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ORIGINAL RESEARCH

Speed, Variability, and Timing of Motor Output in ADHD: Which Measures are Useful for Endophenotypic Research?

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Abstract Attention-Deficit/Hyperactivity Disorder (ADHD) shares a genetic basis with motor coordination problems and probably motor timing problems. In line with this, comparable problems in motor timing should be observed in first degree relatives and might, therefore, form a suitable endophenotypic candidate. This hypothesis was investigated in 238 ADHD-families (545 children) and 147 control-families (271 children). A motor timing task was administered, in which children had to produce a 1,000 ms interval. In addition to this task, two basic motor tasks were administered to examine speed and variability of motor output, when no timing component was required. Results indicated that variability in motor timing is a useful endophenotypic candidate: It was clearly associated with ADHD, it was also present in non-affected siblings, and it correlated within families. Accuracy (under- versus over-production) in motor timing appeared less useful: Even though accuracy was associated with ADHD (probands and affected siblings had a tendency to under-produce the 1,000 ms interval compared to controls), non-affected siblings did not differ from controls and sibling correlations were only marginally significant. Slow and variable motor output without timing component also appears present in ADHD, but not in non-affected siblings, suggesting these deficits not to be related to a familial vulnerability for ADHD. Deficits in motor timing could not be explained by deficits already present in basic motor output without a timing component. This suggests abnormalities in motor timing were predominantly related to deficient motor timing processes and not to general deficient motor functioning. The finding that deficits in motor timing run in ADHD-families suggests this to be a fruitful domain for further exploration in relation to the genetic underpinnings of ADHD.

Keywords ADHD · Siblings · Endophenotype · Motor timing · Motor speed · Motor variability

Introduction

It has become apparent from twin- and adoption studies that the development of the Attention-Deficit/Hyperactivity Disorder (ADHD) (American Psychiatric Association 1994) is strongly genetically based (Faraone et al. 2005; Willcutt, in press). Overall heritability estimates exceed 0.70 (Faraone and Doyle 2000; Smalley 1997) and are fairly constant across studies conducted worldwide (Faraone et al. 2005). Research aimed at the molecular genetic basis of the disorder (genotype) has had success in identifying some susceptibility genes by using information from behaviorally observable symptoms (phenotype) (Faraone et al. 2005). However, the current knowledge about the genetic basis of the disorder is still limited and the causal pathway(s) leading from genotype to phenotype have yet to be revealed.

Both issues have been the aims of investigation in endophenotypic research. Endophenotypes are defined as

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heritable, vulnerability traits that mark a risk for the development of the disorder (Almasy and Blangero 2001; Castellanos and Tannock 2002; Doyle et al. 2005; Gottesman and Gould 2003; Skuse 2001; Waldman 2005; Zobel and Maier 2004). They are conceptualized as forming an intermediate link between the genotype and phenotype and are presumably genetically less complex compared to phenotypic symptoms (Gottesman and Gould 2003; Waldman 2005). Because of these characteristics, it is thought that, compared to phenotypic symptoms, endophenotypes are more suitable for detecting disease genes and for unraveling the modes of actions of these disease genes.

Several criteria have been proposed to discriminate an endophenotype from other biological markers that are not causally involved in the disorder but are merely associated with the disorder (Durston et al. 2004; Gottesman and Gould 2003). Although these criteria do not appear to be universally agreed upon, several key criteria have emerged from the literature (Almasy and Blangero 2001; Castellanos and Tannock 2002; Doyle et al. 2005; Gottesman and Gould 2003; Skuse 2001; Waldman 2005; Zobel and Maier 2004). First, an endophenotype should co-occur with the disorder, although given the heterogeneity of ADHD, it is unlikely that a single endophenotype will occur in all patients with ADHD (Doyle et al. 2005). Second, non-affected relatives should also exhibit the endophenotype to some extent, indicating that the endophenotype contributes to a familial susceptibility for the disorder. Because non-affected relatives share, on average, 50% of their genes with the affected family member, it is theorized that they also carry some of the susceptibility genes of ADHD which translate into subtle abnormalities in the endophenotype (Gottesman and Gould 2003; Waldman 2005). Third, the endophenotype should show familial resemblance, reflected by significant sibling correlations for the endophenotypic measure. In addition to these criteria, several other important characteristics of an endophenotype have been put forward, such as reliability of measurement, stability over time (i.e. expressed regardless whether or not the disorder is currently manifested), and acting as a mediator and/or moderator between genes and disorder (Doyle et al. 2005; Waldman 2005). The focus of our study lies on the first three key criteria of an endophenotype.

Possible endophenotypic candidates might be found in the deficits in motor output associated with ADHD. Fine motor coordination problems as well as gross motor coordination problems are frequently observed in co-occurrence with ADHD (Carte et al. 1996; Korkman and Pesonen 1994; Marcotte and Stern 1997; Piek et al. 1999; Pitcher et al. 2003; Whitmont and Clark 1996). Because of this highly frequent co-occurrence, it is feasible that motor problems might be genetically related to the risk for developing ADHD (Gillberg 2003), which has indeed been reported recently (Martin et al. 2006). This might make motor measures useful endophenotypic candidates, which was underlined by the findings of motor control difficulties in non-affected siblings of children with ADHD (Rommelse et al. 2007a; Slaats-Willemse et al. 2005).

A specific aspect of motor output that might serve as a candidate endophenotype is temporal organization (Castellanos and Tannock 2002; Waldman et al. 2006). Temporal organization of motor output refers to the timing of movements (i.e. motor timing) and seems to be predominantly mediated by the cerebellum and basal ganglia and their reciprocal connections with the cerebral cortex (Handy et al. 2003; Harrington et al. 1998; Ivry 1996; Nenadic et al. 2003). The timing of motor output is hypothesized to consist of two components: a clock component, which reflects central time keeping operations, and a motor delay component, which reflects random variability due to response implementation processes (Harrington et al. 1998; Keele et al. 1985; Wing and Kristofferson 1973). Children with ADHD seem to be predominantly impaired in the clock component, as evidenced by paradigms specifically assessing timing operations independent of motor operations, such as duration discrimination tasks (Keele et al. 1985; see for review Toplak et al. 2006). The motor component is possibly best assessed using simple reaction time tasks and free Tapping tasks in which timing is minimized. Some have found no impairments in children with ADHD (Kalff et al. 2003; Seidman et al. 1997, 2000), others have (Kalff et al. 2005). By combining both components, one can assess timing that is predominantly related to motor output, which reflects the interplay between timing and motor skills. Studies using these motor timing tasks have, however, not revealed consistent results of impairments in children with ADHD, possibly due to inconsistencies in methodological approaches across studies (Toplak et al. 2006). However, greater variability in motor output when a timing component is required is a frequently reported finding in children with ADHD (Leth-Steensen et al. 2000; Pitcher et al. 2002; Rubia et al. 1999, 2003; Toplak et al. 2006; Van Meel et al. 2005). None of these studies, however, used a measure of basic motor speed/variability (without requirements regarding timing/rhythm) in addition to the motor timing measure. Therefore, it remains unclear whether the variability in motor timing is primarily due to variability of motor processes, or due to variability of timing processes or both. Here, we administered two simple motor tasks in addition to the motor timing task, in order to investigate whether deficits were specifically related to the timing of motor output or whether deficits were also observed in tasks that do not require timing of motor output.

The current study is, to our knowledge, the first to examine motor timing abilities in not only children with

ADHD, but also in their siblings, in order to investigate whether motor timing measures might be suitable endophenotypic candidates. Previous studies on related topics have shown that non-affected siblings of children with ADHD have comparable problems in time reproduction skills as their affected siblings (Rommelse et al. 2007b) and that variability in reaction time shows familial overlap with ADHD (Andreou et al. 2007), giving support to the hypothesis that motor timing measures may be suitable endophenotypic candidates. It was expected that (1) children with ADHD would be impaired on motor timing measures and not (or to a lesser extent) on motor measures without a timing component, indicating an association between ADHD and motor timing deficits. Furthermore, we expected (2) to find similar findings in the non-affected siblings of the children with ADHD, suggesting motor timing deficits are not merely associated with the disorder. Last, we expected (3) to find correlations between siblings indicating familial resemblance on motor timing measures.

Method

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 had 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, 238 probands (all with combined subtype of ADHD), 112 affected siblings (64 with combined subtype, 28 with inattentive subtype and 20 with hyperactive-impulsive subtype of ADHD) 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 (see for an overview Tables 1, 2).

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, brain disorders or known genetic disorders, such as Down syndrome or Fragile-X-syndrome.

Within an ADHD-family, both proband and siblings were similarly screened using the standard procedures of the IMAGE project described by 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 [SDQ, Goodman 1997]), were used to identify children with ADHD symptoms. T-scores ≥ 63 on the Conners'-N-scale (DSM-IV total symptom score) and scores $>$ 90th percentile on the SDQ-hyperactivity scale were considered as clinical. For all children within a family scoring clinically on any of the questionnaires, a semi-structured, standardized, 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 internalizing disorders. The section on autistic behaviour traits was administered, if a clinical score (raw score ≥ 15) was obtained on the Social Communication Questionnaire (SCQ; Berument et al. 1999). A standardised algorithm was applied to the PACS and parent rated

Table 1 Distribution of family sizes

Number of siblings within a family	ADHD		Control	
	Families (*n*)	Individuals (*n*)	Families (*n*)	Individuals (*n*)
1	0	0	51	51
2	177	354	72	144
3	53	159	20	60
4	8	32	4	16
Total	238	545	147	271

Note: ADHD = Attention-Deficit/Hyperactivity Disorder

Table 2 Distribution of affected and non-affected siblings within ADHD-families

Total number of children within a family	Diagnostic status			ADHD-families (*n*)
	Proband (*n*)	Affected siblings (*n*)	Non-affected siblings (*n*)	
2	1	1	–	62
	1	–	1	115
3	1	2	–	7
	1	1	1	24
	1	–	2	22
4	1	3	–	2
	1	2	1	1
	1	1	2	4
	1	–	3	1
Total				238

Note: ADHD = Attention-Deficit/Hyperactivity Disorder

Table 3 Sample characteristics

	Probands		Affected siblings		Non-affected siblings		Normal controls		$F_{3,812}$	Contrasts
	$n = 238$		$n = 112$		$n = 195$		$n = 271$			
	M	*SD*	*M*	*SD*	*M*	*SD*	*M*	*SD*		
Age in years	12.0	2.5	12.0	3.4	11.5	3.6	11.6	3.2	ns	
% Right handed	91.1		87.5		89.2		85.5		ns[a]	
% Male	84.5		56.3		45.1		40.6		113.9*[a]	1 > 2,3,4 2 = 3 & 2 > 4 3 = 4
Estimated full scale IQ	97.9	13.0	100.7	10.6	103.8	10.9	106.0	10.2	23.5*	1 = 2 & 1 < 3 = 4 2 = 3 & 2 < 4 3 = 4
Conners' parent DSM-IV										
Inattentive	71.1	8.4	66.0	11.6	47.9	7.0	46.5	4.8	585.4*	1 > 2 > 3 = 4
Hyperactive-impulsive	79.1	9.2	67.8	13.6	49.0	6.9	47.3	5.1	767.3*	1 > 2 > 3 = 4
Total	76.9	8.6	68.3	11.6	48.2	6.8	46.5	4.5	875.7*	1 > 2 > 3 = 4
Conners' teacher DSM-IV										
Inattentive	66.0	9.1	61.7	10.2	48.3	6.0	46.4	4.6	386.3*	1 > 2 > 3 = 4
Hyperactive-impulsive	70.2	10.7	63.5	13.3	48.3	6.5	47.2	5.0	378.1*	1 > 2 > 3 = 4
Total	69.8	9.8	63.8	11.4	48.3	5.8	46.4	4.5	485.8*	1 > 2 > 3 = 4
ADHD diagnosis										
Inattentive	–		28		–		–			
Hyperactive-impulsive	–		20		–		–			
Combined	238		64		–		–			

Note: 1 = Probands; 2 = Affected siblings; 3 = Non-affected siblings; 4 = Normal controls

ADHD = Attention-Deficit/Hyperactivity Disorder; DSM-IV = Diagnostic and Statistical Manual for Mental Disorders (4th edition)

* $P < 0.001$; [a] χ^2; Contrasts based on *p*-values of 0.05

Conners' to derive each of the 18 DSM-IV ADHD items, 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 subscale to generate the total number of hyperactive-impulsive and inattentive symptoms of the DSM-IV. 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 on the ADHD subscale as indicated by teachers on the Conners'. 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 $\leq$ 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 $\leq$ 62). Table 3 provides the characteristics of the four groups.

Measures

Motor Timing Task

This task was designed to measure the accuracy and variability of motor timing (Van Meel et al. 2005). Subjects were instructed to press a button with their preferred index finger when they thought a 1-second time interval had elapsed. The start of the interval was announced by a tone. After the subject's response, visual feedback concerning the accuracy of the response was presented on the screen, 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. Boundaries were set at 500 to 1,500 ms at the beginning of the task. If the response fell within these boundaries, the boundaries of the subsequent trial were narrowed by 100 ms. Likewise, the boundaries of the subsequent trial were widened with 100 ms, if the response on the previous trial fell outside the boundaries.

The practice session consisted of 20 trials, the experimental session of 80 trials. Both sessions were preceded by

presenting 10 times a cartoon figure for exactly 1 s on the screen to demonstrate the duration of 1 s (Van Meel et al. 2005). Dependent measures were accuracy (median of productions in ms, which reflects under- versus over-production) and variability (SD of productions in ms).

Baseline Speed task

This task was designed to measure the speed and variability of motor output in response to an external cue and comparable to a simple reaction time task (De Sonneville 1999). Subjects were required to press a key as quickly as possible, when a fixation cross in the centre of a computer screen changed into a white square. Immediately following the response, the white square changed back into the fixation cross. The time interval between a response and the emergence of the next white square varied randomly between 500 and 2,500 ms in order to prevent anticipation strategies.

A practice session (10 trials) and an experimental session (32 trials) were administered for both hands separately. The task was first practised and executed with the index finger of the non-preferred hand, thereafter practised and executed with the index finger of the preferred hand. Dependent measures were the speed (mean reaction time in ms) and variability (SD of reaction times in ms) of responses.

Tapping task

This task measured the speed and variability of self-generated motor output (without internal or external cues) (De Sonneville 1999). Subjects were required to tap as frequently as possible within an interval of 18 s. The beginning and end of the interval were announced by a tone. During tapping, the number of taps was continuously counted and displayed on the screen.

A practice session (5 s) and an experimental session (18 s) were administered for both hands separately. The task was first practised and executed with the index finger of the non-preferred hand, thereafter practised and executed with the index finger of the preferred hand. Dependent measures were speed (mean intertap interval in ms) and variability (SD of intertap intervals in ms) of motor output.

Intelligence

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

Procedure

Testing of ADHD children and their siblings took place at the VU University Amsterdam or at the Radboud University Nijmegen Medical Centre and was conducted simultaneously for children within a family. Psychostimulants were discontinued for at least 48 h before testing took place (Pelham et al. 1999). Participants that took other medication than stimulants to suppress their symptoms of ADHD were also off medication during testing. The medication of these children was gradually decreased in line with standard procedures to allow for sufficient wash-out. 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.

Analyses

The percentage of missing data was less than 5% for each of the dependent variables. Missing data were replaced by using the Estimation Maximization procedure (Tabachnick and Fidell 2001). None of the dependent variables was normally distributed. Therefore, variables were successfully normalized by applying a Van der Waerden transformation (Statistical Package for the Social Sciences [SPSS] version 14). The Van der Waerden transformation 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 (SPSS version 14). 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. Homogeneity of variance was tested by calculating $F_{\max}$ (ratio of the largest cell variance to the smallest). Since sample sizes were relatively equal (i.e. within a ratio of 4 to 1 or less), an $F_{\max}$ of 10 and lower was acceptable (Tabachnick and Fidell 2001). For all six normalized variables, the ratio was well within acceptable limits (all below 1.37). Alpha was set at .01 for all tests. Following Cohen's guidelines

(Cohen 1988), effect sizes were defined in terms of the percentage of explained variance: 1, 9 and 25% were used to define small, medium, and large effects. These figures translate into η^2-values of 0.01, 0.06 and 0.14.

Linear mixed models were used for the analyses. The linear mixed model expands the general linear model so that the data are permitted to exhibit correlated variability. This model allows for the investigation of group differences while correcting for the non-independency of data (i.e. more than one child participated per family, which resulted in related measurements within groups and between groups). In first instance, we tested the main effects of possible confounders (hand, gender, IQ, and age) on performance on the three different tasks. This was done within the control group to avoid dependency with the factor group. Thereafter, interactions between group and the confounders were examined to investigate whether effects of possible confounders were comparable across groups. In second instance, we investigated whether group differences existed for each task measure. Group was used as factor (four groups: proband, affected sibling, non-affected sibling, and control), age (linear and/or curvilinear) as covariate(s), and family as random effect to account for within family correlation. Pairwise comparisons were used to compare groups and it was analyzed whether a linear trend was present in polynomial group contrasts. It was expected that probands and affected siblings performed worse than controls (mainly on the motor timing measures but not or to a lesser extent on the other motor measures), indicating an association between motor timing deficits and ADHD. It was also expected that the non-affected siblings performed worse than controls and formed an intermediate group in between their affected siblings and controls, suggesting motor timing deficits were related to a familial susceptibility to the disorder. The Conners' Total ADHD scale (averaged across parents and teachers) was used as an additional covariate in the analyses to rule out that possible deficits in the non-affected siblings group could be attributed to sub-clinical ADHD symptoms in this group. Correlations (with 95% confidence intervals) were calculated between siblings to test the familial resemblance of the motor measures (Statistical Analysis for Genetic Epidemiology [S.A.G.E] 5.3.1, 2007).

Results

Testing of possible confounders

Main effects of hand, gender, IQ, and age

We tested for the effects of hand, gender, IQ, and age within the control group to avoid dependency with the factor group. No significant effect of hand was found on the Baseline Speed task ($F(1, 271.0) = 0.05$, $P = .83$, $\eta_p^2 < .01$), but there was a significant effect on the Tapping task ($F(1, 271.0) = 5.99$, $P = .02$, $\eta_p^2 = .02$). Control children were faster and less variable, when performing the Tapping task with their right hand than their left hand, likely reflecting an effect of hand dominance. The Motor Timing task was only performed with the preferred hand. Gender had no effect on the Motor Timing task and Baseline Speed task ($F(1, 241.5) = 0.03$, $P = .87$, $\eta_p^2 < .01$ and $F(1, 229.5) = 0.36$, $P = .55$, $\eta_p^2 < .01$, respectively), but had an effect on the Tapping task ($F(1, 225.1) = 14.91$, $P < .001$, $\eta_p^2 = .05$). Control boys were faster and less variable in their tapping performance than control girls. No effect of IQ was found on the Motor Timing task, Baseline Speed task, or Tapping task ($F(1, 258.4) = 0.20$, $P = .66$, $\eta_p^2 < .01$, $F(1, 254.8) = 0.06$, $P = .81$, $\eta_p^2 < .01$ and $F(1, 259.9) = 0.95$, $P = .33$, $\eta_p^2 < .01$, respectively). In order to assess whether age could be best modeled in linear and/or curvilinear terms, we first analyzed the linear effect of age and then in a second model analyzed the quadratic effect of age, while keeping the linear term for age in the model. In this manner, the incremental contribution of the curvilinear relation with age over and above the linear relation was tested. Age (in linear terms) had a strong effect on the Motor Timing task, Baseline Speed task, and Tapping task ($F(1, 252.7) = 26.65$, $P < .001$, $\eta_p^2 = .22$, $F(1, 239.1) = 292.38$, $P < .001$, $\eta_p^2 = .57$, and $F(1, 244.5) = 278.31$, $P < .001$, $\eta_p^2 = .57$, respectively). Older control children were more accurate, faster and less variable in their motor output. Results indicated that when both age terms were implemented in the model, no curvilinear effect of age was present on the Motor Timing task ($F(1, 259.3) = 1.34$, $P = .25$), but there was on the Baseline Speed task and Tapping task ($F(1, 257.8) = 20.59$, $P < .001$ and $F(1, 258.3) = 12.47$, $P < .001$, respectively). No significant interactions were present between gender and age, whether age was modelled in linear or curvilinear terms.

Interactions between group and possible confounders

Group did not interact with hand on the Baseline Speed task ($F(3, 816.0) = 1.14$, $P = .33$, $\eta_p^2 < .01$), but did interact marginally significantly with hand on the Tapping task ($F(3, 816.0) = 2.73$, $P = .04$, $\eta_p^2 = .01$). Group did not interact with gender on the Motor Timing, Baseline Speed, or Tapping tasks ($F(3, 762.9) = 1.96$, $P = .12$, $\eta_p^2 < .01$, $F(3, 743.3) = 0.52$, $P = .67$, $\eta_p^2 < .01$, and $F(3, 751.8) = 0.53$, $P = .66$, $\eta_p^2 < .01$, respectively) nor with IQ ($F(3, 730.1) = 2.01$, $P = .11$, $\eta_p^2 = .01$, $F(3, 714.3) = 1.28$, $P = .28$, $\eta_p^2 = .01$, and $F(3, 727.2)$

Table 4 Means and standard deviations of the motor measures in ms

Dependent variable	Proband		Affected sibling		Non-affected sibling		Control		η_p^2	Contrasts
	M	*SD*	*M*	*SD*	*M*	*SD*	*M*	*SD*		
Motor timing										
Accuracy	981	99	997	96	1,007	114	1,020	100	.03	1 = 2 > 3 = 4
Variability	389	265	375	265	344	260	295	218	.10	1 = 2 > 3 > 4
Baseline Speed										
Speed	355	75	356	85	353	81	351	78	.02	1 = 2 > 3 = 4
Variability	132	85	131	87	123	82	117	75	.03	1 = 2 > 3 = 4
Tapping										
Speed	239	39	248	48	256	51	249	48	.01	ns
Variability	46	20	48	23	45	20	44	18	.01	ns

Note: 1 = Probands; 2 = Affected Siblings; 3 = Non-Affected Siblings; 4 = Controls. ns = not significant

Scores were averaged across hands for the Baseline Speed and Tapping

Outliers ($|z| > 3$) were removed

= 2.11, $P = .09$, $\eta_p^2 = .01$, respectively), nor with linear age ($F(3, 732.0) = 1.67$, $P = .17$, $\eta_p^2 = .01$, $F(3, 731.1) = 0.88$, $P = .45$, $\eta_p^2 < .01$, and $F(3, 755.2) = 1.36$, $P = .26$, $\eta_p^2 = .01$, respectively), nor with curvilinear age ($F(3, 727.1) = 1.61$, $P = .19$, $\eta_p^2 < .01$, $F(3, 733.2) = 0.51$, $P = .67$, $\eta_p^2 < .01$, and $F(3, 754.4) = 1.21$, $P = .31$, $\eta_p^2 < .01$, respectively).

Based on the results of these analyses, it was decided to average the measures across hands to simplify results, since no group differences were found for the percentage of right- and left-handed (Table 3) and since there was only a marginal significant interaction of small effect between group and hand for one of the tasks (Tapping). Furthermore, not included as covariates were IQ (had no effect on motor performance and did not interact with group) and gender (had only a small effect on one of the tasks and even in the opposite direction i.e. boys performing better than girls, and gender did not interact with group). Both the linear and curvilinear effects of age were included as covariates in the analyses for the Baseline Speed task and Tapping task. Only the linear effect of age was included as covariate in the analyses for the Motor Timing task. Raw means and SDs are presented in Table 4.

Endophenotypic analyses

Motor Timing task

A significant small effect of group was found for *accuracy* ($F(3, 532.9) = 7.21$, $P < .001$, $\eta_p^2 = .03$). Pairwise comparisons indicated that probands and affected siblings did not differ from each other ($P = .21$). Both differed significantly from controls ($P < .001$ and $P = .02$, respectively): probands and (to a lesser extent) affected siblings tended to under-produce the 1,000 ms interval ($M = 981$ ms and $M = 997$ ms, respectively) compared to controls ($M = 1{,}020$ ms). A tendency to under reproduce appeared to be associated with ADHD, but was not convincingly related to a familial predisposition for the disorder, since non-affected siblings did not show this tendency: they differed significantly from probands ($P < .001$), marginally significantly from affected siblings ($P = .02$) but not from controls ($P = .08$) (see Fig. 1). Using the Conners' Total ADHD score as covariate did not change the difference between non-affected siblings and controls ($P = .04$). However, a polynomial group contrast indicated a linear trend to be present (Contrast Estimate [CE] = 0.29, $P < .001$), suggesting probands performed

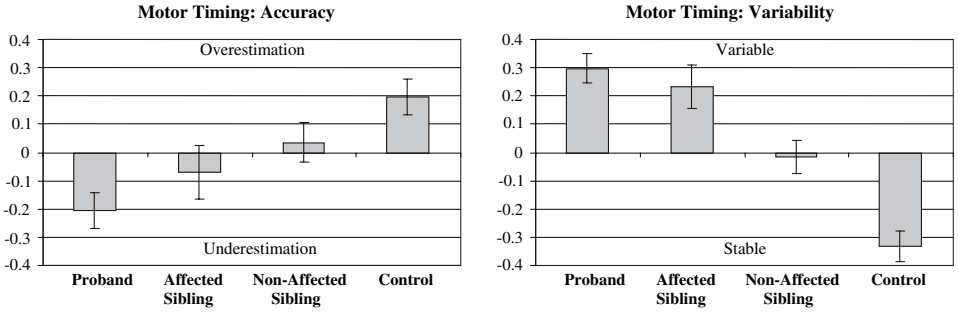

Fig. 1 Accuracy and variability of motor timing (adjusted for the linear effect of age) in probands, affected siblings, non-affected siblings and control children. Error bars represent 1 standard error from the mean

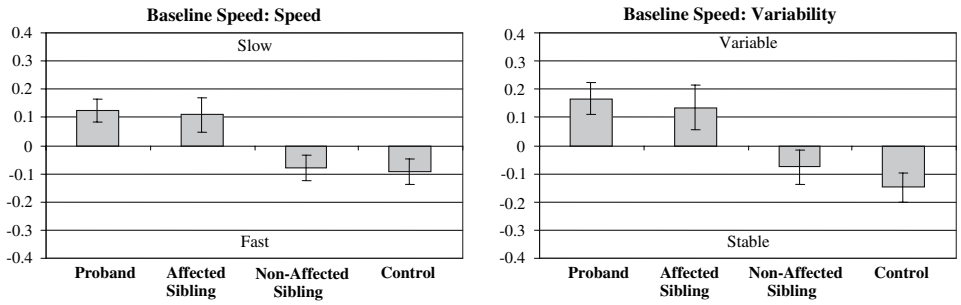

Fig. 2 Speed and variability of Baseline Speed (adjusted for the linear and curvilinear effects age) in probands, affected siblings, non-affected siblings and control children. Error bars represent 1 standard error from the mean. Scores were averaged across hands

most abnormal, followed by affected siblings, then non-affected siblings and then controls. Siblings marginally significantly resembled each other ($r = .11$ confidence interval [CI = .02–.19], $P = .02$).

Groups also differed with respect to the *variability* of motor timing (medium effect) ($F(3, 524.6) = 25.12$, $P < .001$, $\eta_p^2 = .10$). Pairwise comparisons indicated that probands and affected siblings were equally variable ($P = .45$) and both were more variable than controls (both $P < .001$), suggesting ADHD and variability in motor timing were associated. Moreover, variability in motor timing appeared related to a familial predisposition for the disorder, since non-affected siblings formed an intermediate group: They significantly differed from probands, affected siblings, and controls ($P < .001$, $P = .009$ and $P < .001$, respectively). Using the Conners' Total ADHD score as covariate did not change the difference between non-affected siblings and controls ($P = .001$). A linear group contrast was present (CE = −0.49, $P < .001$). A significant familial resemblance was found for variability ($r = .29$ [CI = .20–.38], $P < .001$). These findings lend support for variability of motor timing as endophenotype, though the accuracy of motor timing appears only to be associated with ADHD and not conclusively related to a familial susceptibility for the disorder (Fig. 1).

Baseline Speed task

A small but significant effect of group was found for *speed* ($F(3, 537.2) = 6.92$, $P < .001$, $\eta_p^2 = .02$). Pairwise comparisons revealed that probands and affected siblings did not differ from each other ($P = .82$) and both were slower than controls ($P < .001$ and $P = .007$, respectively), indicating a relationship between speed and ADHD. It appeared that speed was not related to a familial vulnerability for ADHD, since non-affected siblings differed from probands and affected siblings ($P < .001$ and $P = .01$, respectively), but not from controls ($P = .84$). Using the Conners' Total ADHD score as covariate did not change the difference between non-affected siblings and controls ($P = .99$). Nevertheless, polynomial group contrasts indicated a linear trend (CE = −0.14, $P = .001$), suggesting probands to perform most abnormal, followed by affected siblings, then non-affected siblings, and then controls. A significant correlation between siblings was found ($r = .29$ [CI = .20–.38], $P < .001$).

Groups differed somewhat (small effect size) in the *variability* on the Baseline Speed task ($F(3, 555.1) = 6.96$, $P < .001$, $\eta_p^2 = .03$). Pairwise comparisons indicated that probands and affected siblings were equally variable ($P = .74$) and both groups were more variable than normal controls ($P < .001$ and $P = .003$, respectively), signaling an association between ADHD and variability in self generated motor output. Again, non-affected siblings did differ from probands ($P = .003$) and affected siblings ($P = .04$), but not from controls ($P = .38$). Using the Conners' Total ADHD score as covariate did not change the difference between non-affected siblings and controls ($P = .41$). Nevertheless, a linear group contrast was present (CE = −0.22, $P < .001$). Variability correlated between siblings ($r = .16$ [CI = .07–.25], $P < .001$). These findings suggest slow and variable motor output in response to an external cue is associated with ADHD, but probably not related to a familial vulnerability for ADHD, since motor output of non-affected siblings resembles that of normal controls more than that of their affected siblings (Fig. 2).

Tapping Task

No significant effect of group was found for *speed* ($F(3, 547.4) = 1.88$, $P = .13$, $\eta_p^2 = .01$) or *variability* ($F(3, 553.6) = 1.95$, $P = .12$, $\eta_p^2 = .01$). No significant linear trend was present in polynomial group contrasts for speed or variability (CE = 0.10, $P = .04$ and CE = −0.12, $P = .03$, respectively). Siblings did resemble each other in the speed and variability of tapping (speed: $r = .27$ [CI = .18–.36], $P < .001$; variability: $r = .18$ [CI = .09–.27], $P < .001$). These findings indicated that speed and variability in self generated motor output were not familially associated with ADHD (Fig. 3).

Since there were group differences for speed and variability of externally cued motor output (Baseline Speed task), the issue was raised whether the deficits found on the

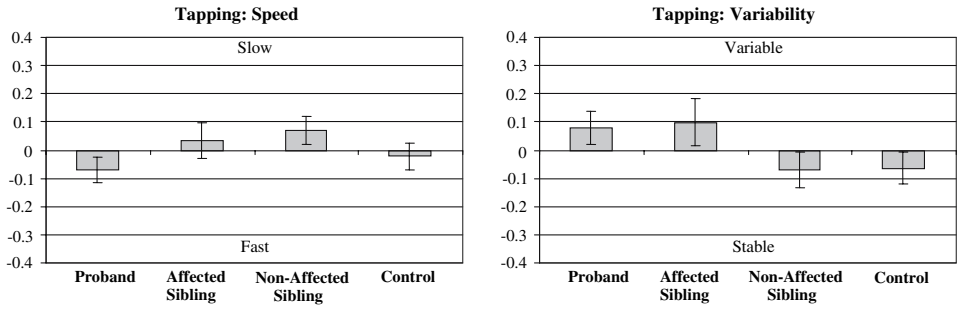

Fig. 3 Speed and variability of tapping (adjusted for the linear and curvilinear effects of age) in probands, affected siblings, non-affected siblings and control children. Error bars represent 1 standard error from the mean. Scores were averaged across hands

Motor Timing task were primarily related to these group differences in basic motor output. Therefore, analyses were undertaken whereby the speed on the Baseline Speed task was used as an additional covariate in the analyses on accuracy on the Motor Timing task. The variability on the Baseline Speed task was used as additional covariate for the analyses on variability on the Motor Timing task.

The effect of group on *accuracy* on the Motor Timing task remained significant after accounting for speed on the Baseline Speed task ($F(3, 532.4) = 7.51$, $P < .001$, $\eta_p^2 = .03$). The unadjusted means of the raw (unstandardized) data of the accuracy on the Motor Timing task for probands, affected siblings, non-affected siblings, and controls were: 981, 997, 1,007, and 1,020 ms, respectively. The adjusted means after covarying for speed on the Baseline Speed task were: 979, 998, 997, and 1,018 ms, respectively.

The same was true for *variability* of motor timing: the medium effect of group remained significant after accounting for variability on the Baseline Speed task ($F(3, 528.2) = 21.72$, $P < .001$, $\eta_p^2 = .09$). The unadjusted means of the raw (unstandardized) data of the variability on the Motor Timing task for probands, affected siblings, non-affected siblings, and controls were: 389, 375, 344, and 295 ms, respectively. The adjusted menas after covarying for the variability on the Baseline Speed task were: 438, 428, 424, and 316 ms, respectively. Group contrasts for accuracy and variability as reported above also remained unchanged. These findings suggest that the deficits found on the Motor Timing task can not be explained by the deficits found in basic motor output.

Discussion

There was investigated whether accuracy and variability of motor timing were viable endophenotypic candidates as reflected by poor performance on these measures in children with ADHD (i.e. indicating an association between the deficits and the disorder), reflected by poor performance in non-affected siblings in between their affected siblings and controls (i.e. suggesting a relation between the deficits and a familial susceptibility for the disorder), and reflected by sibling correlations (i.e. signalling familial resemblance for deficits). We administered two motor tasks in addition to a motor timing task, in order to investigate whether deficits were specifically related to the timing of motor output or whether deficits were also observed in tasks requiring motor output without any timing demands.

Probands and affected siblings were dissociated from controls with respect to accuracy of motor timing. Both groups tended to under-produce the 1,000 ms compared to control children (who tended to over-produce the interval). This finding has been reported previously using exactly the same task (Van Meel et al. 2005) and is comparable to some other studies documenting on under estimation/(re)production in patients with ADHD compared to controls (see for review Toplak et al. 2006). These findings suggest a relation between under reproduction (possibly reflecting a somewhat speeded internal clock and/or impulsivity) and ADHD. The findings were less convincing with respect to non-affected siblings: despite a linear trend in group contrasts, their accuracy of motor timing was more like controls than that of affected siblings. Furthermore, correlations between siblings on accuracy were also modest suggesting familial resemblance for accuracy was present but not strongly. Therefore, accuracy of motor timing seems not to be a strong endophenotypic candidate.

Variability of motor timing, however, convincingly met all characteristics of an endophenotype as investigated in our study: Probands and affected siblings were clearly more variable in their motor output than controls, non-affected siblings also differed significantly from controls and had variability scores in between their affected siblings and controls, and greater variability in motor timing was evidently familial. Greater variability in motor timing in children with ADHD compared to controls concurs with previous studies (Pitcher et al. 2002; Rubia et al. 1999, 2003; Toplak et al. 2006; Van Meel et al. 2005) and suggests variability in motor timing is characteristic of ADHD. Our study adds important knowledge to this topic, showing that non-affected siblings portray a similar type of variability in their motor timing and that siblings resemble each other in the variability of motor timing. These

findings suggest the variability in motor timing is not only associated with the disorder, but is related to familial vulnerability for ADHD, which may make it a useful tool in future studies aimed at unraveling the genetic underpinnings of ADHD.

All in all, variability of motor timing may form a fruitful endophenotypic candidate. However, group differences were also present on motor measures that did not require a timing component, suggesting motor deficits not to be specifically related to timing but to be more generalized. Probands and affected siblings were significantly slower and more variable than controls concerning motor output in response to an external cue (Baseline Speed). These findings of slow and variable responding are in line with a study using the same task in young children at risk for ADHD (Kalff et al. 2005) and suggests slow and variable responding are characteristic of ADHD. However, in contrast to variability of motor timing, non-affected siblings did not differ from controls with respect to speed and variability of externally cued motor output. So, despite the finding that slow and variable motor output is associated with ADHD, it does not appear to be convincingly associated with a familial vulnerability for the disorder.

Given that poor motor output was observed in probands and affected siblings (Baseline Speed), it was surprising that no such abnormalities were found in self-generated motor output (Tapping). Probands and affected siblings had a normal speed and variability in self generated motor output. The discrepancy in results between both tasks may lie in the suggestion that Baseline Speed may have required some form of cognitive processing (i.e. registering a stimulus and responding to it), whereas Tapping only required executing a motor action. The normal performance of children with ADHD on the Tapping task is in line with some studies (Seidman et al. 1997, 2000), but in contrast with others (Toplak et al. 2006). This might be explained by the important difference in timing requirements necessary in the Tapping task used here and in some previous studies. Here, no timing was required to execute the Tapping task. The instruction was simply to press the button as often as possible within a certain time interval. However, in other studies the child was required to modify his/her tapping rate to be in synchrony with the stimulus and maintain the rhythm in the absence of the stimulus (Rubia et al. 1999; Toplak et al. 2006). These tasks load differently on timing processes. Our findings suggest that self-generated motor output does not form a viable area of endophenotypic research, even though speed and variability of self-generated motor output correlate within families.

Since group differences were not only present on measures of motor timing, but also on measures of motor output (Baseline Speed), it was investigated whether motor timing impairments may be due to deficits in basic motor output. This appeared not to be the case. Even when speed and variability of basic motor output were used as covariates in the analyses on motor timing, group differences for motor timing remained. These findings suggest abnormalities in the accuracy and variability of motor timing are relatively independent of general deficits in basic motor output (Keele et al. 1985) and suggest abnormalities in motor timing are predominantly related to timing operations and not to motor functioning. Since motor timing appears predominantly regulated by the cerebellum, basal ganglia and their reciprocal connections with the cerebral cortex (Handy et al. 2003; Harrington et al. 1998; Ivry 1996; Nenadic et al. 2003), subcortical regions in addition to cortical regions might be important in the etiology of ADHD (Halperin and Schulz 2006).

Limitations

We did not administer the PACS interview for nonaffected siblings. This might have resulted in undetected ADHD cases in the nonaffected sibling group, which in turn might explain the deficits of this group. However, we do not believe this to be the case, because (1) all siblings were thoroughly screened and, if they scored clinically on any of the screening questionnaires, the PACS interview was administered, and (2) even when symptom severity was used as a covariate, group differences between nonaffected siblings and controls remained significant. Furthermore, including measures aimed at isolating aspects of timing performance, such as time estimation and reproduction paradigms, in addition to the measure of time production would have enhanced the comprehensiveness of our findings with respect to the internal clock. Some previous studies using time estimation and reproduction tasks have reported that children with ADHD performed abnormally (see for review Toplak et al. 2006). We documented previously on time reproduction deficits present in both children with ADHD as well as their non-affected siblings (Rommelse et al. 2007b), suggesting familial deficits in timing in ADHD generalize across timing paradigms and extent beyond motor timing as reported in the current study.

Conclusions

Variability in motor timing appears a useful endophenotypic candidate: It is clearly associated with ADHD, it is also present in non-affected siblings, and it correlates within families. Accuracy (under- versus over production) in motor timing appears less useful: even though accuracy is associated with ADHD (probands and affected siblings

have a tendency to under-produce compared to controls), non-affected siblings did not exhibit this tendency and sibling correlations were only marginally significant. There were group differences in motor speed and variability (Baseline Speed task): probands and affected siblings were slower and more variable in their motor output as response to an external cue. Even though siblings resembled each other in their speed and variability, non-affected siblings performed more like controls. These findings suggest that speed and variability of externally cued motor output are associated with having ADHD, but probably not related to a familial vulnerability for the disorder. Interestingly, the speed and variability in self-generated motor output (Tapping) is normal in probands and affected siblings, making it unsuitable to unravel underlying vulnerabilities leading up to ADHD. Deficits in motor timing cannot be explained by deficits already present in basic motor output without a timing component (Baseline Speed), suggesting abnormalities in motor timing are predominantly related to deficient timing operations but not to deficient motor functioning. The finding that deficits in motor timing run in ADHD-families suggests this to be a fruitful domain for further exploration in relation to the genetic underpinnings of ADHD.

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References

Almasy L, Blangero J (2001) Endophenotypes as quantitative risk factors for psychiatric disease: rationale and study design. Am J Med Genet 105:42–44

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

Andreou P, Neale BM, Chen W, Christiansen H, Gabriels I, Heise A, Meidad S, Muller U, Uebel H, Banaschewski T, Manor I, Oades R, Roeyers H, Rothenberger A, Sham P, Steinhausen H-C, Asherson P, Kuntsi J (2007) Reaction time performance in ADHD: improvement under fast-incentive condition and familial effects. Psychol Med 37:1703–1715

Berument SK, Rutter M, Lord C, Pickles A, Bailey A (1999) Autism screening questionnaire: diagnostic validity. Br J 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. Mol Psychiatry 11:934–953

Carte ET, Nigg JT, Hinshaw SP (1996) Neuropsychological functioning, motor speed, and language processing in boys with and without ADHD. J Abnorm Child Psychol 24:481–498

Castellanos FX, Tannock R (2002) Neuroscience of attention-deficit/hyperactivity disorder: the search for endophenotypes. Nat Rev Neurosci 3:617–628

Cohen J (1988) Statistical power analysis for the behavioral sciences, 2nd edn. Erlbaum, Hillsdale

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

De Sonneville LMJ (1999) Amsterdam neuropsychological task: a computer-aided assessment program. In: Den Brinker BPLM, Beek PJ, Brand AN, Maarse SJ, Mulder LJM (eds) Cognitive ergonomics, clinical assessment and computer-assisted learning: Computers in psychology. (vol. 6). Swets & Zeitlinger, Lisse, pp 204–217

Doyle AE, Faraone SV, Seidman LJ, Willcutt EG, Nigg JT, Waldman ID, Pennington BF, Peart J, Biederman J (2005) Are endophenotypes based on measures of executive functions useful for molecular genetic studies of ADHD? J Child Psychol Psychiatry 46:774–803

Durston S, Hulshoff Pol HE, Schnack HG, Buitelaar JK, Steenhuis MP, Minderaa RB, Kahn RS, Van Engeland H (2004) Magnetic resonance imaging of boys with attention-deficit/hyperactivity disorder and their unaffected siblings. J Am Acad Child Adolesc Psychiatry 43:332–340

Faraone SV, Doyle AE (2000) Genetic influences on attention deficit hyperactivity disorder. Curr Psychiatry Rep 2:143–146

Faraone SV, Perlis RH, Doyle AE, Smoller JW, Goralnick J, Holmgren MA, Sklar P (2005) Molecular genetics of attention deficit hyperactivity disorder. Biol Psychiatry 57:1313–1323

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

Goodman R (1997) The strengths and difficulties questionnaire: a research note. J Child Psychol Psychiatry 38:581–586

Gottesman II, Gould TD (2003) The endophenotype concept in psychiatry: etymology and strategic intentions. Am J Psychiatry 160:636–645

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

Halperin JM, Schulz KP (2006) Revisiting the role of the prefrontal cortex in the pathophysiology of attention-deficit/hyperactivity disorder. Psychol Bull 132:560–581

Handy TC, Gazzaniga MS, Ivry RB (2003) Cortical and subcortical contributions to the representation of temporal information. Neuropsychologia 41:1461–1473

Harrington DL, Haaland KY, Hermanowicz N (1998) Temporal processing in the basal ganglia. Neuropsychology 12:3–12

Ivry RB (1996) The representation of temporal information in perception and motor control. Curr Opin Neurobiol 6:851–857

Kalff AC, De Sonneville LMJ, Hurks PPM, Hendriksen JGM, Kroes M, Feron FJM, Steyaert J, Van Zeben TMCB, Vles JSH, Jolles J (2003) Low- and high-level controlled processing in executive

motor control tasks in 5–6-year-old children at risk of ADHD. J Child Psychol Psychiatry 44:1049–1057
Kalff AC, De Sonneville LMJ, Hurks PPM, Hendriksen JGM, Kroes M, Feron FJM, Steyaert J, Van Zeben TMCB, Vles JSH, Jolles J (2005) Speed, speed variability, and accuracy of information processing in 5 to 6-year old children at risk of ADHD. J Int Neuropsychol Soc 11:173–183
Keele SW, Pokorny RA, Corcos DM, Ivry R (1985) Do perception and motor production share common timing mechanisms: a correlational analysis. Acta Psychol 60:173–191
Korkman M, Pesonen A (1994) A comparison of neuropsychological test profiles of children with attention deficit-hyperactivity disorder and/or learning disorder. J Learn Disabil 27:383–392
Lehmann EL (1975) Nonparametrics: statistical methods based on ranks. Holden-Day, San-Francisco
Leth-Steensen C, Elbaz ZK, Douglas VI (2000) Mean response times, variability, and skew in the responding of ADHD children: a response time distributional approach. Acta Psychol 104: 167–190
Marcotte AC, Stern C (1997) Qualitative analysis of graphomotor output in children with attentional disorders. Child Neuropsychol 3:147–153
Martin NC, Piek JP, Hay D (2006) DCD and ADHD: a genetic study of their shared aetiology. Hum Mov Sci 25:110–124
Nenadic I, Gaser C, Volz H-P, Rammsayer T, Häger F, Sauer H (2003) Processing of temporal information and the basal ganglia: new evidence from fMRI. Exp Brain Res 148:238–246
Pelham WE, Aronoff HR, Midlam JK, Shapiro CJ, Gnagy EM, Chronis AM, Onyango AN, Forehand G, Nguyen A, Waxmonsky J (1999) A comparison of Ritalin and aderall: efficacy and time-course in children with attention-deficit/hyperactivity disorder. Pediatrics 103:e43
Piek JP, Pitcher TM, Hay DA (1999) Motor coordination and kinaesthesis in boys with attention deficit-hyperactivity disorder. Dev Med Child Neurol 41:159–165
Pitcher TM, Piek JP, Barrett NC (2002) Timing and force control in boys with attention deficit hyperactivity disorder: subtype differences and the effect of comorbid developmental coordination disorder. Hum Mov Sci 21:919–945
Pitcher TM, Piek JP, Hay DA (2003) Fine and gross motor ability in males with ADHD. Dev Med Child Neurol 45:525–535
Rommelse NNJ, Altink ME, Oosterlaan J, Buschgens CJM, Buitelaar J, De Sonneville LMJ (2007a) Motor control in children with ADHD and non-affected siblings: deficits most pronounced using left hand. J Child Psychol Psychiatry 48:1071–1079
Rommelse NNJ, Oosterlaan J, Buitelaar J, Faraone SV, Sergeant JA (2007b) Time reproduction in children with ADHD and their non-affected siblings. J Am Acad Child Adolesc Psychiatry 46:582–590
Rubia K, Taylor A, Taylor E, Sergeant J (1999) Synchronization, anticipation, and consistency in motor timing of children with dimensionally defined attention deficit hyperactivity behavior. Percept Mot Skills 89:1237–1258
Rubia K, Noorloos J, Smith A, Gunning B, Sergeant J (2003) Motor timing deficits in community and clinical boys with hyperactive behavior: the effect of methylphenidate on motor timing. J Abnorm Child Psychol 31:301–313
S.A.G.E. 5.3.1 (2007) Statistical analysis for genetic epidemiology http://www.darwin.cwru.edu/sage/
Seidman LJ, Biederman J, Faraone SV, Weber W, Ouellette C (1997) Toward defining a neuropsychology of attention deficit-hyperactivity disorder: performance of children and adolescents from a large clinically referred sample. J Consult Clin Psychol 65:150–160
Seidman LJ, Biederman J, Monuteaux MC, Weber W, Faraone SV (2000) Neuropsychological functioning in nonreferred siblings of children with attention deficit/hyperactivity disorder. J Abnorm Psychol 109:252–265
Skuse DH (2001) Endophenotypes and child psychiatry. Br J Psychiatry 178:395–396
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. Biol Psychiatry 58:233–238
Smalley SL (1997) Genetic influences in childhood-onset psychiatric disorders: autism and attention-deficit/hyperactivity disorder. Am J Hum Genet 60:1276–1282
Tabachnick BG, Fidell LS (2001) Using multivariate statistics, 4th edn. Allyn and Bacon, Needham Heights
Taylor EA (1986) Childhood hyperactivity. Br J Psychiatry 149: 562–573
Toplak ME, Dockstader C, Tannock R (2006) Temporal information processing in ADHD: findings to date and new methods. J Neurosci Methods 151:15–29
Van Meel CS, Oosterlaan J, Heslenfeld DJ, Sergeant JA (2005) Motivational effects on motor timing in ADHD. J Am Acad Child Adolesc Psychiatry 44:451–460
Waldman ID (2005) Statistical approaches to complex phenotypes: evaluating neuropsychological endophenotypes for attention-deficit/hyperactivity disorder. Biol Psychiatry 57:1347–1356
Waldman ID, Nigg JT, Gizer IR, Park L, Parrley MD, Friderici K (2006) The adrenergic receptor α-2A gene (ADRA2A) and neuropsychological executive functions as putative endophenotypes for childhood ADHD. Cogn Affect Behav Neurosci 6: 18–30
Wechsler D (2000) WAIS-III Nederlandstalige bewerking. Technische handleiding. The Psychological Corporation, London
Wechsler D (2002) WISC-III Handleiding. The Psychological Corporation, London
Whitmont S, Clark C (1996) Kinaesthetic acuity and fine motor skills in children with attention deficit hyperactivity disorder: a preliminary report. Dev Med Child Neurol 38:1091–1098
Willcutt E (in press) The etiology of ADHD: behavioral and molecular genetic approaches. In: Barch D (ed) Cognitive and affective neuroscience of psychopathology. Oxford University Press, Oxford
Wing AM, Kristofferson AB (1973) Response delays and the timing of discrete motor responses. Percept Psychophys 14:5–12
Zobel A, Maier W (2004) Endophänotypen- ein neues konzept zur biologischen charakterisierung psychischer störungen. Nervenarzt 75:205–214