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Evaluating the Endophenotype Model of ADHD Neuropsychological Deficit: Results for Parents and Siblings of Children With ADHD Combined and Inattentive Subtypes

Joel T. Nigg, Lisa G. Blaskey, Julie Ann Stawicki, and Jennifer Sachek
Michigan State University

Neurogenetic models predict neuropsychological weaknesses in the relatives of children with attention-deficit/hyperactivity disorder (ADHD). The authors examined executive and regulatory measures in 386 relatives (307 parents, 79 siblings) of children with ADHD combined type, ADHD inattentive type, and controls. Predicted deficits were seen on trailmaking (relatives of ADHD combined type only), stop-signal reaction times (relatives of girls only), and response variability (mothers only) but not on naming or output speed. Effects generally held, even with relatives' ADHD status controlled. A neuropsychologically impaired subgroup of children with ADHD had relatives with clear neuropsychological weaknesses. The authors conclude that a neurogenetic model of ADHD etiology is supportable only for a subset of executive functions and that neuropsychological heterogeneity warrants more examination in ADHD.

Attention-deficit/hyperactivity disorder (ADHD) denotes an impairing (Hinshaw, 2002), common, and costly child syndrome characterized by age-inappropriate extremes of activity, impulsivity, and inattentive, disorganized behavior. The *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (*DSM–IV*; American Psychiatric Association, 1994) specifies three working subtypes: predominantly hyperactive, predominantly inattentive (ADHD-PI), and combined (ADHD-C). The etiological relationship of these subtypes to one another remains in question (Milich, Balentine, & Lynam, 2001). Moreover, there is substantial concern about whether the taxonomy is as apt for girls as for boys (Gaub & Carlson, 1997), with uncertainty about similarity of deficits in boys and girls (Seidman, Biederman, Faraone, & Weber, 1997) and the potential for distinct etiological processes in boys and girls with ADHD (Rhee, Waldman, Hay, & Levy, 2001). Both issues were echoed in our prior neuropsychological report, in which subtype effects were moderated by child sex (Nigg, Blaskey, Huang-Pollock, & Rappley, 2002). Finally, nosologists are increasingly concerned that frequently occurring comorbid conditions, especially conduct disorder (CD) and, to a lesser extent, oppositional defiant disorder (ODD), may signify distinct etiological subgroups (Jensen, Martin, & Cantwell, 1997).

ADHD has long been shown to be familial (Biederman, Faraone, Keenan, Knee, & Tsuang, 1990; Faraone, Biederman, Keenan, & Tsuang, 1991), with recent replication for *DSM–IV* (Stawicki, Nigg, & von Eye, 2004). Twin studies suggest substantial heritability for the behavior domains and at least some of the subtypes (Sherman, Iacono, & McCue, 1997; Willcutt, Pennington, & DeFries, 2000). However, in light of evidence that in childhood the hyperactive subtype is less heritable than the others (Willcutt et al., 2000) and is not familial (Todd et al., 2001), we excluded it while retaining ADHD-C and ADHD-PI for study.

The Basic Neurogenetic or Endophenotype Model

Theorists of ADHD's developmental mechanisms consistently have sought to integrate heritability with theoretical conceptions that emphasize neuropsychological vulnerabilities. The specific neuropsychological focus of these conceptual framings has varied somewhat, with emphases including executive functions and inhibitory control (Barkley, 1997; Pennington & Ozonoff, 1996); working memory, timing, and response variability (Castellanos & Tannock, 2002); state regulation factors such as effort or activation (Sergeant, Oosterlaan, & van der Meere, 1999); and abnormal reward response (Sagvolden, Aase, Zeiner, & Berger, 1998). Each idea can draw on substantial neuropsychological (Barkley, 1997; Nigg, 2001), neuroimaging (Giedd, Blumenthal, Molloy, & Castellanos, 2001), and physiological (Barry, Clark, & Johnstone, 2003) literatures, though consensus on core mechanisms is far from at hand.

However, the guiding logic governing all of these hypotheses and theories is essentially the same in form, with differences only in the content: Unknown etiological factors (e.g., a set of genes or Genotype × Experience interactions) interfere with normal neural development. These abnormal neural processes, probed with cognitive–neuropsychological laboratory tasks, mediate the development of ADHD by interfering with behavioral control. However, in the absence of known etiology, demonstrating that this causal sequence occurs is extremely difficult in humans.

Joel T. Nigg, Lisa G. Blaskey, Julie Ann Stawicki, and Jennifer Sachek, Department of Psychology, Michigan State University.

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Correspondence concerning this article should be addressed to Joel Nigg, Department of Psychology, 115-C Psychology Building, Michigan State University, East Lansing, MI 48824-1116. E-mail: nigg@msu.edu

Nonetheless, testable predictions follow. Central is the idea of the endophenotype, introduced to psychopathology research 3 decades ago by Gottesman and Shields (1972) and much discussed currently (Almasy & Blangero, 2001; Gottesman & Gould, 2003). The idea is that a predisposing vulnerability should (a) be correlated with ADHD symptoms or disorder in the probands, (b) help to identify more etiologically pure phenotypes for genetic and other etiological research, (c) be familial, and (d) appear in unaffected relatives. A causal cognitive (or other) marker should appear in some unaffected relatives because it presumably combines with other factors in only some family members to cause the full disorder. Failing this test, the cognitive marker may only be another symptom of the disorder but not causal or at least not related to the genetic causal processes. This basic idea has been somewhat promising in the study of schizophrenia (Asarnow et al., 2002; Gottesman & Gould, 2003). However, in the case of ADHD, demonstration of the latter two key familial predictions is lacking.

Prior Cognitive Studies of Relatives of ADHD Children and Need for the Current Study

Siblings

In an early study, Welner, Welner, Stewart, Palkes, and Wish (1977) reported lower IQ and achievement in siblings of hyperactive than control boys, but they did not control for sibling ADHD status. Faraone et al. (1993) were unable to show reliable differences between siblings of clinic-referred boys with *Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised* (*DSM–III–R*; American Psychiatric Association, 1987) ADHD and control boys on IQ and achievement tests after a correction for multiple comparisons, although male siblings of probands tended to have lower IQ scores than male siblings of control boys. Seidman, Biederman, Monuteaux, Weber, and Faraone (2000) studied the same group of siblings of male probands 4 years later with a more differentiated battery of executive functions that included the Stroop Test, Wisconsin Card Sort Test, California Verbal Learning Test, Auditory Continuous Performance Test, Letter Cancellation Test, and Rey–Osterreith Complex Figure. They found similar negative results: Siblings with ADHD showed some executive deficits, but the non-ADHD siblings of ADHD children did not (except list learning).

Parents

Only a few studies have examined parental cognitive function in ADHD. Alberts-Corush, Firestone, and Goodman (1986) found weaker performance in biological but not adoptive parents of hyperactive and control children (gender composition of the child sample was not reported) on the Span of Apprehension Task (working memory) and a delayed reaction time (RT) task but not on Porteus Mazes. Effects were stronger for mothers than for fathers. In a similar design, Nigg, Swanson, and Hinshaw (1997) examined biological and adoptive parents of boys with *DSM–III–R* ADHD on a visual orienting task. Children with ADHD and their biological but not adoptive parents had slow orienting to left-sided targets, implicating an endophenotype for the alerting function of the right-brain lateralized vigilance neural system described by Posner and Peterson (1990). However, parental ADHD status was not reported in either study, and subsequent studies have not consistently replicated the child alerting deficit (Huang-Pollock & Nigg, 2003). Murphy and Barkley (1996) studied 75 parents of 51 children (all but 3 were boys) classified by *DSM–III–R* as severe ADHD, mild ADHD, and controls on the Wisconsin Card Sort Test, the Digit Span Test, a continuous performance test (CPT), and a verbal memory (verbal selective-reminding) task, with null results on all cognitive variables, possibly because of low power. Asarnow et al. (2002) examined parents of a larger sample of children identified with *DSM–III–R* ADHD and community controls but found no effects on a degraded-stimulus CPT (vigilance), Trailmaking B (set shifting), or the Span of Apprehension Test (working memory).

Conclusion

In all, these seven prior studies were mixed at best with regard to the basic hypothesis that neurocognitive deficits are part of the genetically influenced causal process leading to ADHD. Indeed, no study of relatives has ever shown an endophenotype effect while controlling relatives' ADHD status (i.e., all studies that showed family effects failed to control for relatives' ADHD status). However, this literature is in its infancy. It is striking that no study has assessed neurocognitive performance in relatives of probands with *DSM–IV* ADHD. Furthermore, nearly all prior data are on boys, and no study systematically examined proband gender effects. Finally, several of the most currently theorized endophenotypes have yet to be studied, including response inhibition (Barkley, 1997) and response variability (Castellanos & Tannock, 2002), whereas other executive and regulatory measures have been only sparsely studied.

Importance of Neuropsychological Heterogeneity in ADHD

A key issue when considering family transmission of risk concerns neuropsychological heterogeneity (Sonuga-Barke, 2002). For convenience, investigators usually refer to ADHD as though it were unitary (e.g., within the combined subtype). They thus confine discussion to the meaning of group mean differences (or lack thereof) on a given cognitive task. However, neuropsychological group effects are due to abnormal performance by only some of the children with ADHD (Doyle et al., 2000). As a result, family transmission studies might fail if they rely only on the behavioral or *DSM–IV* phenotype. One remedy is to examine cognitive phenotypes as an alternative way to evaluate the endophenotype concept (Crosbie & Schachar, 2001). We also illustrate a variant of this approach in our data analysis.

Candidate Endophenotypes for the Current Study

A wide range of potential endophenotypes arguably is available for study, as cited earlier. We necessarily focused on only a subset of this sizeable universe. First, we considered executive functions (Barkley, 1997). The model guiding our work recognizes that parallel frontal–thalamic–striatal neural loops (Middleton & Strick, 2001) may represent different operations that enable integrated behavioral control (Casey, Tottenham, & Fossella, 2002). Both imaging studies (Casey et al., 2002) and statistical analyses

of phenotypic measures (Miyake, Friedman, Emerson, Witzki, & Howerter, 2000) suggest that executive functions reflect distinct, yet related, processes. Our selection of executive constructs therefore drew from a multicomponent neuropsychological model that includes response suppression (behavioral inhibition; see Barkley, 1997; Nigg, 2001), set shifting, planning (relying on visual working memory), and interference control (Pennington, 1997).

In addition, we considered two output control domains that are outside this particular executive framework but are suggested in ADHD. Response variability is viewed as an important potential marker of ADHD. It may reflect problems in timing and motor control (Castellanos & Tannock, 2002) or arousal regulation (Sergeant et al., 1999). Of importance, it already has shown familiality (Kuntsi & Stevenson, 2001). Output speed is often viewed as an index of effort or activation (Sergeant et al., 1999). It was included in the form of raw decision RT and in the form of naming speed (Carte, Nigg, & Hinshaw, 1996) to broaden the battery.

The endophenotype model suggests the following hypothesis: Relatives of children with ADHD will have weaker marker functioning than control relatives, even when relatives' ADHD status is controlled. A neuropsychological heterogeneity model suggests an alternative hypothesis: Relatives of children with ADHD plus neuropsychological deficit will have weaker performance than relatives of other children with ADHD and controls. Because of dispute about the etiological relation of ADHD-C and ADHD-PI, we designed the data analysis to first pool relatives across these subtypes and then to compare the two subtypes. We also considered that endophenotype effects might be moderated by child gender (Rhee et al., 2001) and comorbid CD (Jensen et al., 1997). We also checked other comorbidity effects while testing the hypotheses in biological parents and in a smaller group of siblings.

Method

Participants

A total of 386 relatives participated, including 176 biological mothers, 131 biological fathers, and 79 full siblings of children participating in our study of ADHD subtypes. Probands were 176 children in three groups: ADHD-C ($n = 62$), ADHD-PI ($n = 35$), and non-ADHD controls ($n = 79$).

To maximize generalizablity, we followed a generally, but not exclusively, community-based recruitment strategy. Families with a child in the first through sixth grades were recruited from mass-mailed invitation letters and public advertisements, with a small percentage (10%) recruited from a local pediatric clinic specializing in ADHD referrals and from a local support group for parents of children with ADHD. To the extent possible, we matched control families on sex, age, and recruitment source (a neighboring general pediatric clinic or the same local school districts). A multistage screening process was used to select children (described next).

Diagnostic assignment of index children. Index children were considered as possible ADHD-C or ADHD-PI if they either (a) passed prescreen cutoffs on both parent and teacher versions of common ADHD rating instruments (the Child Behavior Checklist or Teacher Report Form [Achenbach, 1991], Behavior Assessment Scale for Children [Reynolds & Kamphaus, 1992], Conners [1997] Rating Scale, or the Swanson, Nolan, and Pelham rating scale for ADHD for *DSM–IV* [SNAP–IV; Swanson et al., 2000] or the ADHD Rating Scale [DuPaul, G.J., Power, T.J., Anastopoulos, A.D., & Reid, R. (1998)], depending on year of the study), or (b) were diagnosed as ADHD (any type) by a physician or psychologist in the community who utilized teacher and parent ratings to arrive at their diagnosis. Children were considered as possible controls if they were below cutoffs on all parent and teacher scales and were never diagnosed with ADHD.

Child diagnosis then was confirmed using a parent structured diagnostic interview (the Diagnostic Interview Schedule for Children—IV; DISC–IV; Shaffer, Fisher, & Lucas, 1997) supplemented by an "or" algorithm following the *DSM–IV* field trials validity data (Lahey et al., 1994). Prior versions of the DISC have exhibited acceptable reliability and validity. The "or" algorithm was implemented as follows. If children met age of onset, duration, impairment, and cross-situational criteria, then diagnostic assignment was determined by counting a symptom as present if it was endorsed by the parent (on the DISC–IV) or the teacher (as "sometimes" or "often" present) on the symptom checklist.

Control children were negative for ADHD (all types) on the basis of the above criteria, with four or fewer symptoms in either domain by the "or" algorithm. Families were excluded from all groups if the target child yielded five symptoms of inattention or overactivity, based on the field trial data indicating that these borderline cases might have ADHD-C or ADHD-PI (Lahey et al., 1994). Key proband comorbid disorders were also assessed. ODD or CD were assigned on the basis of DISC–IV algorithms. We excluded reading disorder (RD) at screen in most years, but 8 children were allowed in with RD in the final year of the study. RD was assigned if (a) absolute level of average Wechsler (1992) Individual Achievement Test Reading and Spelling were less than or equal to a standard score of 85 and (b) full scale IQ minus reading–spelling average was at least 15 points. IQ was estimated with a reliable and valid five-test short form of the Wechsler (1991) Intelligence Scale for Children, Third Edition (WISC–III; Sattler, 2001).

Diagnostic assignment of parents. Parent ADHD status was assessed with the National Institute of Mental Health Diagnostic Interview Schedule—IV (Robins et al., 1995), supplemented by a *DSM–IV* symptom checklist. Because we identified families on the basis of child probands, we could not exclude parents with borderline symptom levels. Adults with childhood ADHD may tend to underreport their childhood symptoms (Barkley, Fischer, Smallish, & Fletcher, 2002). In view of this, the *DSM–IV* field trial results cited earlier, and our priority on avoiding false negatives in identifying parents with prior ADHD to test the endophenotype model, we checked results while controlling parent ADHD defined as the *DSM–IV* required six-symptom, as well as a more liberal five-symptom, cutoff. We also used the interview data to assign ADHD subtypes to parents for secondary data checks. Parent IQ was estimated with a two-subtest short form of the Wechsler Adult Intelligence Scale—III (WAIS–III; Sattler, 2001).

Diagnostic assignment of siblings. For a subset of families, funds were available to assess one sibling. We selected the sibling nearest in age to the target child, provided the sibling was old enough to complete the neuropsychological measures (at least 6 years of age). We were unable to obtain teacher ratings on most of the siblings, so rely here on parent ADHD Rating Scale scores. We again sought primarily to avoid false negatives in estimating ADHD status for siblings. To do so, we used the 80th percentile as our rule in for ADHD (Power et al., 1998). We expected this cut point to slightly overselect ADHD in siblings, consistent with the purpose of our study to rule out ADHD as an explanation for relatives' cognitive performance. Although the sibling sample size was considerably smaller than the parent sample size, we include those data here.

Exclusion criteria. Families and children were excluded from all groups if the target child had mental retardation, autistic disorder, Tourette syndrome, current major depressive episode, bipolar disorder, or physical or neurological handicap ascertained by parent report. Siblings with any of those conditions were excluded as well. Children with CD or RD were excluded from the control group. Parents were excluded if they had a history of head injury with loss of consciousness ($n = 1$) or psychosis. All children and their parents were native English speakers, had normal hearing and normal or corrected vision, and had a valid full scale IQ > 75.

Adoptive parents and stepparents were excluded, as were biological parents who were estranged from the family, abusive, imprisoned, deceased, or refused to participate. Failure of biological fathers to participate was nonrandom: It was associated with higher levels of child hyperactivity ($p = .02$), ODD symptoms ($p = .01$), and child CD symptoms ($p = .01$). Therefore, the parental data may underestimate impairment on the neuropsychological battery. Underrepresentation of fathers is typical in such studies (e.g., Murphy & Barkley, 1996).

Procedure and Measures

All evaluations were conducted at Michigan State University in a standardized sequence. Test administrators and diagnostic interviewers were carefully trained, followed practiced scripts in providing test instructions, had their test administration procedures checked via videotape in a periodic quality-control procedure, and were naive to child or parent diagnostic status and study hypotheses. The following measures were obtained.

Behavioral inhibition. *Behavioral inhibition*, or suppression of a prepotent motor response, is postulated to require activation of a circuit linking basal ganglia and orbitoprefrontal cortex (Casey et al., 2002) and is often suggested as an ADHD endophenotype (Barkley, 1997; Crosbie & Schachar, 2001; Holmes et al., 2002). It was operationalized with the tracking version of the Stop Task using the same procedures as Logan, Schachar, and Tannock (1997) and Nigg (1999). The Stop Task is a computerized choice RT task. Following two blocks of 32 practice trials, four blocks of 64 trials were administered. In the tracking version of this task, stop-signal RT (the index of inhibitory control) is estimated by subtracting mean stop-signal latency from mean go response time (Logan et al., 1997). Simulation data show the estimated stop-signal RT to be reliable with four blocks of trials and robust to violations of the statistical and theoretical assumptions underlying the task (Band, van der Molen, & Logan, 2003).

Set shifting. The ability to rapidly alternate mental set was operationalized with the Trailmaking Test Form B from the Halstead–Reitan Neuropsychological Battery (Reitan, 1979). Trailmaking B requires the subject to trace a path between alternating letters and numbers as rapidly as he or she can without making errors. Parents completed the more difficult adult version of this task, which is similar in structure to the child version; siblings completed the child version. The primary executive measure was time to complete Form B, whereas Form A time was viewed as a warm-up task and was not further analyzed.

Planning–working memory. The term *planning* here entails manipulation of visual information using the visual working memory system, thus placing demands on prefrontal cortex in adults and children (Levin et al., 1994). It was operationalized with the Tower of London (Krikorian, Bartok, & Gay, 1994). Participants viewed boards having three wooden pegs of unequal heights on which three wooden balls of different colors were to be moved one at a time, from a standard start position, to match pictured positions. The 12 problems increased in difficulty from two to five moves, with a possible total score of 36 points based on number of trials needed to solve each problem. Prior studies suggest that similar tasks differentiate ADHD-C and control groups (Klorman et al., 1999; Nigg et al., 2002). The outcome variable was the total score (range = 0–36).

Interference control. *Interference control* refers to the ability to monitor response conflict and suppress a competing response to carry out a primary response. It entails activation of anterior cingulate and dorsolateral prefrontal cortex (Cabeza & Nyberg, 1997). It was operationalized with the Stroop Color–Word Interference Test (Golden, 1978). The Stroop test is a widely used neuropsychological measure (MacLeod, 1991). The paper-and-pencil version of the task was administered, with 45 s per trial. To evaluate interference control apart from naming speed, we created a residual score by regressing color–word naming on color and word naming. This score correlated at .94 with the traditional interference score in parents and at .99 in children but was more normally distributed.

Response variability. Variability in output speed on fast tasks is a candidate endophenotype emphasized in a recent neuroscience model of ADHD (Castellanos & Tannock, 2002) because of its ramifications for timing and motor control; it also has ramifications for models of arousal and output regulation (Posner & Peterson, 1990). It was assessed by the within-subject RT standard deviation on the go trials on the Stop Task (Logan et al., 1997).

Response and naming speed. These measures provide one commonly cited index of effort or activation (Posner & Peterson, 1990; Sergeant et al., 1999), although naming speed also entails retrieval processes. We assessed output speed in two ways. One variable was the mean RT on the go trials of the Stop Task (Logan et al., 1997). The other was naming speed (Carte et al., 1996), here derived by creating an average of the standardized Stroop Test word and color naming scores (for parents they correlated at .69, yielding an alpha of .80; the composite correlated at $> .87$ with both scores; figures were similar for children).

Data Reduction

Missing data. To evaluate whether missing data were systematically related to variables of interest, we computed for each case a dummy-coded "amount of missing neuropsychological data variable" (Cohen & Cohen, 1983) and correlated this variable with relatives' cognitive and symptom variables (the seven neuropsychological scores, IQ, and inattention and hyperactivity ratings). For mothers, 1 of 10 correlations was significant (response variability, $r = .17$, $p = .02$). The rest ranged in absolute value from $< .01$ to .13. For fathers, 1 of 10 correlations was significant (Trailmaking B, $r = .19$, $p = .04$), whereas the remainder ranged in absolute value from $< .01$ to .09. In view of the small number of significant correlations and the small magnitude of correlations overall, we opted to estimate missing data and to covary the amount of missing data variable from variables correlated with it (Cohen & Cohen, 1983). We imputed missing data using the estimation maximization algorithm, which is one form of maximum-likelihood estimation. Maximum-likelihood imputation methods are generally viewed as superior to older alternatives, such as listwise deletion or regression estimation (Rovine & Delaney, 1990; Shafer & Graham, 2002), because they preserve parameter estimates (in our data, mean F change with imputation was < 0.05 for both fathers and mothers). We imputed data separately within fathers and within mothers. Overall, this led to the estimation of 7.3% of data for fathers (excluding nonparticipating fathers, as described earlier) and 2.7% of data points for mothers (for a total of $< 5\%$ imputed data points). We considered this level of data estimation well within the acceptable range in view of the robustness of the estimation method. We similarly imputed missing data points for the 79 participating siblings, resulting in estimation of 11% of their data points; one sibling extreme outlier score was discarded and not replaced (Trailmaking B, > 5 min). Other outliers were viewed as acceptable in the data sets.

Pooling of relatives' data. Consistent with existing literature, assortative mating was present for parent IQ (mother and father $r = .33$, $p < .001$) but not for symptoms of ADHD in parents (inattention, $r = -.06$, *ns*; hyperactivity $r = .07$, *ns*). Parent neuropsychological performance likewise was uncorrelated, with all same-task correlations ranging from –.07 to .12. We therefore combined all parents for our main analyses, following the procedures used in prior endophenotype studies of ADHD (e.g., Asarnow et al., 2002). However, in view of the nonrandom missingness of fathers, we included interaction terms in our models to evaluate whether effects were dependent on parent sex. We report sibling data separately from parent data for the primary analyses for consistency with the literature. However, we pooled all relatives for the neuropsychological subtype analysis in view of their exploratory nature to reduce Type I error.

Validity of distinguishing the seven dependent measures. Some conceptual (and thus empirical) overlap among the cognitive measures was expected (Miyake et al., 2000), yet they were also expected to be sufficiently distinct that their separate evaluation was warranted. Consistent

with this picture, correlations among our seven dependent variables ranged in absolute value from .01 (stop-signal RT with Tower of London) to .61 (go response time and response variability). All remaining pairwise correlations among the seven dependent measures were below .41, indicating that all of these pairs of variables shared less than one fifth of their variance. The average correlation across the 21 pairwise intercorrelations was .14. Overall, the pattern of correlations was consistent with the executive and regulator function literature (Pennington, 1997). In light of strong theoretical predictions specific to response variability, we kept it distinct from output speed. In addition, in light of the remaining correlations and to facilitate comparison with other studies, we opted not to attempt further data reduction.

Plan of data analysis. To be included in the primary data analyses, candidate endophenotypes had to (a) differentiate ADHD from non-ADHD probands and (b) be familial (nonzero proband to relative correlations). Variables that survived those screens were subjected to hypothesis tests. Comparisons among the relatives were conducted using a regression approach (Aiken & West, 1991). Orthogonal contrast codes were used to compare (a) all parents of children with ADHD with control parents and (b) parents of ADHD-C with parents of ADHD-PI. These contrasts were entered together after the covariates; their unique effects in the simultaneous model are therefore reported. Proband and parent sex were dummy coded and included in all models at Step 3, with the four multiplicative interaction terms (the two contrasts by the two sex variables) entered at the final step for parents (two interactions, with proband sex, were entered in an otherwise identical model for siblings). We covaried relatives' age in all diagnostic group comparisons because mothers differed in age (see Table 1) and sibling performance was related to age. IQ was modestly correlated with most of the executive measures (ranging in absolute value from $r = .14$ to $r = .35$). In light of controversy over whether IQ should be covaried in studies of this nature (see Miller & Chapman, 2001), we checked models with and without IQ as a covariate; the footnotes of Table 1 indicate any changes in results based on covarying IQ.

Power. Using Cohen's (1988) methods, with $n = 307$ for the parent analyses, power to detect a single between-group contrast in a simultaneous regression model (assuming $k = 5$ covariates) was ~.80 to detect $f^2 = .026$ (approximate $\beta = .15$), which is a small effect in Cohen's nomenclature. Estimating the power for the Sex × Contrast interactions depends on more assumptions (see Cohen & Cohen, 1983, p. 373), but power was .80 to detect interactions of approximately $f^2 = .04$ (approximate $\beta = .20$). Power, of course, was lower for sibling analyses and slightly higher when pooling all relatives.

Results

Preliminary Examination of the Data

Sample description. Table 1 provides demographic details of the samples. As shown, parent groups did not differ in IQ or reading ability. The mothers of children with ADHD-C were younger than mothers of control children ($p < .02$, Tukey test), causing a significant three-group effect of parent age for mothers. A companion article (Stawicki et al., 2004) described parent psychopathology in these samples in detail. Parents and siblings of ADHD probands were more likely to meet criteria for ADHD than relatives of control children. As the bottom of Table 1 shows, all of the candidate endophenotypes showed effects in the proband groups using our regression contrast approach, although effects for go RT were dependent on an interaction.

Correlations between relatives' and probands' cognitive performance. Table 2 presents the on-diagonal (same-task) correlations between relative and proband child scores. IQ scores and ADHD symptoms are included for comparative purposes because their heritability is well described. As can be seen, significant associations appeared between proband and relatives' performance for five of the seven neuropsychological measures. Two measures were not familial in the pooled data (Tower of London, interference control) and were thus dropped from further analysis. This left five dependent measures as candidate endophenotypes: response variability, response suppression, set shifting, naming speed, and response speed. Notably, cognitive effects were about half as large as the benchmark effect of IQ, perhaps because of the tendency for assortative mating for IQ but not for the other cognitive measures.

Hypothesis 1: Relatives of Probands With and Without ADHD

Table 3 provides the univariate data for parents and siblings, analyzed separately. All analyses were implemented via the regression contrast approach described earlier. Thus, a single regression model was computed for each of the five dependent variables that remained. Age of relative was covaried in all models, and results for IQ are noted in the table. As Table 3 shows, endophenotype effects were replicated for Trailmaking B for parents and siblings (holding for ADHD-C, regardless of model or covariates) and were apparent for stop-signal RT for girls after decomposition of an interaction in the parent data. Response variability also exhibited an effect after decomposition of interactions, but the simple effect depended on covarying IQ. As a contrast or control variable not predicted to have a causal influence on ADHD development, we checked models for parent IQ. As expected, even though IQ was highly familial, results were nonsignificant (first contrast $\beta = -.07$, *ns*; second contrast $\beta = -.08$, *ns*; no interactions).

Consideration of covariates, however, remained crucial. First, if neuropsychological vulnerability is a marker of biological risk for ADHD, then it should be present even when the influence of relatives' ADHD on their neuropsychological performance is statistically removed. Otherwise, poor neuropsychological performance may be merely another correlate of ADHD but deserving of no special status in etiological theory. Lifetime ADHD (any subtype) was assigned to parents and siblings in the percentages shown in Table 1. Effects that were significant in Table 3 were reanalyzed with relative ADHD status added as a covariate, thus removing its influence from the analysis. All effects that were significant remained so, whether ADHD was defined using a strict six-symptom cutoff or a more generous five-symptom cutoff, except that variability dropped below significance in one model. Thus, these effects generally held up as potential endophenotypes. We also rechecked significant effects within subtype (proband and parent ADHD-C), with no change in results.

However, comorbid child conditions still might be carrying these effects. To evaluate this possibility for the most important confound, CD (Jensen et al., 1997), we inserted child CD status as a covariate, again with no change in any significant effects. The same held when proband RD was covaried (the sample only included 8 probands with learning disability (LD), all boys; $n = 2$ with ADHD-PI and $n = 6$ with ADHD-C). ODD was highly correlated with ADHD ($r = .47$; 50% of cases with ADHD had ODD vs. 3% of controls), so perhaps it was unsurprising that when ODD was covaried, all effects were nonsignificant. This might

Table 1
Demographic Overview of Parent and Sibling Samples: Mean (and Standard Deviation) Scores by Proband Diagnosis

Variable	Control	ADHD		Three-group *F* test *p*
		Combined	Inattentive	
Mothers				
n	62	79	35	
Age (years)	38.2 (5.0)	35.5 (6.0)	37.8 (6.0)	.017
IQ	109.2 (14.0)	107.6 (13.0)	110.9 (15.0)	*ns*
Race (% White)	82	85	79	*ns*
Avg inattentive sym	0.48 (1.4)	1.75 (3.0)	1.39 (2.8)	.01
Avg hyperactive sym	0.28 (0.9)	1.37 (2.4)	0.96 (2.0)	.005
% ADHD (any type)	3	23	11	.002
Fathers				
n	53	50	28	
Age (years)	39.9 (5.0)	38.5 (6.0)	39.9 (6.0)	*ns*
IQ	109.4 (15.0)	111.8 (13.0)	115.6 (15.0)	*ns*
Race (% White)	84	81	79	*ns*
Avg inattentive sym	1.09 (2.0)	2.85 (3.4)	1.71 (2.6)	.009
Avg hyperactive sym	0.26 (0.7)	2.65 (3.5)	0.43 (1.2)	< .001
% ADHD (any type)	8	30	18	.011
Siblings				
n	26	36	17	
Age (years)	9.8 (2.3)	10.0 (3.0)	10.6 (3.4)	.80
IQ	111.1 (12.9)	114.9 (14.0)	100.0 (10.7)	.06
% boys	58	43	29	.18
Avg inattentive sym	2.7 (2.8)	8.2 (6.8)	6.6 (4.5)	.001
Avg hyperactive sym	3.5 (3.5)	7.7 (7.2)	6.1 (3.9)	.006
% ADHD (any type)	15	48	50	.007
Probands				
n	62	79	35	
Age (years)	9.7 (1.2)	9.6 (1.3)	9.9 (1.2)	*ns*
IQ	109.5 (15.0)	104.1 (13.0)	105.6 (17.0)	.08
Race (% White)	82	85	79	*ns*

Measure	Control	ADHD		Regression coefficients			
		Combined	Inattentive	Con1	Con2	Int1	Int2
Trailmaking B	43.6 (21)	52.8 (32)	64.9 (47)	−.23**	−.13†	.09	.21
Stop-signal RT[a]	307.4 (96)	414.0 (148)	371.6 (143)	−.32**	.07	−.51*	−.54*
Response variability[b]	180.4 (48)	217.4 (51)	213.2 (63)	−.31**	.03	−.57*	−.13
Tower of London	28.3 (3)	26.5 (3)	26.9 (3)	.25**	−.04	.26	.16
Stroop interference (*z*)	.20 (1)	−.01 (.9)	−.32 (1)	.18*	.12	.34	−.06
Stroop naming speed (*z*)[b]	.33 (.9)	−.18 (.8)	−.18 (.9)	.27**	−.00	.44*	−.28
Response speed[b]	693.7 (121)	722.0 (105)	724.0 (124)	−.13	.02	−.52*	−.06

Note. IQ is based on a two-subtest short form of the Wecshler Adult Intelligence Scale—Revised for parents and on a five-subtest short form of the Wechsler Intelligence Scale for Children—Third Edition for probands and their siblings. The average number of *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (*DSM–IV*) symptoms (Avg inattentive-hyperactive sym) is based on structured interview of childhood symptoms experienced by the parents and on parent checklist ratings of siblings. Parent attention-deficit/hyperactivity disorder (ADHD) diagnosis is based on the Diagnostic Interview Schedule for *DSM–IV* and the modified (SNAP–IV) checklist. Sibling diagnosis is estimated from symptom counts provided by parent checklist ratings. Con1 = regression contrast control versus all ADHD; Con2 = ADHD combined type versus ADHD inattentive type; Int1 = Contrast 1 × Child Gender interaction; Int2 = Contrast 2 × Child Gender interaction.

[a] For boys: ADHD combined type > control ($p < .01$); ADHD inattentive type = control ($F < 1.0$); ADHD combined type > ADHD inattentive type ($p < .05$). For girls: ADHD combined type > control ($p < .01$); ADHD inattentive type > control ($p < .001$); ADHD combined type = ADHD inattentive type ($p = .20$). [b] Main effect larger in boys than in girls after interaction decomposed; response speed: boys, $p < .05$.

† $p < .10$. * $p < .05$. ** $p > .01$.

Table 2
On-Diagonal Correlations of Parent and Child Neuropsychological Scores

Variable	All relatives (N = 386)	All parents (n = 307)	Mothers (n = 171)	Fathers (n = 131)	Siblings (n = 79)
Stop task variability	.16**	.16**	.16*	.19*	.29**
Stop-signal RT	.19**	.09	.13*	.02	.45**
Trailmaking B	.09*	.10*	.18**	.04	.08
Tower of London	.03	.02	−.01	−.05	.18
Stroop interference ctrl	.03	−.07	.16*	.01	.02
Stroop naming speed	.15**	.11*	.05	.21**	.26*
Stop Task go RT	.13**	.16**	.07	.26**	−.08
Full scale IQ	.39**	.37**	.37**	.36**	.51**
Attention symptoms	.23**	.21**	.19**	.25**	.35**
Hyperactivity symptoms	.26**	.31**	.24**	.42**	.31**

Note. RT = reaction time; ctrl = control.
* $p < .05$. ** $p < .01$.

suggest that all effects were at least partially due to the presence of ODD in the ADHD samples or that ODD is an integral part of the neuropsychological element of the ADHD syndrome.

Hypothesis 2: Heterogeneity—The Neuropsychologically Affected Subgroup

The second hypothesis addressed neuropsychological heterogeneity in the ADHD children. If neuropsychological endophenotypes are related to risk for ADHD, then dividing children by neuropsychological risk status should predict relatives' neuropsychological status for those putative endophenotypes. Support for this hypothesis would thus help to validate a neuropsychologically affected subtype (Sonuga-Barke, 2002). We conducted these analyses for each neuropsychological variable. We defined affected on the neuropsychological tasks as worse than the 10th percentile in the control group. However, because of tie scores, the actual cut points varied from the 8th to the 13th percentile. To combine parent and sibling data for these exploratory analyses, we standardized the dependent measures within parents and within siblings and then combined the standardized data. We converted the z scores to T scores to ease table readability. Table 4 thus provides

Table 3
Relatives' Neuropsychological Scores Means, (and Standard Deviations) by Child Group And Coeffients from Regression Contrasts and Interactions

		ADHD		β		Interaction			
	Control	Combined	Inattentive	Control vs. all ADHD	ADHD-C vs. ADHD-I	Child Gender × Contrast		Parent Gender × Contrast	
Parents									
Response variability[bcg]	122.6 (32)	126.5 (37)	125.2 (47)	.04 (.15*)	.01	−.12	−.05	−.16*	.10
Stop signal RT[afg]	212.7 (48)	213.9 (54)	221.4 (52)	.13 (.34*)	−.13	−.21*	.12	−.26*	.12
Trails B[fgh]	54.5 (20)	62.6 (30)	54.8 (20)	.11*	.18**	−.10	−.18	.00	.13
Stroop naming speed (z)[efg]	.02 (.9)	.03 (.9)	−.10 (.9)	−.04	.04 (.15*)	−.15	.24*	−.03	−.13
Output speed (Go RT)[dfg]	657.5 (129)	658.4 (132)	622.6 (142)	−.05	.13*	.17	.03	.06	.10
Siblings									
Response variability	171.0 (60)	192.8 (83)	179.6 (82)	.15	.02	.17	−.04	—	—
Stop signal RT	309.1 (178)	377.4 (191)	310.1 (158)	.13	.11	.24	.21	—	—
Trails B[fg]	30.4 (11)	42.2 (27)	43.0 (22)	.29**	−.07	−.26	−.17	—	—
Stroop naming speed (z)	.05 (.7)	.01 (1)	−.10 (.9)	−.11	.10	.22	−.05	—	—
Output speed (Go RT)	716.7 (114)	703.0 (136)	702.0 (117)	−.02	.03	−.01	.23	—	—

Note. Superscripts summarize simple effects and covariate effects. ADHD = attention-deficit/hyperactivity disorder; RT = reaction time; LD = learning disability; CD = conduct disorder.
[a] Simple effect for mothers of girls only; interaction for Parent Gender × Contrast occurs in model within girls ($p = .05$; when parent IQ covaried, $p = .02$). [b] Contrast × Parent Gender interaction not significant if IQ is covaried ($p = .06$). [c] Simple effect significant only for mothers, only when parent IQ covaried ($p = .03$) but not when IQ not covaried ($p = .06$). [d] Contrast main effect significant when parent IQ is not covaried ($p < .05$) but not when parent IQ is covaried ($p = .07$). [e] Simple effect for parents of boys when parent IQ is covaried; when parent IQ not covaried ($\beta = .14$, $p = .07$). No effect for parents of girls. [f] Significant effect shown survives covarying of relatives' ADHD status defined as five symptoms, six symptoms, or ADHD-C subtype. [g] Significant effect shown survives covarying of proband LD, CD. [h] Control vs. ADHD β to $p = .057$ when missingness is covaried.
* $p < .05$. ** $p < .01$.

Table 4
Child Neuropsychological Subtype Analysis: Cut Points, Percentage Selected, Parental and Sibling Cognitive Mean (and Standard Deviation) Scores

	Percentage probands affected				Relatives *T* scores by new proband types			Regression contrasts (all)		
Variable	Cut point	Ctrl	A-C	A-I	Crtl	ADHD-N	ADHD-IM	Interaction	0 vs. 1	all vs. 2
Variability	>219 ms	13	48	46	48.8 (8)	48.7 (10)	52.7 (12)[b]	*ns*	−.09	.26***
Stop RT	>410 ms	8	51	40	48.6 (9)	49.0 (9)	52.1 (11)[b]	*ns*	−.08	.23**
Trails B	>67 s	11	27	34	47.7 (8)	50.5 (10)	52.7 (13)[b]	*ns*	.13*	.14*
Stroop naming	< −.75	10	15	23	50.5 (9)	50.3 (10)	48.4 (11)[b]	*ns*	−.02	−.07
Output speed[a]	>841 ms	8	17	14	50.5 (9)	49.4 (10)	51.4 (12)[b]	.19*	.01	.12[c]

Note. Controls with abnormal scores were excluded from the new groupings. Relatives' scores are standardized *T* scores, calculated within parents and within siblings and then combined across all parents and siblings. Ctrl = Control; A-C = ADHD Combined type, A-I = ADHD Primarily Inattentive Type. ADHD-N = child with ADHD with neuropsychological scores within the normal range or within cut points noted; ADHD-IM = child with ADHD with neuropsychological scores outside the cut points noted in the table. Stop RT = stop signal reaction time. Regression Contrast 1 compared controls with ADHD-normal; Contrast 2 compared ADHD-impaired with all others and is the key test of the heterogeneity model.
[a] Indicates that because of the interaction. Only results for boys are displayed (results for girls were nonsignificant; boys' effect, $p = .052$). All Contrast 1 × Sex interactions were not significant and are not displayed for Stroop naming, low = poor performance; for all other measures a low score = good performance. [b] Signifies the worst-performing group for each variable. [c] $p < .06$.

the proband cut points, percentage of impaired probands in each diagnostic group of children (relatives of affected control children were excluded from regression models), mean *T* scores for relatives of children in the new ADHD groupings, and results of the regression models with contrasts for each variable for parents and siblings.

The proband groups in Table 4 therefore are stratified as follows: (a) parents of control children with "normal" neuropsychological scores, (b) parents of children with ADHD (either combined or inattentive) with normal cognitive scores, and (c) parents of children with ADHD with impaired neuropsychological scores. The first regression contrast compared parents of controls with parents of ADHD normal children; the model would not predict that these two groups would differ. The second contrast compared those first two groups with the parents of the ADHD impaired children, wherein an effect was predicted by the model.

Results as displayed in Table 4 indicated a valid (familial) neuropsychological endophenotype exactly fitting predictions for response variability and stop-signal RT. Results partly fit predictions for Trailmaking B (the impaired group was the weakest group, but both sets of relatives of ADHD youngsters were worse than controls). Results were shy of significance for go RT and naming speed. The positive results survived the covarying of relatives' IQ, proband CD, and proband ODD and RD. Overall, these results provided good support for the heterogeneity model for output regulation measures and partial support for the set-shifting measure.

Effects of Diagnostic Algorithms

Although our diagnostic "or" algorithm to assign proband ADHD status should maximize validity by following the field trials, it could overselect ADHD-C, weakening subtype comparison effects. We therefore also checked results using a more stringent (though less well validated) algorithm that requires that full criteria be met by the DISC–IV, with agreement based on teacher 90th percentile normative ratings. No new effects emerged, except that ADHD-C and ADHD-PI were distinguished on naming speed.

Discussion

Cognitive and neuropsychological measures are attractive potential endophenotypes because they provide objective, continuous measures that are correlated with the ADHD behavioral phenotype (Almasy & Blangero, 2001). All of the five measures analyzed in hypothesis tests showed effects in the proband children in our sample and were familial. The general model of neuropsychological involvement in ADHD predicts that selected cognitive markers can serve as endophenotypes in etiological (e.g., genetic) studies. The core prediction from this model—presence of the marker in unaffected relatives—has never been fully tested for ADHD and, as a result, has never been demonstrated for ADHD. Only a handful of studies have even examined cognitive performance in first-degree relatives of children with ADHD, all using earlier definitions of the disorder, with weak results, as we noted in our introduction. None examined relatives of children identified by *DSM–IV* criteria, considered child gender, or examined currently theorized endophenotypes of response inhibition, response variability, or interference control. In addition, this was the first study to consider familiality of a hypothesized neuropsychologically impaired ADHD subtype.

In general, our results admit three conclusions. First, there was some support for the endophenotype model, even with relatives' ADHD status controlled. The endophenotype effect was most unequivocal for Trailmaking B but also held up for stop-signal RT (however, only for relatives of girls) and response variability (but only for mothers and only if IQ was covaried). Second, the failure of key measures, notably stop inhibition, to hold up in relatives of boys while showing effects in girls raises important questions about sex moderation of etiological effects. Third, and importantly, in light of the mixed results for the *DSM–IV* model, data supported a model of etiological heterogeneity in which a subgroup of children with ADHD are affected by a familial weakness in key cognitive functions. The findings thus suggest the need to further consider gender-specific transmission of risk and provide new data to fuel discussion of multiple etiological pathways to ADHD. We consider each of these conclusions in turn.

Status of Endophenotype Effects

We did find some endophenotype effects but not many. It was notable that interference control and planning were not even familial and that output speed measures performed poorly as potential endophenotypes. These findings provide a cautionary reminder that neuropsychological correlates of ADHD are not necessarily part of a causal developmental chain or promising markers for genetic studies.

Even those measures that did show some promise as endophenotypes require replication for several reasons. Our most robust findings using the *DSM–IV* model were for Trailmaking B. This low-cost set-shifting measure requires rapid motor control, sequencing, and planning, thus representing a conceptually attractive endophenotype (Castellanos & Tannock, 2002). However, in contrast to our results, Asarnow et al. (2002) failed to find effects in parents of ADHD children on Trailmaking B. It is unclear why the two studies differed. Differences could be due to sample composition (e.g., our use of *DSM–IV* vs. their use of *DSM–III–R* to identify probands) or specific methodology in administering the measure. Ours is the first report of response inhibition using the Stop Task in a family study of this type. It might be encouraging for the basic executive inhibition theory (Barkley, 1997) that we found some results, but contrary to that theory, we did not find results for boys. Underscoring the need for replication of any family findings at this stage, Kuntsi and Stevenson (2001) failed to find family correlations for stop inhibition in their twin study but found the best support for response speed and variability (regulation) measures. We also found response variability effects, but they were somewhat weak in that they were only present for mothers and depended on covarying IQ. We did not have positive findings for go RT.

Most of the endophenotypes we studied are more often theorized to be causal in ADHD-C than in ADHD-PI. However, as Table 1 illustrated, most of these measures failed to differentiate the ADHD subtypes in the probands, with the exception of stop-signal RT. Our design therefore did not assume that these subtypes are etiologically distinct but did include comparisons between them to check that hypothesis. In general, relatives of the two subtypes did not consistently differ, lending support to the position that the two subtypes are not entirely etiologically distinct, at least as they are defined in *DSM–IV*. However, they did differ on Trailmaking B, consistent with claims that the subtypes are partially differentiable. Overall, our results suggest that response inhibition, set shifting, and response variability may serve as endophenotypes for genetic studies of ADHD but that this conclusion depends on proband gender, especially for response inhibition.

Gender and Endophenotypes for ADHD

Why might we have found clearer results for girls than for boys on response inhibition? Aside from calling into question the role of response inhibition in etiology for boys, this finding raises the question of differential processes in boys and girls. The prior literature on children with ADHD has suggested that girls with ADHD show greater cognitive impairments than boys with ADHD (Gershon, 2002), even though behavioral severity is milder. It therefore may not be surprising that greater cognitive impairment would also be found in relatives of girls. This pattern of findings could be consistent with a process in which, before they exhibit ADHD, girls undergo greater etiological risk (or greater risk "loading") than boys. If girls are protected from exhibiting ADHD on the basis of hormonal, socialization, or other factors, then it would make sense that those showing the disorder have greater cognitive familial risk loading than affected boys.

A second possible interpretation of these data is that there are a larger percentage of phenocopies of ADHD among boys than girls. In other words, more boys may exhibit ADHD because of emotional or other causes that are not related causally to these neuropsychological mechanisms. Instead, it may be that for a higher percentage of boys, neuropsychological weaknesses are a consequence of ADHD rather than a causal mechanism, and the reverse may be true for girls. If so, it would be difficult to identify endophenotypes in family studies of ADHD using the *DSM–IV* system. Indeed, the literature we reviewed earlier clearly shows such identification has been difficult. Overall, our finding echoes recent reports in the literature that suggest that both genetic (Rhee et al., 2001) and cognitive (Hartung, Milich, Lynam, & Martin, 2002) processes may differ for boys and girls in the development of ADHD. Taking these studies together with the current one, it may be that causal models involving neuropsychological deficits are easier to demonstrate in girls with ADHD, who may exhibit a clearer cognitive deficit and fewer phenocopies than affected boys. Moreover, our response variability finding was apparent only in mothers, lending more weight to the need to consider sex-specific transmission patterns both in children and in their parents in genetic studies of ADHD.

Etiological Heterogeneity and Endophenotypes

The observation that many children with ADHD do not evidence cognitive or neuropsychological impairment (Barkley & Grodzinsky, 1992; Doyle et al., 2000) lends a crucial, often overlooked, caveat to developmental models. As a result, theorists have begun to suggest neuropsychologically based multiple-pathway models (Sonuga-Barke, 2002). Our findings regarding neuropsychological heterogeneity in ADHD represent a new empirical contribution to such thinking, in that this is the first analysis to evaluate familiality of a putative cognitively affected subgroup of children with ADHD (see Crosbie & Schacher, 2001, for a related finding). Pooled data across all available relatives provided strong evidence that a neuropsychologically impaired subtype was familial, at least for the two key endophenotypes of response inhibition and response variability. Our results, like those of Crosbie and Schacher (2001), suggest that consideration of neuropsychological heterogeneity in children with ADHD, in particular those with impaired versus normal function, can shed light on the effort to explore familial and genetically relevant endophenotypes for ADHD etiology. Doing so may improve detection of genetic pathways to the disorder from what can be achieved with the behaviorally defined *DSM–IV* classifications. Future work should evaluate the extent to which indicators can be consolidated to identify one or more affected groups, a task beyond the scope of our report.

These findings and our emphasis on neurocognitive and etiological heterogeneity in ADHD samples thus are consistent with recent conceptual discussions in the literature suggesting that

executive inhibitory control may be one process, whereas other processes, such as motivational response or reward gradient, may be a second process involved in ADHD (Nigg, 2001; Sonuga-Barke, 2002). It is also possible that one subgroup may have neuropsychological impairment (perhaps in several areas), whereas another group may be a behavioral phenocopy without meaningful neuropsychological impairment. As the frequencies shown in Table 4 underscore, only a percentage of children with ADHD could be meaningfully classified as impaired on any one neuropsychological measure. This may help to explain the difficulty in identifying endophenotypes when relying solely on the *DSM–IV* behavioral classification system. Along these lines, it is interesting to recall the findings of Swanson et al. (2000). They divided children on the basis of genotype, finding that response speed deficits were apparent only in one of the groups of children with ADHD. It will be worthwhile to repeat such analyses with the endophenotypes that obtained at least provisional support herein. Our measures likely reflect multiple and potentially distinct neurotransmitter systems. Therefore, pairing theorized endophenotypes with genotypes relevant to the related neurotransmitter systems could lead to a more differentiated picture of heterogeneity and subtyping and help advance this line of work.

Limitations

Several limitations in these data should be noted. First, like prior family studies, we had underrepresentation of affected fathers. This could have led to missing some effects. Second, if gender-specific patterns are the rule, then powerful designs able to detect interaction effects are needed; our study had a respectable sample size, but power to detect interactions was less than for main effects. Some small, but potentially important, interactions (and thus some simple effects) could have been missed. Conversely, the use of multiple dependent measures, analysis of parents and siblings, and checks on covariates resulted in potential inflation of Type I error; we have already noted the need for replication of these initial findings. Finally, our assessment of ADHD in relatives was limited to parent report. Positive findings require further analysis in this regard.

Conclusion

The findings provide new data by which to evaluate the general claim that neuropsychological correlates of ADHD are part of the causal processes leading to development of the disorder. Findings provide only minimal support for the *DSM–IV* conception of a neuropsychologically caused disorder for boys, with somewhat more support for girls. Results suggest that fitting neuropsychological processes into causal models will require consideration of child gender. Moreover, findings suggest that a more promising direction for understanding etiological pathways in ADHD is to examine child subtypes on the basis of etiologically informative process distinctions, such as neuropsychological impairment. Heterogeneity models should be further explored in family and other etiologically informative designs.

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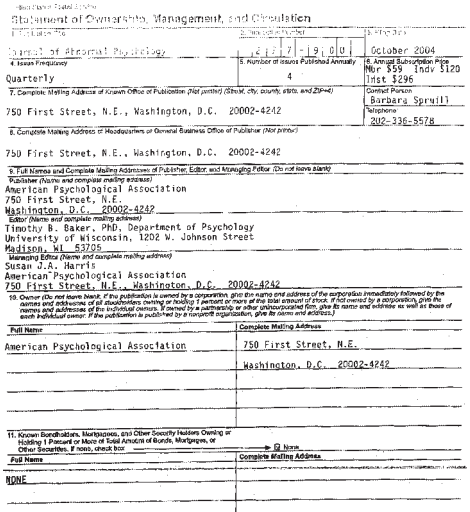

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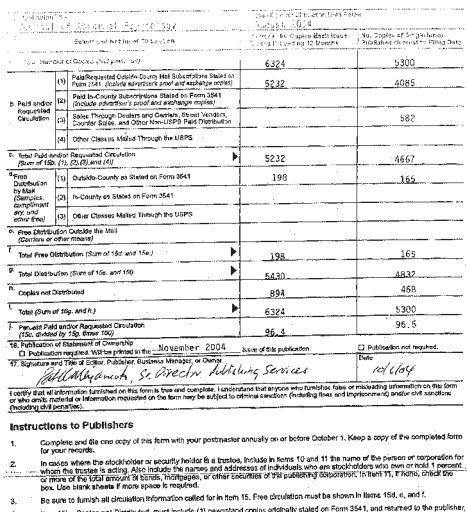

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