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

Jonna Kuntsi, PhD; Alexis C. Wood, PhD; Frühling Rijdsdijk, PhD; Katherine A. Johnson, PhD; Penelope Andreou, PhD; Björn Albrecht, PhD; Alejandro Arias-Vasquez, PhD; Jan K. Buitelaar, MD, PhD; Gráinne McLoughlin, PhD; Nanda N. J. Rommelse, PhD; Joseph A. Sergeant, PhD; Edmund J. Sonuga-Barke, PhD; Henrik Uebel, MD; Jaap J. van der Meere, PhD; Tobias Banaschewski, MD, PhD; Michael Gill, MRCPsych, PhD; Iris Manor, MD; Ana Miranda, MD; Fernando Mulas, MD; Robert D. Oades, PhD; Herbert Roeyers, PhD; Aribert Rothenberger, MD; Hans-Christoph Steinhausen, MD, PhD, DMSc; Stephen V. Faraone, PhD; Philip Asherson, MRCPsych, PhD

**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.

*Arch Gen Psychiatry.* 2010;67(11):1159-1167

**A**TENTION-DEFICIT/HYPER-activity disorder (ADHD) is a common neurodevelopmental disorder affecting around 5% of children.<sup>1</sup> 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.<sup>2,3</sup> 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.<sup>4</sup>

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.<sup>5,6</sup> Among the various cognitive variables investigated, reaction time (RT) variability (RTV) is one of the best to discriminate between ADHD and control samples,<sup>7-9</sup> although several other behavioral and cognitive measures are associ-

Author Affiliations are listed at the end of this article.

ated with the condition. Cognitive theories differ in whether they propose a single underlying cause for the widespread behavioral and cognitive impairments associated with ADHD or, alternatively, multiple etiological pathways.<sup>10-16</sup>

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<sup>17,18</sup> and IQ.<sup>19</sup> However, we do not know whether these apparent multiple impairments share etiological roots or whether separate etiological pathways exist.<sup>20</sup> A particularly powerful approach, which goes beyond simple sibling designs that look for significant differences on task performance between unaffected siblings and controls,<sup>21</sup> 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.<sup>22-24</sup> 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.<sup>25</sup> 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, epilepsy, 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 ap-

plied 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<sup>26</sup> 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 345 individuals. The final total sample therefore consisted of 1265 individuals, which comprised 580 complete sibling pairs and 105 singletons. Of the 1265 individuals, 524 with combined-subtype ADHD were classified as affected, 16 who met criteria for the hyperactive-impulsive or inattentive subtypes were classified as a “sub-threshold 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, 355 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<sup>27,28</sup> 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.<sup>26</sup> Impairment criteria were based on the severity of symptoms identified in the PACS. Across the International Multicenter ADHD Genetics sites, a mean  $\kappa$  coefficient of 0.88 and an average agreement of 96.6% were obtained for ADHD diagnostic categories.<sup>29</sup>

#### 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<sup>30</sup> were used to obtain an estimate of IQ.

**The Go/No-Go Task.** On each trial in this task,<sup>31,32</sup> 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<sup>24</sup>), matched for length of time on task. Herein we present data from the slow condition, with an interstimulus interval of 8 seconds and consisting of 72 trials, and the fast condition, with an interstimulus interval of 1 second and consisting of 462 trials. The order of presentation of the slow and fast conditions varied randomly across participants. The variables obtained from the task are mean RT (MRT), standard deviation of RTs, commission errors, and omission errors.

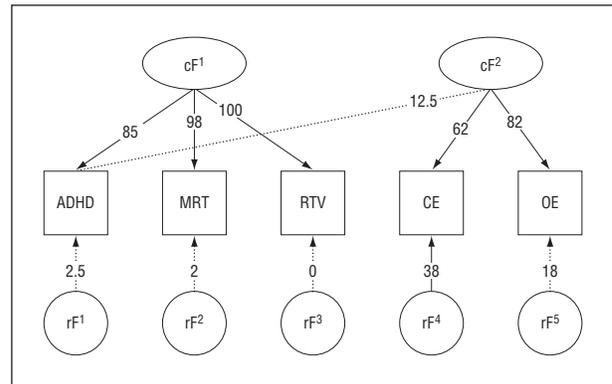
**The Fast Task.** The baseline condition, with a fore period of 8 seconds and consisting of 72 trials,<sup>22,33</sup> followed a standard warned 4-choice RT task. A warning signal (4 empty circles, arranged side by side) first appeared on the screen. At the end of the fore period (presentation interval 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 in position to the location of the target stimulus. After a response, the stimuli disappeared from the screen and a fixed intertrial interval of 2.5 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<sup>22</sup>). The variables obtained from the task are MRT and standard deviation of RTs, herein reported for the baseline condition.

**The Maudsley Index of Childhood Delay Aversion.** Two conditions, each with 20 trials, were administered (in random order across participants).<sup>23,33</sup> 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<sup>34</sup> 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 inte-



**Figure.** Percentages of familial variance due to common (cF<sup>1</sup>-cF<sup>2</sup>) and residual (rF<sup>1</sup>-rF<sup>5</sup>) familial factors. Significant parameters are indicated with solid lines ( $P < .05$ ) and nonsignificant parameters with dotted lines. ADHD indicates attention deficit/hyperactivity disorder; CE, commission errors; MRT, mean reaction time; OE, omission errors; and RTV, reaction time variability.

gration 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 familiarity 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.<sup>35</sup>

### 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-

**Table 1. Background and Cognitive Variables in Probands With ADHD, Siblings of Probands, and Controls**

	Mean (SD)		
	Probands With ADHD	Siblings of Probands	Controls
Male sex, No. (%) <sup>a,b,c</sup>	413 (89.01)	227 (49.78)	243 (70.43)
Age, y <sup>a,c</sup>	11.45 (2.73)	11.38 (2.96)	12.07 (2.47)
IQ <sup>a,c</sup>	102.02 (15.44)	103.43 (13.59)	108.91 (13.71)
Conners' <i>DSM-IV</i> ADHD subscale score			
Parent-rated <sup>a,b,c</sup>	78.87 (8.51)	54.80 (13.62)	52.20 (10.83)
Teacher-rated <sup>a,b,c</sup>	71.20 (10.70)	56.54 (12.41)	50.32 (9.17)
MRT, ms			
Fast task, baseline condition <sup>a,c</sup>	924.01 (352.18)	879.75 (401.17)	672.08 (208.34)
Go/no-go task, slow condition <sup>a,b,c</sup>	645.70 (233.85)	538.97 (184.81)	495.26 (118.44)
Final MRT, mean score <sup>a,b,c</sup>	756.92 (255.18)	706.07 (253.90)	582.00 (152.24)
RTV, ms			
Fast task, baseline condition <sup>a,b,c</sup>	455.39 (343.55)	357.82 (323.58)	202.58 (178.50)
Go/no-go task, slow condition <sup>a,b,c</sup>	312.79 (221.37)	225.48 (169.37)	143.54 (103.73)
Final RTV, mean score <sup>a,b,c</sup>	368.54 (230.83)	277.24 (212.26)	171.45 (123.09)
Commission errors, %			
Go/no-go task, slow condition <sup>a,b,c</sup>	52.84 (23.57)	43.48 (24.79)	37.64 (22.53)
Go/no-go task, fast condition <sup>a,b,c</sup>	53.92 (17.89)	44.39 (18.97)	41.28 (17.84)
Final commission errors, mean score <sup>a,b,c</sup>	53.31 (18.44)	43.89 (19.88)	39.30 (18.13)
Omission errors, %			
Go/no-go task, slow condition <sup>a,b,c</sup>	13.04 (14.39)	8.15 (10.93)	3.56 (5.47)
Go/no-go task, fast condition <sup>a,b,c</sup>	18.81 (13.53)	10.82 (10.14)	7.69 (7.84)
Final omission errors, mean score <sup>a,b,c</sup>	15.67 (11.77)	9.18 (8.78)	5.62 (5.57)
Choice impulsivity, % <sup>a,c,d</sup>	72.22 (32.72)	76.65 (29.23)	86.43 (23.75)

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; MRT, mean reaction time; RTV, reaction time variability.

<sup>a</sup>Significant difference between probands and controls ( $P < .05$ ).

<sup>b</sup>Significant difference between probands and siblings ( $P < .05$ ).

<sup>c</sup>Significant difference between siblings and controls ( $P < .05$ ).

<sup>d</sup>Percentage of choices for the larger reward, in the no-postreward-delay condition of the Maudsley index of childhood delay aversion task; a lower percentage of such choices indicates greater choice impulsivity.

trixes for the underlying F and E influences. On the basis of these analyses, data were simulated for 1000 participants within an exploratory factor analysis in STATA version 10 (StataCorp, Houston, Texas) (not presented but available from the authors on request). Exploratory factor analysis approaches give an indication of the underlying factor structure, but no specification of the underlying variance/covariance matrixes can be deduced.<sup>36</sup> Therefore, factors with an eigenvalue of greater than 1 and the strongest factor loadings (those that were more than half alternative factor loadings) were specified separately for F and E influences in a confirmatory familial factor model (see the **Figure**). The exception was ADHD, which was specified to load onto both factors because we aimed to investigate the etiology of the association of ADHD with the cognitive variables.

## RESULTS

Mean values for background and cognitive variables in probands with ADHD, siblings of probands, and controls are given in **Table 1**.

### SELECTION OF COGNITIVE TASK VARIABLES FOR MV ANALYSES

Task variables, which showed the highest phenotypic correlation with ADHD, were selected for the MV analysis (see also previous phenotypic analyses with subsamples of this sample<sup>22-24</sup>). To limit the total number of variables and to create psychometrically robust variables,<sup>33</sup> mean scores were obtained across 2 tasks or conditions,

where 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. Such mean scores were obtained for MRT and RTV (across fast task baseline condition and go/no-go task slow condition;  $r_f = 0.76$  and  $0.75$ , respectively) and omission and commission errors (across go/no-go task slow and fast conditions;  $r_f = 0.81$  and  $0.73$ , respectively). We did not include IQ as a separate variable in the analysis because of the limit on the number of variables and given that our earlier analyses indicated that the majority of familial influences shared between ADHD and cognitive variables were independent of those shared with IQ.<sup>37</sup> However, to control for any small mediating effects of IQ, each variable used in the analysis was 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 ( $r_{ph} = 0.89$ ), familial ( $r_f = 1.00$ ), 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

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,<sup>38</sup> 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 familiarity. 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 struc-

**Table 2. Phenotypic, Familial, and Individual-Specific Environmental Correlations**

	ADHD	MRT	RTV	Commission Errors	Omission Errors
Phenotypic correlations					
MRT	0.36 <sup>a</sup>				
RTV	0.39 <sup>a</sup>	0.80 <sup>a</sup>			
Commission errors	0.19 <sup>a</sup>	−0.16 <sup>a</sup>	0.05		
Omission errors	0.22 <sup>a</sup>	0.34 <sup>a</sup>	0.49 <sup>a</sup>	0.42 <sup>a</sup>	
Choice impulsivity	−0.10	−0.23 <sup>a</sup>	−0.21 <sup>a</sup>	0.01	−0.25 <sup>a</sup>
Familial correlations					
MRT	0.61 <sup>a</sup>				
RTV	0.74 <sup>a</sup>	0.91 <sup>a</sup>			
Commission errors	0.45 <sup>a</sup>	−0.04	0.30		
Omission errors	0.48 <sup>a</sup>	0.11	0.43	0.76 <sup>a</sup>	
Choice impulsivity	−0.39 <sup>b</sup>	−0.23	−0.44	−0.09	−0.50
Individual-specific environmental correlations					
MRT	0.27 <sup>a</sup>				
RTV	0.28 <sup>a</sup>	0.76 <sup>a</sup>			
Commission errors	0.09 <sup>b</sup>	−0.20 <sup>a</sup>	−0.02		
Omission errors	0.18 <sup>a</sup>	0.41 <sup>a</sup>	0.50 <sup>a</sup>	0.44 <sup>a</sup>	
Choice impulsivity	−0.03	−0.24 <sup>a</sup>	−0.17 <sup>b</sup>	0.00	−0.21 <sup>a</sup>

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; MRT, mean reaction time; RTV, reaction time variability.

<sup>a</sup>  $P \leq .001$ .

<sup>b</sup>  $P \leq .05$ .

ture, 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.

### COMMENT

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<sup>24</sup> and a separate twin sample<sup>9</sup> 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.<sup>24</sup> 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.<sup>7</sup> In a longitudinal investigation, high RTV was observed in both ADHD persisters and ADHD remitters, whereas compromised accuracy was observed in ADHD persisters only.<sup>39</sup>

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.<sup>38</sup> The nature of the underlying processes involved in high RTV in ADHD is the subject of much current research activity.<sup>9,40-42</sup> 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<sup>43</sup> and skin conductance<sup>44</sup> measures. In the study by O'Connell et al,<sup>44</sup> 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.<sup>9,22,24,45</sup> 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.<sup>41,46,47</sup> 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.<sup>48</sup>

Our findings may also link to a developmental framework established by Halperin and colleagues,<sup>16,39</sup> 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<sup>16,39</sup> further predicts that the extent to which ex-

ecutive 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.<sup>10,44,49,50</sup> This model, influenced by Posner and Petersen,<sup>51</sup> Paus et al,<sup>52</sup> and Robertson et al<sup>53</sup> 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,<sup>10,44,49,50</sup> incorporating the prefrontal, temporal, and parietal cortices.<sup>48,54</sup> 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<sup>50</sup>), 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.<sup>55-57</sup>

However, previous studies on the arousal-attention model suggest that both RTV (specifically slow-frequency RTV) and omission errors separate from commission errors.<sup>10,49</sup> 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<sup>16,39</sup> and the attention-arousal model<sup>10,44,49,50</sup> 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-

tor; it did not emerge as a significant separate factor and hence was excluded from the final model. Interpretation of choice impulsivity within this model is difficult because of its more modest association with ADHD and substantial nonfamilial influences, which may partly reflect measurement error due to ceiling effects.<sup>33</sup> Our recent study on a large population sample similarly indicated small yet significant effects for performance on the same choice-delay task but raised the possibility that these may be specific to inattention symptoms.<sup>58</sup>

The existence of the 2 familial factors needs to be replicated in additional samples and with other ADHD-sensitive cognitive measures, including tasks capturing aspects of reward, motivational, temporal, and memory processes. Although existing evidence suggests that the familial influences identified in this study are likely to reflect largely genetic rather than shared environmental influences,<sup>33,59</sup> this finding should be confirmed directly in a twin study. The replication of our previous finding on the separation of the etiological influences on IQ from those that ADHD shares with other cognitive variables across a general-population twin sample,<sup>38</sup> the current sample,<sup>37</sup> and a separate ADHD sample<sup>60</sup> is promising in suggesting that findings are not specific to samples or measures.

One limitation is that we were not able to evaluate the relationship of the cognitive factors to comorbid disorders associated with ADHD because the PACS diagnostic interview was completed only for ADHD cases. Furthermore, we do not know whether the findings reported herein are specific to ADHD or may be generalizable to other disorders in which similar cognitive impairments are observed. The focus on across-disorders comparisons is an important direction for future research, especially in light of the growing evidence from quantitative and molecular genetic studies of shared genetic influences with disorders comorbid with ADHD.<sup>61,62</sup> A specific limitation of the current analyses is that some centers used only 2 of the 3 tasks, leading to some missing data. Nonetheless, we still had power to establish significant familial factor loadings in the final factor model, with the exception of the loading of ADHD onto the second familial factor. Further analyses should investigate whether this loading emerges as significant in larger samples. An additional limitation is that potential indicators of sustained attention were measured only indirectly in the omission errors of the go/no-go task; in future research, tasks should be included that specifically target sustained attention, such as continuous performance or vigilance tasks.

In summary, the importance of these findings is in demonstrating 2 sets of etiological influences on different aspects of cognitive performance in ADHD, which together account for 97.5% of the familial influences on ADHD. The 2 familial factors identified herein may further influence other processes not directly measured in this study, or the genetic factors that underlie the 2 familial factors may have pleiotropic effects on additional processes.<sup>63</sup> Although genome-wide association studies promise to discover new molecular pathways for ADHD, initial studies have not yielded statistically significant findings.<sup>64-67</sup> Genome-wide association studies of ADHD should search for genes underlying these 2 processes sepa-

rately, starting with the analysis of RTV because it was the variable most strongly correlated with ADHD. This is a feasible endeavor because many of the groups involved in genome-wide association-mapping studies of ADHD have collected comparable RT data. Finally, from a clinical perspective, the developmental model of Halperin and colleagues<sup>16,39</sup> needs to be further explored because it has important implications for the types of interventions at different ages. Once the underlying genetic mechanisms are better understood, there is also potential for the development of novel drugs that target different stages of development and aspects of cognitive impairments in ADHD.

**Submitted for Publication:** September 29, 2009; final revision received May 19, 2010; accepted June 2, 2010.

**Author Affiliations:** MRC Social, Genetic, and Developmental Psychiatry Centre, Institute of Psychiatry, King's College London, London, United Kingdom (Drs Kuntsi, Wood, Rijdsdijk, Andreou, McLoughlin, and Asherson); Department of Epidemiology and Section on Statistical Genetics, University of Alabama at Birmingham (Dr Wood); Department of Psychiatry, Trinity Centre for Health Sciences, St James's Hospital, Dublin, Ireland (Drs Johnson and Gill); School of Psychology, Queen's University Belfast, Belfast, Northern Ireland (Dr Johnson); Child and Adolescent Psychiatry, University of Göttingen, Göttingen, Germany (Drs Albrecht, Uebel, and Rothenberger); Department of Psychiatry, Donders Institute for Brain, Cognition, and Behavior, Centre for Neuroscience (Drs Arias-Vasquez, Buitelaar, and Rommelse), and Department of Human Genetics (Dr Arias-Vasquez), Radboud University Nijmegen Medical Center, Nijmegen, the Netherlands; Department of Clinical Neuropsychology, Vrije Universiteit, Amsterdam, the Netherlands (Dr Sergeant); Developmental Brain-Behaviour Laboratory, University of Southampton, Southampton, United Kingdom (Dr Sonuga-Barke); Department of Experimental Clinical and Health Psychology, Ghent University, Ghent, Belgium (Drs Sonuga-Barke and Roeyers); Department of Developmental and Experimental Clinical Psychology, University of Groningen, Groningen, the Netherlands (Dr van der Meere); Department of Child and Adolescent Psychiatry and Psychotherapy, Central Institute of Mental Health, University of Heidelberg, Mannheim, Germany (Dr Banaschewski); Research Department, S. Herzog Memorial Hospital, Jerusalem, Israel (Dr Manor); Department of Developmental and Educational Psychology, University of Valencia (Dr Miranda), and Department of Neuropaediatrics, La Fe University Hospital (Dr Mulas), Valencia, Spain; Clinic for Child and Adolescent Psychiatry and Psychotherapy, University of Duisburg-Essen, Essen, Germany (Dr Oades); Department of Child and Adolescent Psychiatry, University of Zurich, Zurich, Switzerland (Dr Steinhausen); Child and Adolescent Clinical Psychology, Institute of Psychology, University of Basel, Basel, Switzerland (Dr Steinhausen); Child and Adolescent Psychiatry, Psychiatric Hospital Aalborg, University Hospital Aarhus, Aalborg, Denmark (Dr Steinhausen); and Departments of Neuroscience and Psychiatry, State University of New York Upstate Medical University, Syracuse (Dr Faraone).

**Correspondence:** Jonna Kuntsi, PhD, MRC Social, Genetic, and Developmental Psychiatry Centre, Institute of Psychiatry, King's College London, London SE5 8AF, United Kingdom (jonna.kuntsi@kcl.ac.uk).

**Financial Disclosure:** Dr Kuntsi has received a speaker's fee from Eli Lilly and Company that has been used for educational and research activities. Dr Buitelaar has in the past 3 years been a consultant to, member of advisory boards of, and/or speaker for Bioprojet, Bristol-Myers Squibb, Eli Lilly and Company, Janssen-Cilag BV, Medice, Organon/Shering Plough, Pfizer, Shire, UCB Pharma, and Servier. Dr Sergeant is a member of an advisory board to Eli Lilly and Company and Shire and has received research funding from Eli Lilly and Company; educational grants from Eli Lilly and Company, Janssen-Cilag, and Shire; and speaker's fees from Eli Lilly and Company, Janssen-Cilag, and Shire. Dr Sonuga-Barke is a member of advisory boards to Astra Zeneca, Flynn Pharma, Shire, and UCB Pharma; has received research support from Janssen-Cilag, Qbtech, and Shire and conference support from Shire; is on a speakers' board for Shire and UCB Pharma; and has been a consultant for Shire and UCB Pharma. Dr Uebel received conference attendance support or was paid for public speaking by Eli Lilly and Company, Janssen-Cilag, and Medice and received research support from Schwabe and Shire. Dr Miranda is an advisor to Eli Lilly and Company. Dr Oades has received support for investigator-initiated studies from UCB GmbH. Dr Roeyers is a member of an advisory board to Shire and has received research funding and conference attendance support from Eli Lilly and Company. Dr Rothenberger is on the advisory board and speakers' bureau of Eli Lilly and Company, Medice, Novartis, and Shire; has received educational grants from Medice and Shire; and has received research support from Schwabe and Shire. Dr Steinhausen has served as an advisor and speaker to Eli Lilly and Company, Janssen-Cilag, Novartis, Shire, and UCB Pharma. In the past year, Dr Faraone has received consulting fees and has been on advisory boards for Eli Lilly and Company, Ortho-McNeil, and Shire and has received research support from Eli Lilly and Company, Pfizer, Shire, and the National Institutes of Health (NIH). In previous years, Dr Faraone has received consulting fees, been on advisory boards, or been a speaker for Eli Lilly and Company, Janssen, McNeil, Novartis, Pfizer, and Shire and has received research support from Eli Lilly and Company, Pfizer, Shire, and the NIH. Dr Asherson has received funding for educational and research activities from Janssen-Cilag and Shire and has received consultancy and speaker fees from Eli Lilly and Company, Flynn Pharma, Janssen-Cilag, and Shire that have been used for educational and research activities.

**Funding/Support:** This work was supported in part by National Institutes of Health grants R01MH62873 and R01MH081803 (Dr Faraone) and, in London, by Medical Research Council grant G03001896 (Dr Kuntsi).

**Additional Contributions:** We thank all the families who kindly participated in this research. We thank additional team members at data collection sites of Dublin, Ireland; Essen, Germany; Ghent, Belgium; Goettingen, Germany; London; Tel Aviv, Israel; Valencia, Spain; and Zurich, Switzerland, for their important contributions.

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