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Motor control in children with ADHD and non-affected siblings: deficits most pronounced using the left hand

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Background: Attention-deficit/hyperactivity disorder (ADHD) is strongly influenced by heritability. Identifying heritable vulnerability traits (endophenotypes) that mark a relatively high risk of developing the disorder can contribute to the identification of risk genes. A fruitful area for the search for such endophenotypes may be motor control in children with ADHD, since the disorder is frequently accompanied by motor problems. **Method:** The current study used a large sample of 350 children with ADHD, 195 non-affected siblings and 271 normal controls aged 5–19 years. Children were administered two computerised motor control tasks in which they had to trace a path between two circles (Tracking task) and follow a randomly moving target (Pursuit task). Both tasks were performed with both the right and the left hand. **Results:** Children with ADHD were less precise and stable than controls. Non-affected siblings also deviated from controls, but only on the Tracking task. Group differences were modulated by the use of the right versus the left hand: no group differences emerged when the right hand was used, yet group differences did emerge when the left hand was used. Performance on both tasks was significantly familial. **Conclusions:** Imprecision and instability of movements in children with ADHD and in their non-affected siblings as measured by the Tracking task might be suitable endophenotypic candidates: these deficits are familially present in children having ADHD as well as in their non-affected siblings. Motor performance might be best assessed in children using their left hand, because motor control deficits are most pronounced using the left hand. This might relate to right hemispheric brain pathology in children with ADHD (and possibly in their non-affected siblings) that is related to the control of the left hand and/or relate to differential effects of daily life practice on both hands, which may be smaller on the left hand. **Keywords:** ADHD, non-affected sibling, motor control, endophenotype. **Abbreviations:** ANT: Amsterdam Neuropsychological Tasks; IMAGE: International Multicenter ADHD Genes study; SCQ: Social Communications Questionnaire; SDQ: Strengths and Difficulties Questionnaire.

The heritability of attention-deficit/hyperactivity disorder (ADHD) explains on average 73% of the phenotypic variance of the disorder (Faraone et al., 2005; Willcutt, in press). In combination and interaction with environmental risk factors, this causes siblings of an affected child to have a 6 to 8 times higher risk of developing the disorder themselves (Willcutt, in press). The identification of precursors of the disorder, such as susceptibility genes, not only contributes to early identification of children at risk, but also sheds light on the etiology of the disorder. However, the search for genes that are involved in ADHD has been hampered by the heterogeneity of the disorder (Buitelaar, 2005). That is, even though affected individuals qualify for the same diagnosis as established by standard nosological frameworks, such as the fourth edition of the *Diagnostic and Statistical Manual for Mental Disorders* (DSM-IV; American Psychiatric Association [APA], 1994), they may differ widely from one another in the severity and number of symptoms expressed. It is possible, therefore, that the genetic pathways leading to the disorder may be diverse, which adds to the complexity of gene identification.

Reducing this complexity in gene identification is one of the main goals of endophenotypic research. An endophenotype for a particular disorder is conceptualised as a quantitative, heritable, vulnerability trait that is more strongly linked to disease genes for that disorder compared to the phenotypic symptoms of that disorder (Almasy & Blangero, 2001; Castellanos & Tannock, 2002; Gottesman & Gould, 2003; Waldman, 2005). Inheriting multiple vulnerability traits may predispose an individual to developing a disorder. Since first-degree relatives and an affected individual share, on average, 50% of their genes, first-degree relatives will show the same vulnerability trait to some extent, even in the absence of the disorder. Studying endophenotypes in affected individuals and their first-degree relatives may form, therefore, a powerful tool in genetic research.

A fruitful area in the search for ADHD-endophenotypes may be motor functioning. Previous research has shown that many children with ADHD

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experience problems in gross (Carte, Nigg, & Hinshaw, 1996; Piek, Pitcher, & Hay, 1999) and fine motor skills (Korkman & Pesonen, 1994; Marcotte & Stern, 1997; Pitcher, Piek, & Hay, 2003; Whitmont & Clark, 1996) and that these problems are already apparent in preschool children at risk for ADHD (Kalff et al., 2003; Yochman, Ornoy, & Parush, 2006). A substantial number of children with ADHD fulfil the criteria for the Developmental Coordination Disorder (DCD; Gillberg & Rasmussen, 1982; Kadesjö & Gillberg, 1998; Piek et al., 1999; Sergeant, Piek, & Oosterlaan, 2006), a disorder marked by impairment in the development of fine and gross motor coordination (Mandich & Polatajko, 2003). Motor problems might be partly related to abnormalities in structure and/or function of the cerebellum and basal ganglia found in ADHD (Barquin et al., 1998; Castellanos et al., 1996).

It is feasible that the co-occurrence of ADHD and motor problems might be genetic in origin (Gillberg, 2003; Martin, Piek, & Hay, 2006). If this is true, one would expect non-affected siblings of a child with ADHD to experience, to some extent, the same problems in motor functioning as the affected child. This has rarely been investigated and the available findings are inconsistent. Seidman, Biederman, Monuteaux, and Weber (2000) found no difference between non-affected siblings of children with ADHD and control siblings for accuracy on a figure copy test. More recently, however, Slaats-Willemse, De Sonneville, Swaab-Barneveld, and Buitelaar (2005) did find differences between non-affected siblings and controls on a computerised Pursuit task, in which children had to pursue a randomly moving target as precisely as possible. Non-affected siblings appeared to be less precise and more variable in their movements compared to controls, even to the extent that they performed as poorly as their affected siblings. However, non-affected siblings performed normally on a computerised Tracking task, in which they had to trace a path between an inner and an outer circle. Slaats-Willemse et al. (2005) interpreted these intriguing findings in terms of differential demands on higher-order cognitive processing in the two tasks: pursuing a moving target would load more heavily on cognitive processing than tracing a path between two lines (Huijbregts et al., 2003; Slaats-Willemse et al., 2005). They concluded that higher-order controlled motor deficits might be associated with genetic susceptibility to ADHD.

Studies on motor functioning in non-affected siblings of children with ADHD are scarce and results are difficult to compare due to differences in the assessment of motor functioning used in the two available studies (paper and pencil versus computer). Neither of the two studies made a distinction in movement accuracy between the right and left hand, yet this distinction might be valuable, because both hands are unequally practiced in daily life (Annett, Hudson, & Turner, 1974; Peters, 1981), which might influence results.

The current study was aimed at replicating and extending the findings reported by Slaats-Willemse et al. (2005) by using the exact same computerised motor tasks but with a substantially larger sample. In line with the results of Slaats-Willemse et al. (2005), it was hypothesised that children with ADHD would be less precise and stable in their performance on both the Tracking and Pursuit tasks compared to controls, whereas the non-affected siblings would only perform worse on the Pursuit task compared to controls. It was hypothesised that these group differences would be best observed in the performance of the left hand, because this hand is probably less influenced by practice for most children. We also tested whether performance on both tasks would show familial overlap between siblings.

Method

Subjects

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. Within the ADHD-families there were 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. Control-families consisted of 271 children. No additional control sibling could be recruited for 51 control children, because the sibling was either unwilling to participate or because the control-family consisted of only one child.

All children were between the ages of 5 and 19 years 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 children already clinically diagnosed with ADHD and their siblings were similarly screened using the standard procedures of the IMAGE project, described fully elsewhere (Brookes et al., 2006). 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 on the Conners' ADHD-subscales (L, M and N) and scores >90th percentile on

the SDQ-hyperactivity scale were considered as clinical. Concerning all children within a family rated clinically on the Conners' or SDQ completed either by parents or teachers, a semi-structured, standardised, investigator-based interview was administered separately for each child: the Parental Account of Children's Symptoms (PACS; Taylor, 1986). The PACS covers DSM-IV symptoms of ADHD, conduct disorder, oppositional defiant disorder, anxiety, mood, and other internalising disorders. The section on autistic behaviour traits was administered if a clinical score (raw score ≥15) was obtained on the Social Communication Questionnaire (Berument, Rutter, Lord, Pickles, & Bailey, 1999). A standardised 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') on the teacher-rated Conners' ADHD subscales (L, M and N) 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 (L, M and N) as indicated by the teachers on the Conners' questionnaire. For purposes of analysis here, siblings were regarded as non-affected, if they obtained scores in the non-clinical range on both the parent and teacher questionnaires (Conners' N-scale: *T*-score ≤62, SDQ <90th percentile). No PACS interview was administered concerning non-affected siblings.

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 (Conners' N-scale: *T*-score ≤62). Table 1 provides the characteristics of the three groups.

Materials

The Tracking and Pursuit tasks are computerised subtests of the Amsterdam Neuropsychological Tests (ANT; De Sonneville, 1999) and were designed to measure motor control. These tasks have been used in other studies to examine motor control (Buizer, De Sonneville, Van den Heuvel-Eibrink, Njiokiktjien, & Veerman, 2005; Kalff et al., 2003; Koekkoek et al., 2006; Huijbregts et al., 2003; Slaats-Willemse et al., 2005). Both tasks were completed first with the non-preferred hand followed by the preferred hand. Hand preference was ascertained by asking the child with which hand he/she preferred to write/draw. One practice and one experimental session were administered for both hands separately. Children were instructed to place their elbow on the armchair and to lay their wrist on the table. Children were not required to activate any mouse key but only to move the mouse.

Tracking. In this task, an invisible midline (radius 8 cm) had to be traced with a mouse cursor between an outer (radius 8.5 cm) and inner circle (radius 7.5 cm), clockwise with the right hand and counter clockwise with the left hand. Children were instructed to trace the invisible midline as quickly and precisely as possible. The circle was divided in 60 equal parts and for each part the distance (in mm) between the cursor and the invisible midline was calculated automatically by the computer. The mean distance and SD of distances (both in mm) and completion time (in s) were calculated. The average completion time was approximately 20 seconds. Mean distance is referred to as precision, SD of

Table 1 Sample characteristics

	Children with ADHD, $n = 350$		Non-affected siblings, $n = 195$		Normal controls, $n = 271$			
	M	*SD*	*M*	*SD*	*M*	*SD*	$F_{2,800}$	*p*
Age in years	12.0	2.8	11.5	3.6	11.6	3.2	26.7	.06
% Right handed	90.0		89.2		85.5		5.1[a]	.27
% Male	75.4		45.1		40.6		89.2[a]	<.001[b]
Estimated Full Scale IQ	99.1	11.7	103.8	10.9	106.0	10.2	31.7	<.001[b]
Conners' Parent DSM-IV								
Inattentive	69.5	9.8	47.9	7.0	46.5	4.8	808.5	<.001[b]
Hyperactive-Impulsive	75.5	12.0	49.0	6.9	47.3	5.1	907.7	<.001[b]
Total	74.2	10.4	48.2	6.8	46.5	4.5	1101.6	<.001[b]
Conners' Teacher DSM-IV								
Inattentive	64.6	9.6	48.3	6.0	46.4	4.6	547.9	<.001[b,c]
Hyperactive-Impulsive	68.0	12.0	48.3	6.5	47.2	5.0	508.6	<.001[b]
Total	67.8	10.7	48.3	5.8	46.4	4.5	662.1	<.001[b,c]
ADHD Diagnosis								
Inattentive	28		–		–			
Hyperactive-Impulsive	20		–		–			
Combined	302		–		–			

Note. ADHD = Attention-deficit/hyperactivity disorder; DSM-IV = *Diagnostic and Statistical Manual for Mental Disorders* (4th edition).

[a] χ^2.

[b]The ADHD group differs significantly from the non-affected siblings group and the control group ($p < .05$).

[c]The non-affected siblings group differs significantly from the control group ($p < .05$).

the distances is referred to as stability and completion time is referred to as speed.

Pursuit. This task required the child to 'catch' a randomly moving target (asterisk) by moving a mouse cursor on top of the asterisk. The cursor moved at a constant speed of 10 mm/s. Children were instructed to follow the randomly moving target as precisely as possible. The task was required to be executed for 60 s for both hands separately. The distance between the cursor and the moving target (in mm) was calculated automatically per second. The mean distance (precision) and SD of the distances (stability) were calculated (both in mm).

Intelligence. Full-scale IQ was estimated by four subtests of the WISC-III (Wechsler, 2002) or WAIS-III (Wechsler, 2000) (depending on the participants' age): Vocabulary, Similarities, Block Design, and Picture Completion. These subtests are known to correlate between .90 and .95 with the Full-scale IQ (Groth-Marnat, 1997).

Procedure

The tasks described in this study were part of a broader neuropsychological assessment battery used in the Dutch part of the IMAGE study (Rommelse, Oosterlaan, Buitelaar, Faraone, & Sergeant, 2007), consisting of cognitive, timing and motor tasks that were presented in different order (Latin square). Administration of the whole battery (including breaks) took three to four hours. Testing of children with ADHD and their siblings took place at the Vrije Universiteit Amsterdam or at the Radboud University Nijmegen Medical Centre and was conducted simultaneously for all children within a family. Psychostimulants were discontinued for at least 48 hours 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.

Data analyses

The percentage of missing data was less than 5% for each of the dependent variables. Missing data were replaced by means of expectation maximisation (Tabachnick & Fidell, 2001). Alpha was set at .05. Variables were normalised by applying a natural log transformation.

Gender and age both can have an effect on motor functioning (Thomas & French, 1985). Therefore, their effects were studied, but only within the control group since group and gender were confounded (most children with ADHD were boys). A mixed model was used with gender as between-subject factor, age as a covariate, and family as random effect to account for within-family correlation. Precision and stability were separately analysed. Analyses were simultaneously conducted for the Tracking and Pursuit tasks. Gender did not affect precision or stability ($F(1, 220.3) = .74$, $p = .39$ and $F(1, 203.9) = 2.13$, $p = .15$, respectively) and was, therefore, omitted from further analyses. Age did influence precision and stability ($F(1, 257.5) = 218.39$, $p < .001$ and $F(1, 271.2) = 109.14$, $p < .001$, respectively). Overall, older children performed more precisely and stably than younger children. The group by age interaction was not significant for precision and stability ($F(2, 575.2) = 2.06$, $p = .13$ and $F(2, 586.3) = 1.89$, $p = .15$, respectively), indicating that the effect of age was comparable across groups. Therefore, only the main effect of age was included in the model.

To address the main questions of the study, a mixed model was used to test whether (1) children with ADHD and their non-affected siblings would be less precise and stable in their movements than normal controls and whether (2) these group differences would be larger in the performance of the left hand than the right hand and whether (3) motor performance would show familiality within families. Group was used as a fixed factor (3 groups: children with ADHD, non-affected siblings and controls), hand as repeated measure (right and left hand), age as a covariate and family as random effect. The group by hand interaction was implemented in the model to test whether group differences were comparable across hands. Pairwise comparisons were used to examine group differences. Analyses were separately conducted for the Tracking and Pursuit tasks. For both the Tracking and the Pursuit tasks, precision and stability were highly correlated (Tracking: $r = .95$ [right hand], $r = .95$ [left hand]; Pursuit: $r = .89$ [right hand], $r = .94$ [left hand]) and were, therefore, analysed simultaneously. Completion time of the Tracking task was analysed as an auxiliary dependent variable to test whether groups differed in speed with which they completed the Tracking task.

Results

Tracking task

Raw data is presented in Table 2. A mixed model with group as main effect, hand as repeated measure, the group by hand interaction, age as a covariate and family as random effect indicated a significant effect of group on precision and stability of movement ($F(2, 384.3) = 5.14$, $p = .006$). However, the group by hand interaction was significant as well ($F(2, 816.0) = 5.61$, $p = .004$), indicating that group differences should be interpreted separately per hand. Pairwise comparisons indicated that using the right hand, children with ADHD and their non-affected siblings did not differ from controls ($p = .09$ and $p = .28$, respectively) or from each other ($p = .61$). Using the left hand, however, both children with ADHD and their non-affected siblings were less precise and stable than controls ($p < .001$ and $p = .03$, respectively). Children with ADHD were less precise and stable than their non-affected siblings ($p = .04$).

A mixed model with group as main effect, hand as repeated measure, the group by hand interaction, age as a covariate and family as random effect indicated a significant effect of group on speed ($F(2, 410.8) = 10.30$, $p < .001$). The group by hand interaction was, however, not significant ($F(2, 816.0 =$

Table 2 Means and standard deviations of the untransformed task measures

	Children with ADHD $n = 350$		Non-affected siblings $n = 195$		Normal controls $n = 271$	
	M	*SD*	*M*	*SD*	*M*	*SD*
Tracking task						
Precision in mm						
Right hand	1.9	1.6	1.8	1.5	1.6	1.6
Left hand	2.8	2.2	2.5	1.8	2.1	1.9
Stability in mm						
Right hand	1.4	1.0	1.4	.8	1.3	1.0
Left hand	2.1	1.4	1.9	1.1	1.7	1.3
Speed in seconds						
Right hand	15.4	7.3	17.3	8.1	18.9	9.6
Left hand	19.4	8.4	20.6	9.7	23.2	10.7
Pursuit Task						
Precision in mm						
Right hand	4.0	4.1	4.1	3.4	3.9	2.0
Left hand	6.1	4.7	6.0	4.1	5.6	3.9
Stability in mm						
Right hand	2.6	3.1	2.6	2.7	2.6	2.2
Left hand	4.0	3.3	3.9	3.7	3.6	3.1

Note. ADHD = Attention-Deficit/Hyperactivity Disorder.

2.74, $p = .07$), indicating that group differences were present regardless of the hand that was used to perform the task. Overall, children with ADHD completed the task faster than controls ($p < .001$) and their non-affected siblings ($p = .02$). Non-affected siblings were as fast as controls ($p = .07$).

Since children with ADHD took less time to complete the Tracking task compared to controls and non-affected siblings, the analyses on precision and stability were repeated with speed as a second covariate. When speed was taken into account, group differences remained non-significant for the performance of the right hand ($F(2, 398.3) = .39$, $p = .68$) and significant for the performance of the left hand ($F(2, 779.5) = 3.32$, $p = .04$). Group contrasts for performance of the left hand were somewhat attenuated: children with ADHD still performed less precisely and stably than controls ($p = .01$). Non-affected siblings formed an intermediate group, since they did not differ from their affected siblings or controls ($p = .12$ and $p = .47$, respectively). This suggested that the imprecision and instability in children with ADHD and their non-affected siblings when performing with their left hand could not be explained by differences in speed.

Table 3 Test of the significance of covariances between siblings

Dependent measure	EC (95%CI)	Wald *Z*	*p*
Tracking task			
Right hand			
Precision	.01 (.01–.04)	2.19	.03
Stability	.01 (.00–.02)	2.43	.02
Speed	.02 (.01–.08)	1.58	.12
Left hand			
Precision	.03 (.01–.05)	3.13	.002
Stability	.01 (.00–.03)	2.26	.02
Speed	.04 (.02–.06)	3.75	<.001
Pursuit task			
Right hand			
Precision	.01 (.00–.02)	2.02	.04
Stability	.02 (.01–.04)	2.51	.01
Left hand			
Precision	.03 (.02–.04)	4.57	<.001
Stability	.05 (.03–.07)	5.67	<.001

Note. EC = estimate of covariance; CI = confidence interval.

Siblings resembled each other in their precision, stability and speed on the Tracking task, except for speed of the right hand (Table 3). Figure 1 illustrates the precision, stability and speed of the performance of both hands separately for the three groups.

Pursuit task

A mixed model with group, hand, the group by hand interaction, age as a covariate and family as random

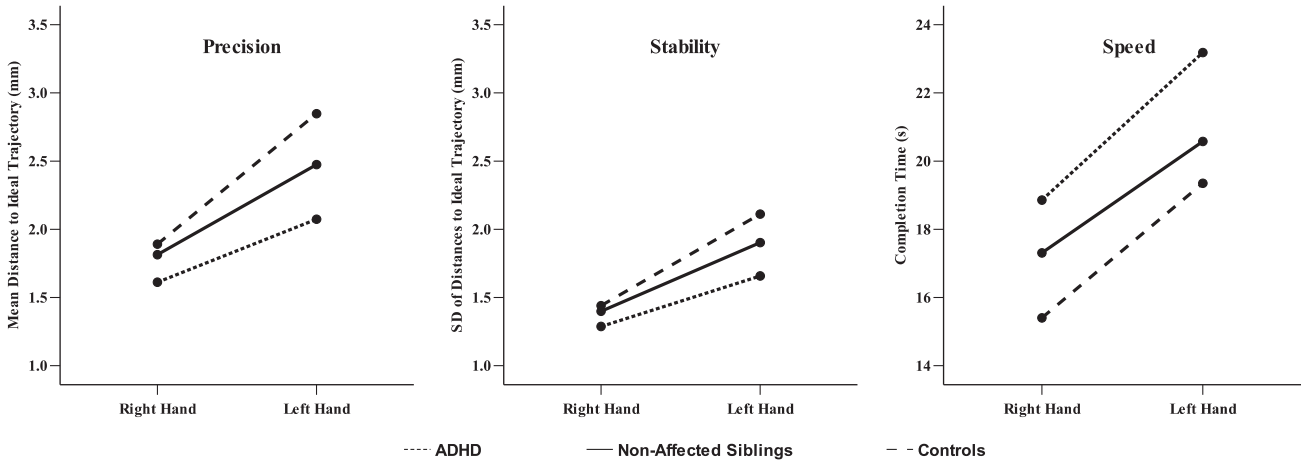

Figure 1 Precision, stability and speed of movement with the right and left hand on the tracking task in children with ADHD, non-affected siblings and controls

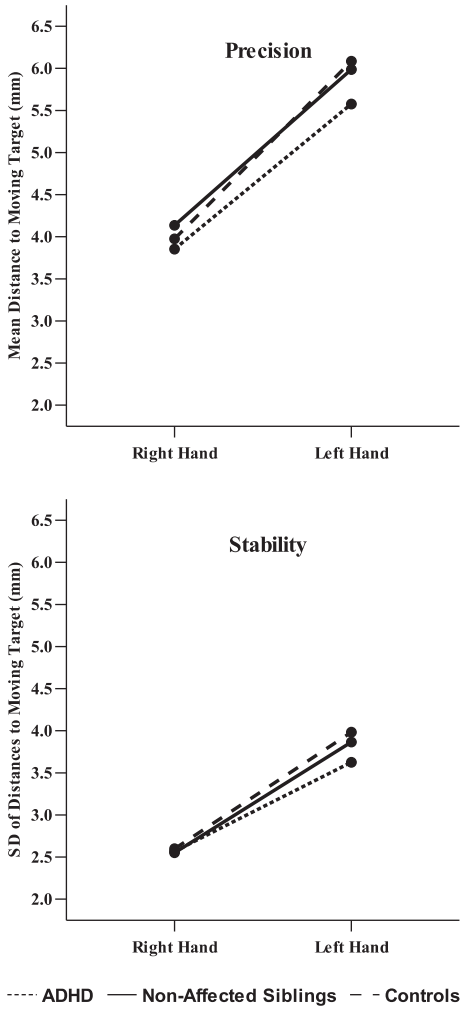

Figure 2 Precision and stability of movement with the right and left hand on the pursuit task in children with ADHD, non-affected siblings and controls

effect indicated that group differed in precision and stability of movement ($F(2, 413.6) = 3.46$, $p = .03$). The group by hand interaction was also significant, however, suggesting that the effect of group should be interpreted separately for each hand ($F(2, 816.0) = 4.42$, $p = .01$). Pairwise comparisons indicated that using the right hand, children with ADHD and their non-affected siblings did not differ from controls ($p = .83$ and $p = .28$) or each other ($p = .34$). However, using the left hand, children with ADHD performed less precisely and stably than controls ($p < .001$) and their non-affected siblings ($p = .03$). Non-affected siblings did not differ from controls ($p = .21$). Furthermore, precision and stability on the Pursuit task were familial (Table 3). The results for the Pursuit task are presented in Figure 2.

Discussion

Problems in motor coordination are often associated with ADHD (Carte et al., 1996; Gillberg & Rasmussen, 1982; Kadesjö & Gillberg, 1998; Korkman & Pesonen, 1994; Marcotte & Stern, 1997; Piek et al., 1999; Pitcher et al., 2003; Sergeant et al., 2006; Whitmont & Clark, 1996) and may be put forward as a heritable, vulnerability trait (endophenotype) for the disorder. The current study attempted to replicate previous findings suggesting motor control problems in children with ADHD and their non-affected siblings (Slaats-Willemse et al., 2005).

Overall, children with ADHD were less precise and stable in their movements than controls. This is in line with the majority of studies reporting on motor problems (Korkman & Pesonen, 1994; Marcotte & Stern, 1997; Pitcher et al., 2003; Slaats-Willemse et al., 2005; Whitmont & Clark, 1996) and spatial inconsistency (Aase, Meyer, & Sagvolden, 2006; Aase & Sagvolden, 2006) in children with ADHD. The findings of comparable problems in non-affected siblings on the Tracking task are interesting. This might imply that problems in precision and stability of movement picked up by the Tracking task are related to a familial risk for developing ADHD. This was further underlined by the significant resemblance in motor performance between siblings. This suggests that the measures were familial, and also, possibly heritable. The findings of motor control problems in children with ADHD as well as in their non-affected siblings might be useful for genetic research into ADHD and more specifically into the comorbidity of ADHD with motor coordination problems, such as DCD, with which ADHD shares a common genetic basis (Martin et al., 2006). Non-affected siblings performed normally, however, on the Pursuit task. This might contradict the presence of motor control problems in non-affected siblings, although this may also be explained by an insensitivity of the Pursuit task to detect problems related to motor functioning.

The effect of group on motor performance was unequal for the right and left hand: group differences were non-significant for the right hand as opposed to the left hand. The reason for the discrepant findings for the right and left hand might be attributed to brain pathology that is specifically related to the control of coordination of the left hand and/or the discrepancy in practice of both hands. With respect to the first explanation, ADHD has been hypothesised as being a predominantly 'right hemispheric disorder' (Sandson, Bachna, & Morin, 2000; Stefanatos & Wasserstein, 2001) and the reported volume reductions of the cerebellum seem to be somewhat more pronounced in the left cerebellar hemisphere (Castellanos et al., 1996). Furthermore, the lateralised readiness potential (LRP), considered to reflect motor activation (Masaki, Wild-Wall, Sangals, & Sommer, 2004), appears to be weaker for the left-handed responses in ADHD (Steger, Imhof, Steinhausen, & Brandeis, 2000). This, in sum, may lead to more profound motor control problems in the left hand as compared to the right hand. Considering the second explanation, for the majority of children, the

right hand has greater utilisation in performing certain movements (Annett et al., 1974; Peters, 1981) and is predominantly used when handling a computer mouse. Practice, in turn, can lead to performance gains (Annett et al., 1974; Peters, 1981), which might mask subtle motor control deficits in the right hand. This raises the possibility that practice effects attenuate group differences for the right hand. Nevertheless, the performance of both the right and left hands showed significant resemblance between siblings, which suggests that both are in theory useful for endophenotypic research.

Compared to the findings reported by Slaats-Willemse et al. (2005) on children with ADHD, we reported similar findings for imprecision and instability of movements, yet discrepant findings for speed of movement. Children with ADHD performed significantly faster than their non-affected siblings and controls, which was not reported by Slaats-Willemse et al. (2005). When speed was entered as a covariate, group differences remained. This indicates that the imprecision and instability in children with ADHD cannot be explained by the higher speed with which they completed the Tracking task. Therefore, the findings of imprecision and instability of movements in children with ADHD reported by Slaats-Willemse et al. (2005) seemed to be replicated by us.

Our findings were, however, discrepant with regard to the performance of non-affected siblings previously reported by Slaats-Willemse et al. (2005). They reported non-affected siblings to be less precise and stable on the Pursuit task, yet not on the Tracking task. This finding was interpreted as suggestive of motor flexibility problems as a marker for genetic susceptibility to ADHD. However, we found the opposite pattern: non-affected siblings performed worse than controls on the Tracking task, but not on the Pursuit task. The discrepancy in findings between the current study and that of Slaats-Willemse et al. (2005) could not be explained by differences in the analytical approach, because when we conducted the same analyses as described by Slaats-Willemse et al. (2005) we still found no differences between non-affected siblings and controls on the pursuit task.

Some limitations of this study should be noted. Although it is possible that practice effects attenuated group differences for the right hand, this explanation has not been studied. Future research should clarify whether practice of motor control can indeed attenuate group differences by systematically studying the effects of prolonged practice on motor skills. Furthermore, we used computerised tasks to measure motor control. These tasks are not properly validated as motor tasks and because no additional, validated motor tasks were used, it remains uncertain what aspects of motor coordination are actually assessed by these tasks. However, the tasks do seem to detect some aspects of motor problems associated with ADHD, because both here and previously (Slaats-Willemse et al., 2005), children with ADHD were less precise and stable in their movements.

It may be concluded that imprecision and instability of movements in children with ADHD and in their non-affected siblings as measured by the Tracking task might be suitable endophenotypic candidates, since these deficits are present in children having ADHD as well as in their non-affected siblings genetically at risk. Motor control might best be studied in children using their left hand to complete the task, because this enhances group differences. This might relate to right hemispheric brain pathology in children with ADHD (and possibly in their non-affected siblings) that is related to the control of the left hand and/or relate to differential effects of daily life practice on both hands, which might be smaller on the left hand.

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References

Aase, H., Meyer, A., & Sagvolden, T. (2006). Moment-to-moment dynamics of ADHD behaviour in South African children. *Behavioural and Brain Functions*, *2*, 11.

Aase, H., & Sagvolden, T. (2006). Infrequent, but not frequent, reinforcers produce more variable responding and deficient sustained attention in young children with attention-deficit/hyperactivity disorder (ADHD). *Journal of Child Psychology and Psychiatry*, *47*, 457–471.

Almasy, L., & Blangero, J. (2001). Endophenotypes as quantitative risk factors for psychiatric disease: Rationale and study design. *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics*, *105*, 42–44.

American Psychiatric Association. (1994). *Diagnostic and statistical manual for mental disorders* (4th edn). Washington, DC: American Psychiatric Press.

Annett, M., Hudson, P.T.W., & Turner, A. (1974). The reliability of differences between the hands in motor skill. *Neuropsychologia*, *12*, 527–531.

Barquin, P.C., Giedd, J.N., Jacobsen, L.K., Hamburger, S.D., Krain, A.L., Rapoport, J.L., & Castellanos, F.X. (1998). Cerebellum in attention-deficit hyperactivity

disorder: A morphometric MRI study. *Neurology*, *50*, 1087–1093.

Berument, S.K., Rutter, M., Lord, C., Pickles, A., & Bailey, A. (1999). Autism screening questionnaire: Diagnostic validity. *British Journal of Psychiatry*, *175*, 444–451.

Brookes, K., Xu, X., Chen, W., Zhou, K., Neale, B., Lowe, N., Anney, R., Franke, B., Gill, M., Ebstein, R., Buitelaar, J., Sham, P., Campbell, D., Knight, J., Andreou, P., Altink, M., Arnold, R., Boer, F., Buschgens, C., Butler, L., Christiansen, H., Feldman, L., Fleischman, K., Fliers, E., Howe-Forbes, R., Goldfarb, A., Heise, A., Gabriels, I., Korn-Lubetzki, I., Johansson, L., Marco, R., Medad, S., Minderaa, R., Mulas, F., Muller, U., Mulligan, A., Rabin, K., Rommelse, N., Sethna, V., Sorohan, J., Uebel, H., Psychogiou, L., Weeks, A., Barrett, R., Craig, I., Banaschewski, T., Sonuga-Barke, E., Eisenberg, J., Kuntsi, J., Manor, I., McGuffin, P., Miranda, A., Oades, R., Plomin, R., Roeyers, H., Rothenberger, A., Sergeant, J., Steinhausen, H., Taylor, E., Thompson, M., Faraone, S., & Asherson, P. (2006). The analysis of 51 genes in DSM-IV combined type attention deficit hyperactivity disorder: Association signals in *DRD4, DAT1* and 16 other genes. *Molecular Psychiatry*, *11*, 934–953.

Buitelaar, J.K. (2005). ADHD: Strategies to unravel its genetic architecture. *Journal of Neural Transmission Supplementary*, *69*, 1–17.

Buizer, A.I., De Sonneville, L.M.J., Van den Heuvel-Eibrink, M.M., Njiokiktjien, C., & Veerman, A.J.P. (2005). Visuomotor control in survivors of childhood acute lymphoblastic leukemia treated with chemotherapy only. *Journal of the International Neuropsychological Society*, *11*, 554–565.

Carte, E.T., Nigg, J.T., & Hinshaw, S.P. (1996). Neuropsychological functioning, motor speed, and language processing in boys with and without ADHD. *Journal of Abnormal Child Psychology*, *24*, 481–498.

Castellanos, F.X., Giedd, J.N., Marsh, W.L., Hamburger, S.D., Vaituzis, A.C., Dickstein, D.P., Sarfatti, S.E., Vauss, Y.C., Snell, J.W., Lange, N., Kaysen, D., Krain, A.L., Ritchie, G.F., Rajapakse, J.C., & Rapoport, J.L. (1996). Quantitative brain magnetic resonance imaging in attention-deficit hyperactivity disorder. *Archives of General Psychiatry*, *53*, 607–616.

Castellanos, F.X., & Tannock, R. (2002). Neuroscience of attention-deficit/hyperactivity disorder: The search for endophenotypes. *Nature Reviews Neuroscience*, *3*, 617–628.

Conners, K. (1996). Rating scales in ADHD. *Duke University Medical Center*.

De Sonneville, L.M.J. (1999). Amsterdam Neuropsychological Task: A computer-aided assessment program. In B.P.L.M. Den Brinker, P.J. Beek, A.N. Brand, S.J. Maarse, & L.J.M. Mulder (Eds.), *Cognitive ergonomics, clinical assessment and computer-assisted learning: Computers in psychology* (vol. 6, pp. 204–217). Lisse, The Netherlands: Swets & Zeitlinger.

Faraone, S.V., Perlis, R.H., Doyle, A.E., Smoller, J.W., Goralnick, J., Holmgren, M.A., & Sklar, P. (2005). Molecular genetics of attention deficit hyperactivity disorder. *Biological Psychiatry*, *57*, 1313–1323.

Gillberg, C. (2003). ADHD and DAMP: A general health perspective. *Child and Adolescent Mental Health*, *8*, 106–113.

Gillberg, C., & Rasmussen, P. (1982). Perceptual, motor and attentional deficits in six-year-old children: Background factors. *Acta Paediatrica Scandinavica*, *71*, 121–129.

Goodman, R. (1997). The strengths and difficulties questionnaire: A research note. *Journal of Child Psychology and Psychiatry*, *38*, 581–586.

Gottesman, I.I., & Gould, T.D. (2003). The endophenotype concept in psychiatry: Etymology and strategic intentions. *American Journal of Psychiatry*, *160*, 636–645.

Groth-Marnat, G. (1997). *Handbook of psychological assessment* (3rd edn). New York: Wiley.

Huijbregts, S.C.J., De Sonneville, L.M.J., van Spronsen, F.J., Berends, I.E., Licht, R., Verkerk, P.H., & Sergeant, J.A. (2003). Motor functioning under lower and higher controlled processing demands in early and continuously treated phenylketonuria. *Neuropsychology*, *17*, 369–379.

Kadesjö, B., & Gillberg, C. (1998). Attention deficits and clumsiness in Swedish 7-year-old children. *Developmental Medicine and Child Neurology*, *40*, 796–804.

Kalff, A.C., De Sonneville, L.M.J., Hurks, P.P.M., Hendriksen, J.G.M., Kroes, M., Feron, F.J.M., Steyaert, J., Van Zeben, T.M.C.B., Vles, J.S.H., & Jolles, J. (2003). Low- and high-level controlled processing in executive motor control tasks in 5–6-year-old children at risk of ADHD. *Journal of Child Psychology and Psychiatry*, *44*, 1049–1057.

Koekkoek, S., Eggermont, L., De Sonneville, L., Jupimai, T., Wicharuk, S., Apateerapong, W., Chuenyam, T., Lange, J., Wit, F., Pancharoen, C., Phanuphak, P., & Ananworanich, J. (2006). Effects of highly active antiretroviral therapy (HAART) on psychomotor performance in children with HIV disease. *Journal of Neurology*, *253*, 1432–1459.

Korkman, M., & Pesonen, A. (1994). A comparison of neuropsychological test profiles of children with attention deficit-hyperactivity disorder and/or learning disorder. *Journal of Learning Disabilities*, *27*, 383–392.

Mandich, A., & Polatajko, H.J. (2003). Developmental coordination disorder: Mechanisms, measurement and management. *Human Movement Science*, *22*, 407–411.

Marcotte, A.C., & Stern, C. (1997). Qualitative analysis of graphomotor output in children with attentional disorders. *Child Neuropsychology*, *3*, 147–153.

Martin, N.C., Piek, J.P., & Hay, D. (2006). DCD and ADHD: A genetic study of their shared aetiology. *Human Movement Science*, *25*, 110–124.

Masaki, H., Wild-Wall, N., Sangals, J., & Sommer, W. (2004). The functional locus of the lateralized readiness potential. *Psychophysiology*, *41*, 220–230.

Pelham, W.E., Aronoff, H.R., Midlam, J.K., Shapiro, C.J., Gnagy, E.M., Chronis, A.M., Onyango, A.N., Forehand, G., Nguyen, A., & Waxmonsky, J. (1999). A comparison of Ritalin and Adderall: Efficacy and time-course in children with attention-deficit/hyperactivity disorder. *Pediatrics*, *103*, e43.

Peters, M. (1981). Handedness: Effect of prolonged practice on between hand performance differences. *Neuropsychologia*, *19*, 587–590.

Piek, J.P., Pitcher, T.M., & Hay, D.A. (1999). Motor coordination and kinaesthesis in boys with attention

deficit-hyperactivity disorder. *Developmental Medicine and Child Neurology*, *41*, 159–165.
Pitcher, T.M., Piek, J.P., & Hay, D.A. (2003). Fine and gross motor ability in males with ADHD. *Developmental Medicine and Child Neurology*, *45*, 525–535.
Rommelse, N.N.J., Oosterlaan, J., Buitelaar, J., Faraone, S.V., & Sergeant, J.A. (2007). Time reproduction in children with ADHD and their nonaffected siblings. *Journal of the American Academy of Child and Adolescent Psychiatry*, *46*, 582–590.
Sandson, T.A., Bachna, K.J., & Morin, M.D. (2000). Right hemisphere dysfunction in ADHD: Visual hemispatial inattention and clinical subtype. *Journal of Learning Disabilities*, *33*, 83–90.
Seidman, L.J., Biederman, J., Monuteaux, M.C., & Weber, W. (2000). Neuropsychological functioning in nonreferred siblings of children with attention deficit hyperactivity disorder. *Journal of Abnormal Child Psychology*, *109*, 252–265.
Sergeant, J.A., Piek, J.P., & Oosterlaan, J. (2006). ADHD and DCD: A relationship in need of research. *Human Movement Science*, *25*, 76–89.
Slaats-Willemse, D., De Sonneville, L., Swaab-Barneveld, H., & Buitelaar, J. (2005). Motor flexibility problems as a marker for genetic susceptibility to attention-deficit/hyperactivity disorder. *Biological Psychiatry*, *58*, 233–238.
Stefanatos, G.A., & Wasserstein, J. (2001). Attention deficit/hyperactivity disorder as a right hemisphere syndrome. *Annals of the New York Academy of Sciences*, *931*, 172–195.
Steger, J., Imhof, K., Steinhausen, H-C, & Brandeis, D. (2000). Brain mapping of bilateral interactions in attention deficit hyperactivity disorder and control boys. *Clinical Neurophysiology*, *111*, 1141–1156.
Tabachnick, B.G., & Fidell, L.S. (2001). *Using multivariate statistics* (4th edn). Needham Heights: Allyn & Bacon.
Taylor, E.A. (1986). Childhood hyperactivity. *British Journal of Psychiatry*, *149*, 562–573.
Thomas, J.R., & French, K.E. (1985). Gender differences across age in motor performance: A meta-analysis. *Psychological Bulletin*, *98*, 260–282.
Waldman, I.D. (2005). Statistical approaches to complex phenotypes: Evaluating neuropsychological endophenotypes for attention-deficit/hyperactivity disorder. *Biological Psychiatry*, *57*, 1347–1356.
Wechsler, D. (2000). *WAIS-III Nederlandstalige bewerking. Technische handleiding*. London: The Psychological Corporation.
Wechsler, D. (2002). *WISC-III Handleiding*. London: The Psychological Corporation.
Whitmont, S., & Clark, C. (1996). Kinaesthetic acuity and fine motor skills in children with attention deficit hyperactivity disorder: A preliminary report. *Developmental Medicine and Child Neurology*, *38*, 1091–1098.
Willcutt, E. (in press). The etiology of ADHD: Behavioral and molecular genetic approaches. In D. Barch (Ed.), *Cognitive and affective neuroscience of psychopathology*. Oxford: Oxford University Press.
Yochman, A., Ornoy, A., & Parush, S. (2006). Perceptuomotor functioning in preschool children with symptoms of attention deficit hyperactivity disorder. *Perceptual and Motor Skills*, *102*, 175–186.

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