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Testing for Neuropsychological Endophenotypes in Siblings Discordant for ADHD

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Abstract

Objective—Neurocognitive deficits associated with attention deficit-hyperactivity disorder (ADHD) may 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) in order 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— ADHD subjects show significant impairment on executive function, processing speed, and response variability measures compared to control subjects. Unaffected cotwins of ADHD subjects are significantly impaired on nearly all the same measures as their ADHD siblings, even when subclinical symptoms of ADHD are controlled.

Conclusion—Executive function, processing speed, and response variability deficits may be useful endophenotypes for genetic studies of ADHD.

Keywords

ADHD; endophenotype; genetics; neuropsychology; executive function; processing speed

Introduction

The genetics and neuropsychology of ADHD

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 may 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.

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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

Due to the neuropsychological complexity of ADHD, several authors have suggested that neuropsychological measures may 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 may 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 may 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 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 6 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 controls, 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 controls on only two measures, suggesting that the specific measures administered in this study may 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 ADHD. In summary, these previous studies provide some support for neuropsychological measures as endophenotypes for ADHD, but suggest that results may differ in males and females.

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 cotwins would exhibit significant

neuropsychological weaknesses in comparison to twins without ADHD on at least a subset of these measures.

Method

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 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 based on 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 due 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 prior to age seven 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 paper.

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 cotwin 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 cotwins 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 (16 years old and younger; WISC-R; 30) or the Wechsler Adult Intelligence Scale (17 and 18 years old; WAIS; 40), and reading achievement was assessed with the Peabody Individual Achievement Test (PIAT; 41). To simplify interpretation a reading composite score was created based on 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. Due to space constraints an abbreviated description of each task is provided in Table 1. All measures are described in detail in previous papers (15,28).

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 two 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 prior to 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; 59), and IQ scores of the probands with ADHD and their unaffected cotwins were significantly below the mean of the comparison group (Table 2). As expected based on 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 controls. 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 prior to any additional analyses. Outliers were defined as scores that fell more than three standard deviations (SD) from the mean of the overall sample and more than 0.5 SD beyond the next most extreme score. Each outlier was adjusted to a score 0.5 SD units beyond the next highest score, with multiple outliers rescored to 0.1 SD apart.

Analyses

An initial multivariate analysis of covariance 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., 60, 61). On the other hand, ADHD symptoms may 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, as 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 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 cotwins 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 to the control twins on all EF, processing speed, and response variability measures, but none of the motivation or delay aversion measures. The unaffected cotwins 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 cotwins 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 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 measures that were initially significant (Table 3). In contrast, the unaffected cotwins of probands with ADHD remained significantly impaired relative to the control group for stop-signal reaction time (SSRT) and standard deviation of Go trial reaction time only.

Gender

Because some previous studies suggest that girls with ADHD are at stronger familial risk for ADHD and may exhibit greater neurocognitive weaknesses (e.g., 62, 63), a final series of analyses was conducted to test if non-ADHD cotwins of male and female probands differed on any of the neuropsychological measures. These analyses revealed only one significant sex difference, such that unaffected cotwins of female probands exhibited more impairment on Time Estimation than cotwins of male probands ($p=.03$).

Discussion

To test the utility of neuropsychological measures as endophenotypes for ADHD, measures of executive function (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 cotwins. Consistent with previous research, performance of probands with ADHD is significantly impaired compared to controls on all EF, processing speed, and response variability measures. The performance of cotwins without ADHD differed significantly from controls 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 may be promising endophenotypes for ADHD. In

contrast to previous studies (6,17), neither the probands or their cotwins exhibited significant weaknesses on the measures of delay aversion or other motivational processes.

SSRT and the standard deviation 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 may 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 may 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. (64) measured the neuroanatomy of unaffected siblings of ADHD probands and found that the unaffected siblings have reduced right prefrontal gray matter volume relative to controls. 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 (65). Taken together, these findings suggest that further research into the genetic and neurophysiological influences on SSRT and overall arousal regulation may 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 sex differences in the neuropsychological correlates of ADHD (20,66). These inconsistent results suggest that additional research with larger samples is needed to clarify questions of sex moderation of neuropsychological effects in probands and unaffected relatives.

While 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 analyses of the present sample that suggest that weaknesses in EF and response variability are heritable phenotypes that share genetic variance with ADHD (67).

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 cotwins of probands with ADHD performed significantly worse than controls on 16 of 18 measures, far more than would be expected by chance alone.

Twins with reading disability 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 disorders. Therefore, our results warrant replication in a study that examines ADHD alone.

ADHD was defined based on 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 cotwins 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 may be influenced by both developmental changes and magnitude of reward (e.g., 68). In comparison to 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 if any explain the null results in the current sample.

Finally, EF and processing speed deficits have also been found in other disorders which are frequently comorbid with ADHD, such as learning disabilities (28), antisocial behavior (69), 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 cotwins 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 stop-signal reaction time, response variability, and measures of perceptual and naming speed, suggesting that these tasks may be useful endophenotypes for molecular genetic studies of ADHD.

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Neuropsychological Measures.

Table 1

Measure	Description ¹	Reference ²
Executive Functions		
<i>Response inhibition</i>		
CPT commission errors	Commission errors on an 18 minutes 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
<i>Vigilance</i>		
CPT omission errors	Omission errors on an 18 minute CPT task.	49
<i>Interference Control</i>		
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 trial containing both word and color information.	48
<i>Set-shifting</i>		
Wisconsin Card Sorting Test	Sort cards based on 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
<i>Working Memory</i>		
WISC-R Digit Span	In the first half the participant repeats verbatim a series of numbers presented by the examiner. The second 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 seconds, 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 based on 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 fifteen seconds.	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

Measure	Description ¹	Reference ²
Response Variability		
Stop-signal Go trial RT SD	Standard deviation 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 nine 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 two second delay and a larger reward (\$0.50) provided after a 30 second delay. The task includes 20 trials no matter which reward is selected on each trial.	57

¹ inhibition, interference, working memory, and set-shifting tasks are described in detail by Willcutt et al. (2005b), processing speed tasks are described by Shanahan et al. (2006).

² Numbers indicate references: 1.43. Barkley et al., 1997; 2.44. Case et al., 1982; 3.45. Decker, 1989; 4.46. DeFries, et al., 1978; 5. 47. Denckla and Rudel, 1976; 6.48. Golden, 1978; 7. 49. Gordon, 1983; 8. 50. Heaton, 1981; 9.51. Logan et al., 1997, 10.52. Owen et al., 1996, 11.53. Quay, 1988, 12. 54. Reitan & Wolfson, 1985; 13.55 Shankweiler, et al., 1979; 14.56 Siegel & Ryan, 1989; 15.57. Solanto et al., 2001, 16.39. Wechsler, 1974, 17.58. Wechsler, 1991.

Table 2

Descriptive Characteristics of Twins

	Control siblings M (SD)	non-ADHD siblings of ADHD probands M (SD)	ADHD probands M (SD)	<i>F</i> ^a
<i>Demographic Variables</i>				
<i>N</i>	332	228	266	
Sex	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 [*]
Socioeconomic status	3.3 _a (1.0)	3.0 _b (1.2)	2.9 _b (1.2)	4.9 [*]
<i>WISC-R</i>				
Full Scale IQ	113.5 _a (12.5)	106.7 _b (13.6)	101.8 _c (12.7)	66.8 [*]
Verbal IQ	114.5 _a (13.1)	106.7 _b (14.0)	102.3 _c (14.7)	62.8 [*]
Performance IQ	109.7 _a (13.0)	105.4 _b (13.0)	101.1 _c (12.2)	35.5 [*]
<i>Academic Achievement</i>				
Reading ability composite	1.4 _a (1.3)	.6 _b (1.4)	.1 _c (1.5)	76.7 [*]
<i>ADHD Symptoms</i>				
Inattention	.8 _a (1.4)	1.2 _b (1.6)	7.7 _c (1.1)	2329.0 [*]
Hyperactivity – impulsivity	.4 _a (.9)	.9 _b (1.4)	3.6 _c (3.0)	241.7 [*]
Total symptoms	1.2 _a (1.8)	2.1 _b (2.4)	11.3 _c (3.5)	1377.7 [*]

Note. PIAT = WISC-R = Wechsler Intelligence Scale for Children, Revised.

^a df = 2, 871. Means with different subscripts are significantly different, $p < .01$.

* indicates significance, $p < .01$

Table 3

Sibling correlations and neuropsychological performance of the groups

Measure	Sibling Correlation ¹	Control M (SD)	Non-ADHD cotwins of ADHD probands M (SD)	ADHD Probands M (SD)	Effect Sizes for Group Comparisons			Significant Group Differences after covariance ²		
					Control vs. ADHD	Control vs. non- ADHD cotwins	Non- ADHD cotwins vs. ADHD	IQ	Reading Ability	ADHD Symptoms
Executive Function										
<i>Response inhibition</i>										
CPT commissions	.07/.09	9.2 (15.5)	20.3 (47.6)	27.4 (44.2)	.55***	.31*	.15***	C>P	C>P	C>S
SSRT	.30***/.47***	285.9 (109.4)	354.5 (144.5)	380.1 (159.7)	.73***	.51**	.22***	C>S,P	C>S,P	C>S
<i>Vigilance</i>										
CPT omissions	.35***/.22***	11.0 (11.6)	15.4 (16.0)	18.3 (15.7)	.53***	.31**	.18**	None	C,S>P	C>S,P
<i>Interference Control</i>										
Stroop	.04/.19***	-1.5 (.80)	.03 (.90)	.07 (.79)	.28**	.21*	.05	C>P	C>P	C>S
<i>Set-shifting</i>										
WCST ³	.20**/.27***	13.3 (9.9)	15.7 (9.3)	20.0 (17.8)	.46***	.25*	.30***	C,S>P	C,S>P	C,S>P
Trailmaking Part B	.21***/.28***	34.1 (19.1)	41.3 (24.8)	52.6 (33.0)	.69***	.33***	.39***	C,S>P	C,S>P	C>S>P
<i>Working Memory</i>										
Digit Span	.31***/.32***	11.2 (2.9)	10.1 (2.9)	9.3 (3.0)	.59***	.32***	.27**	C>P	C>P	C>S,P
Counting Span	.26***/.36***	7.6 (2.4)	6.6 (2.7)	6.1 (2.4)	.61***	.39***	.19**	C>P	C>P	C>S,P
Sentence Span	.23***/.39***	5.9 (2.0)	5.1 (2.3)	4.8 (2.3)	.54***	.36**	.16**	C>P	None	C>S,P
CANTAB errors ³	.29***/.39***	32.2 (16.1)	39.7 (17.6)	44.7 (18.6)	.72***	.45*	.28***	C>P	C,S>P	C>P
Time Estimation ^{4,5}	.48***/.42**	-20 (.58)	.12 (.86)	.25 (1.01)	.54***	.42*	.15	None	None	None
Processing Speed										
Coding	.22***/.23***	10.5 (2.8)	9.9 (3.0)	8.0 (3.0)	.86***	.20**	.63***	C,S>P	C,S>P	C>P
Symbol Search ³	.31***/.22***	12.9 (3.4)	12.1 (3.3)	10.7 (3.4)	.66***	.23*	.43***	C,S>P	C,S>P	C>P
Rapid Naming ⁵	.36***/.20***	.06 (1.01)	-38 (1.0)	-89 (1.1)	.71***	.24**	.47***	C,S>P	C,S>P	C>S>P
Perceptual Speed ⁵	.38***/.29***	-02 (1.1)	-36 (1.1)	-1.1 (1.1)	1.0***	.31***	.71***	C,S>P	C,S>P	C>S>P
Response variability										
Go RT SD	.18***/.47***	166.0 (45.6)	196.3 (66.6)	213.9 (76.1)	.76***	.53***	.25***	C>S>P	C>S>P	C>S,P
Motivation/Delay Aversion										

Measure	Sibling Correlation ¹	Control M (SD)	Non-ADHD cotwins of ADHD probands M (SD)	ADHD Probands M (SD)	Effect Sizes for Group Comparisons			Significant Group Differences after covariance ²		
					Control vs. ADHD	Control vs. non- ADHD cotwins	Non- ADHD cotwins vs. ADHD	IQ	Reading Ability	ADHD Symptoms
Doors Task ⁴	.16 ^{*/.24***}	61.3 (29.1)	63.8 (29.7)	59.9 (29.5)	.05	.08	.13	None	None	None
Delay Aversion ⁴	.20 ^{*/.29***}	32.7 (5.5)	32.7 (5.5)	31.7 (5.6)	.17	.00	.17	None	None	S>P

* indicates significance after covarying age and sex,

* p < .05;

** p < .01;

*** p < .001.

¹ Intraclass sibling correlation. Correlations in control pairs are left of the slash, and correlations between pairs with an ADHD proband are right of the slash.

² C=control twins, S=siblings of ADHD probands without ADHD, P=ADHD probands, None indicates there were no group differences when covariate was included in the model. All scores are rescaled so that > indicates that the group(s) on the left of the symbol had better performance. ^{3, 4} These six tasks were added later on in the battery and have the following N's:

³ Controls (n=236), Siblings (n=136), ADHD probands (n=156),

⁴ Controls (n=190), Siblings (n=92), ADHD probands (n=106).

⁵ Composite measures are residualized scores controlling age and sex.