Separation of Cognitive Impairments in Attention-Deficit/Hyperactivity Disorder Into 2 Familial Factors

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Context: Attention-deficit/hyperactivity disorder (ADHD) is associated with widespread cognitive impairments, but it is not known whether the apparent multiple impairments share etiological roots or separate etiological pathways exist. A better understanding of the etiological pathways is important for the development of targeted interventions and for identification of suitable intermediate phenotypes for molecular genetic investigations.

Objectives: To determine, by using a multivariate familial factor analysis approach, whether 1 or more familial factors underlie the slow and variable reaction times, impaired response inhibition, and choice impulsivity associated with ADHD.

Design: An ADHD and control sibling-pair design.

Setting: Belgium, Germany, Ireland, Israel, Spain, Switzerland, and the United Kingdom.

Participants: A total of 1265 participants, aged 6 to 18 years: 464 probands with ADHD and 456 of their siblings (524 with combined-subtype ADHD), and 345 control participants.

Main Outcome Measures: Performance on a 4-choice reaction time task, a go/no-go inhibition task, and a choice-delay task.

Results: The final model consisted of 2 familial factors. The larger factor, reflecting 85% of the familial variance of ADHD, captured 98% to 100% of the familial influences on mean reaction time and reaction time variability. The second, smaller factor, reflecting 13% of the familial variance of ADHD, captured 62% to 82% of the familial influences on commission and omission errors on the go/no-go task. Choice impulsivity was excluded in the final model because of poor fit.

Conclusions: The findings suggest the existence of 2 familial pathways to cognitive impairments in ADHD and indicate promising cognitive targets for future molecular genetic investigations. The familial distinction between the 2 cognitive impairments is consistent with recent theoretical models—a developmental model and an arousal-attention model—of 2 separable underlying processes in ADHD. Future research that tests the familial model within a developmental framework may inform developmentally sensitive interventions.

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Attention-deficit/hyperactivity disorder (ADHD) is a common neurodevelopmental disorder affecting around 5% of children. The disorder is characterized by inattentive, hyperactive, and impulsive behaviors that persist into adulthood in around 65% of cases and is associated with high levels of clinical, psychosocial, and economic burden. Because of the high heritability of ADHD, which averages around 76%, etiological research has focused in particular on the role of genetic factors and the neurobiological processes that mediate genetic effects on behavior.

One approach to understanding the neurobiology of ADHD is to investigate brain function through performance on cognitive tasks that delineate the underlying cognitive processes. Cognitive studies find widespread impairments in both children and adults with ADHD, with deficits particularly on executive function tasks, especially those measuring response inhibition and sustained attention. Among the various cognitive variables investigated, reaction time (RT) variability (RTV) is one of the best to discriminate between ADHD and control samples, although several other behavioral and cognitive measures are associ-
ADHD or, alternatively, multiple etiological pathways.\textsuperscript{10-16}

A key approach to delineating etiological mechanisms is to identify the cognitive processes that mediate between genes and behavior. When specific measures of cognitive function have been studied separately, family and twin designs have provided evidence of shared genetic or familial influences with ADHD, particularly for RTV, inhibition, and other executive dysfunctions, including aspects of attention\textsuperscript{17,18} and IQ.\textsuperscript{19} However, we do not know whether these apparent multiple impairments share etiological roots or whether separate etiological pathways exist.\textsuperscript{20} A particularly powerful approach, which goes beyond simple sibling designs that look for significant differences on task performance between unaffected siblings and controls,\textsuperscript{21} is the use of genetic multivariate (MV) model fitting. Genetic MV methods delineate the architecture of genetic and environmental influences underlying the association between ADHD and task performance while simultaneously addressing the etiological influences on several separately measured cognitive processes and, further, indicating their relative importance.

In this study we adopted an empirical MV approach, focusing on cognitive variables that we previously reported to be associated with ADHD and siblings of probands with ADHD.\textsuperscript{22-24} Specifically, we used MV familial factor analysis in a large sample of ADHD and control sibling pairs to address the question of whether 1 or more familial factors underlie the slow and variable RTs, impaired response inhibition, and choice impulsivity (preference for smaller, immediate rewards, incorporating “delay aversion”) that are associated with ADHD.

**METHODS**

**SAMPLE**

**ADHD Probands and Siblings**

Participants were recruited from specialist clinics in Belgium, Germany, Ireland, Israel, Spain, Switzerland, and the United Kingdom through the International Multicenter ADHD Genetics project.\textsuperscript{25} All participants were of white European descent and aged 6 to 18 years. All probands had a clinical diagnosis of combined-subtype ADHD and had a full sibling (unselected for clinical phenotype) and biological parents available for ascertainment of clinical information and DNA. Exclusion criteria for both probands and siblings included an IQ of less than 70, autism, general learning difficulties, brain disorders, and any genetic or medical disorder associated with externalizing behaviors that might mimic ADHD. Sibling selection was based first on sex and second on nearest age to the index proband.

**Control Sample**

The control group was recruited from primary (ages 6-11 years) and secondary (ages 12-18 years) schools in the United Kingdom, Germany, and Spain, aiming for an age and sex match with the clinical sample. The same exclusion criteria were applied as for the clinical sample. In addition, 1 child subsequently withdrew after testing and 3 were excluded for having an IQ of less than 70. An additional 10 controls were excluded for having both parent and teacher subscale T scores on the Conners ADHD/DSM-IV Scale\textsuperscript{26} of more than 63, to exclude potential undiagnosed ADHD cases.

**Final Sample**

The ADHD proband and sibling sample consisted of 920 individuals (464 ADHD probands and 456 siblings of ADHD probands) and the control sample of 343 individuals. The final total sample therefore consisted of 1265 individuals, which comprised 380 complete sibling pairs and 105 singletons. Of the 1265 individuals, 324 with combined-subtype ADHD were classified as affected, 16 who met criteria for the hyperactive-impulsive or inattentive subtypes were classified as a “subthreshold group,” and an additional 664 individuals were unaffected siblings and controls. The ADHD status was therefore included in the analyses in an ordinalized manner. Sixty-one participants had cognitive data but no clinical data, and their ADHD status was coded as missing. Of the 524 individuals with combined-subtype ADHD, there was an overlap of comorbid disorders: 151 had conduct disorder, 335 had oppositional defiant disorder, and 63 had possible mood disorder (excluding bipolar disorder), derived as part of the Parental Account of Child Symptoms (PACS) parental interview (see the “Measures” section). Ethical approval was obtained from local ethical review boards.

**PROCEDURE**

The assessments of the proband and sibling were carried out in separate rooms. Short breaks were given as required, and the total length of the test session was 2½ to 3 hours. A minimum of a 48-hour medication-free period was required for cognitive testing.

**MEASURES**

**ADHD Diagnosis**

The PACS interview\textsuperscript{27,28} was conducted with the parents to derive the 18 DSM-IV symptoms for ADHD index cases plus siblings who were thought, on the basis of parents’ descriptions of behavior or Conners scores of 65 or greater, to have ADHD. Situational pervasiveness was defined as some symptoms occurring within 2 or more different situations from the PACS, as well as the presence of 1 or more symptoms scoring 2 or more from the DSM-IV ADHD subscale of the teacher-rated Conners subscale.\textsuperscript{29} Impairment criteria were based on the severity of symptoms identified in the PACS. Across the International Multicenter ADHD Genetics sites, a mean $k$ coefficient of 0.88 and an average agreement of 96.6% were obtained for ADHD diagnostic categories.\textsuperscript{30}

**Cognitive Tasks**

Wechsler Intelligence Scales for Children, Third Edition. The vocabulary, similarities, picture completion, and block design subtests from the Wechsler Intelligence Scales for Children\textsuperscript{31} were used to obtain an estimate of IQ.

The Go/No-Go Task. On each trial in this task,\textsuperscript{31,32} 1 of 2 possible stimuli appeared for 300 milliseconds in the middle of the computer screen. The participant was instructed to respond only...
to the “go” stimuli and to react as quickly as possible but to maintain a high level of accuracy. The proportion of “go” stimuli to “no-go” stimuli was 4:1. The participants performed the task under 3 conditions (slow, fast, and incentive)

The Fast Task. The baseline condition, with a fore period of 8 seconds and consisting of 72 trials, followed a standard warned 4-choice RT task. A warning signal (4 empty circles, arranged side by side) first appeared on the screen. At the end of the fore period (presentation interval for the warning signal), the circle designated as the target signal for that trial was filled (colored in). The participant was asked to make a compatible choice by pressing the response key that directly corresponded to the location of the target stimulus. After a response, the stimuli disappeared from the screen and a fixed intertrial interval of 2.9 seconds followed. Speed and accuracy were emphasized equally. If the child did not respond within 10 seconds, the trial was terminated. A comparison condition with a fast event rate (1 second) and incentives followed the baseline condition (further details in Andreou et al).

The Maudsley Index of Childhood Delay Aversion. Two conditions, each with 20 trials, were administered (in random order across participants). In each trial, the participant had a choice between a smaller, immediate reward (1 point, involving a 2-second prereward delay) and a larger, delayed reward (2 points, involving a 30-second prereward delay). In the condition with no postreward delay, choosing the small reward led immediately to the next trial; in the postreward delay condition, this led to a delay period of 30 seconds, whereas choosing the large reward led to a delay period of 2 seconds before the next trial. The variable obtained from the task is the percentage of choices for the larger reward, for each condition separately; a lower percentage of such choices indicates greater choice impulsivity.

STATISTICAL ANALYSES

Familial Structural Equation Models

The structural equation-modeling program Mx was used to conduct the MV genetic analyses and estimation of phenotypic correlations. To account for the selected nature of the sample, the selection variable (ADHD status) was included in all models with its parameters fixed. This inclusion necessitated ordinal data analysis for all variables with the age-, IQ- and sex-regressed residual scores of the cognitive variables ordinalized into 5 equal-sized categories. Ordinal data analysis assumes the combination of ordered categories to reflect measurements of an underlying MV normal distribution of the traits. In our models, this ordered categorical approach was reflected in 1 fixed threshold for ADHD (fixed to expected population prevalence) and 4 thresholds for the cognitive data, which gave rise to ordered categories on which the polychoric sibling correlations were conducted. A limitation of this approach is that it is very computationally intensive, with the numerical integration increasing exponentially as the number of variables increases. This computational demand places a limit on the number of variables that can be included in ordinal data analysis; in these analyses, 5 variables in addition to the selection variable (ADHD, included in all models to correct for ascertainment bias) was the maximum number that could be included in any one model. Furthermore, the computational demands of ordinal data analysis herein precluded the presentation of 95% confidence intervals, but the significance of parameters was tested by dropping each parameter of interest in turn and looking for a drop in fit compared with the full (nonreduced) model at the P < .05 level, with a 1-df test.

The threshold for ADHD status was fixed to give a population prevalence of 5% (z score set at 1.64), and familiality parameters were fixed to expected population estimates (heritability assumed to be 80%, with a sibling correlation of 0.40) by means of a method developed and validated in an earlier simulation study.

Phenotypic Correlations

Sibling correlations were estimated from a constrained phenotypic correlation model to give maximum likelihood correlations between the phenotypic variance in each measure for each sibling and to allow additional constraints. The first imposed constraint was fixing the sibling correlation for ADHD status to 0.40 to correct for ascertainment bias. Further constraints reflect the assumptions of the familial model: that phenotypic correlations across traits are the same across siblings and that cross-trait cross-sibling correlations are independent of sibling status (birth order).

Familial Models: Cholesky Decomposition

Using the information that siblings reared together share, on average, 50% of their segregating alleles, MV models use cross-trait cross-sibling correlations to decompose the covariation between traits into familial (referred to as F and composed of 50%-100% of additive genetic [A] + 100% of common environmental [C]) influences and individual-specific environmental (E) influences, which include possible measurement error.

Confirmatory Familial Factor Analysis

Preliminary model-fitting analysis, using a correlated-factors solution of the Cholesky model, gives separate correlation ma-
Mean values for background and cognitive variables in probands with ADHD, siblings of probands, and controls are given in Table 1.

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<th>Table 1. Background and Cognitive Variables in Probands With ADHD, Siblings of Probands, and Controls</th>
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<td>Final omission errors, mean scorea,b,c</td>
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<td>Choice impulsivity, %a,b,c</td>
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Abbreviations: ADHD, attention-deficit/hyperactivity disorder; MRT, mean reaction time; RTV, reaction time variability.

Mean data were fabricated for intellectual analysis, and all variables were regressed for IQ as well as for age and sex. An additional preliminary bivariate model-fitting analysis between choice impulsivity (here referring to performance in the no-postreward-delay condition of the Maudsley index of childhood delay aversion task) and a variable we called “delay aversion” (choice impulsivity while controlling for performance in the postreward delay condition) indicated a high degree of phenotypic overlap (\( r_f = 0.89 \)) and child-specific environmental (\( r_e = 0.88 \)) overlap, suggesting that either variable could be used because both indexed the same underlying familial etiology (or liability). We focused on variables available and where supported by bivariate model-fitting analyses. The latter was indicated when there was evidence of a large degree of familial overlap across the 2 variables (defined as high familial correlation, \( r_f \)), suggesting they were measuring largely the same underlying liability.
the choice impulsivity variable in the analyses, which showed a stronger association with ADHD.

MISSING DATA

Some data are missing because 2 of the teams did not administer the go/no-go task, 2 did not administer the fast task, and there were occasional technical problems with equipment. Go/no-go data were available from 922 participants, fast task data from 687 participants, and delay aversion task data from 988 participants. Mx uses raw data maximum likelihood estimation, which incorporates all available data points (and therefore no listwise or pairwise deletion is applied in cases of missing data). We additionally reran the analyses using imputation for missing data. Results with imputed data showed a similar overall pattern and, thus, are not presented herein.

PHENOTYPIC, FAMILIAL, AND CHILD-SPECIFIC ENVIRONMENTAL CORRELATIONS

The phenotypic correlations (Table 2) indicate the strongest associations with ADHD for RTV (0.39) and MRT (0.36), followed by omission errors (0.22) and commission errors (0.19), then choice impulsivity (0.10). The familial correlations (Table 2) similarly indicate strongest association with ADHD for RTV (0.74) and MRT (0.61). Furthermore, the familial correlation between RTV and MRT is high at 0.91, mirroring results in a general-population twin sample, indicating that these variables cannot be distinguished at the familial level. The familial correlation between omission errors and commission errors is also high at 0.76. The individual-specific environmental correlations (Table 2) are generally lower, but a high correlation of 0.76 was observed between MRT and RTV.

FACTOR ANALYSES

The factor-loading structure (shown in the Figure for F factors) reflects factor loadings that accounted for most of the shared variance in each phenotype. For each variable, only 1 factor loading was included, except for omission errors, which loaded onto both E factors in the E factor analysis.

Given that, with sibling data only, it is not possible to ascertain the exact amount of phenotypic variance accounted for by the sum of additive genetic and shared environmental influences, we focus in this report on the proportions of overall familiality. The 2 familial factors loaded separately onto the RT variables (MRT and RTV) and the error variables (commission and omission errors). The majority of familial influences underlying task variables could be explained by the 2 common familial factors (62%-100%), which further, in sum, accounted for 97.5% of the familial variance underlying ADHD.

The factor structure at the individual-specific environmental level (not shown in the Figure) was similar to that at the familial level. Two main factors were extracted, in total accounting for 21% to 98% of the E variance in cognitive variables. Similar to the F factor structure, within the E factor analysis the RT variables loaded onto the first factor and the error variables onto the second. The only difference was that omission errors loaded onto both E factors but only the second F factor, with the first E factor accounting for 35% of the underlying E variance for omission errors.

A penultimate model included the choice impulsivity variable. The Cholesky model indicated nonsignificant familial correlations between choice impulsivity and other variables (Table 2). This pattern of correlations is difficult to specify in a confirmatory factor analysis; nevertheless, choice impulsivity did not account for a third separate factor. Furthermore, because the phenotypic correlation with ADHD was not significant in the constrained saturated phenotypic model (Table 2), a model without this variable therefore more closely matched the observed data structure, and choice impulsivity was excluded in the final model. The overall factor structure remained the same whether including or excluding choice impulsivity. With choice impulsivity included (the penultimate model), it loaded onto familial factor 2 (9%) but not onto familial factor 1. Most other factor loadings remained the same, and none changed by more than 16% of the overall phenotypic variance.

Results from MV familial analyses on a large sample of ADHD and control sibling pairs indicate the presence of 2 familial cognitive impairment factors in ADHD. The larger factor, reflecting 85% of the familial variance of ADHD, captured all familial influences on RTV and 98% of those on MRT. The second, smaller factor, reflecting 13% of the familial variance of ADHD, captured 82% of the familial influences on omission errors on the go/
no-go task and 62% of those on commission errors. These findings argue against a single familial pathway to cognitive impairments in ADHD, highlight the importance of the RT factor, and indicate promising cognitive targets for molecular genetic investigations.

The familial separation between RT and accuracy performance in ADHD fits with recent data that have indicated phenotypic separation between, in particular, RTV and commission errors. Previous analyses on the current sample and a separate twin sample showed how incentives led to ADHD-sensitive improvement in RTV but not in commission errors. In addition, sex effects emerged for commission errors only and not for RTV. A psychometric analysis across several cognitive measures indicated a large unitary RTV construct, but ADHD-control group differences remained on commission errors after controlling for RTV, suggesting coexistence of 2 separate impairments. In a longitudinal investigation, high RTV was observed in both ADHD persisters and ADHD remitters, whereas compromised accuracy was observed in ADHD persisters only.

The emergence of the major RT familial factor highlights the importance of understanding the causes of the slow and variable RTs in ADHD. With a familial correlation of 0.91, RTV and MRT were indistinguishable at the familial level, replicating recent findings from a general-population twin sample. The nature of the underlying processes involved in high RTV in ADHD is the subject of much current research activity. One proposal is that the association between increased RTV and ADHD results from a deficit in arousal processes. Direct evidence of this association comes from studies using electrophysiological and skin conductance measures. In the study by O’Connell et al, block-by-block increases in RTV were accompanied by gradual decreases in arousal, suggesting a vigilance decrement. Furthermore, RTV in ADHD is not stable but shows greater than expected improvements under specific task manipulations, such as incentives or the presentation rate of stimuli. An alternative line of evidence suggests that increased RTV might arise from inadequate suppression during task performance of the “default-mode network,” a network incorporating the medial prefrontal, posterior cingulate, anterior temporal, and lateral parietal cortices. Abnormal activation of the superior and middle temporal cortices, the anterior cingulate, the basal ganglia, and the thalamus may also underlie the observed increase in RTV in ADHD.

Our findings may also link to a developmental framework established by Halperin and colleagues, which proposes that RTV reflects poor state regulation, perceptual sensitivity, and/or weak arousal mechanisms. Overall, the model makes a distinction between 2 neurocognitive processes: proposed subcortical dysfunction, linked to the etiology of ADHD and reflected in RTV, and prefrontally mediated executive control, linked to persistence or desistence of ADHD during adolescence. As such, one possible interpretation of the 2 familial factors is that the first factor (RT) represents the core enduring deficit and the second factor (errors) represents prefrontally mediated executive control dysfunctions. The developmental model further predicts that the extent to which executive control functions, which develop throughout childhood and adolescence, can compensate for the more primary and enduring subcortical deficits determines the degree of recovery from ADHD symptoms. Future research could apply the current model of 2 familial factors within a longitudinal design to test the predictions emerging from the developmental model, as well as within a functional magnetic resonance imaging design, to directly test the proposed links to brain areas.

We also noted a possible link from our model of 2 familial factors to another recent proposal, the arousal-attention model of ADHD. This model, influenced by Posner and Petersen, Paus et al., and Robertson et al, and supported by electrophysiological, medication response, and comparative disorder data, suggests a distinction between bottom-up influences from subcortical arousal structures, reflected in continuous response control measures such as RTV, and top-down cortical control of the sustained attention system, incorporating the prefrontal, temporal, and parietal cortices. Hence, the 2 proposed components of the arousal-attention model consist of a vigilance decrement, linked to gradual decreases in arousal, and fluctuations in top-down control of attention over very brief periods. Given that our data indicate a largely shared familial etiology between omission and commission errors and that sustained attention is a prerequisite for successful inhibition (whereas the opposite is not the case), one possibility is that the second familial factor represents brief reductions in the top-down control of sustained attention, leading to secondary inhibition deficits. This conjecture would be consistent with electrophysiological studies (including a study by G.M., B.A., T.B., A.R., Daniel Brandeis, PhD, P.A., and J.K., unpublished data, November 2008) that indicate that abnormal inhibitory processing in both children and adults with ADHD is typically preceded or accompanied by attentional processing deficits.

However, previous studies on the arousal-attention model suggest that both RTV (specifically slow-frequency RTV) and omission errors separate from commission errors. Our factor analyses indicated that, at the level of individual-specific environmental influences, omission errors contributed to both factors, and only at the familial level both omission and commission errors loaded onto the second factor. This illustrates how the present findings on etiologic associations cannot be directly compared with previous studies focusing on phenotypic (observable) associations.

Although the evidence in support of 2 familial factors was strong, the separation of the 2 familial factors is likely to be relative rather than absolute. This observation is also indicated in the individual familial correlations across pairs of measures, which were largely moderate rather than zero for variables that familial factor analysis separated into different factors. Both the developmental model and the attention-arousal model predict interactions between the 2 partially separable processes.

In our penultimate model, choice impulsivity (preference for smaller, immediate rewards) showed a low loading onto the error factor and no loading onto the RT fac-
Attention-deficit/hyperactivity disorder (ADHD) is a chronic condition characterized by symptoms of inattention, hyperactivity, and impulsivity. The underlying mechanisms of ADHD are complex and involve genetic and environmental factors. Recent research has suggested that there may be a specific genetic component to ADHD, particularly involving inattention symptoms. This finding is supported by studies that have identified familial influences on ADHD, with some suggesting that these influences are specific to inattention symptoms.

The identification of familial factors in ADHD is promising as it may help to elucidate the genetic basis of the disorder. Genome-wide association studies (GWAS) have been used to identify genetic variants associated with ADHD, but these studies have had mixed results. One limitation of GWAS is that they often involve large sample sizes and may not capture small yet significant effects.

In the current study, the authors replicated previous findings that ADHD is associated with specific cognitive measures, including tasks capturing aspects of reward, motivational, temporal, and memory processes. This replication is important as it helps to validate the findings and further supports the hypothesis that ADHD is associated with specific cognitive impairments.

However, the authors also note that the findings presented in the current study are specific to ADHD and may not be generalizable to other disorders with similar cognitive impairments. This is an important consideration as it highlights the need for further research to understand the specificity of ADHD-related cognitive impairments.

One limitation of the study is that it was not able to evaluate the relationship of the cognitive factors to comorbid disorders associated with ADHD. The authors note that this is a significant limitation as it means that the findings reported herein may be specific to ADHD or may be generalizable to other disorders in which similar cognitive impairments are observed. This highlights the importance of future research in this area.

In summary, the findings of this study are promising as they suggest that ADHD is associated with specific cognitive impairments, particularly inattention symptoms. However, further research is needed to understand the specificity of these impairments and to elucidate the underlying mechanisms of ADHD.

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