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Neuropsychological measures probably facilitate heritability research of ADHD

Nanda N.J. Rommelse [a,b,*], Marieke E. Altink [b], Neilson C. Martin [c], Cathelijne J.M. Buschgens [b], Jan K. Buitelaar [b], Joseph A. Sergeant [a], Jaap Oosterlaan [a]

[a] *Department of Clinical Neuropsychology, VU University Amsterdam, Amsterdam, The Netherlands*
[b] *Department of Psychiatry, Radboud University Nijmegen Medical Center, The Netherlands*
[c] *School of Psychology, Curtin University of Technology, Perth, Western Australia, Australia*

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Abstract

Previous studies, in which cognitive and motor neuropsychological tasks were administered to 816 children from Attention-Deficit/Hyperactivity Disorder (ADHD)- and control-families, showed that various of these measures appeared useful for genetic research in ADHD by forming candidate endophenotypes: underlying, heritable, vulnerability traits that mark an enhanced liability for developing ADHD. The current study extends these findings by showing that six of these ten measures correlate more strongly between siblings than an ADHD composite, suggesting these measures may have a larger heritability than ADHD itself. Significant sibling cross-correlations also suggested that six of ten neuropsychological measures related to similar familial (and heritable) factors as ADHD, suggesting these measures to be useful for ADHD genetic research. An aggregated neuropsychological composite appeared to be the most powerful, since it correlated more strongly between siblings than most individual task measures. These findings suggest heritability research in ADHD will probably be facilitated by including neuropsychological measures.

Keywords: Endophenotype; Phenotype; ADHD; Heritability; Neuropsychology; Siblings

1. Introduction

Neuropsychological research may aid in the discovery of genes and their influence on neuropsychiatric disorders. It has been hypothesized that neuropsychological deficits may form more direct expressions of disease genes than phenotypic symptoms (Castellanos & Tannock, 2002; Doyle, Faraone, et al., 2005; Rommelse, Oosterlaan, Buitelaar, Faraone, & Sergeant, 2007; Waldman, 2005). In this framework, neuropsychological deficits act as 'endophenotypes': underlying, heritable, vulnerability traits that mark an enhanced liability for developing a disorder (Almasy & Blangero, 2001). Using endophenotypes can facilitate gene detection by forming more homogeneous subgroups of patients all being impaired on a specific endophenotype and/or by linking specific gene variations to endophenotypes.

* Corresponding author at: Department of Psychiatry, Radboud University Nijmegen Medical Center, Reinier Postlaan 12, 6525 GC Nijmegen, The Netherlands. Tel.: +31 24 3512222; fax: +31 24 3512211.
E-mail address: n.lambregts-rommelse@psy.umcn.nl (N.N.J. Rommelse).

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Not all neuropsychological deficits are automatically suitable as endophenotypes. Various criteria have been postulated to define an endophenotype. The most frequently cited ones are: the neuropsychological deficit (1) should be associated with the disorder, (2) should be present in non-affected relatives to a higher degree compared to controls, (3) should correlate between biological family-members, and (4) should (partly) arise from the same heritable factors that also influence the phenotype (Almasy & Blangero, 2001; Castellanos & Tannock, 2002; Doyle, Faraone, et al., 2005; Gottesman & Gould, 2003; Rommelse, Oosterlaan, et al., 2007; Skuse, 2001; Waldman, 2005). Thus, in order to examine whether certain neuropsychological deficits may be useful as endophenotypes, it is necessary to include both affected individuals and their non-affected relatives.

The current study deals specifically with candidate neuropsychological endophenotypes of Attention-Deficit/Hyperactivity Disorder (ADHD; American Psychiatric Association, 1994). Numerous studies have been conducted in the past decades, which have shown that a wide variety of neuropsychological deficits are associated with ADHD. Deficits have been observed in executive functions such as inhibition, working memory, set shifting and planning (Barkley, 1997; Boonstra, Oosterlaan, Sergeant, & Buitelaar, 2005; Clark, Prior, & Kinsella, 2000; Doyle, 2006; Pennington & Ozonoff, 1996; Sergeant, Geurts, & Oosterlaan, 2002; Willcutt, Doyle, Nigg, Faraone, & Pennington, 2005), attentional skills (Barkley, 1997; Brodeur & Pond, 2001; Losier, McGrath, & Klein, 1996), time (re)production and estimation (Barkley, Edwards, Laneri, Fletcher, & Metevia, 2001; Kerns, McInerney, & Wilde, 2001; Toplak, Dockstader, & Tannock, 2006), (oculo)motor speed, variability, timing, and coordination (Leth-Steensen, Elbaz, & Douglas, 2000; Pitcher, Piek, & Barrett, 2002; Rubia, Noorloos, Smith, Gunning, & Sergeant, 2003; Sergeant, Piek, & Oosterlaan, 2006; Toplak et al., 2006; Van der Stigchel et al., 2007; Van Meel, Oosterlaan, Heslenfeld, & Sergeant, 2005), and sensory–motor integration (Yordanova, Banaschewski, Kolev, Woermer, & Rothenberger, 2001). However, since relatively few studies have included non-affected relatives of patients with ADHD, it is unclear whether these neuropsychological deficits may be useful as endophenotypes. The available studies that have included non-affected relatives targeted mainly executive functions as candidate endophenotypes. Two studies found no conclusive evidence of executive dysfunctioning in non-affected siblings (Nigg, Blaskey, Stawicki, & Sachek, 2004; Seidman, Biederman, Monuteaux, Weber, & Faraone, 2000), but another study did (Bidwell, Willcutt, DeFries, & Pennington, 2007). Other studies specifically targeting inhibition or interference control, found evidence for these executive functions as endophenotypes (Crosbie & Schachar, 2001; Doyle, Faraone, et al., 2005; Schachar et al., 2005; Slaats-Willemse, Swaab-Barneveld, De Sonneville, & Buitelaar, 2005; Slaats-Willemse, Swaab-Barneveld, De Sonneville, Van der Meulen, & Buitelaar, 2003). Less attention has been given to studying functions outside the executive domain. Previous studies have shown that non-affected siblings have (subtle) problems, similar to their affected siblings, in stability of motor control (Slaats-Willemse, De Sonneville, Swaab-Barneveld, & Buitelaar, 2005), in motor/response variability (Andreou et al., 2007; Bidwell et al., 2007), and speed of oculomotor control (Van der Stigchel et al., 2007).

In five recent studies including 816 children (aged 5–19 years) from ADHD- and control-families (Rommelse, Altink, De Sonneville, et al., 2007; Rommelse, Altink, Oosterlaan, Beem, et al., 2008; Rommelse, Altink, Oosterlaan, Buschgens, et al., 2007; Rommelse, Oosterlaan, et al., 2007; Rommelse, Altink, Oosterlaan, Buschgens, et al., 2008), both cognitive and motor endophenotypes were investigated. It was found that the well-known executive dysfunctions associated with ADHD (i.e. impairments in inhibition [longer Stop Signal Reaction Times] and verbal [fewer Digit Span backwards] and visuo-spatial working memory [fewer number of correctly identified visual-spatially presented targets in the correct order]) were also present in non-affected siblings (Rommelse, Altink, Oosterlaan, Buschgens, et al., 2008). Moreover, these deficits appeared to arise from similar familial sources, because inhibition impairments in a child were related to working memory impairments in his/her siblings and vice versa. Also, accuracy in Time Reproduction (measured as the total absolute deviation between the time in seconds of the stimulus and the time in seconds of the response], a function heavily related to executive functions, was highly familial and impaired in children with ADHD and their non-affected siblings (Rommelse, Oosterlaan, et al., 2007), as well as was the tendency to commit errors on a task measuring inhibition and cognitive flexibility (Rommelse, Altink, De Sonneville, et al., 2007). Evidence for endophenotypes in the motor domain was also found. Variability in Motor Timing appeared strongly familial and sensitive to a genetic risk for ADHD (Rommelse, Altink, Oosterlaan, Beem, et al., 2008). Variability in self-generated motor output and externally cued motor output was abnormal in affected children and, even though familial, generally unimpaired in non-affected siblings (Rommelse, Altink, Oosterlaan, Beem, et al., 2008). Nevertheless, evidence for familially determined impairments in the precision of motor control was found (Rommelse, Altink, Oosterlaan, Buschgens, et al., 2007). Though informative, three issues remained unanswered in these five studies regarding the utility of these neuropsychological measures as endophenotypes and are the aims of the current study.

First, it is expected that candidate neuropsychological endophenotypes are more strongly linked to heritable factors than the ADHD phenotype itself. If so, sibling correlations should be higher for the neuropsychological measures than for the ADHD symptoms. Second, it is expected that neuropsychological measures form a link between disease genes and the ADHD phenotype (Kuntsi & Stevenson, 2001). If true, the neuropsychological measures will relate to the same familial (and with that, heritable) factors as the ADHD phenotype. In that case, neuropsychological performance of a child will be correlated with ADHD in his/her siblings. Third, it is expected that the most powerful neuropsychological instrument is a composition score of individual neuropsychological measures, since a composition score entails less error variance than individual measures. If so, this composite will show better results in the analyses of the first and second research aim than the individual task measures. These three issues will be investigated in the current study.

2. Method

2.1. Participants

Families with at least one child with the combined subtype of ADHD (proband) and at least one additional sibling (regardless of possible ADHD-status) were recruited in order to participate in the Dutch part of the International Multicenter ADHD Genes study (IMAGE). The IMAGE project is an international collaborative study that aims to identify genes that increase the risk for ADHD using QTL linkage and association strategies (Brookes et al., 2006). Additional control-families were recruited from primary and high schools from the same geographical regions as the participating ADHD-families. Controls and their first degree relatives were required to have no formal or suspected ADHD diagnosis. A total of 238 ADHD-families and 147 control-families fulfilled inclusion and exclusion criteria encompassing a sample of 816 children in total. Within the ADHD-families, 238 probands (all with combined subtype ADHD), 112 affected siblings (64 with combined subtype, 28 with inattentive subtype and 20 with hyperactive-impulsive subtype) and 195 non-affected siblings participated. Control-families consisted of 271 children. For 51 control children, no additional control sibling could be recruited for the study, because the sibling was unwilling to participate or because the control-family consisted of only one child.

All children were between the ages of 5 and 19 years (average 11 years and 9 months) and were of European Caucasian descent. Participants were excluded, if they had an IQ < 70, a diagnosis of autism, epilepsy, general learning difficulties, brain disorders or known genetic disorders, such as Down syndrome or Fragile-X-syndrome.

Both the proband and his/her siblings were similarly screened using the standard procedures of the IMAGE project described elsewhere (Brookes et al., 2006; Rommelse, Oosterlaan, et al., 2007). Briefly, screening questionnaires (parent and teacher Conners' long version rating scales [Conners, 1996] and parent and teacher Strengths and Difficulties Questionnaires [Goodman, 1997]) were used to identify children with ADHD symptoms. *T*-scores ≥63 (90th percentile) on the Conners' ADHD-subscales (DSM-IV Inattention, DSM-IV Hyperactive-Impulsive, and DSM-IV Total) and scores >90th percentile on the SDQ-hyperactivity scale were considered clinical. A semi-structured, standardized, investigator-based interview was administered for the child with ADHD: The Parental Account of Children's Symptoms (PACS) (Taylor, 1986). A standardized algorithm was applied to the PACS to derive each of the 18 *DSM-IV* ADHD-symptoms, providing operational definitions for each behavioural symptom. These were combined with items that were scored 2 (pretty much true) or 3 (very much true) in the teacher-rated Conners ADHD subscales DSM-IV Inattention, DSM-IV Hyperactive-Impulsive, and DSM-IV Total) to generate the total number of hyperactive-impulsive and inattentive symptoms of the *DSM-IV* symptom list. Situational pervasiveness was defined as at least one symptom occurring within two or more different situations, as indicated by the parents in the PACS interview, as well as the presence of at least one symptom scoring 2 or 3 from the ADHD subscales (DSM-IV Inattention, DSM-IV Hyperactive-Impulsive, and DSM-IV Total) as indicated by the teachers on the Conners questionnaire. The Conners' long version for both parents and teachers was completed for control children. Control children had to obtain non-clinical scores on both the parent and teacher version on all subscales (Conners DSM-IV Total: *T*-score ≤ 62).

Full-scale IQ was estimated by four subtests of the WISC-III or WAIS-III (depending on the child's age): Vocabulary, Similarities, Block Design and Picture Completion (Wechsler, 2000; Wechsler, 2002). These subtests are known to correlate between .90 and .95 with the full-scale IQ (Groth-Marnat, 1997). IQ testing took place while the children were off medication.

2.2. Experimental tasks

The ten experimental tasks described in this study have been fully described elsewhere (Rommelse, Altink, De Sonneville, et al., 2007; Rommelse, Altink, Oosterlaan, Beem, et al., 2008; Rommelse, Altink, Oosterlaan, Buschgens, et al., 2007; Rommelse, Oosterlaan, et al., 2007; Rommelse, Altink, Oosterlaan, Buschgens, et al., 2008). All ten tasks used in this study have been used frequently in ADHD research aiming to explore the neuropsychological deficits in ADHD. For example, six of the ten tasks, namely Shifting Attentional Set, Visual–Spatial Sequencing, Pursuit, Tracking, Tapping, and Baseline Speed are part of a sound neuropsychological battery (Amsterdam Neuropsychological Tasks) of which the validity and reliability has been confirmed (De Sonneville, 1999). Digit Span is widely known and used as measure for verbal working memory as part of the WISC/WAIS of which validity and reliability have been confirmed (Wechsler, 2000, 2002). The Stop Task is based on a thoroughly investigated paradigm (Logan, 1994) and this particular Stop Task has been successfully used in multiple ADHD studies at our department of Clinical Neuropsychology. Likewise, the tasks tapping into Motor Timing and Time Reproduction have been frequently used before by experts in the ADHD field (Barkley, 1998; Van Meel et al., 2005) and their utility has been proven. Based on previous results (Rommelse, Altink, De Sonneville, et al., 2007; Rommelse, Altink, Oosterlaan, Beem, et al., 2008; Rommelse, Altink, Oosterlaan, Buschgens, et al., 2007; Rommelse, Oosterlaan, et al., 2007; Rommelse, Altink, Oosterlaan, Buschgens, et al., 2008), the variable per task that showed most optimal results in the endophenotypic analyses was chosen for the current analyses (see also Section 1) (Table 1).

2.3. Procedure

Testing of children with ADHD and their siblings took place at the VU University Amsterdam or at the Radboud University Nijmegen Medical Center and was conducted simultaneously for all children in a family. Psychostimulants were discontinued for at least 48 h before testing took place (Pelham et al., 1999). Children were motivated with small breaks. At the end of the session, a gift worth approximately €4, was given. Control children were tested in a similar way in a quiet room at their school. The study had medical–ethical approval.

2.4. Data analyses

Neuropsychological task variables with less than 5% missing data were subjected to expectation maximization to replace the missing data (Tabachnick & Fidell, 2001). The percentage of missing data on the Stop Task (9.2%) was considered too large to replace in this manner. Some variables of the neuropsychological tasks were changed in sign, so that the scores of all variables would imply the same meaning: higher scores being indicative of a poor performance. An ADHD composite was derived by summing the raw scores obtained on the Conners parent and teacher and dividing this number by two. It was chosen to perform all analyses on this ADHD composite, instead of performing the analyses separately for parent and teacher ratings of ADHD, because inter-rater agreement was high ($r = .69$, $p < .001$) and the correlations between parent ratings and the neuropsychological measures, on the one hand, and teacher ratings and the neuropsychological measures, on the other hand, were very similar (correlations can be obtained from the corresponding author). Therefore, we believe creating an ADHD composite is a sensible approach, because it will generate an overall picture of findings and will reduce the number of correlations needing to be calculated by half.

Normalization and standardization of all task variables and the ADHD composite was performed in SPSS using a Van der Waerden transformation (Statistical Package for the Social Sciences version 14). This transformation is also used in similar types of research (Anokhin, Heath, & Ralano, 2003). The Van der Waerden transformation is a standard option in SPSS and transforms raw scores into z-scores corresponding to the estimated cumulative proportion of the distribution corresponding to a particular rank. It is defined by the formula $r/(w+1)$, in which w is the sum of the case weights and r is the rank, ranging from 1 to w (Lehmann, 1975). Cases are given different weights by means of simulated replication. The value of the new standardized variable equals the sum of case weights. This transformation has two important advantages: It handles the (extreme) influence outliers may have on the data, by ranking them as (very) high or low within the normal distribution, and the comparison between the variables was facilitated since the variables were all depicted on the same scale.

The sample allowed us to calculate a total of 540 sibling (cross-) correlations: a family consisting of two children allows calculation of one sibling correlation (sibling A − sibling B); a family of three children allows calculation of three

Table 1
Short description of the neuropsychological tasks fully described in Rommelse, Altink, De Sonneville, et al. (2007), Rommelse, Altink, Oosterlaan, Beem, et al. (2008), Rommelse, Altink, Oosterlaan, Buschgens, et al. (2007), Rommelse, Oosterlaan, et al. (2007) and Rommelse, Altink, Oosterlaan, Buschgens, et al. (2008)

Name and aim task	Task components	Performance measures
Stop Task	*Task description*: Go-trials (drawing of a plane) that was either pointing to the right or to the left. Stop-trials were identical to the go-stimulus but in addition a stop-signal was presented (drawing of a cross that was superimposed on the plane).	Latency of the stop-process: the Stop Signal Reaction Time (SSRT).
Motor inhibition of an ongoing response	*Task requirements*: Participants pressed a response button that corresponded to the direction of the stimulus as quickly and as accurately as possible. For the stop-signal children were required to withhold their response.	
Shifting Attentional Set	*Task description*: Stimuli consisted of a horizontal gray bar with green or red moving squares. The task consisted of three blocks. In the first block, the moving square was coloured green, and compatible responses were required. In the second block, the moving square was coloured red, and incompatible responses were required. In the third block, the colour of the moving square alternated randomly between green and red, and both compatible and incompatible responses were required.	Percentage errors across blocks.
Motor inhibition and cognitive flexibility	*Task requirements*: Participants were instructed to press a response button as quickly and as accurately as possible that corresponded to the direction in which the stimulus moved and was required.	
Time Test	*Task description*: Stimuli (4, 8, 12, 16, 20 s) were randomly presented in two separate modalities: visual (light bulb) and auditory (tone).	Precision of the reproduction (operationalized as the absolute discrepancy between the response length and the stimulus length) averaged across trials and modalities.
Time reproduction	*Task requirements*: Participants were required to press a button to reproduce stimuli.	
Visuo-Spatial Sequencing	*Task description*: Nine circles symmetrically organized in a square (3×3). On each trial, a sequence of circles was pointed at by a computer-driven hand.	Total number of correct targets in the correct order.
Visuo-spatial working memory	*Task requirements*: Participants were instructed to replicate the exact same sequence of circles, by pointing to them with a small, self-driven hand.	
Digit Span	*Task description*: Forward: repeating a sequence of numbers in the same order. Backward: repeating the numbers in the opposite order.	Maximum Digit Span backwards.
Verbal working memory	*Task requirements*: Participants were instructed to reproduce sequences as accurately as possible.	
Pursuit	*Task description*: The stimulus consisted of a randomly moving target (asterisk) at a constant speed of 10 mm/s.	Precision (mean distance in mm between target and cursor calculated per second and averaged across the 60 s experimental session) of the left hand.
Motor control under continuous adaptation	*Task requirements*: Child was required 'catch' the target as precisely as possible by moving a mouse cursor on top of the asterisk.	
Tracking	*Task description*: The stimulus consisted of an inner and outer circle (radius 7.5 and 8.5 cm, respectively).	Precision (mean distance to midline in mm averaged across 60 equal parts of the circle) of the left hand.

Table 1 (*Continued*)

Name and aim task	Task components	Performance measures
Motor control without continuous adaptation required	*Task requirements* Participants were instructed to trace an invisible midline (radius 8 cm) between the inner and outer circle as quickly and precisely as possible with a mouse cursor with both hands (clockwise with the right hand and counter clockwise with the left hand).	
Tapping	*Task description*: Two conditions: index finger of the non-preferred hand, the index finger of the preferred hand.	Variability (S.D. of intertap intervals in ms) averaged across hands.
Self-generated motor output	*Task requirements*: Participants were required to tap as frequently as possible within a certain time period. Administration took about 3 min.	
Baseline Speed	*Task description*: A fixation cross in the center of a computer screen changed unpredictably into a white square. The time interval between a response and the emergence of the next white square varied randomly between 500 and 2500 ms.	Variability (S.D. of reaction times in ms) of responses averaged across hands.
Motor output as response to an external cue	*Task requirements*: Participants were required to press a key when the white square emerged, first practised and executed with the index finger of the non-preferred hand, thereafter with the index finger of the preferred hand.	
Motor Timing	*Task description*: The start of a 1-s interval was announced by a tone (80 db, 50 ms).	Variability (S.D. of productions in ms).
Timing of motor output	*Task requirements*: Subjects were instructed to produce as accurately as possible the 1-s interval. After the subject's response, visual feedback was given, indicating whether the response was correct, too short or too long. A response was regarded as correct, if it fell between the lower and upper boundary set by a dynamic tracking algorithm.	

sibling correlations (sibling A − sibling B, sibling A − sibling C, and sibling B − sibling C); a family of four children allows calculation of six sibling correlations (sibling A − sibling B, sibling A − sibling C, sibling A − sibling D, sibling B − sibling C, sibling B − sibling D, and sibling C − sibling D). Correlations were calculated using S.A.G.E. (Statistical Analysis for Genetic Epidemiology version 5.3.1). Significance levels were corrected for the non-independency of sib-pairs (i.e. more than one sib-pair per family contributing to the analyses, if the family consisted of three or four children). Correction for multiple comparisons according to the False Discovery Rate (FDR) controlling procedure was applied to the analyses with a q-value setting of 0.05 (Benjamini & Hochberg, 1995). The following three terms were used: correlation (referring to a correlation between two variables in the same subject), sibling correlation (referring to a correlation between siblings for the same variable), and sibling cross-correlation (referring to a correlation between siblings for two different variables).

First, to establish whether the neuropsychological measures were more strongly familially determined than the ADHD composite, sibling correlations were calculated to estimate the degree of familiality of all measures. Sibling correlations for the neuropsychological measures were compared with the sibling correlation for the ADHD composite using dependent correlations one-sided t-tests (Chen & Popovich, 2002). Second, to analyze whether shared familial influences affected both the neuropsychological measures and the ADHD composite, we calculated sibling cross-correlations (neuropsychology of a child with ADHD composite of his/her siblings). An estimation of the percentage of shared genetic factors between the neuropsychological measures and the ADHD composite was performed. Even though it is not possible to estimate reliably heritability coefficients in a sibling-design, since siblings share both half of the additive genetic factors as well as their shared environment, the assumption might be made that sibling

similarity is due to additive genetic factors (Andreou et al., 2007), because virtually all twin studies on ADHD have indicated that shared environment does not seem to influence ADHD (Waldman & Gizer, 2006; Waldman & Rhee, 2002). Heritability coefficients were calculated by multiplying the sibling cross-correlation by two and dividing this score by the correlation between the neuropsychological measure and the ADHD composite, as has been done previously (Andreou et al., 2007). Third, in order to investigate whether a neuropsychological composite would provide a better endophenotype instrument than individual task measures, a principal component analysis was run on the ten neuropsychological measures. The composite was subjected to the same analyses as described above and the sibling correlations and sibling cross-correlations were compared between the composite and each neuropsychological measure by means of dependent correlations one-sided *t*-tests (Chen & Popovich, 2002).

3. Results

3.1. Familiality of neuropsychological measures and ADHD composite

Siblings resembled each other significantly on all neuropsychological measures (with sibling correlations ranging from .14 to .31, Table 2) and on the ADHD composite ($r = .11$, Table 2). The sibling correlations for all neuropsychological measures were at least as large as the sibling correlation for the ADHD composite. Six of ten neuropsychological measures revealed sibling correlations that were even significantly larger than the sibling correlation for the ADHD composite (Table 2), suggesting these neuropsychological measures showed stronger patterns of familiality (and thus heritability) than the ADHD composite.

3.2. Shared familial (and heritable) influences on the neuropsychological measures and ADHD composite

In order for neuropsychological measures to be useful for molecular genetic research, the measures should relate to similar familial (and heritable) influences as the ADHD composite. If this is the case, the neuropsychological measures of a child should correlate with the ADHD composite of his/her siblings (i.e. sibling cross-correlation). Six of ten neuropsychological measures showed significant sibling cross-correlations, suggesting similar familial factors influenced neuropsychological task performance and the ADHD composite (Table 3). On the assumption that shared familiality is entirely due to additive genetic factors (since shared environmental factors do not seem to influence ADHD [Andreou et al., 2007]) heritability estimates were made of the six neuropsychological measures that showed familial overlap with the ADHD composite (2 × sibling cross-correlation/correlation task measure with ADHD composite,

Table 2
Sibling correlations for the neuropsychological measures compared to sibling correlation for the ADHD composite

	Sibling correlation		Compared with sibling correlation for ADHD composite	
	r (95% CI)	*p*	t_{537}	*p*
Cognitive measures				
Stop Task (SSRT)	**.22 (.12–.33)**	**<.001**	**1.98**	**.02**
Shifting Attentional Set (% errors)	**.23 (.14–.32)**	**<.001**	**2.08**	**.02**
Time Reproduction (absolute deviation)	**.25 (.16–.34)**	**<.001**	**2.53**	**.006**
Visuo-Spatial Sequencing (*N* correct targets)	**.20 (.11–.29)**	**<.001**	1.58	.06
Digit Span (backwards)	**.18 (.09–.27)**	**<.001**	1.21	.11
Motor measures				
Pursuit (precision)	**.28 (.19–.37)**	**<.001**	**2.98**	**.002**
Tracking (precision)	**.22 (.13–.31)**	**<.001**	**1.95**	**.03**
Tapping (variability)	**.18 (.09–.27)**	**<.001**	1.22	.11
Baseline Speed (variability)	**.14 (.05–.23)**	**.002**	0.51	.31
Motor Timing (variability)	**.31 (.22–.40)**	**<.001**	**3.73**	**<.001**

Note: SSRT, Stop Signal Reaction Time. Sibling correlation for the ADHD composite: $r = .11$ (.02–.20), $p = .02$. Findings in bold are significant after correction for multiple comparisons.

Table 3
Sibling cross-correlations indicating common familial influences on neuropsychological measures and ADHD composite

	Sibling cross-correlation		Correlation with ADHD composite		% heritability
	r (95% CI)	*p*	*r* (95% CI)	*p*	
Cognitive measures					
Stop Task (SSRT)	**.12 (.05–.20)**	**.002**	**.24 (.17–.31)**	**<.001**	(.12 × 2)/.24 = 100%
Shifting Attentional Set (% errors)	.05 (−.02–.12)	.16	**.20 (.13–.27)**	**<.001**	
Time Reproduction (absolute deviation)	**.12 (.05–.19)**	**.001**	**.31 (.25–.37)**	**<.001**	(.12 × 2)/.31 = 77%
Visuo-Spatial Sequencing (*N* correct targets)	**.08 (.01–.15)**	**.03**	**.26 (.20–.33)**	**<.001**	(.08 × 2)/.26 = 62%
Digit Span (backwards)	.06 (−.01–.13)	.08	**.21 (.14–.28)**	**<.001**	
Motor measures					
Pursuit (precision)	.04 (−.03–.11)	.23	**.15 (.08–.22)**	**<.001**	
Tracking (precision)	**.09 (.02–.16)**	**.01**	**.27 (.21–.33)**	**<.001**	(.09 × 2)/.27 = 67%
Tapping (variability)	**.08 (.02–.15)**	**.02**	.06 (−.01–.13)	.07	(.08 × 2)/.06 = >100%
Baseline Speed (variability)	.06 (−.01–.12)	.09	**.13 (.06–.20)**	**<.001**	
Motor Timing (variability)	**.14 (.07–.21)**	**<.001**	**.28 (.22–.34)**	**<.001**	(.14 × 2)/.28 = 100%

Note: SSRT, Stop Signal Reaction Time. Heritability was calculated using the formula: (sibling cross-correlation × 2)/correlation task measure with ADHD composite. Heritability estimates are based on the assumption that sibling resemblance is entirely due to genetic factors (and not shared environmental factors). Findings in bold are significant after correction for multiple comparisons.

Table 3). Approximately 62–100% of the variance of the six neuropsychological measures was related to heritable factors that also affected the ADHD composite.

3.3. Results of the neuropsychological composite

Neuropsychological measures are not free of measurement error. This can negatively influence the results of familiality and heritability. Combining the measures into a composite score might reduce measurement error. A principal component analysis was run on the variance–covariance matrix to combine all ten neuropsychological measures. One major composite emerged explaining 47% of the variance. The neuropsychological composite correlated significantly between siblings ($r = .34$ [.23–.44], $p < .001$), which was more strongly than the sibling correlation for the ADHD composite ($t = 4.33$, $p < .001$), suggesting the neuropsychological composite to be more familial (and possibly heritable) then the ADHD composite. The neuropsychological composite also showed a significant sibling cross-correlation with the ADHD composite ($r = .14$ [.06–.22], $p = .001$), indicating similar familial factors influenced the neuropsychological composite and the ADHD composite. If these shared familial factors were complete reflections of additive genetic factors, than 82% (i.e. .14 × 2/.34 = 82) of the neuropsychological composite reflected heritable factors that also influenced ADHD.

In order to investigate whether the composite was more suitable as endophenotypic instrument than the individual task measures, the sibling correlations and sibling cross-correlations were compared between the composite and each neuropsychological measure. The sibling correlation using the composite was significantly larger than the sibling correlations for eight of ten single neuropsychological measures (*t*-values between 1.85 and 3.96 with *p*-values between .03 and <.001). Only the sibling correlations for Pursuit and Motor Timing were as large as the sibling correlation for the composite ($t = 1.24$, $p = .11$ and $t = 0.64$, $p = .26$, respectively). However, the composite did not have a significant larger sibling cross-correlation with the ADHD composite than most individual task measures (*t*-values between 0.00 and 1.46 with *p*-values between .07 and .50), except for Shifting Attentional Set ($t = 1.70$, $p = .04$) and Pursuit ($t = 1.95$, $p = .03$). These findings suggest that a neuropsychological composite is overall more strongly familial determined than most individual task measures, though the shared familial overlap with ADHD appears roughly comparable to that of most individual task measures.

4. Discussion

This study extends previous findings on the utility of neuropsychological measures as candidate endophenotypes for ADHD (Rommelse, Altink, De Sonneville, et al., 2007; Rommelse, Altink, Oosterlaan, Beem, et al., 2008; Rommelse,

Altink, Oosterlaan, Buschgens, et al., 2007; Rommelse, Oosterlaan, et al., 2007; Rommelse, Altink, Oosterlaan, Buschgens, et al., 2008) by (1) examining whether neuropsychological measures show a stronger degree of familiality than an ADHD composite, (2) investigating whether similar familial (and heritable) factors influence neuropsychological measures and an ADHD composite, and (3) testing whether a composite of neuropsychological measures is a more powerful endophenotypic instrument than individual task measures.

Results indicated that all neuropsychological measures correlated at least as strongly between siblings as an ADHD composite, with six of ten measures correlating even more strongly between siblings than the ADHD composite. These findings suggest that most neuropsychological tasks, specifically the Stop Task, Shifting Attentional Set, Time Reproduction (cognitive tasks) and Pursuit, Tracking, Motor Timing (motor tasks), may be more heritable than the ADHD phenotype itself. This concurs with the concept of (neuropsychological) endophenotypes as being more strongly related to genetic factors (disease genes) than the phenotype (Almasy & Blangero, 2001; Castellanos & Tannock, 2002; Doyle, Faraone, et al., 2005; Gottesman & Gould, 2003; Rommelse, Oosterlaan, et al., 2007; Skuse, 2001; Waldman, 2005) and underlines the usefulness of certain neuropsychological measures for detecting underlying familially related dysfunctions. However, some neuropsychological tasks (Visuo-Spatial Sequencing, Digit Span [cognitive tasks] and Tapping and Baseline Speed [motor tasks]) showed comparable degrees of familiality as the ADHD composite. This may imply that these neuropsychological measures are equally strongly linked to disease genes as the ADHD phenotype and do not form a more powerful instrument to detect these disease genes (Braff & Freedman, 2002). However, they may still prove useful in ADHD molecular research, when they are linked to a smaller number of genes than the ADHD phenotype (Doyle, Willcutt et al., 2005) and if they facilitate the forming of more homogeneous subgroups of patients having a common neuropsychological deficit.

Further support for the utility of neuropsychological measures was found when the sibling cross-correlations were analyzed: six of ten neuropsychological tasks (Stop Task, Time Reproduction, Visuo-Spatial Sequencing [cognitive tasks] and Tracking, Tapping, Pursuit [motor tasks]) measured in a child were positively and significantly related to the degree of ADHD in his/her siblings. This indicates that similar familial influences have an effect on these neuropsychological measures and the ADHD composite (Andreou et al., 2007; Kuntsi & Stevenson, 2001). Therefore, these neuropsychological measures may facilitate understanding the mode of action of certain risk genes in ADHD: linking a neuropsychological measure to specific genes, may give insight into how these genes act on the ADHD phenotype (Kuntsi & Stevenson, 2001). However, since it is not possible to separate reliably heritable factors from shared environmental factors within a non-twin design, the sibling cross-correlations may also stem from shared environmental influences instead of heritability (Andreou et al., 2007). Still, since the vast majority of twin studies in ADHD have indicated that shared environment does not seem to play a significant role in determining the degree of ADHD (Faraone & Doyle, 2001; Van't Ent et al., 2007; Waldman & Rhee, 2002), it has been suggested that resemblance between siblings may be entirely due to genetic factors (Andreou et al., 2007). Calculations based on this assumption showed that six of ten neuropsychological measures overlapped genetically with the ADHD composite between 62 and 100%, making these measures potentially useful for future molecular genetic research in ADHD. The other four neuropsychological measures did not show significant sibling cross-correlations, despite findings of significant sibling correlations. This may suggest that, even though these neuropsychological measures are familial, their familial overlap with ADHD is too weak to be useful as instruments in molecular genetic research of ADHD.

In order to investigate whether a composite of the neuropsychological measures led to an improvement in results, a principal component analysis was run to combine all measures. This neuropsychological composite appeared to be more strongly correlated between siblings (.34) than eight of ten individual measures (between .14 and .31), suggesting a neuropsychological composite is overall more strongly familially determined than most individual task measures. However, most sibling cross-correlations (eight of ten) were comparably large between the composite and individual task measures, signalling the shared familial overlap of the composite with the ADHD composite appears roughly comparable to that of most individual task measures. These findings suggest that a neuropsychological composite may prove a more powerful endophenotypical instrument than some individual task measures, possibly because they entail less error variance than individual measures (Rushton, Brainerd, & Pressley, 1983), though their power is equivalent to some other individual task measures.

Almost all correlations calculated were small and some were of medium size (Cohen, 1988). This suggests that the familial effects on the neuropsychological measures are modest. However, we did not expect to find large correlations for several reasons. First, it is likely that multiple genes relate to the ADHD phenotype (polygenetically determined disorder), each having a small effect (Faraone & Biederman, 1998) with no single gene being necessary or sufficient

to cause ADHD. It was expected that sibling correlations and sibling cross-correlations for familially determined neuropsychological deficits would also be small. Second, previous research on neuropsychological functioning in patients with ADHD has shown that a substantial proportion of patients does not perform abnormally on neuropsychological measures (Nigg, Willcutt, Doyle, & Sonuga-Barke, 2005), resulting in an overall small association between neuropsychological deficits and ADHD. Nevertheless, in the task battery we administered, six of ten measures and the composite score showed a higher degree of familiality (and heritability) than the ADHD composite, lending support to the utility of these measures in heritability research of ADHD.

Sibling correlations for the ADHD composite (.11) were lower than one would expect based on previously reported DZ twin correlations on the same ADHD scale (Conners') (around −.01 to .47) (Hudziak, Derks, Althoff, Rettew, & Boomsma, 2005; Kuntsi, Gayán, & Stevenson, 2000; Martin, Scourfield, & McGuffin, 2002). There may be several explanations for this. First, in this study, the sibling correlation was calculated based on the raw scores (not matched for age and gender) to allow direct comparison with 'raw' neuropsychological scores (of which no age and gender scaled scores were available). When the scaled Conners' score was used, the sibling correlation became larger (.17), yet still somewhat lower than previously reported DZ correlations. An alternative explanation might be that the low correlation was due to the nature of the selected sample studied here (ADHD-families and control-families) in contrast to other (mostly twin) studies which employed population-based samples. This might have resulted in a restricted range in ratings and hence, to lower correlations. A third explanation might be that DZ twins are not directly comparable to siblings, since DZ twin correlations tend to be larger than non-twin sibling correlations on a range of cognitive and behavioural measures (Koeppen-Schomerus, Spinath, & Plomin, 2003). This might be related to the fact that DZ-twins are of the same age, whereas siblings are not. It is feasible, therefore, that DZ twins are perceived as more alike than siblings resulting in higher DZ correlations than sibling correlations. In addition to this, being dissimilar in age, siblings will probably be more often rated by different teachers than DZ twins. Correlations between ratings of different observers are generally lower than correlations between ratings of the same observer (Dale, Harlaar, & Plomin, 2005).

4.1. Limitations

The ADHD composite was obtained by averaging ADHD ratings across parents and teachers to reduce the number of correlations that needed to be calculated and to obtain a more stable and reliable phenotypic measure of ADHD (Conners et al., 2001; Schwarz, Barton-Henry, & Pruzinsky, 1985). However, this may have masked rater-specificity of results. This did not appear to be the case, because the correlations between the neuropsychological measures and ADHD ratings were very similar for ratings made by the parents and teachers and because none of the sibling correlations and sibling cross-correlations between the neuropsychological measures and parental ADHD ratings, on the one hand, and between the neuropsychological measures and teachers ADHD ratings, on the other hand, differed significantly from each other. This is in line with a study showing comparable latent classes underlie Conners' ratings of parents and teachers (Althoff et al., 2006). However, overall correlations appeared somewhat larger (though not significantly so) when parental ratings of ADHD were used compared to teacher ratings, which may be related to the fact that siblings are dissimilar in age and, consequently, were often rated by different teachers, which may have introduced extra error variance in the teacher ratings (Dale et al., 2005). A second limitation may be that not all measures were obtained from all participants: the PACS interview was only administered for affected children, but not for non-affected siblings or controls. This might have resulted in undetected ADHD cases in the non-affected sibling and control group. However, we do not believe this to be the case, because all siblings were thoroughly screened and if they scored clinically at any of the screening questionnaires, the PACS interview was administered. In addition, it is highly unlikely that a child will score normal on all rating scales, but abnormal on a clinical interview. But even if that would be the case, in this study we used quantitative measures of ADHD symptomatology and not a categorical diagnostic variable. Thus, non-affected siblings scoring slightly above the average of control children were also recorded in that manner. Lastly, the presence of comorbid disorders may have been of influence to the results. However, we screened for multiple comorbid problems (oppositional behaviours, autism, anxiety, reading and motor coordination problems) and have examined the relationship between these measures and the neuropsychological measures (unpublished data). Even when covarying for all of these comorbidities, the relationship between ADHD measures and the neuropsychological measures remained significant. Therefore, we do not believe the presence of comorbid disorders has substantially influenced the results in the present manuscript.

4.2. Conclusions

The current study finds support for the hypothesis that neuropsychological measures may aid in the discovery of the genetic underpinnings of ADHD. Results indicated that all ten neuropsychological measures correlated significantly between siblings, indicating familiality of neuropsychological tasks. Six of ten measures appeared more strongly familial than the ADHD composite, suggesting these measures may be more heritable than ADHD. Significant sibling cross-correlations suggested that six of ten neuropsychological measures were related to similar familial (and heritable) factors as the ADHD composite, suggesting these neuropsychological measures to be useful in heritability research in ADHD. An aggregated neuropsychological composite appeared to be the most powerful, since it correlated more strongly between siblings than most individual task measures. These findings suggest heritability research in ADHD will probably be facilitated by including neuropsychological measurements.

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