^gcontrol subjects (n = 190); siblings (n = 92); ADHD probands (n = 106).

^hComposite measures are residualized scores controlling age and gender.

disorders. Therefore, our results warrant replication in a study that examines ADHD alone.

Attention-deficit/hyperactivity disorder was defined on the basis of the algorithm that was used in the DSM-IV field trials to combine parent and teacher ratings (32), and the inattentive and combined subtypes were analyzed together, because preliminary analyses revealed few differences between the subtypes. However, because statistical power is lower to detect differences between subtypes, future research in larger samples is needed to test definitively whether the utility of neuropsychological endophenotypes varies for different diagnostic algorithms or diagnostic subtypes of ADHD.

In contrast to the results of several previous studies (12), neither probands with ADHD nor their co-twins without ADHD differed significantly from the control group on the delay aversion task. Several factors could account for this failure to replicate previous studies. Recent studies suggest that sensitivity to delay might be influenced by both developmental changes and magnitude of reward (e.g., 67). In comparison with previous studies of delay aversion, the current sample is older, the delay aversion task included a larger reward, and participants had already completed other tasks in which it was possible to earn a reward. We plan to systematically manipulate each of these factors in the future to test whether any explain the null results in the current sample.

Finally, EF and processing speed deficits have also been found in other disorders that are frequently comorbid with ADHD, such as learning disabilities (28), antisocial behavior (68), and autism (11). Because ADHD and most other childhood disorders have polygenic, multifactorial etiologies, it is perhaps not surprising that some neuropsychological risk factors would be associated with multiple disorders. Future studies are needed to clarify which genetic and neuropsychological risk factors are specific to ADHD and which are more general risk factors that increase susceptibility to ADHD and other disorders.

Conclusions

Unaffected co-twins of probands with ADHD performed worse than control participants on 78% of the measures administered in an extensive battery of neurocognitive tasks. Results were most robust for SSRT, response variability, and measures of perceptual and naming speed, suggesting that these tasks might be useful endophenotypes for molecular genetic studies of ADHD.

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1. Faraone SV, Doyle AE (2001): The nature and heritability of attention-deficit/hyperactivity disorder. *Child Adolesc Psychiatr Clin N Am* 10:299–316.
2. Willcutt EG, Carlson CL (2005): Diagnostic validity of attention-deficit/hyperactivity disorder. *Clinical Neuroscience Review* 5:219–232.

3. Faraone SV, Khan SA (2006): Candidate gene studies of attention-deficit/hyperactivity disorder. *J Clin Psychiatry* 67(suppl 8):13–20.
4. Willcutt EG, Pennington BF, Olson RK, DeFries JC (2007): Understanding comorbidity: A twin study of reading disability and attention-deficit/hyperactivity disorder. *Am J Med Genet B Neuropsychiatr Genet* Apr 17; doi:10.1002/ajmg.b.30310 [Epub ahead of print].
5. Nigg JT (2005): Neuropsychologic theory and findings in attention-deficit/hyperactivity disorder: The state of the field and salient challenges for the coming decade. *Biol Psychiatry* 57:1424–1435.
6. Sonuga-Barke EJ (2005) Causal models of attention-deficit/hyperactivity disorder: From common simple deficits to multiple developmental pathways. *Biol Psychiatry* 57:1231–1238.
7. Willcutt EG, Doyle AE, Nigg JT, Faraone SV, Pennington BF (2005): Validity of the executive function theory of attention-deficit/hyperactivity disorder: A meta-analytic review. *Biol Psychiatry* 57:1336–1346.
8. Barkley RA (1997): *ADHD and the Nature of Self-Control*. New York: Guilford Press.
9. Barkley RA (1997): Behavioral inhibition, sustained attention, and executive function: Constructing a unified theory of ADHD. *Psychol Bull* 121:65–94.
10. Nigg JT (2000): On inhibition/disinhibition in developmental psychopathology: Views from cognitive and personality psychology and a working inhibition taxonomy. *Psychol Bull* 126:220–246.
11. Pennington BF, Ozonoff S (1996): Executive functions and developmental psychopathology. *J Child Psychol Psychiatry* 37:51–87.
12. 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* 42:1335–42.
13. Castellanos F X, Sonuga-Barke E J S, Scheres A, Di Martino A, Hyde C, Walters J R (2005): Varieties of attention-deficit/hyperactivity disorder-related intra-individual variability. *Biological Psychiatry* 57:1416–1423.
14. Sergeant J A, Geurts H, Huijbregts S, Scheres A, Oosterlaan J (2003): The top and bottom of ADHD: a neuropsychological perspective. *Neuroscience and Biobehavioral Reviews* 27:583–592.
15. Shanahan MA, Pennington BF, Yerys BE, Scott A, Boada R, Willcutt EG, Olson RK, DeFries JC (2006): PS Deficits in Attention Deficit/Hyperactivity Disorder and Reading Disability. *J Abnorm Child Psychol*. Epub Jul 19.
16. Hartung CM, Milich R, Lynam DR, Martin CA (2002): Understanding the relations among gender, disinhibition, and disruptive behavior in adolescents. *J Abnorm Psychol* 111: 659–664.
17. Luman M, Oosterlaan J, Sergeant J A (2006): The impact of reinforcement contingencies on AD/HD: A review and theoretical appraisal. *Clinical Psychology Review* 25:183–213.
18. Scheres A, Oosterlaan J, Sergeant JA (2001): Response execution and inhibition in children with AD/HD and other disruptive disorders: The role of behavioural activation. *J Child Psychol Psychiatry* 42:347–357.
19. Doyle AE, Faraone SV, Seidman LJ, Willcutt EG, Nigg JT, Waldman I, *et al.* (2005): Are endophenotypes based on measures of executive functions useful for molecular genetic studies of ADHD? *J Child Psychol Psychiatry* 46:774–803.
20. Seidman LJ, Biederman J, Monuteaux MC, Weber W, Faraone SV (2000): Neuropsychological functioning in nonreferred siblings of children with attention deficit/hyperactivity disorder. *J Abnorm Psychol* 109:252–265.
21. Gottesman II, Gould TD (2003) The endophenotype concept in psychiatry: Etymology and strategic intentions. *Am J Psychiatry* 160:636–645.
22. Almasy L, Blangero J (2001): Endophenotypes as quantitative risk factors for psychiatric disease: Rationale and study design. *Am J Med Genet* 105:42–44.
23. Nigg JT, Blaskey LG, Stawicki JA, Sachek J (2004): Evaluating the endophenotype model of ADHD neuropsychological deficit: Results for parents and siblings of children with ADHD combined and inattentive subtypes. *J Abnorm Psychol* 113:614–625. Review.
24. Plomin R, DeFries J, McClearn G (1990): *Behavioral Genetics: A Primer*, 2nd ed. New York: Freeman.
25. Slaats-Willemse D, Swaab-Barneveld H, de Sonneville L, Van Der Meullen E, Buitelaar J (2003): Deficient response inhibition as a cognitive endophenotype of ADHD. *J Am Acad Child Adolesc Psychiatry* 42:1242–1248.
26. Schachar RJ, Crosbie J, Barr CL, Ornstein TJ, Kennedy J, Malone M, *et al.* (2005): Inhibition of motor responses in siblings concordant and discordant for attention deficit hyperactivity disorder. *Am J Psychiatry* 162: 1076–1082.

27. DeFries JC, Filipek PA, Fulker DW, Olson RK, Pennington BF, Smith SD, Wise BW (1997): Colorado Learning Disabilities Research Center. *Learning Disabilities: A Multidisciplinary Journal* 8:7–19.
28. Willcutt EG, Pennington BF, Olson RK, Chhabildas N, Hulslander J (2005): Neuropsychological analyses of comorbidity between reading disability and attention deficit hyperactivity disorder: In search of the common deficit. *Dev Neuropsychol* 27:35–78.
29. Semrud-Clikeman M, Biederman J, Sprich-Buckminster S, Lehman BK, Faraone SV, Norman D (1992): Comorbidity between ADHD and LD: A review and report in a clinically referred sample. *J Am Acad Child Adolesc Psychiatry* 31:439–448.
30. Barkley RA, Murphy K (1998): *Attention-Deficit Hyperactivity Disorder: A Clinical Workbook, 2nd ed.* New York: Guilford Press.
31. Pelham WE, Gnagy EM, Greenslade KE, Milich R (1992): Teacher ratings of DSM-III-R symptoms for the disruptive behavior disorders. *J Am Acad Child Adolesc Psychiatry* 31:210–218.
32. Lahey BB, Applegate B, McBurnett K, Biederman J, Greenhill L, Hynd GW, *et al.* (1994): DSM-IV field trials for attention deficit hyperactivity disorder in children and adolescents. *Am J Psychiatry* 151:1673–1685.
33. Dishion T (1990): The peer context of troublesome child and adolescent behavior. In Leone PE, editor. *Understanding Troubled and Troubling Youth.* Newbury Park, California: Sage.
34. DuPaul GJ, Power TP, Anastopoulos AD, Reid R (1998): *ADHD Rating Scale-IV.* New York: Guilford Press.
35. Willcutt EG, Chhabildas N, Pennington BF (2001): Validity of the DSM-IV subtypes of ADHD. *The ADHD Report* 9:2–5.
36. Chhabildas NA, Pennington BF, Willcutt EG (2001): A comparison of the cognitive deficits in the DSM-IV subtypes of ADHD. *J Abnorm Child Psychol* 29:529–540.
37. Schmitz M, Cadore L, Paczko M, Kipper L, Chaves M, Rohde LA, Moura C, Knijnik M (2002): Neuropsychological performance in DSM-IV ADHD subtypes: An exploratory study with untreated adolescents. *Canadian Journal of Psychiatry* 47: 863–869.
38. Willcutt EG, Brodsky K, Chhabildas N, Shanahan M, Yerys B, Scott A, Pennington BF (2005c): The neuropsychology of ADHD: validity of the executive function hypothesis. In D Gozal and D L Molfese (eds.), *Attention deficit hyperactivity disorder: from genes to patients*, pp. 185–213. Humana Press: Totowa, NJ.
39. Wechsler D (1974): *Examiner's Manual: Wechsler Intelligence Scale for Children – Revised.* New York: The Psychological Corporation.
40. Wechsler D (1981): *Manual for the Wechsler Adult Intelligence Scale—Revised.* San Antonio: The Psychological Corporation.
41. Dunn LM, Markwardt FC (1970): *Examiner's manual: Peabody Individual Achievement Test.* Circle Pines, MN: American Guidance Service.
42. DeFries JC (1985): Colorado reading project. In DB. Gray, JF Kavanagh (Eds.), *Biobehavioral measures of dyslexia* (pp. 107–122). Parkton, MD: York Press.
43. Barkley RA, Koplowitz S, Anderson T, McMurray M (1997): Sense of time in children with ADHD: Effects of duration, distraction, and stimulant medication. *Journal of the International Neuropsychological Society* 3:359–369.
44. Case R, Kurland M, Goldberg J (1982): Operational efficiency and the growth of short-term memory span. *Journal of Experimental Child Psychology* 33:386–404.
45. Decker SN (1989): Cognitive processing rates among disabled and normal reading young adults: A nine year follow-up study. *Reading and Writing: An interdisciplinary Journal* 1:123–134.
46. DeFries JC, Singer SM, Foch TT, Lewitter FI (1978): Familial nature of reading disability. *Br J Psychiatry* 132:361–7.
47. Denckla MB, Rudel R (1976): Rapid automatized naming (R.A.N.): Dyslexia differentiated from other learning disabilities. *Neuropsychologia* 14:471–479.
48. Golden JC (1978): *Stroop Color and Word Test.* Stoelting Company: Chicago, IL.
49. Gordon M (1983): *The Gordon Diagnostic System.* DeWitt, NY: Gordon Systems.
50. Heaton RK (1981): *Wisconsin Card Sorting Test Manual.* Odessa, FL: Psychological Assessment Resources.
51. Logan GD, Schachar RJ, Tannock R (1997): Impulsivity and inhibitory control. *Psychological Science* 8:60–64.
52. Owen AM, Doyon J, Petrides M, Evans AC (1996): Planning and spatial working memory: A positron emission tomography study in humans. *European Journal of Neuroscience* 8:353–364.
53. Quay HC (1988): Attention deficit disorder and the behavioral inhibition system: The relevance of the neuropsychological theory of Jeffrey A Gray. In L M Bloomingdale (Ed.), *Attention Deficit Disorder. Vol. 3: New research in attention, treatment, and psychopharmacology* (pp. 176–186). Oxford, England: Pergamon Press.
54. Reitan R, Wolfson D (1985): *The Halstead-Reitan Neuropsychological Test Battery: Theory and Clinical Interpretation.* Tucson: Neuropsychology Press.
55. Shankweiler D, Lieberman IY, Mark LS, Fowler CA, Fischer FW (1979): The speech code and learning to read. *Journal of Experimental Psychology: Human Learning and Memory* 5:531–545.
56. Siegel LS, Ryan EB (1989): The development of working memory in normally achieving and subtypes of learning disabled children. *Child Development* 60:973–980.
57. Solanto MV, Abikoff H, Sonuga-Barke EJ, Schachar R, Logan GD, Wigal T, Hechtman L, Hinshaw S, Turkel E (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.
58. Wechsler D (1991): *Manual for the Wechsler Intelligence Scale for Children, 3rd ed.* San Antonio, Texas: The Psychological Corporation.
59. Lahey BB, Pelham WE, Stein M, Loney J, Trapani C, Nugent K, *et al.* (1998): Validity of DSM-IV attention-deficit/hyperactivity disorder for young children. *J Am Acad Child Adolesc Psychiatry* 37:695–702.
60. Werry JS, Elkind GS, Reeves JS (1987): Attention deficit, conduct, oppositional, and anxiety disorders in children: III. Laboratory differences. *J Abnorm Child Psychol* 15:409–428.
61. Faraone SV, Tsuang D, Tsuang MT (1999): *Genetics and Mental Disorders: A Guide for: Students, Clinicians, and Researchers.* New York: Guilford.
62. Gershon J (2002): A meta-analytic review of gender differences in ADHD. *J Atten Disord* 5:143–154.
63. Durston S, Hulshoff Pol HE, 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.
64. Aron AR, Poldrack RA (2005): The cognitive neuroscience of response inhibition: Relevance for genetic research in attention-deficit/hyperactivity disorder. *Biol Psychiatry* 57:1285–1292.
65. Seidman LJ, Biederman J, Monuteaux MC, Valera E, Doyle AE, Faraone SV (2005): Impact of gender and age on executive functioning: Do girls and boys with and without attention deficit hyperactivity disorder differ neuropsychologically in preteen and teenage years? *Dev Neuropsychol* 27:79–105.
66. Willcutt EG, Chhabildas NA, Bidwell LC, Pennington BF (submitted): A twin study of the validity of the executive function theory of ADHD. *J Child Psychol Psychiatry*
67. Scheres A, Dijkstra M, Ainslie E, Balkan J, Reynolds B, Sonuga-Barke E, Castellanos FX (2006) Temporal and probabilistic discounting of rewards in children and adolescents: Effects of age and ADHD symptoms. *Neuropsychologia* 44:2092–2103.
68. Dolan M, Park I (2002): The neuropsychology of antisocial personality disorder. *Psychol Med* 32:417–427.