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Are Motor Inhibition and Cognitive Flexibility Dead Ends in ADHD?

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Abstract Executive dysfunction has been postulated as the core deficit in ADHD, although many deficits in lower order cognitive processes have also been identified. By obtaining an appropriate baseline of lower order cognitive functioning light may be shed on as to whether executive deficits result from problems in lower order and/or higher order cognitive processes. We examined motor inhibition and cognitive flexibility in relation to a baseline measure in 816 children from ADHD and control families. Multiple children in a family were tested in order to examine the familiality of the measures. No evidence was found for deficits in motor inhibition or cognitive flexibility in children with ADHD or their nonaffected siblings: Compared to their baseline speed and accuracy of responding, children with ADHD and their (non)affected siblings were not disproportionally slower or inaccurate when demands for motor inhibition or cognitive flexibility were added to the task. However, children with ADHD and their (non)affected siblings were overall less accurate than controls, which could not be attributed to differences in response speed. This suggests that inaccuracy of responding is characteristic of children having (a familial risk for) ADHD. Motor inhibition and cognitive flexibility as operationalized with mean reaction time were found to be familial. It is concluded that poorer performance on executive tasks in children with ADHD and their (non)affected siblings may result from deficiencies in lower order cognitive processes and not (only) from higher order cognitive processes/executive functions.

Keywords Inhibition · Set shifting · Endophenotype · Affected and nonaffected siblings · Familiality

Attention-Deficit/Hyperactivity Disorder (ADHD) (American Psychiatric Association [APA] 1994) is associated with impairments in the fronto–striatal–basal ganglia neurocircuitry (Casey et al. 1997; Dickstein et al. 2005; Durston et al. 2003; Giedd et al. 2001). These impairments are hypothesized to be (causally) related to deficits in higher order cognitive processes/executive functions (Barkley 1997; Casey et al. 1997; Fuster 2002; Lovejoy et al. 1999; Mehta et al. 2004; Rubia et al. 1999). Executive deficits in working memory, (motor) inhibition, cognitive flexibility and planning are frequently found in children, adolescents and adults with ADHD (Barkley 1997; Boonstra et al. 2005b; Oosterlaan et al. 1998; Oosterlaan and Sergeant 1998; Pennington and Ozonoff 1996; Sergeant et al. 2003; Sergeant et al. 2002; Willcutt et al. 2005). As the term 'higher order cognitive processes' suggests, there are also lower order cognitive processes on which higher order cognitive processes build (Halperin and Schulz 2006; Sergeant 2000; Sergeant et al. 2003; Shallice et al. 1996). Lower order cognitive processes, such as encoding, search, decision and response organization are less complex than higher order cognitive processes (Domin 1999; Parisi 1997; Sergeant 2000) and form necessary components for higher order cognitive operations (Baddeley and Della Sala

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higher order ? Why some are higher order.

1996; Domin 1999; Holyoak and Kroger 1995; Rubinstein et al. 2001; Sergeant 2000). Impairments in executive functions can theoretically result not only from deficits in higher order cognitive processes, but also from deficits in lower order cognitive processes (Baddeley and Della Sala 1996; Cools et al. 2001; Halperin and Schulz 2006; Ríos et al. 2004; Sergeant et al. 2002). A contribution may be made to the origin of executive deficits found in ADHD by distinguishing between lower order and higher order cognitive processes.

Although the hierarchical distinction between lower order and higher order cognitive processes is far from new, accounting for deficits in lower order cognitive processes, when studying higher order cognitive processes, is not a standard procedure in studies with ADHD patients. For instance, tasks that have been frequently used to examine executive functions, such as the Wisconsin Card Sorting Test, Verbal Fluency, Matching Familiar Figures Test, and Mazes (Sergeant et al. 2002) do not all allow for determining a useful baseline (i.e. measure of lower order cognitive processes) with which the higher order cognitive function can be compared. Furthermore, on computerized tasks that do allow for baseline measures of speed and accuracy, such as the Go NoGo task and Stop task (Logan and Cowan 1984; Oosterlaan et al. 1998; Trommer et al. 1988), these baselines may be somewhat confounded because of the mixture of go and stop trials. That is, the speed and accuracy on go trials are used as baseline measures, although these measures may be influenced by a preceding stop trial: The triggering of inhibition processes on a preceding stop trial may influence speed and accuracy on the following go trial. Speed and accuracy on go-trials may not, therefore, form a pure baseline measure. Obtaining a baseline for higher order cognitive processes is a complex and possibly somewhat arbitrary undertaking, although may prove to be valuable in clarifying the hierarchical origin of executive deficits in patients with ADHD. That is, whether executive deficits in these patients stem from deficits in lower order cognitive processes and/or from deficits in higher order processes.

Evidence for deficits in lower order (cognitive) processes in ADHD patients is strong. Deficits have been reported in encoding, perception, language, visuomotor integration, motor functioning, learning, memory, temporal processing, word-reading, color-naming, and pattern- and spatial recognition (August and Garfinkel 1989; Banaschewski et al. 2005; Blondis 1999; Boonstra et al. 2005b; Carte et al. 1996; Dowson et al. 2004; Garcia-Sanchez et al. 1997; Halperin and Schulz 2006; Johnson et al. 2001; Kadesjo and Gillberg 1999; Mangeot et al. 2001; Purvis and Tannock 1997; Raggio 1999; Rhodes et al. 2005; Rucklidge 2006; Sergeant 2000; Sergeant and Van der Meere 1990; Tannock et al. 2006; Van Mourik et al. 2005). It thus seems valuable to acquire some measures of baseline functioning in patients with ADHD, when studying higher order cognitive processes.

Apart from determining a baseline when studying executive functions, it is valuable to measure both speed and accuracy. It has been previously demonstrated that ADHD patients (and impulsive adults) might trade accuracy for speed (Barkley 1990; Dickman and Meyer 1988; Sergeant and Scholten 1985; Sonuga-Barke et al. 1996). Strictly speaking, such results do not indicate a process deficit in ADHD patients, but may reflect difficulties in the maintenance of an effective response set, aversion to delay, deficits in response inhibition, or differences in speed accuracy trade-off (Sonuga-Barke 2002).

The current study examines motor inhibition and cognitive flexibility in relation to a baseline measure of speed and accuracy in children and adolescents with ADHD. The particular task used in our study allows for a baseline measure of speed and accuracy and has previously been used successfully to study motor inhibition and cognitive flexibility in various clinical groups (Buizer et al. 2005; De Sonneville et al. 2002; Huijbregts et al. 2002; Mennes et al. 2006). In addition, the affected and non-affected siblings of children with ADHD and the siblings of control children were administered the task, in order to examine the familiality of possible deficits brought to light by the task. By studying the performance of relatives, it can be assessed whether deficits are familial and can serve as endophenotypes for the disorder. Endophenotypes are defined as heritable, vulnerability traits that heighten the risk for developing a disorder (Almasy and Blangero 2001; Castellanos and Tannock 2002; Gottesman and Gould 2003; Waldman 2005). They are hypothesized as forming an intermediate link between the genotype and phenotype of an individual. Since siblings share on average 50% of their genes, it is possible that nonaffected siblings carry risk genes for the disorder without the expression of the disorder in the phenotype. Because the endophenotype is theorized as having a stronger link with disease genes than the phenotype, it is possible that their enhanced genetic risk expresses itself in their endophenotypic status. In that case, nonaffected siblings will show the same deficits, probably to a lesser extent than their affected siblings, which has been previously reported for executive and non-executive functions (Nigg et al. 2004; Rommelse et al. 2007; Seidman et al. 2000; Slaats-Willemse et al. 2005; Slaats-Willemse et al. 2003). Such familially based deficits may prove useful for genetic research (Gottesman and Gould 2003).

The aim of this study was threefold. First, to examine whether children with ADHD and their nonaffected siblings showed deficits in motor inhibition and cognitive flexibility in relation to a baseline measure of speed and accuracy of responding. Second, to investigate whether possible differ-

ences in accuracy between groups were explained by differences in speed (speed accuracy trade-off). Third, to determine whether motor inhibition and cognitive flexibility were familial.

Materials and 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 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. In the ADHD-families, 238 probands (all with combined subtype ADHD), 112 affected siblings (64 with combined subtype, 28 with inattentive subtype and 20 with hyperactive-impulsive subtype) and 195 nonaffected siblings participated. Control-families consisted of 271 children. For 51 control children, no additional control sibling could be recruited for the study, because the sibling was unwilling to participate or because the control-family consisted of only one child.

All children were between the ages of 5 and 19 years 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.

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

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 in a family that were rated clinically on any of the questionnaires completed either by parents or teachers, 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 raw score of ≥15 was obtained on the Social Communication Questionnaire (SCQ; Berument et al. 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') in 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 in 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 nonaffected siblings.

The Conners' long version for both parents and teachers was completed for control children. Control children were required to obtain non-clinical scores on both the parent and teacher version (Conners'-N-scale: *T*-score ≤62) to be accepted in the study. Table 1 provides the characteristics of the four groups.

Procedure

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 in a family. Psychostimulants were discontinued for at least 48 h before testing took place (Pelham et al. 1999). Children were motivated with small breaks. At the end of the session, a gift worth approximately € 4, was given. Control children were tested in a similar way in a quiet room at their school. The study had medical–ethical approval.

The tasks described in this study were part of a broader neuropsychological assessment battery used in the Dutch

Table 1 Sample characteristics

	Probands		Affected siblings		Nonaffected siblings		Normal controls		$F_{3,812}$	Contrasts based on p-values of 0.05
	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 and 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 and 1<3=4 2=3 and 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	–			–			

1 = Probands, 2 = Affected siblings, 3 = Nonaffected 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.

part of the IMAGE study (Rommelse et al. 2007), consisting of cognitive, timing and motor tasks that were presented in different order (Latin square). Administration of the whole battery (including breaks) took about 3–4 h.

Experimental Task

The task consisted of three blocks and was designed to measure motor inhibition and cognitive flexibility (De Sonneville 1999). The first block was designed to acquire a baseline of the speed and accuracy of responding with which the performance on the two succeeding blocks could be compared. In all blocks, a horizontal bar consisting of ten grey squares (26×26 mm each, 4 mm distance between squares) was presented permanently at the centre of the screen. From trial to trial, a coloured square moved across the bar in a random direction (either one square to the right or to the left). In the first trial of every block, the square was coloured green and started at the fifth position from the right. Responses were required to be initiated between 150 and 5,000 ms after a square moved one position, otherwise a trial was replaced. The task was self-paced with post-response intervals of 250 ms. Children were instructed before each block.

In **Block 1** (ten practice trials, 40 experimental trials), the moving square was coloured green, and *compatible responses* were required: Children were instructed to press a response button as quickly and accurately as possible that corresponded to the direction in which the stimulus moved. This block was used to acquire a baseline of speed and accuracy of responding.

In **Block 2** (ten practice trials, 40 experimental trials), the moving square was coloured red, and *incompatible responses* were required: Children were instructed to press a response button as quickly and accurately as possible in the direction opposite to which the stimulus moved. The suppression of the automatic compatible response, in order to generate a non-automatic incompatible response, was hypothesized as requiring motor inhibition. Motor inhibition was operationalized as the difference in mean reaction time or percentage of errors between Blocks 1 and 2.

In **Block 3** (16 practice trials, 80 experimental trials), the colour of the moving square alternated randomly between green and red, and *both compatible and incompatible responses* were required. Thus, both the direction and the colour of the square were unpredictable. The colour of the square simultaneously changed, when the square moved

one position. When the colour of the square was green and the square had moved one position, a compatible response was required (as in Block 1). When the colour of the square was red and the square had moved one position, an incompatible response was required (as in Block 2). The mixture of both compatible and incompatible trials was hypothesized as requiring higher levels of cognitive flexibility (Los 1996). Cognitive flexibility was operationalized as the difference in mean reaction time or percentage of errors between Block 1 and the compatible trials of Block 3. Both in Blocks 1 and 3, compatible responses were required. The difference between both blocks lay in the fact that in Block 3, the participant did not know on forehand that a compatible response was required, whereas the participant did in Block 1.

The main dependent measures were mean reaction time and percentage of errors. An auxiliary dependent measure was the speed with which errors were committed. This measure was not used as a main dependent measure, since data on this variable was limited to children who actually committed errors.

Data Analyses

The missing data for mean reaction time and errors was less than 5%. Missing data were replaced by means of Expectation Maximization (Tabachnick and Fidell 2001). Alpha was set at 0.05. Variables were successfully normalized by applying a natural log transformation (SPSS version 14).

Main effects of possible confounders gender, age and IQ were examined only in the control group to avoid dependence with the main factor group. Gender was used as fixed factor, age and IQ as covariates and family as random effect. The interactions between group and the confounders were tested to investigate whether the possible confounders could be used as simple covariates. The mean reaction times and the percentage of errors were analysed across blocks.

In order to address the first question of the paper, we tested whether groups differed for motor inhibition and cognitive flexibility. A mixed model was used with group as fixed factor (four groups: probands, affected siblings, nonaffected siblings, and controls), block as repeated measure, age as covariate and family as random effect to account for within family correlation. Importantly, the group by block interaction was implemented in the model, in order to test whether group differences for reaction time and errors would be larger in Block 2 versus Block 1 (reflecting motor inhibition) and larger on compatible trials in Block 3 versus Block 1 (reflecting cognitive flexibility). Second, to examine whether possible inaccuracy in children with ADHD and their nonaffected siblings was due to an enhanced speed with which they committed errors, group differences were calculated for mean reaction time on errors. A mixed model was used with group as fixed factor, age as covariate, and family as random effect. Third, familiality of motor inhibition and cognitive flexibility was investigated by calculating the covariances between siblings in a family.

Results

Testing of Possible Confounders Gender, Age, and IQ

IQ did not affect mean reaction time or errors (F (1, 265.0)= 0.07, p=0.79 and F (1, 265.6)=0.39, p=0.53). The same was true for gender (mean reaction time: F (1, 269.0)=2.51, p=0.11 and errors: F (1, 258.8)=2.57, p=0.11). IQ and gender did not interact with group and were, therefore,

Table 2 Means and SDs of the untransformed task variables

	Probands		Affected siblings		Nonaffected siblings		Normal controls	
	M	SD	*M*	SD	*M*	SD	*M*	SD
Block 1								
Mean reaction time	447.8	128.9	453.2	200.3	477.5	178.0	439.1	138.0
Percentage of errors	6.3	7.1	5.7	7.7	4.6	5.4	3.6	4.6
Block 2								
Mean reaction time	680.0	232.0	700.4	331.0	753.4	300.9	714.3	320.4
Percentage of errors	14.9	13.2	13.4	14.3	13.2	12.9	10.4	12.1
Block 3								
Mean reaction time								
Compatible trials	984.8	290.3	1,047.3	371.3	1,069.2	367.5	1,043.6	373.2
Incompatible trials	1,070.7	336.1	1,114.8	392.2	1,163.3	431.6	1,119.0	424.2
Percentage of errors								
Compatible trials	19.7	17.1	16.7	14.9	18.1	17.5	14.0	15.0
Incompatible trials	21.6	17.3	19.0	16.6	20.4	17.1	15.7	14.1

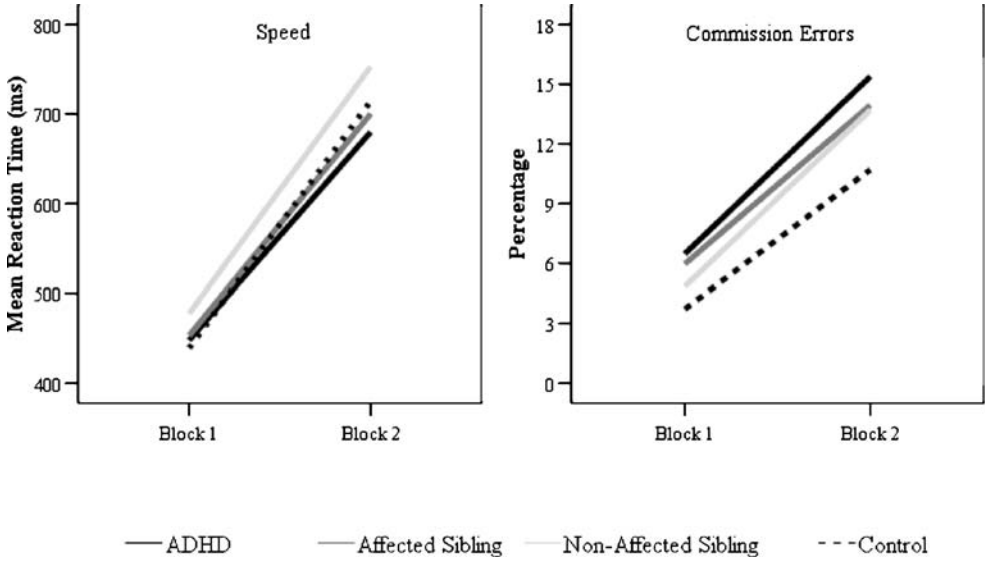

Fig. 1 Motor inhibition in probands, affected siblings, nonaffected siblings and controls as reflected by differences in reaction time and percentage errors between the presentation of incompatible trials (Block 2) compared to the presentation of compatible trials (Block 1)

omitted from further analyses (mean reaction time: IQ F (3, 533.1)=0.62, p=0.60, gender F (3, 671.3)=0.51, p=0.68; errors: IQ F (3, 521.4)=0.71, p=0.55, gender F (3, 692.7)= 0.23, p=0.87). Age, however, strongly influenced both the mean reaction time and errors (F (1, 233.2)=376.16, p< 0.001 and F (1, 216.0)=60.64, p<0.001, respectively). Older subjects performed faster and more accurately than younger subjects. To test whether the effect of age was comparable across groups and could be used as a simple covariate, the interaction between group and age was tested. The interaction group by age was significant for mean reaction time (F (3, 611.0)=2.65, p=0.05), suggesting the effect of age was not entirely comparable across groups and, as a consequence, both the main effect of age as well as the interaction group by age were implemented in the further analyses on mean reaction time. The group by age interaction was not significant, however, for errors (F (3, 608.0)=1.29, p=0.28), suggesting possible group differences were comparable across the age range studied. Therefore, age could be used as a simple covariate for analyses of errors. Raw data is presented in Table 2.

Motor Inhibition and Cognitive Flexibility

Motor Inhibition

A significant main effect was found for block on *mean reaction time* (F (1, 816.0)=2159.72, p<0.001), indicating reaction times were slower in Block 2 compared to Block 1, which suggested Block 2 was found to be more difficult than Block 1 and indicated our task manipulation succeeded. No significant effect of group was found (F (3, 632.2)=

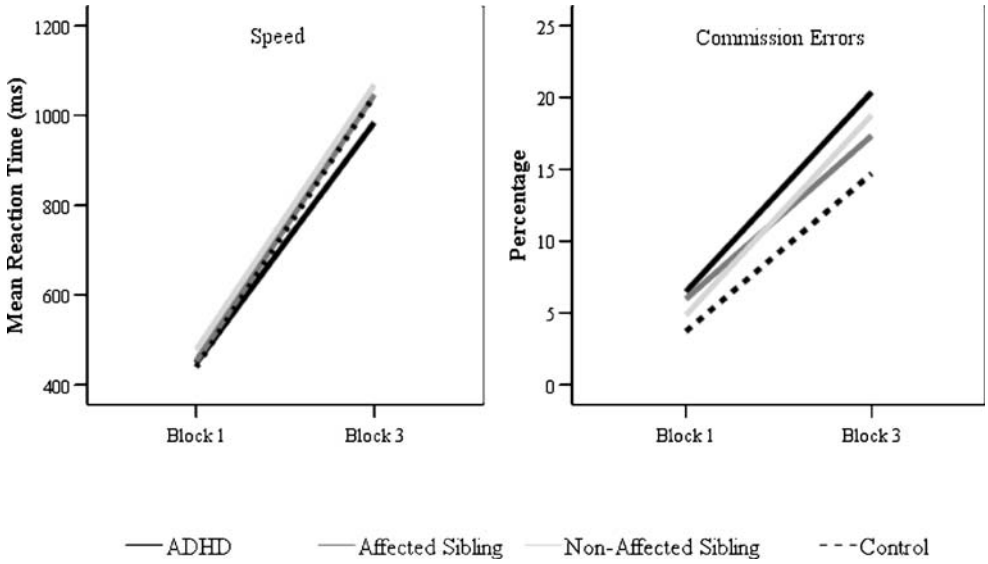

Fig. 2 Cognitive flexibility in probands, affected siblings, nonaffected siblings and controls as reflected by differences in mean reaction time and percentage of errors between the presentation of a mixture of compatible and incompatible trials (Block 3, compatible trials) compared to the presentation of compatible trials (Block 1)

2.59, p=0.18). Importantly, no significant group by block interaction was present (F (3, 816.0)=1.68, p=0.17), indicating probands, affected siblings, and nonaffected siblings were not disproportionally slow in Block 2 versus Block 1 compared to controls.

Again, a significant main effect of block was found when the *errors* were analyzed (F (1, 816.0)=299.14, p< 0.001), indicating more errors were made in Block 2 compared to Block 1. A significant effect of group was found (F (3, 725.8)=14.59, p<0.001). Pairwise comparisons indicated that probands, affected siblings and nonaffected siblings committed more errors than controls (p< 0.001, p=0.003, and p=0.02, respectively). Probands made more errors than their affected and nonaffected siblings (p= 0.04 and p<0.001, respectively). Affected and nonaffected siblings did not differ (p=0.35). The interaction group by block was not significant (F (3, 816.0)=0.21, p=0.89), indicating that the elevated percentage of errors of probands, affected siblings, and nonaffected siblings was already evident in the baseline measure (Block 1) and did not disproportionally increase in Block 2 compared to controls. Thus, there was no evidence for motor inhibition deficits in children with ADHD or their siblings either for mean reaction time or for errors (see Fig. 1).

Cognitive Flexibility

As expected, *mean reaction times* were significantly slower in Block 3 (compatible trials) compared to Block 1 (F (1, 816.0)=6380.12, p<0.001). Groups differed in mean reaction time (F (3, 620.4)=2.78, p=0.04). Pairwise comparisons revealed that nonaffected siblings were marginally slower than controls (p=0.06) but none of the other comparisons were significant. A significant group by block interaction was present (F (3, 816.0)=2.96, p=0.03). Post hoc comparisons revealed, however, no significant differences between individual groups.

With respect to *errors*, more errors were made in Block 3 (compatible trials) compared to Block 1 (F (1, 816.0)= 571.12, p<0.001). Groups differed in the percentage of errors (F (3, 423.2)=20.29, p<0.001). Pairwise comparisons indicated that probands, affected siblings, and nonaffected siblings made more errors than controls (p<0.001, p=0.001, and p=0.002, respectively). Probands produced more errors than their affected and nonaffected siblings (p=0.006 and p<0.001). Affected and nonaffected siblings did not differ (p=0.51). No significant group by block interaction was present (F (3, 816.0)=0.21, p=0.89), indicating that the elevated number of errors was already present in the baseline measure (Block 1) and did not increase in Block 3. Therefore, there was no evidence of cognitive flexibility problems in children with ADHD or their siblings either for mean reaction time or for errors (see Fig. 2).

Group Differences for Speed on Errors

In Block 1, reaction times of errors did not differ significantly from the general mean reaction times (F (1, 816.1)= 2.08, p=0.15) and groups did not differ in the speed with which they committed errors (F (3, 650.4)=0.14, p=0.94). This ruled out a fast guess or impulsive strategy difference between groups. The larger percentage of errors of probands and their (non)affected siblings in the baseline measure was thus not attributable to differences in speed between the groups.

In Block 2, reaction times for errors were slower than the mean reaction times (F (1, 816.1)=161.42, p<0.001), but groups did not differ in the speed with which they made errors (F (3, 604.4)=0.06, p=0.98). The larger percentage of errors of probands and their (non)affected siblings in Block 2 could, therefore, not be attributed to differences in strategy.

In Block 3, the reaction time on errors was faster than the mean reaction time (F (1, 816.0)=3458.0, p<0.001). Groups differed in the speed with which errors were made (F (3, 806.6)=5.19, p=0.001). Pairwise comparisons revealed that probands, affected siblings and nonaffected siblings had slower errors than controls (p<0.001, p=0.002 and p= 0.007, respectively). Probands committed errors at the same speed as their affected siblings (p=0.42) and slower than their nonaffected siblings (p=0.05). Affected and nonaffected siblings did not differ (p=0.44). Since probands, affected and nonaffected siblings were not faster than controls in making their errors, their greater percentage of errors could not be attributed to fast/impulsive responding.

Familiality of the Task Measures

Motor inhibition and cognitive flexibility were operationalized by subtracting the mean reaction time and percentage of errors of Block 1 from the mean reaction time and percentage of errors of Block 2 (motor inhibition) and on compatible trials in Block 3 (cognitive flexibility). Siblings resembled each other in motor inhibition and cognitive flexibility for mean reaction time (motor inhibition: Wald Z=2.63, p=0.009, EC [Estimation of Covariance]=0.09, 95% CI [Confidence Interval]: 0.04–0.18 and cognitive flexibility: Wald Z=6.90, p<0.001, EC=0.11, 95% CI: 0.08–0.14). Siblings did not resemble each other in motor inhibition or cognitive flexibility regarding the percentage of errors. This appeared to be due to the restriction of variance of this measure.

Discussion

In this study we examined whether children with ADHD and their nonaffected siblings were impaired in motor inhibition and cognitive flexibility, whether possible differ-

ences in accuracy were related to differences in speed with which errors occurred, and whether motor inhibition and cognitive flexibility were familial.

No evidence was found for deficits in motor inhibition or cognitive flexibility in probands, affected siblings, or nonaffected siblings compared to controls: Children with ADHD and their nonaffected siblings were not disproportionally affected compared to a baseline measure. It appears that their inaccuracy of responding stems from more basic deficiencies already apparent in the baseline measure. This suggests that impairments in the higher order cognitive processes of motor inhibition and cognitive flexibility may depend upon deficits in lower order cognitive processes. These findings challenge the proposition of disinhibition or executive dysfunction as the core deficit in ADHD (Barkley 1997; Pennington and Ozonoff 1996). These findings are discrepant with some studies reporting on problems in motor inhibition and cognitive flexibility in which baseline functioning was taken into account, such as the Stop task or Go NoGo (Logan and Cowan 1984; Oosterlaan et al 1998; Trommer et al. 1988). These discrepancies might be related to differences in task paradigms: The Stop task and Go NoGo tasks require children to withhold a prepotent response on some trials, whereas in our paradigm children had to execute a response on every trial. Withholding from reacting on some trials (Stop task and Go NoGo task) or withholding an automatic/compatible response on all trials while executing a controlled/incompatible response (our paradigm) might rely on different cognitive processes, which may be differentially impaired in ADHD. Similarly, cognitive flexibility as assessed by the Wisconsin Card Sorting Test might rely on different processes than cognitive flexibility in our paradigm: The Wisconsin Card Sorting test requires a subject to extract the problems solving rules, which also change during the test without the subject's knowledge, whereas in our paradigm the problem solving rule is known to the subject and constant during the test.

The implications of the absence of deficits in motor inhibition and cognitive flexibility may be profound. The hypothesis that executive deficits form the core basis of (neuro)psychological dysfunctions in ADHD has dominated the literature of the past decade (Barkley 1997; Castellanos and Tannock 2002; Oosterlaan et al. 1998; Oosterlaan and Sergeant 1998; Pennington and Ozonoff 1996; Schachar et al. 2000; Sergeant et al. 2002; Tannock 1998; Willcutt et al. 2005). Undoubtedly, many children, adolescents and adults suffer from deficits in one or more domains of executive functioning (Boonstra et al. 2005b; Doyle 2006). However, whether these executive deficits stem from problems in the higher order cognitive processes or lower order cognitive processes, as our findings suggest, remains still a vital issue in need of research. How this absence of executive dysfunction in our study relates to the presence of anatomical and functional abnormalities found in the (pre)frontal lobe in ADHD patients, is a complex theoretical issue. It might be that the (pre)frontal lobes are not causally involved in the disorder, but contribute to the age related recovery of symptoms frequently observed in ADHD patients (Halperin and Schulz 2006). Just like abnormalities in the frontal lobe in patients with ADHD may result from dysfunctions in earlier developing brain areas, executive deficits may result from non-executive deficits. Our findings suggest that executive dysfunctions in ADHD may results from deficits in lower order cognitive processes and not (only) from deficits in higher order cognitive processes. This calls into question the theories stating executive dysfunctions are the primary deficits in ADHD, which explain ADHD deficits as solely/primarily out of executive dysfunctions.

The inaccuracy of performance of probands, affected siblings, and nonaffected siblings could not be attributed to possible group differences in processing speed, previously documented in self-paced tasks (Koschack et al. 2003; Sonuga-Barke et al. 1996). Overall, groups did not differ in the speed with which they performed the task and did not differ in the speed with which they committed errors, except in Block 3. Contrary to expectations based on a speed accuracy trade-off, children with ADHD and their nonaffected siblings were slower, not faster, than control children when committing an error, which has been previously reported (Sergeant and Van der Meere 1990). It thus appears that the elevated number of errors on the task was clearly not related to an impulsive response style in children with ADHD and their nonaffected siblings. The comparable speed of children with ADHD, their nonaffected siblings and controls may be explained by the self-paced character of the task: The next trial started 250 ms after the response on the previous trial. In contrast to externally paced tasks, participants can determine their own response speed. It appears that children with ADHD and their nonaffected siblings are not impaired in their reaction time, when the pace of stimuli depends on their own speed of responding (Sonuga-Barke et al. 1996).

The familiality of both motor inhibition and cognitive flexibility were estimated in order to examine the usefulness of both measures as heritable, vulnerability traits. Mixed results have been obtained regarding the usefulness of both processes as endophenotypes. On the one hand, both motor inhibition as well as cognitive flexibility, as operationalized by mean reaction times, appeared significantly familial. This opens up avenues for using these processes to unravel the underlying cognitive vulnerabilities that give rise to an enhanced risk of having ADHD. On the other hand, children from ADHD families were unimpaired in motor inhibition and cognitive flexibility, which suggests that both measures may be unsuitable for

revealing an underlying deficit in ADHD families. Furthermore, only mean reaction times and not errors were familial. This latter finding might be related to metric limitations of errors: Even when normalization procedures were applied to errors, the normal distribution and variance remained restricted. Sufficient variation within a measure is required for estimation of covariance between siblings. Errors, though, seemed a characteristic deficiency in children with ADHD and children having a familial risk for ADHD and seem to be related to the severity of (a familial risk for) ADHD, with probands committing the most errors, followed by their affected siblings, and then their nonaffected siblings. The higher rate of errors in children with ADHD is a consistent finding across studies using widely different neuropsychological tasks (Boonstra et al. 2005a; Losier et al. 1996; Oosterlaan and Sergeant 1998; Trommer et al. 1991). The source of this general inaccuracy of performance, reflected by an elevated amount of errors on virtually all neuropsychological domains, may lie in basic deficiencies in the processing of incoming signals and/or deficiencies in the organization of a response (Sergeant 2000). What is evident, though, is that general inaccuracy of performance is an important feature of ADHD, appears present in non-affected family-members as well, and may thus shed light on the familiality of underlying basic processing difficulties.

With respect to the clinical implications of our work, the results suggest that children with ADHD experience problems in basic response output. This may imply that even when they have to perform simple tasks or chores, errors are likely to occur. Since children with ADHD were not faster (i.e. hastier) than controls when making an error, it appears their error-prone performance is not caused by their hastiness to get the task done. The same appears to be true for non-affected brothers and sisters of children with ADHD. Even though they do not portray obvious symptoms of inattention and hyperactivity-impulsivity, they appear to share at least some of the underlying neuropsychological difficulties characterising of ADHD, which may be easily overlooked in the absence of clear ADHD symptoms.

Taken together, no evidence was found for deficits in motor inhibition or cognitive flexibility in children with ADHD or their nonaffected siblings: Compared to their baseline speed and accuracy of responding, they were not disproportionally slow or inaccurate, when demands for motor inhibition or cognitive flexibility were added to the task. Overall, however, probands, affected, and nonaffected siblings were less accurate than controls, which could not be attributed to differences in speed. This suggests inaccuracy of responding is characteristic of children having (a familial risk for) ADHD. Motor inhibition and cognitive flexibility as operationalized with mean reaction time were familial. It may be concluded that poorer performance on executive tasks in children with ADHD and their nonaffected siblings may result from deficiencies in lower order cognitive processes and not (only) from higher order cognitive processes/executive functions.

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