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The relationship between ADHD and key cognitive phenotypes is not mediated by shared familial effects with IQ — Source link

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ABSTRACT

Background Twin and sibling studies have identified specific cognitive phenotypes that may mediate the association between genes and the clinical symptoms of attention deficit hyperactivity disorder (ADHD). ADHD is also associated with lower IQ scores. We aimed to investigate whether the familial association between measures of cognitive performance and the clinical diagnosis of ADHD is mediated through shared familial influences with IQ.

Method Multivariate familial models were run on data from 1265 individuals at ages 6-18, which comprised of 920 participants from ADHD-sibling pairs and 345 control participants. Cognitive assessments included a four-choice reaction time (RT) task, a go/no-go task, a choice-delay task and an IQ assessment. The analyses focused on the cognitive variables of mean RT, RT variability, commission errors (CE), omission errors (OE), and choice impulsivity (CI).

Results Significant familial association was confirmed between cognitive performance and both ADHD (rF:.41-.71) and IQ (rF:-.25--.49). The association between ADHD and cognitive performance was largely independent (80-87%) of any contribution from aetiological factors shared with IQ. The exception was for CI, where 49% of the overlap could be accounted for by the familial variance underlying IQ.

Conclusions The aetiological factors underlying lower IQ in ADHD appear to be distinct from those between ADHD and RT / error measures. This suggests that lower IQ does not account for the key cognitive impairments observed in ADHD. The results have implications for molecular-genetic studies designed to identify genes involved in ADHD.

INTRODUCTION

Research on attention deficit hyperactivity disorder (ADHD) has identified specific cognitive measures, such as reaction time (RT) performance and commission errors on go/no-go tasks, as potential intermediate phenotypes that may mediate the association between genes and behavioural symptoms (Kuntsi et al. 2004; Rommelse 2008). ADHD is also associated with lower IQ, and this association has been shown to be due largely to shared genetic influences (Kuntsi et al., 2004; Polderman et al., 2006). Yet it remains unclear to what extent impairment in general cognitive function can explain the observed associations with the other cognitive indices. Here we investigate, using a genetic model fitting approach, the role of IQ in relation to cognitive impairments that are known to be associated with ADHD and share familial (genetic) influences with the clinical disorder

Previous research has evaluated the suitability of cognitive performance measures as potential intermediate phenotypes using five main criteria (Gottesman & Shields 1973; Gottesman & Gould 2003). Two of the initial criteria are that the cognitive performance measures show a phenotypic association with the clinical disorder and, that the cognitive performance measures share overlapping genetic influences with the disorder or symptoms of the disorder in the general population. Until recently, ADHD research has mainly used a proband-sibling design to nominate potential intermediate phenotypes, comparing the means of affected ADHD probands, unaffected siblings of probands and controls. Shared familial influences are implied when the sibling mean is significantly different from the control group mean, in the direction of the proband mean. While this method can provide an estimate of the size of the familial effects (Andreou et al., 2007), it cannot be used to investigate the extent to which multiple cognitive measures share the same familial effects.

An alternative approach is to use structural equation modelling (SEM) which provide estimates of the size of shared familial influences between the experimental measure and the clinical disorder and allows

comparison between two or more potential intermediate phenotypes. SEM approaches in twin studies have found little or no evidence for shared environmental effects on either ADHD or the associated cognitive variables (Burt, 2009; Wood et al 2009b), so it can be assumed that the familial effects are genetic in origin (Andreou et al., 2007). The multivariate SEM approach to the analysis of putative intermediate phenotypes will allow us to describe the underlying familial architecture and the degree to which cognitive variables share etiological influences with each other and with the clinical phenotype. These results will also facilitate reducing the number of measures to take forward into genetic mapping studies, where multiple testing is a major problem.

ADHD is associated with impairments on executive function tasks, especially those measuring reaction time (RT), response inhibition (indexed by commission errors) and sustained attention (indexed by omission errors) (Johnson, et al 2009; Klein et al. 2006;Kuntsi et al. 2009;Willcutt et al. 2005; Wood et al. 2009b). A strong association has emerged between ADHD and RT variability (Klein et al 2006; Kuntsi et al 2009; Rommelse et al. 2008; Wood et al 2009b), and in our own research, we previously showed an association with combined type ADHD on subsets of the current sample for commission and omission errors on a go/no-go task (Uebel et al, 2009), as well as mean RT and RT variability on the go/no-go and a four-choice RT task (Andreou et al. 2007; Uebel et al, 2009), and with 'choice impulsivity' (preference for smaller-immediate rewards, incorporating 'delay aversion'; Marco et al. 2009). Using identical tasks, similar findings emerged in a large general population twin sample (ages 7-10) for the RT variables, commission errors[1] (Kuntsi, et al 2009) and choice impulsivity (Paloyelis, et al 2009).

[1] Omission errors were not investigated due to small number of such errors made in this general population sample

We observed improvements in RT mean and variability under incentive or combined fast/incentive conditions that was greater in cases than controls, suggesting an important role for motivational or energetic factors on the processes that underlie the response time measures (Andreou, et al 2007; Uebel et al. 2009). In contrast, case-control differences in omission and commission errors were not altered under the different conditions, suggesting a potentially different underlying cognitive process that was not influenced by motivational or energetic factors for these variables (Uebel et al 2009).

Using the population twin sample we estimated the heritability of mean RT and RT variability to be around 50-60%, (Wood, et al 2009b). Furthermore, the estimates increased to around 70% when corrected for measured test-retest unreliability (Kuntsi, et al 2006), nearing the average 'broad sense' heritability for ADHD of 70% (Burt 2009). Quantifying results from other studies that report shared familial variance between RT data and ADHD (Bidwell et al. 2007a; Nigg et al. 2004), the genetic correlation between the RT variables and ADHD symptom scores was estimated at around 0.7 (Wood, et al 2009b), indicating that approximately 70% of the genes that influence ADHD also influence RT performance, and that the familial variance in sibling studies represents largely genetic influence. Previous analyses on a subset of the present ADHD-proband and control sibling-pair sample similarly indicated that 58-70% of the covariation between ADHD and RT variables was due to shared familial influences (Andreou, et al 2007). In other analyses, performance on the stop signal reaction time from the stop task (Bidwell et al. 2007b; Schachar et al. 2005; Rommelse et al, 2008; Waldman et al. 2006) and commission errors on the continuous performance task (Bidwell, et al 2007b) also indicated shared familial variance with ADHD, as indicated by mean scores in unaffected siblings or parents of ADHD-probands that were significantly different from those of controls. Using the go/no-go task, twin data indicated heritability estimates of up to 45% for error data (Kuntsi, et al 2006) and ADHD-unaffected sibling-control means comparisons further suggested

shared familial variance with ADHD, assumed to be largely genetic, as above (Andreou, et al 2007; Slaats-Willemse et al. 2003; Uebel et al 2009).

ADHD is also associated with lower IQ and twin data indicate that this is also mainly the result of shared genetic influences (Kuntsi, et al 2004; Polderman et al. 2006). An important clinical question therefore is whether IQ deficits, and their underlying processes, drive some of the more specific cognitive performance deficits found in ADHD. A recent investigation in ADHD sibling pairs suggested independent familial segregation of executive functioning and IQ in ADHD families (Rommelse, et al 2008) which concurred with results using SEM on the twin sample (7-10 years). Most of the genetic covariance (66-82%) between RT variables and ADHD symptom scores was due to genetic factors that are not shared with IQ, with 92-95% of the overall phenotypic covariance arising independently of etiological (genetic and environmental) factors shared with IQ (Wood, et al 2009b). Establishing whether this translates to a clinical sample is a key aim in the current analyses.

To address this question in a more clinically relevant sample, we now extend our previous IQ-related model-fitting analyses on the twin sample to a large clinical sample of ADHD probands, their siblings and a control sibling-pair sample, and further extend the analysis to additional cognitive variables. Using familial multivariate model fitting, we aimed to investigate whether the familial association between five measures of cognitive performance (mean RT, RT variability, omission errors, commission errors and choice impulsivity) and a clinical diagnosis of ADHD is mediated through shared familial influences with IQ. A measure of choice impulsivity was included in light of recent findings which suggest that (unlike the RT data findings) covariation between ADHD and reward preference may, at least in part, be explained by the covariation between ADHD and IQ (Bitsakou et al., 2009; Marco et al., 2009). We aimed to examine this at the etiological level. An additional aim is to examine if there is justification for aggregating across measures

of the same cognitive index, gained either from different tasks (RT variables) or different conditions of the same task (accuracy variables). Such aggregation across measures is likely to be beneficial for future genetic analyses, as psychometrically robust variables are created (Kuntsi, et al. 2006) and the overall number of variables is reduced.

METHODS

Sample

ADHD probands and siblings: Participants were recruited from eight specialist clinics in seven European countries (Belgium, Germany, Ireland, Israel, Spain, Switzerland and United Kingdom), through the International Multicentre ADHD Genetics (IMAGE) project (see Chen et al. 2008 for detailed description of ascertainment and diagnostic procedures). 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 one or more full siblings and biological parents available for ascertainment of clinical information and DNA. Siblings were unselected for clinical phenotype. Exclusion criteria applying to both probands and siblings included IQ less than 70, autism, epilepsy, general learning difficulties, brain disorders and any genetic or medical disorder associated with externalizing behaviours that might mimic ADHD. Where families had more than two siblings, the ADHD index cases were matched to only one of the siblings, to maintain a simple proband-sibling structure for all families included in this analysis. 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. 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. An additional 61 participants had cognitive data, but no clinical data, and their affection status was coded as missing. Ethical approval was obtained from local ethical review boards.

Procedure

ADHD probands and their siblings were invited to the research centre for the cognitive assessments and for the parent interview. A minimum of a 48-h medication-free period was required for cognitive testing; and patients on non-stimulant medications were not excluded from the study. The assessments of the proband and sibling were carried out in separate rooms either at the research centre or in schools. Children were given short breaks as required and the total length of the test sessions, including breaks, was approximately 2.5–3 h.

Measures

Diagnosis

The Parental Account of Child Symptoms (PACS) interview (Taylor et al. 1986b) 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 behaviour 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' (Conners et al. 1998). 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 (Asherson et al. 2008).

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; Wechsler 1991) were used to obtain an estimate of the child's IQ.

The go/no-go task: On each trial of the go/no-go task (Borger & van der Meere 2000; Kuntsi et al. 2005), one of two possible stimuli appeared for 300 ms in the middle of the computer screen. The child 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 children performed the task under three conditions (slow, fast and incentive; see Uebel et al. in press), 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 children. The variables obtained from the task are mean RT (MRT), standard deviation (SD) of RTs (RTV), commission errors (CE) and omission errors (OE).

The fast task: The baseline condition of the fast task (Andreou, et al 2007; Kuntsi, et al 2006), with a fore period of 8 s and consisting of 72 trials, followed a standard warned four-choice RT. 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 child 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 Andreou, et al 2007). The variables obtained from the task are MRT and SD of RTs; here reported for the baseline condition.

The choice-impulsivity task (Maudsley index of childhood delay aversion): Two conditions, each with 20 trials, were administered (Kuntsi, et al 2006; Marco, et al 2009). In each trial, the child 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, reducing the overall length of the condition. In the post-reward delay condition, choosing the small reward led to a delay period of 30 seconds, and choosing the large reward led to a delay period of 2 seconds before the next trial; therefore, the overall delay was constant and independent of choice made. The order of the two conditions was randomly chosen for each participant. Here, we report data for 'choice impulsivity': the percentage of choices for the larger reward in the no post-reward delay condition (reverse scored).

Selection of cognitive task variables for model fitting analyses: RT data were available from the go/no-go and fast tasks: mean RT and RT variability were obtained from baseline (slow) conditions, where a strong association with ADHD is observed (Andreou, et al 2007; Kuntsi, et al 2009; Uebel et al 2009). Commission and omission error data were available from the go/no-go task: data were obtained from slow and fast

conditions, as associations with ADHD are observed in both these conditions (Kuntsi, et al 2009;Uebel et al 2009). Choice impulsivity data were obtained from the no post-reward delay condition of the choice-delay task, as this reflects the strongest association with ADHD from this task over and above 'delay aversion' (Marco, et al 2009; Paloyelis, et al 2009),.

Analyses

Familial structural equation models The structural equation-modeling program Mx (Neale et al. 2006) was used to conduct the genetic analyses and to estimate phenotypic correlations. To account for the selected nature of the sample, the selection variable (ADHD status) is included in all models with its parameters fixed. This necessitated ordinal data analysis with the age- 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, with one or more thresholds per liability distribution to distinguish between the ordered categories. The threshold for ADHD status was fixed to a z-value of 1.64 to give a population prevalence of 5%, and its parameters fixed to expected population estimates, with the familiality of ADHD fixed to 80% (sibling correlation of .40; see Rijsdijk et al. 2005 for further explanation and validation of this approach).

Phenotypic correlations (rPh) Sibling correlations are estimated from a phenotypic correlation model specified in a Gaussian decomposition to give maximum likelihood correlations between the phenotypic variance in each measure for each sibling, and to allow additional constraints. In addition to constraints outlined above, 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 (first- or second- born).

Genetic Models: Cholesky decomposition (Figure 1). 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] + 100% common environmental [C]) influences, and individual-specific environmental (E) influences, which include possible measurement error. Without knowing the underlying ratio of A:C influences for each variable, it is not possible to specify a variance/covariance structure that accurately estimates the amount of variance due to A+C influences, and as we are here focusing on shared variance, overall percentages for variance due to F and E parameters for each variable are not presented (although estimates are available in Figure 1).

A triangular, or Cholesky, decomposition is imposed on the data, which allows an estimation of the extent to which traits share common F and E influences. Although the ordering of variables in the Cholesky is often arbitrary for computational reasons, in the multivariate models we assigned IQ to be the first measured variable, to allow an estimation of the extent to which the covariance between cognitive data and ADHD was independent of risk factors shared with IQ. Due to the computational intensity of ordinal data analysis, 95% confidence intervals are not available. However, the significance of parameters in the main model (Figure 1) were tested by dropping, in turn, each parameter and comparing the chi-square of the reduced model to that of the full model with a 1-df test of freedom at the $p<.05$ level. A significant result indicates that the model was a worse fit without this parameter, and thus, the parameter was significant with an alpha level of .05.

RESULTS

Group differences between ADHD-CT probands, siblings of probands and controls existed for gender and parent and teacher ratings of ADHD behaviors; and between probands and controls, and siblings and

controls (but not probands and siblings) for IQ and age. The use of definition variables in Mx was not possible due to the computational intensity of the integration in ordinal data analysis. Accordingly, the data were regressed for age and gender prior to the familial modeling and the age- and sex- corrected residuals used. IQ and ADHD status were included as measured variables.

Multivariate familial models across ADHD and MRT, RTV, CE or OE: To examine whether cognitive variables across similar (theoretically related) tasks, or across different conditions of the same task, reflect similar etiological influences, models were run across two sets of data for each cognitive index (ADHD was also included to correct for ascertainment bias). The similar phenotypic and cross-sibling correlations from the constrained, phenotypic model indicate that shared familial effects underlie task (for MRT and RTV) or condition (for CE and OE) level covariance (Table 2). This is reflected in the high familial correlations between task- or condition- level data on the same cognitive construct of between rF=0.69-0.83 (Table 2).

Multivariate familial models across IQ, ADHD, CI, and mean MRT, RTV, CE or OE scores (Figure 1)

The correlations between ADHD and IQ were -0.20 at the phenotypic level and -0.17 at the familial level. Given the results outlined above, the extent to which etiology of any overlap between cognitive indices and ADHD was independent of etiology shared with IQ was examined using mean scores across the measures of MRT, RTV, CE or OE, using a Cholesky decomposition (Table 3). By summing the contribution of F and E factors that contribute to the covariation between cognitive indices and ADHD that do *not* influence the population variance in IQ, and taking them as a percentage of the total co-variance, we obtain the percentage of the co-variation that is independent of shared etiological influences with IQ.

Etiological (F / E) correlations with ADHD were as expected from task- or condition-specific measures (not presented but available from ACW upon request). The overlap between ADHD and the cognitive indices

was largely independent of any shared etiology between ADHD and IQ. Between 73% and 81% of the familial influences that were shared between ADHD and the cognitive indices were independent of those shared with IQ. The exception was CI, which was lower at 62%, indicating a greater degree of overlap with the familial influences shared between ADHD and IQ. The percentage of the covariation with ADHD that was independent of shared familial influences with IQ was 58% for MRT, 62% for RTV, 67% for CE, 52% for OE and 53% for CI. Overall, the percentage of the covariation with ADHD that was independent of any shared etiological (F+E) influences with IQ was 85% for MRT, 87% for RTV, 84% for CE, 80% for OE and 61% for CI.

DISCUSSION

Data from a large ADHD and control sibling-pair sample showed that the association between ADHD and several cognitive measures (mean RT, RT variability, commission errors and omission errors) is largely (80-87%) independent of etiological influences shared with IQ. This confirms and extends previous model fitting findings on a general population twin sample (Wood, et al 2009b), as well as previous findings from a separate clinical sample using different analytical techniques (Rommelse, et al 2008). The evidence is therefore accumulating that the relationship between ADHD and key cognitive phenotypes is not mediated by shared familial effects with IQ. This suggests that several distinct processes are involved and that impairments in general cognitive ability are unlikely to explain the specific deficits seen in ADHD.

For individual cognitive measures, the high familial correlations (0.69-0.83) obtained *across* conditions or tasks indicate that they are largely measuring the same underlying liability. These results, on familial sharing, indicate that performance appears relatively stable across task and condition, when focusing on the cognitive measures that are associated with ADHD. These results support the aggregation of data across the variables examined here for future genetic mapping analyses. They also suggest that the

individual cognitive measures are indexing the same unitary construct across these two tasks, providing support for combining datasets for meta-analytic studies, where the data was gathered using the different specific tasks. This is important for genetic mapping studies because replication of preliminary findings and pooling of data to reach genomewide levels of significance is essential to confirm the identity of true genetic associations. However, while these results are promising, caution must be advised in considering the exact task parameters. For example, for RT variability we have shown using the current sample (Andreou et al., 2007; Uebel et al., 2009) and a separate population twin sample (Kuntsi et al., 2009) how the strength of association with ADHD depends crucially on task condition parameters, such as event rate and incentives.

Our results across tasks and conditions show a striking similarity with results in a younger, general population twin study (Wood et al, 2009b). An example is the comparability of the genetic correlations between ADHD symptom scores and RT variability in the fast and go/no-go tasks in the twin study (~0.6-0.7) and the familial correlations in the current study (~0.6-0.8). In addition to suggesting that the familial covariance is largely genetic, these findings emphasize the robustness of the methods and findings, which replicate not only across tasks and samples, but also across definitions of ADHD (diagnosis *vs* a continuum of symptoms in the general population); supporting the conceptualization of ADHD as the extreme of a continuously distributed trait. Future analyses will aim to extend this work and examine whether there are separate pathways between the RT and error variables to account, for example, for bottom-up influences from subcortical arousal structures and brief reductions in the top-down control of sustained attention and inhibition (Halperin et al., 2006, 2008; Kuntsi et al. under review). The current data emphasize that these processes do not arise out of pathways shared with the more generalised deficit of lowered IQ.

The familial sharing between ADHD and choice impulsivity was lower (with a familial correlation of -0.14) than that found for the other cognitive variables. The percentage of the covariation with ADHD that was

independent of shared etiological influences with IQ was also lower, at 61%, indicating that choice impulsivity and IQ are more closely related constructs at the etiological level. Research investigating whether there are separate and dissociable mechanisms, underpinned by different neural circuitry (Sonuga-Barke, 2005), may clarify the role of choice impulsivity in ADHD symptomatology.. Overall, the evidence in support of choice impulsivity as an intermediate familial phenotype in ADHD is less strong than for the other cognitive variables investigated here, but it is unclear at present whether this reflects, at least in part, psychometric properties of the particular measure used in this study (in particular ceiling effects; (see Kuntsi, et al 2006) and should therefore be further investigated using alternative measures of this construct.

The current analyses add to the emerging understanding of the genetic architecture of the cognitive and energetic processes that underlie the symptoms of ADHD. For the first time, a clinical sample has been used to quantify that the familial influences ADHD shares with IQ are largely separable from those that ADHD shares with the other key cognitive indices associated with the disorder. The aetiological factors that give rise to lower IQ in ADHD appear to be largely distinct from those that give rise to the association of ADHD with RT variables, commission and omission errors. Lower IQ does not appear to be a general explanation for the impairments in these specific cognitive domains.

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Table 1: Group means (and standard deviations) for sample characteristics and cognitive variables

	ADHD probands	Siblings of ADHD probands	Controls
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 [a 1 2 3]	78.87 (8.51)	54.80 (13.62)	52.20 (10.83)
Teacher-rated Conners' DSM-IV ADHD subscale [a 1 2 3]	71.20 (10.70)	56.54 (12.41)	50.32 (9.17)
MRT			
Fast task (baseline condition)[1]	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 (233.85)
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)
CE			
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)
OE			
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)
CI [1 3]	33.48 (29.83)	30.71 (27.57)	16.95 (24.98)

[a] Ratings from the Conners DSM-IV: ADHD total symptoms subscale

[1] Indicates significant differences between probands and controls ($p<.05$)

[2] Indicates significant differences between probands and siblings ($p<.05$)

[3] Indicates significant differences between siblings and controls ($p<.05$)

Table 2: Maximum likelihood phenotypic, cross-sibling and familial correlations for cross-task[a] or cross-condition[b] data from constrained phenotypic models across ADHD (used for ascertainment correction) and cognitive variables .

	Phenotypic correlation	Cross-sibling correlation	Familial correlation
MRT	.52	.19	.69
RTV	.49	.20	.70
CE	.59	.16	.74
OE	.50	.20	.83

[a] MRT / RTV where data are collected across two tasks: the fast task and the go/no-go task

[b] CE / OE where data are collected across one task (the go/no-go task) but two conditions are associated with ADHD at the phenotypic level

Note: CI is not included as it is collected across only one task

Table 3: Etiological correlations from correlated factors solutions of Cholesky models estimating the etiological influences across IQ, ADHD status, and cognitive variables

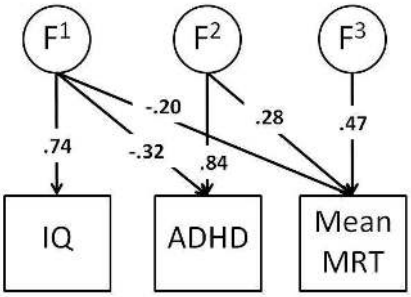
	Phenotypic correlations		Cross-sibling correlations		Familial correlations		Individual –specific correlations	
	ADHD	IQ	ADHD	IQ	ADHD	IQ	ADHD	IQ
MRT[a]	.42	-.24	.22	-.10	.57	-.39	.33	-.13
RTV[a]	.47	-.25	.23	-.11	.71	-.42	.33	-.15
CE[b]	.24	-.16	.12	-.08	.41	-.25	.12	-.12
OE[b]	.33	-.23	.17	-.16	.50	-.49	.25	-.08
CI	-.16	.30	-.03	.22	-.14	.17	-.02	.83

[a]Mean across fast task and slow condition of the go/no-go task

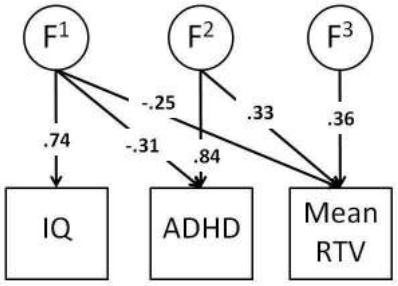
[b]Mean across slow and fast conditions of the go/no-go task

Figure 1: Familial parameter estimates from Cholesky models estimating the etiological influences across IQ, ADHD status, mean reaction time (MRT, panel A), mean reaction time variability (RTV, panel B), mean commission errors (CE, panel C), mean omission errors (OE, panel D) and choice impulsivity (CI, panel E)

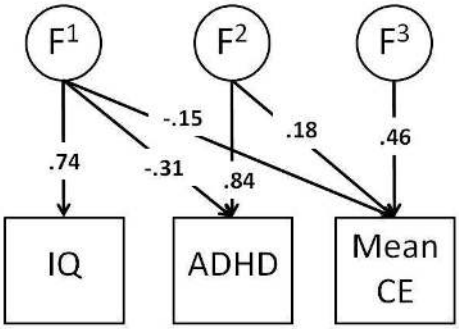
A



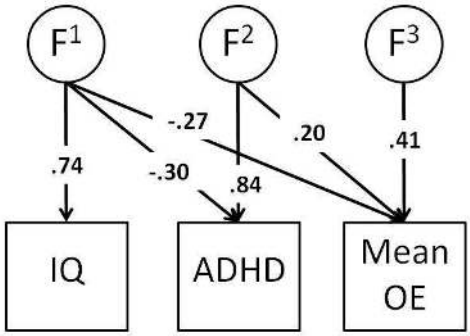
B



C


F1
F2
F3
-.15
.18
.46
.74
-.31
.84
IQ
ADHD
Mean CE

D


F1
F2
F3
-.27
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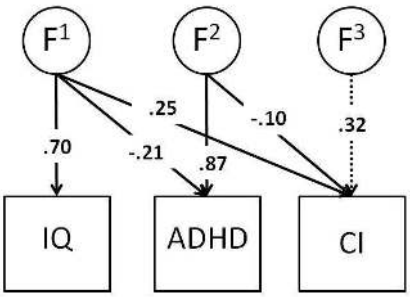
IQ
ADHD
Mean OE

E



Note: Non-significant parameters in dotted lines.