Separation of cognitive impairments in attention deficit hyperactivity disorder into two familial factors

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Abstract

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 whether 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.

Objective To determine, using a multivariate familial factor analysis approach, whether one or more familial factors underlie the slow and variable reaction times (RTs), impaired response inhibition, sustained attention, and choice impulsivity that are associated with ADHD.

Design An ADHD and control sibling-pair design.

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

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

Main Outcome Measures Performance on a four-choice RT task, a go/no-go inhibition task and a choice-delay task.

Results The final model consisted of two familial factors. The larger factor, reflecting 85% of the familial variance of ADHD, captured 98-100% of the familial influences on mean RT and RT variability. The second smaller factor, reflecting 12.5% of the familial variance of ADHD, captured 62-82% of the familial influences on commission and omission errors on the go/no-go task. Choice impulsivity was excluded in the final model, due to poor fit.

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

INTRODUCTION:

Attention deficit hyperactivity disorder (ADHD) is a common neurodevelopmental disorder, affecting around 5% of children [1]. 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[2,3]. 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[4].

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[5, 6]. Among the various cognitive variables investigated, reaction time (RT) variability is one of the best to discriminate between ADHD and control samples [7-9], although several other behavioral and cognitive measures are associated 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 multiple etiological pathways[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 for shared genetic or familial influences with ADHD, particularly for RT variability, inhibition and other executive dysfunctions, including aspects of attention[17, 18] and IQ [19]. Yet we do not know whether these apparent multiple impairments share etiological roots, or whether separate etiological pathways exist [20]. A particularly powerful approach, which goes beyond simple sibling designs that look for significant differences on task performance between unaffected siblings and controls [21], is the use of genetic multivariate (MV) model fitting. 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.

Here we adopt an empirical MV approach, focusing on cognitive variables that we previously reported to be associated with ADHD and siblings of ADHD probands[22-24]. Specifically, we use MV familial factor analysis in a large sample of ADHD and control sibling pairs, to address the question of whether one or more familial factors underlie the slow and variable RTs, impaired response inhibition and sustained attention, 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 United Kingdom, through the International Multicentre ADHD Genetics (IMAGE) project [25]. All participants were of European Caucasian descent and aged 6-18. All probands had a clinical diagnosis of combined subtype ADHD (ADHD-CT) 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 IQ<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 gender 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 UK, 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, one child subsequently withdrew after testing and three were excluded for having an IQ of below 70. A further 10 controls were excluded for having both parent and teacher Conners' DSM-IV ADHD subscale T-scores of over 63, to exclude potential, undiagnosed ADHD cases.

Final sample: The ADHD proband and sibling sample consisted of 920 individuals and the control sample of 345 individuals (see also Table 1). The final total sample therefore consisted of 1265 individuals, which comprised 580 complete sibling pairs and 105 singletons. Of the 1265 individuals, 524 with ADHD-CT were classified as affected, 16 who met criteria for the hyperactive-impulsive or inattentive subtypes were classified as a 'sub-threshold group', and a further 664 individuals were unaffected siblings and controls. ADHD status was therefore included in the analyses in an ordinalized manner. A further 61 participants had cognitive data, but no clinical data, and

their affection status was coded as missing. Of the 524 individuals with ADHD-CT, 151 had conduct disorder, 355 had oppositional defiant disorder and 63 had possible mood disorder (excluding bipolar disorder), derived as part of the PACS parental interview (see below). 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 2.5–3 h. A minimum of a 48-h medication-free period was required for cognitive testing.

MEASURES

ADHD diagnosis

The Parental Account of Child Symptoms (PACS) interview [26, 27] 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 ≥65, to have ADHD. Situational pervasiveness was defined as some symptoms occurring within two or more different situations from the PACS, as well as the presence of one or more symptoms scoring 2 or more from the DSM-IV ADHD subscale of the teacher-rated Conners' [28]. Impairment criteria were based on severity of symptoms identified in the PACS. Across the IMAGE sites a mean kappa coefficient of 0.88 and an average agreement of 96.6% were obtained for ADHD diagnostic categories [29].

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 (WISC-III [30]) were used to obtain an estimate of IQ.

The go/no-go task [31, 32]*:* On each trial, one of two possible stimuli appeared for 300 ms 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 three conditions (slow, fast and incentive [24]), matched for length of time on task. Here we present data from the slow condition, with an inter-stimulus interval (ISI) of 8 s and consisting of 72 trials, and the fast condition, with an ISI of 1 s 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), SD of RTs, commission errors and omission errors.

The fast task [22, 33]*:* The baseline condition, with a fore period of 8 s and consisting of 72 trials, followed a standard warned four-choice RT task. A warning signal (four 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. Following a response, the stimuli disappeared from the screen and a fixed inter-trial interval of 2.5 s followed. Speed and accuracy were emphasized equally. If the child did not respond within 10 s, the trial terminated. A comparison condition with a fast event rate (1 s) and incentives followed the baseline condition (further details in [22]). The variables obtained from the task are MRT and SD of RTs; here reported for the baseline condition.

The Maudsley index of childhood delay aversion [23, 33]*:* 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 (one point involving a 2-second pre-reward delay) and a larger-delayed reward (two points involving a 30-second pre-reward delay). In the no post-reward delay condition, choosing the small reward led immediately to the next trial; in the post-reward delay condition, this led to a delay period of 30 seconds, while 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 [34] 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 necessitated ordinal data analysis for all variables with the age-, IQ- and sex-regressed residual scores of the cognitive variables ordinalized into five equal-sized categories. Ordinal data analysis assumes the combination of ordered categories to reflect measurements of an underlying multivariate normal distribution of the traits. In our models, this was reflected in one fixed threshold for ADHD (fixed to expected population prevalence) and four 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 places a limit on the number of variables that can be included in ordinal data analysis and, in these analyses, five variables in addition to the selection variable (ADHD, included in all models to correct for ascertainment bias) was the maximum number of variables that could be included in any one model. Further, the computational demands of ordinal data analysis here 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 to the full (non-reduced) model at the $p<.05$ level, with a 1-df test.

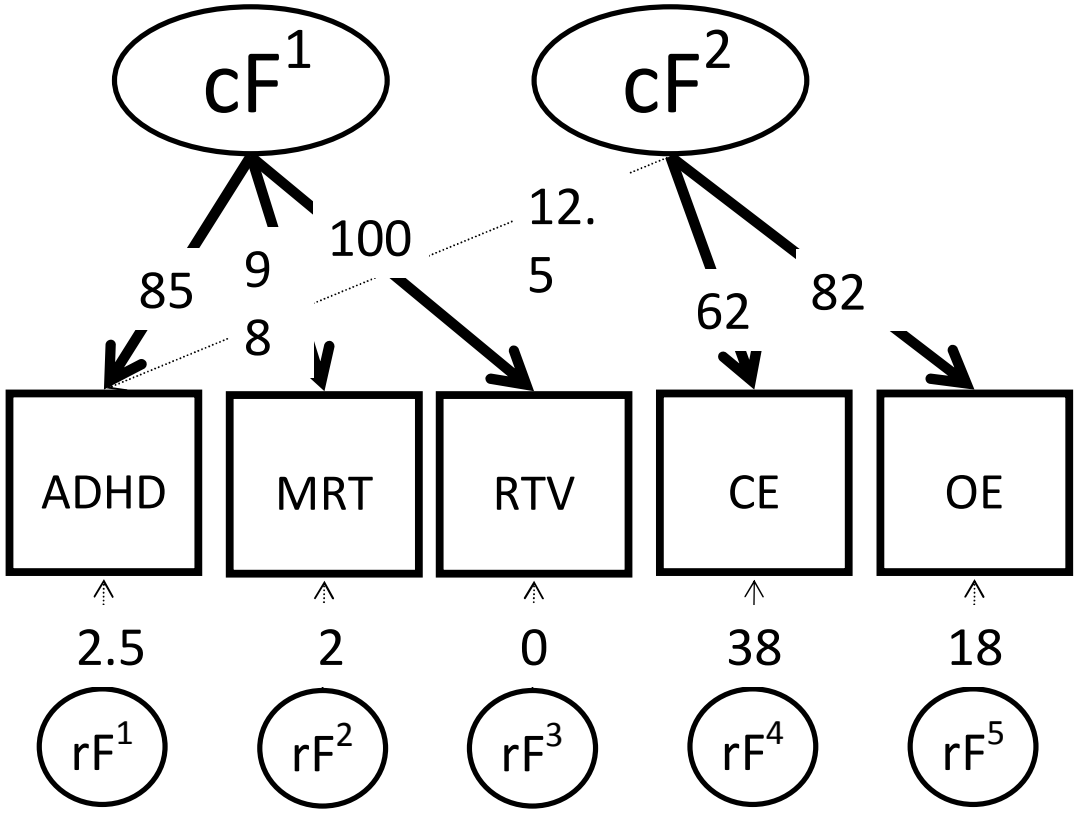
The threshold for ADHD status was fixed to give a population prevalence of 5% (z-score set at 1.64) and further, familiality parameters fixed to expected population estimates (heritability assumed to be 80%, with a sibling correlation of 0.40), using a method developed and validated in an earlier simulation study [35].

Phenotypic correlations: Sibling correlations are 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 is 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, multivariate models use cross-trait cross-sibling correlations to decompose the co-variation between traits into familial (F: 50-100% of additive genetic (A)

Figure.

Percentages of familial variance due to common (cF^1-cF^2) and residual (rF^1-rF^5) familial factors: Significant parameters are indicated with solid lines ($P < .05$) and non-significant 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



+ 100% 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 matrices for the underlying F and E influences. Based on these, data are simulated for 1000 participants within an exploratory factor analysis in STATA v.10 (not presented but available upon request). This gives an indication of the underlying factor structure, but no specification of the underlying variance / covariance matrices can be deduced [36]. Therefore factors with an Eigenvalue of greater than one 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 Figure 1). The exception was ADHD, which was specified to load onto both factors, as we aimed to investigate the etiology of the association of ADHD with the cognitive variables.

Table 1: Means (and standard deviations) for ADHD probands, siblings of ADHD probands and controls on background and cognitive variables

	ADHD probands n = 464	Siblings of ADHD probands n = 456	Controls n = 345
% male [1 2 3]	89.01	49.78	70.43
Age [1 3]	11.45 (2.73)	11.38 (2.96)	12.07 (2.47)
IQ [1 3]	102.02 (15.44)	103.43 (13.59)	108.91 (13.71)
Parent-rated Conners' DSM-IV ADHD subscale [1 2 3]	78.87 (8.51)	54.80 (13.62)	52.20 (10.83)
Teacher-rated Conners' DSM-IV ADHD subscale [1 2 3]	71.20 (10.70)	56.54 (12.41)	50.32 (9.17)
MRT			
Fast task (baseline condition) [1 3]	924.01 (352.18)	879.75 (401.17)	672.08 (208.34)
Go/no-go task (slow condition)[1 2 3]	645.70 (233.85)	538.97 (184.81)	495.26 (118.44)
Final MRT (mean score) [1 2 3]	756.92 (255.18)	706.07 (253.90)	582.00 (152.24)
RTV			
Fast task (baseline condition)[1 2 3]	455.39 (343.55)	357.82 (323.58)	202.58 (178.50)
Go/no-go task (slow condition)[1 2 3]	312.79 (221.37)	225.48 (169.37)	143.54 (103.73)
Final RTV (mean score) [1 2 3]	368.54 (230.83)	277.24 (212.26)	171.45 (123.09)
Commission errors (%)			
Go/no-go task (slow condition)[1 2 3]	52.84 (23.57)	43.48 (24.79)	37.64 (22.53)
Go/no-go task (fast condition)[1 2 3]	53.92 (17.89)	44.39 (18.97)	41.28 (17.84)
Final commission errors (mean score)[1 2 3]	53.31 (18.44)	43.89 (19.88)	39.30 (18.13)
Omission errors (%)			
Go/no-go task (slow condition)[1 2 3]	13.04 (14.39)	8.15 (10.93)	3.56 (5.47)
Go/no-go task (fast condition)[1 2 3]	18.81 (13.53)	10.82 (10.14)	7.69 (7.84)
Final omission errors (mean score)[1 2 3]	15.67 (11.77)	9.18 (8.78)	5.62 (5.57)
Choice impulsivity[1 3 4]	72.22 (32.72)	76.65 (29.23)	86.43 (23.75)

[1] probands and controls ($p<.05$) [2] probands and siblings ($p<.05$) [3] siblings and all controls ($p<.05$) [4] the percentage of choices for the larger reward, in the no post-reward delay condition of the Maudsley index of childhood delay aversion task; a lower percentage of such choices indicates greater 'choice impulsivity'

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 on sub-samples of this sample [22-24]). To limit the total number of variables and to create psychometrically robust variables [33], mean scores were obtained across 2 tasks or conditions, where available and where supported by bivariate model fitting analyses. The latter was indicated where there was evidence of a large degree of familial overlap across the two 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). IQ was not included as a separate variable in the analysis, due to 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 [37]. 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.

A further preliminary bivariate model fitting analysis between 'choice impulsivity' (here referring to performance in the no post-reward 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 post-reward 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, as both indexed the same underlying familial etiology (or liability). We focused on the 'choice impulsivity' variable in the analyses, which showed the strongest 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 list-wise or pair-wise 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). Further, the familial correlation between RTV and MRT is high at 0.91; mirroring results in a general population twin sample[38], 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 is observed between MRT and RTV.

Factor analyses: The factor loading structure (shown in the figure for F factors) reflects factor loadings that accounted for the majority of the shared variance in each phenotype. For each variable, only one factor loading was included, except for omission errors which loaded onto both E factors in the E factor analysis.

Table 2:

Phenotypic, familial and individual-specific environmental correlations

	ADHD	MRT	RTV	Comm-ission errors	Om-ission errors
Phenotypic correlations					
MRT	.36**				
RTV	.39**	.80**			
Commission errors	.19**	-.16**	.05		
Omission errors	.22**	.34**	.49**	.42**	
Choice impulsivity	-.10	-.23**	-.21**	.01	-.25**
Familial correlations					
MRT	.61**				
RTV	.74**	.91**			
Commission errors	.45**	-.04	.30		
Omission errors	.48**	.11	.43	.76**	
Choice impulsivity	-.39*	-.23	-.44	-.09	**-.50**
Individual-specific environmental correlations					
MRT	.27**				
RTV	.28**	.76**			
Commission errors	.09*	-.20**	-.02		
Omission errors	.18**	.41**	.50**	.44**	
Choice impulsivity	-.03	-.24**	-.17*	.00	-.21**

** $p \leq .001$, * $p \leq .05$

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 here focus 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 two 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 21-98% 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 non-significant familial correlations between choice impulsivity and other variables (Table 2). This pattern of correlations is difficult to specify in a confirmatory factor analysis; yet choice impulsivity did not account for a third separate factor. Further, since 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 multivariate familial analyses on a large sample of ADHD and control sibling pairs indicate the presence of two familial cognitive impairment factors in ADHD. The larger factor, reflecting 85% of the familial variance of ADHD, captured all familial influences on RT variability and 98% of those on mean RT. The second smaller factor,

reflecting 12.5% 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 [24] and a separate twin sample [9] showed how incentives led to ADHD-sensitive improvement in RTV but not in commission errors. Further, gender effects emerged for commission errors only and not for RTV [24]. 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 RT variability, suggesting co-existence of two separate impairments [7]. In a longitudinal investigation, high RTV was observed both in ADHD-persisters and ADHD-remitters, whereas compromised accuracy was observed in ADHD-persisters only [39].

The emergence of the major RT familial factor highlights the importance of understanding the causes for 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 [38]. The nature of the underlying processes involved in high RTV in ADHD is the subject of much current research activity [9, 40-42]. One proposal is that the association between increased RTV and ADHD results from a deficit in arousal processes. Direct evidence for this comes from studies employing electrophysiological [43] and skin conductance [44] measures. In the study from O'Connell [44], block-by-block increases in RT variability were accompanied by gradual decreases in arousal, suggesting a vigilance decrement. Further, 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 [9,22,24,45]. An alternative line of evidence suggests that increased RT variability might arise from inadequate suppression during task performance of the "default-mode network"; a network incorporating the medial prefrontal cortex, posterior cingulate, anterior temporal and lateral parietal cortices [41, 46, 47]. Abnormal activation of the superior and middle temporal cortices, the anterior cingulate, the basal ganglia and thalamus may also underlie the observed increase in RTV in ADHD [48].

Our findings may also link to a developmental framework developed by Halperin and colleagues [16, 39], which proposes that RTV reflects poor state regulation, perceptual sensitivity and/or weak arousal mechanisms. Overall, the model makes a distinction between two 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 two 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 [16, 39] 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 two familial factors within a longitudinal design, to test the predictions

emerging from the developmental model, as well as within an fMRI design, to directly test the proposed links to brain areas.

We also note a possible link from our model of two familial factors to another recent proposal, the arousal-attention model of ADHD [10,44,49,50]. This model, influenced by Posner [51], Paus [52] and Robertson [53] and supported by electrophysiological, medication response and comparative disorder data, suggests a distinction between bottom-up separate factor, and hence was excluded influences from subcortical arousal structures, reflected in continuous response control measures such as RTV, and top-down cortical control of the sustained attention system [10, 44, 49, 50], incorpor-ating the prefrontal, temporal and parietal cortices [48, 54]. Hence, the 2 proposed compon-ents 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 time 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 [50]), 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 [55-58].

However, previous studies on the arousal-attention model suggest that both RTV (specifically slow-frequency RT variability) and omission errors separate from commission errors [10, 49]. 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 etiological associations cannot be directly compared to previous studies focusing on phenotypic (observable) associations.

Although the evidence for two familial factors was strong, the separation of the two familial factors is likely to be relative rather than absolute. This is also indicated in the individual familial correlations across pairs of measures, which were largely moderate rather than zero for variables that the familial factor analysis separated into different factors. Both the developmental model [16, 39] and the attention-arousal model [10, 44, 49, 50] predict interactions between the two 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 factor, yet did not emerge as a significant in the final model. Interpretation of choice impulsivity within this model is difficult, due to its more modest association with ADHD and substantial non-familial influences, which may partly reflect measurement error due to ceiling effects [33]. 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 [59].

The existence of the two familial factors needs to be replicated in further 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 [33, 60], this should be investigated 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 [38], the current sample [37] and a separate ADHD sample [61] 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 only completed for ADHD cases. Furthermore, we do not know whether the findings reported here are specific to ADHD or may generalize to other disorders, where similar cognitive impairments are observed. This is an important direction for future research, especially in light of the growing evidence from quantitative and molecular genetic studies for shared genetic influences with disorders comorbid with ADHD [62, 63]. A specific limitation of the current analyses is that some Centers used only two of the three 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 if this loading emerges as significant in larger samples. A task-related limitation relates to the reliance on measurement of omission errors on a go/no-go task with unpredictable order of stimulus presentation; in future research tasks should be used that specifically target sustained attention, such as the sustained attention to response task (SART) with fixed order of stimulus presentation [50].

In summary, the importance of these findings is in revealing two 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 two familial factors identified here may further influence other processes not directly measured in this study, or the genetic factors that underlie the two familial factors may have pleiotropic effects on additional processes [64]. Although genome-wide association studies (GWAS) promise to discover new molecular pathways for ADHD, initial studies have not yielded statistically significant findings [65-68]. GWAS studies of ADHD should search for genes underlying these two processes separately, starting with the analysis of RT variability since this 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 [16, 39] needs to be further explored, since 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.

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