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Performance variability, impulsivity errors and the impact of incentives as gender-independent endophenotypes for ADHD

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Abstract

Background—Attention-deficit hyperactivity disorder (ADHD) is one of the most common and highly heritable child psychiatric disorders. There is strong evidence that children with ADHD show slower and more variable responses in tasks such as Go/Nogo tapping aspects of executive functions like sustained attention and response control which may be modulated by motivational factors and/or state-regulation processes. The aim of this study was (1) to determine if these executive functions may constitute an endophenotype for ADHD; (2) to investigate for the first time whether known modulators of these executive functions may also be familial and (3) to explore whether gender has an impact on these measures.

Methods—Two hundred and five children with ADHD combined type, 173 nonaffected biological siblings and 53 controls with no known family history of ADHD were examined using a Go/Nogo-Task in the framework of a multi-centre study. Performance-measures and modulating effects of event-rate and incentives were examined. Shared familial effects on these measures were assessed, and the influence of gender was tested.

Results—Children with ADHD responded more slowly and variably than nonaffected siblings or controls. Nonaffected siblings showed intermediate scores for reaction-time variability, false alarms and omission errors under fast and slow event rates.

A slower event-rate did not led to reduced performance specific for ADHD. In the incentive condition, mean reaction times speeded-up and became less variable only in children with ADHD

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and their nonaffected siblings, while accuracy was improved in all groups. Males responded faster, but also committed more false alarms. There were no interactions of group by gender.

Conclusions—Reaction-time variability and accuracy parameters could be useful neuropsychological endophenotypes for ADHD. Performance modulating effects of incentives suggested a familially-driven motivational dysfunction which may play an important role on etiologic pathways and treatment approaches for ADHD. The effects of gender were independent of familial effects or ADHD-status, which in turn suggests that the proposed endophenotypes are independent of gender.

Keywords

attention-deficit hyperactivity disorder; ADHD; endophenotype; executive function; reaction time variability; false alarms; state regulation; incentives

Introduction

The core symptoms of Attention-Deficit/Hyperactivity Disorder (ADHD) - age-inappropriate levels of hyperactivity, impulsivity and inattention – are present in at least 3–5% of school-aged children (American-Psychiatric-Association, 1994). They occur independently of cultural background, but are overrepresented in boys (Rohde *et al.*, 2005). Twin and adoption studies yielded heritability rates of 76% (Faraone *et al.*, 2005), but single risk-alleles contribute only slightly to the overall risk for ADHD (Castellanos & Tannock, 2002; Faraone et al., 2005).

Endophenotypes are intermediate phenotypes representing quantitative and heritable vulnerability traits. To clarify the etiologic pathways from genes over gene-environment interactions to the symptoms of ADHD, endophenotypes should be assed at different levels of investigation (e.g. neuropsychology, EEG, MRI) (Buitelaar, 2005; Gottesman & Gould, 2003). Theoretically, genetic effects should be larger for endophenotypes than for the phenotypes used in diagnosis making them better targets for molecular genetic studies (Doyle *et al.*, 2005). Moreover, endophenotypes may serve as useful intermediate constructs to explain the heterogeneity of the ADHD phenotype (Banaschewski *et al.*, 2007; Buitelaar, 2005; Rommelse *et al.*, 2007).

At the level of neuropsychology, numerous studies suggest that ADHD symptoms may be closely related to impairments of executive functions (EF) such as behavioural inhibition or sustained attention (Barkley, 1997; Pennington & Ozonoff, 1996; Sergeant, 2005; Sonuga-Barke, 2005). Children suffering from ADHD perform poorly in a wide range of tasks that require response control (Drechsler *et al.*, 2005; Mason *et al.*, 2005). In general, their responses tend to be slower, more variable and more error-prone (Barkley, 1997; Tannock, 1998). These findings may indicate a suboptimal state of activation (Castellanos *et al.*, 2005; Kuntsi *et al.*, 2001; Sergeant, 2005). They may also, in part, be explained by delay aversion (Scheres et al., 2001; Sonuga-Barke, 2005) or alterations in a delay-of-reinforcement gradient (Luman *et al.*, 2005; Sagvolden *et al.*, 2005). Slow event rates should lead to underactivation and thus to slow and inaccurate responding; fast event rates might induce a fast but inaccurate response style (Sanders, 1983), particularly in ADHD (Sergeant, 2005). Thus, various studies reported that slow event-rates can impair performance in ADHD-compared to normal control children (Sergeant, 2005; van der Meere *et al.*, 1995a). Further, children with ADHD seem to be highly sensitive to reward (Douglas & Parry, 1994), and some studies found improved performance if incentives were given within due time (Sagvolden et al., 2005; Slusarek *et al.*, 2001). Recently, it was reported that certain performance parameters of a four-choice reaction time task (e.g. reaction-time variability)

seemed to reflect an endophenotype, although it remained unclear whether the modulators of performance, event-rate and incentives, were familial (Andreou *et al.*, 2007).

Hence, several models of ADHD impairment can explain poorer performance, slower reaction times (RT) and higher reaction-time variability (RT-SD) and their modulation by event-rates and incentives. The Go/Nogo task has been found to be adequate to assess sustained attention and response control and for investigation of the influence of the above mentioned conditions (Borger & van der Meere, 2000).

The aim of this study was to examine whether general aspects of task performance such as speed, accuracy or performance homogeneity represent endophenotypes. Further, the influence of modulating factors like event-rate and incentives on these parameters was investigated. Finally, we tested whether there were effects of age and gender independent of performance differences between groups.

METHODS AND MATERIALS

Sample

Recruitment of participants was conducted as part of the International Multi-Center ADHD Gene study (Asherson, 2004; Kuntsi *et al.*, 2006). Families with more than three biological members including at least one child with ADHD symptoms were recruited from ADHD outpatient clinics or specialized private practices in Germany, Ireland, Israel, Spain and United Kingdom. The control group was recruited from primary and secondary schools in London, UK, and in Göttingen, Germany. Participants had to be 6–18 years of age at the time of entry into the study. Exclusion criteria included autism, epilepsy, IQ below 70, brain disorders and any genetic or medical disorder that may mimic ADHD. Ethical approval for this study was obtained from local ethical review boards.

Overall, datasets from 445 children aged 6–18 years either diagnosed with a research diagnosis of ADHD combined type, or nonaffected siblings of ADHD children or unrelated controls without a clinical diagnosis or known family history of ADHD as described below were available. Due to technical problems, datasets of 14 ADHD-participants had to be excluded. Therefore, the sample analysed consisted of 53 (38 boys) controls, 173 (75 boys) nonaffected siblings of ADHD-participants and 205 (186 boys) participants with a diagnosis of ADHD combined-type (see also Table 1 of the supplementary online material). Outlying task performance was defined as two standard deviations over the mean target RT and with the false alarm rate below the grand mean or vice versa. No outliers with such extreme speed-accuracy trade-offs were found. As females were outnumbered in the ADHD-group ($\chi^2_{(2)}$=99.3, p<.01), analyses controlled for gender effects. There were no group or gender differences in age (both $F_{(1/2, 425)}$<.1, p>.9); but control children showed higher estimated IQs than nonaffected siblings and participants with ADHD ($F_{(2, 425)}$=4.7**, p<.01). In addition, the males' estimated IQs were higher than females' ($F_{(2, 425)}$=5.2**, p=.02). The proportion of children with an estimated IQ lower than 80 was small (6%) and did not differ among groups ($\chi^2_{(2)}$=2.4, p=.31). As indicated by the Strengths and Difficulties Questionnaire (SDQ), participants with ADHD displayed more behaviour problems than both controls and nonaffected siblings (all $F_{(2, 423/411)}$>8.3, p<.01; see Figure 1). Nonaffected siblings were rated as slightly more hyperactive than control children by teachers, but the mean ratings lay in the normal range (Woerner *et al.*, 2004). Parents and teacher reported girls as less hyperactive (both $F_{(1, 423/411)}$>7.9, p<.01) and more prosocial (both $F_{(2, 423/411)}$>5.3, p<.05).

Procedure

Families that came into consideration were contacted. In case of interest, detailed information material and clinical questionnaires as screening instruments for ADHD and global psychological background (Long versions of Conners rating scales for parents, CPRS-R:L and teachers CTRS-R:L (Conners *et al.*, 1998a, 1998b), parent and teacher version of the Strengths and Difficulties Questionnaire (SDQ) (Goodman, 1997; Woerner et al., 2004), Social Communication Questionnaire (SCQ) (Berument *et al.*, 1999) were provided for all children. If T-scores on the Conners ADHD scale (N) exceeded 63 and scores on the SDQ Hyperactivity scale exceeded the 90th percentile, a semi-structured clinical interview (PACS (Chen & Taylor, 2006)) was conducted with one parent by trained investigators in order to verify ADHD diagnosis and to confirm the presence or absence of symptoms from other child psychiatric disorders. To ensure that unrelated control children recruited from primary and secondary schools were free of a susceptibility for ADHD, children with T-scores exceeding 63 on both parent and teacher rated Conners DSM-IV ADHD total symptoms scales or with a family history of ADHD as obtained by non-structured clinical interviews were excluded. The Go/Nogo-Task reported here was part of a neuropsychological test-battery that also contained two other neuropsychological tests described elsewhere (Andreou et al., 2007; Marco *et al.*, 2009) and several subtests from the WISC/WAIS (vocabulary, similarities, picture completion, and block design) in order to obtain an estimate of the child's IQ (Sattler, 1992). Prior to cognitive testing children were free of medication for at least 48 hours. Blood samples were also taken for subsequent DNA extraction. The neuropsychological testing took place in noise shielded rooms in the respective departments. At the end of the session, all children earned small prizes; parents did not receive any financial reward for participation except reimbursement.

Stimuli and Task

On each trial of the Go/No-Go Task (Borger et al., 1999; Kuntsi *et al.*, 2005; van der Meere et al., 1995b), one of two possible stimuli (letters X or O) appeared for 300 ms in the middle of the computer screen. The children were instructed to respond only to the 'go' stimuli (letter X) and to react as quickly as possible, but to maintain a high level of accuracy. The proportion of 'go' to 'no-go' stimuli was 4:1.

The children performed the task under three different conditions. The fast condition consisted of 462 trials with an inter-stimulus-interval (ISI) of 1 s. The ISI increased to 8 s in the slow presentation condition, which consisted of 72 trials. The order of the slow and fast conditions varied randomly across children. During practice-sessions (with 18 trials for fast and 6 trials for the slow condition), the tester ensured that the child had understood the instructions and gave feedback. The incentive condition was always administered last at the centres in Göttingen and London. This condition is a modification of the incentive condition used in the study of the stop task by Slusarek (Slusarek et al., 2001). Each correct response to the letter X and each correct non-response to the letter O earned one point, but for each omission error (failure to respond to X) and for each failure to respond within 2 s one point was lost. Each false alarm (incorrect response to O) led to the loss of five points. The points were shown in a box, immediately right of the screen centre that was updated continuously throughout. The task started with a deposit of 40 points to avoid the possibility of a negative tally. The children were asked to earn as many points as possible, as the points would be exchanged for a real prize after the game ended. This condition was intended to be comparable to the slow condition and thus consisted of 72 trials and had an ISI of 8 s.

Altogether, fast, slow and incentive condition lasted approximately 11 minutes each. A preliminary reliability study revealed moderate-to-good retest reliability(Kuntsi et al., 2005).

Analyses

All analyses were conducted using SPSS 12.0.2. Since the dependant variables RT, intraindividual variability of RT (RT-SD), percentage of false-alarms and percentage of omission-errors for both fast and slow condition show developmental trends, age was taken as a covariate in every comparison.

Repeated-measure ANCOVAs with the within-subject factor “condition” (slow vs. fast) and between-subject factors “group” (controls, nonaffected siblings, participants with ADHD) and “gender” together with Sidak-adjusted post-hoc-tests were conducted for all dependent variables. For significant interaction effects “condition*group”, a post-hoc ANCOVA with dependent variable “difference between conditions” was performed. Effects of the incentive condition were analysed for the Göttingen and London sub-sample separately with repeated measure ANCOVAs for all dependant variables with within-subject factor “condition” (slow vs. incentive) and between-subject factor “group” and “gender”.

As four performance parameters were tested in each analysis, following the Sidak procedure a significance level of $p<.013$ retains the overall significance level of $p<.05$. Moreover, additional nonparametric statistics (overall Kruskal-Wallis tests, followed by post-hoc Mann-Whitney U-tests) for the boys-only subsample were performed in order to provide a statistic free of assumptions about the distribution of the data.

To address effects of familiality, trend analyses across groups were performed to test whether non-affected siblings were located intermediately between ADHD and control children. This would be indexed by a linear trend in the absence of a residual quadratic trend. A residual quadratic component would indicate that the non-affected siblings were either more similar to the control or more similar to the ADHD group (Albrecht *et al.*, 2008; Hager, 1996; Slaats-Willemse *et al.*, 2003).

Results

Impact of event-rate

Go mean reaction-time—Reaction times were generally slower for the slow compared to the fast event-rate condition (“condition”, $F_{(1, 424)}= 135.9$, $p>.01$, see Figure 2 and Table 2 of the supplementary material) and are subject to developmental effects (“Age”, $F_{(1, 424)}=225.3$, $p<.01$). The difference between conditions was smaller with increasing age (“condition*age”, $F_{(1, 424)}=43.1$, $p<.01$). Groups differed in mean RT ($F_{(2, 424)}=9.9$, $p<.01$), with controls and nonaffected siblings responding generally faster than individuals with ADHD, which was confirmed by nonparametric analyses of the boys-only sub-sample ($\chi^2_{(2)}=14.9$, $p<.01$). Generally, boys responded faster than girls ($F_{(1, 424)}=6.2$, $p=.01$), and this effect of gender was additive in both groups and conditions (interaction-effects revealed in any case $F_{(1/2, 424)}<1$, $p>.38$). Total mean RT showed a linear ($p<.01$) but also a quadratic trend ($p=.02$) whilst the total RT-difference between fast and slow condition showed no linear trend ($p=.20$) but a tendency towards a quadratic trend ($p=.09$) across groups which indicates that nonaffceted siblings’ performance was distributed near that of controls.

Reaction-time variability—Analyses of RT-SD showed a similar pattern of results to the analyses of RT, with the exception that no gender-differences were found. RT-SD decreased with age ($F_{(1, 424)}=155.9$, $p<.01$) and was higher in the slow compared to the fast condition ($F_{(1, 424)}=68.9$, $p<.01$); however, with increasing age this effect was less pronounced (“Condition*Age”, $F_{(1, 424)}=42.5$, $p<.01$). Furthermore, controls showed the lowest and participants with ADHD showed the highest RT-SD with nonaffected siblings located

intermediate ("Group", $F_{(2, 424)}$=17.4, p<.01, confirmed by the nonparametric analyses of the boy-only subsample, $\chi^2_{(2)}$=38.6, p<.01).

Trend analyses across groups revealed for total mean RT-SD a linear (p<.01) and not a quadratic trend (p=.47) which indicates that nonaffceted siblings did show a degree of RT-SD intermediate between the controls and participants with ADHD. For the RT-SD-difference between conditions no clear trends across groups were found.

Percentage of false alarms—The percentage of false alarms decreased with increasing age ($F_{(1, 424)}$=54.4, p<.01). Both event-rates yielded the same proportion of false alarms ($F_{(1, 424)}$=1.1, p=.30) and no interaction with group ($F_{(2, 424)}$=.3, p=.77). Participants with ADHD and nonaffected siblings committed more false alarms than controls ($F_{(2, 424)}$=11.9, p<.01; confirmed nonparametrically for boys-only, $\chi^2_{(2)}$=13.3, p<.01). Girls generally committed fewer false alarms than boys ($F_{(1, 424)}$=19.9, p<.01), which again was additive, i.e. did not show any interactions with group or condition ($F_{(1/2, 424)}$<1.1, p>.29).

Analyses of the total mean false alarms rate revealed a linear (p<.01) without a quadratic trend across groups (p>.47).

Percentage of omission errors—Omission errors also decreased with age ($F_{(1, 424)}$=117.0, p<.01). There was an interaction effect between condition and group which indicated that omission-error rate was particularly reduced rather than enhanced by the slow event-rate in participants with ADHD compared to controls ($F_{(1, 424)}$=4.3, p=.01). Subsequent univariate ANOVAs revealed for both conditions that participants with ADHD made more omission errors than their nonaffected siblings and controls, but for the fast condition even nonaffected siblings omitted more trials than controls (both $F_{(2, 424)}$>6.3, p<.01). This was confirmed by nonparametric analyses of the boys-only subsample (both $\chi^2_{(2)}$>9.4, p<.01). No influences of gender were found.

Both total mean as well as the impact of event-rate showed linear (both p<.01) and no quadratic trends (p>.82) across groups, thus nonaffected siblings showed intermediate effects.

Impact of incentives

Data from 2 nonaffected siblings and 3 participants with ADHD were not available, so a total of 308 participants from London or Göttingen entered this comparison (Figure 3 and Table 3 of the supplementary material). Neither groups nor genders differed in age (both $F_{(2, 302)}$<1, p>.7), but lower IQs were found in participants with ADHD compared to controls ($F_{(2, 302)}$=4.4, p=.01) and in females compared to males ($F_{(1, 302)}$=4.4, p=.04).

Go mean reaction-time—Reaction-times were faster in older children ($F_{(1, 301)}$=75.3, p<.01) and for boys compared to girls ($F_{(1, 301)}$=4.9, p=.03). Furthermore, mean RT differed for both, conditions ($F_{(1, 301)}$=55.9, p<.01) and groups ($F_{(2, 301)}$=6.2, p<.01) with significant interactions condition*group ($F_{(2, 301)}$=6.1, p<.01) as well as condition*age ($F_{(1, 301)}$=44.7, p<.01, the main effect of faster mean RT in the incentive compared to the slow condition diminished with increasing age). Additional Sidak-adjusted post-hoc tests revealed that only participants with ADHD improved their mean RT if incentives were given. Subsequent nonparametric analyses for boys-only confirmed the findings on mean RT ($\chi^2_{(2)}$>7.6, p=.02), but the impact of incentives revealed a trend only ($\chi^2_{(2)}$=4.4, p=.10).

Similar to the outcome of the fast vs. slow event-rate comparison, mean RTs showed linear and quadratic trends across groups (both p<.05). However, the impact of incentives showed solely a linear trend (p<.01 and p=.27, respectively).

Reaction-time variability—Generally, intra-individual RT-SD decreased with increasing age ($F_{(1, 301)}$=99.8, p<.01), and was larger in the slow compared to the incentive condition, particularly in younger children ("condition" $F_{(1, 301)}$=38.5, p<.01 and "condition*age" $F_{(1, 301)}$=22.9, p<.01). The ADHD-group showed the highest RT-SD ($F_{(2, 301)}$=13.0, p<.01).

Total mean RT-SD revealed linear and quadratic trends across groups (both p<.04).

Percentage of false alarms—False alarm rates ($F_{(1, 301)}$=58.4, p<.01) and the impact of incentives decreased with increasing age ("Condition*Age" ($F_{(1, 301)}$=6.3, p=.01)). Controls committed fewer false alarms than both nonaffected siblings and participants with ADHD which did not differ ($F_{(1, 301)}$=8.2, p<.01). In a nonparametric analysis of boys-only this overall group-effect on mean false alarms was diminished towards a trend ($\chi^2_{(2)}$=4.6, p<.10), although nonparametric post-hoc Mann-Whitney-U-tests confirmed higher error-rates for the ADHD alone with respect to the controls (p=.03). Additionally, boys committed more false alarms than girls ($F_{(1, 301)}$=8.3, p<.01). Total false-alarm rates revealed a clear linear trend across groups only (p>.01), and the impact of incentives on it revealed neither a linear nor quadratic trend across groups (p>.1).

Percentage of omission errors—Fewer omission errors were made in the incentive compared to the slow condition ($F_{(1, 301)}$= 74.0, p<.01), but this effect diminished with increasing age ($F_{(1, 301)}$=41.6, p<.01). Generally groups differed ($F_{(2, 301)}$=5.5, p<.01), but there was also an interaction "Condition*Group" ($F_{(2, 301)}$=4.3, p=.01). Additional analyses revealed that all groups showed reduced omission error rates in the incentive compared to the slow condition, but improvement was larger for participants with ADHD compared to both their nonaffected siblings and unrelated controls (see Table 3 of the supplementary material). Additional nonparametric analyses of the boys-only sub-sample confirmed group-differences ($\chi^2_{(2)}$=14.6, p<.01), but revealed larger improvement for the ADHD group as compared to Controls only (p=.02). There were no significant gender differences or interactions (all $F_{(1/2, 301)}$<1.3, p>.27).

Both total mean omission-error rate as well as the impact of incentives on it revealed linear (both p<.01) but no quadratic (p>.26) trends across groups.

Discussion

In this multi-centre study we examined aspects of executive functioning, in particular neuropsychological parameters of sustained attention and response control in a Go/Nogo task and their modulation by event-rate or incentives as candidates for endophenotypes in children with ADHD. It was hypothesised that task performance operationalised by reaction times of correct responses, intra-individual reaction-time variability and error rates were diminished in children with ADHD, and that their nonaffected siblings show intermediate impairments as compared to controls without a family history of ADHD.

Performance without modulators

As expected, children with ADHD displayed poorer performance in terms of slower mean RT as well as higher percentages of false alarms and omission errors compared to unrelated healthy controls which is in line with many studies (Albrecht et al., 2008; Banaschewski *et al.*, 2003; Oosterlaan *et al.*, 1998).

Further, increased RT-SD was demonstrated in ADHD subjects. Although a good theoretical account for RT-SD is still lacking (Castellanos et al., 2005), it may index temporal processing deficits (Castellanos & Tannock, 2002) or more general problems in maintaining an alert and focussed state over time (Russell *et al.*, 2006). In addition, nonaffected siblings

were found to respond more variably than controls, but still less variably than children suffering from ADHD, thus being located in an intermediate position. This is convergent with results from recent studies concluding that RT-SD may be a suitable endophenotype (Andreou et al., 2007; Doyle et al., 2005).

Children with ADHD committed more false alarms than controls, with nonaffected siblings in an intermediate position as confirmed by statistical trend analyses across groups. Again, particularly for the fast condition, nonaffected siblings show more false alarms than controls, but less than ADHD which again suggests that an impulsive response style may constitute an endophenotype for ADHD (Oades *et al.*, 2008). It remains questionable, whether RT-SD and false alarms are like two sides of the same coin. However, since false alarms but not RT-SD showed gender effects, this seems unlikely, and thus these parameters may indeed reflect separable processes.

Event-rates and performance

Manipulation of event-rate to impact energetic state using event-rates yielded expected task-related effects: given a slow stimulus presentation rate, mean reactions were generally slower but not more accurate. While this may indicate a suboptimal activation state in the slow condition, children with ADHD were not particularly impaired as proposed by the cognitive-energetic model of ADHD (Sergeant, 2005). Instead, participants with ADHD showed under slow event-rates a substantial reduction in omission errors compared to controls. It remains unclear, whether this is due to a more basic effect. Since in the fast condition, the density of go-responses in time is much higher than in the slow condition, the tendency to respond may become more prepotent, and mean RT decreased accordingly. Thus, the Nogo-part of the task becomes more difficult with fast event rates. Given that the false alarm-rate did not change between conditions, one may speculate that the increase in difficulty have been compensated for by omissions, in order to avoid commission errors. However, our results do not support the view that performance deficits in children with ADHD during the Go/Nogo-task may be explained by underactivation as induced by event-rate, and thus question the cognitive-energetic explanation for this experiment.

Incentives and performance

Under low event-rate conditions, incentives led to enhanced performance concerning speed or accuracy, particularly in younger children. Furthermore, false alarms, omission errors, mean RT and RT-SD decreased particularly in participants with ADHD and to a lesser extent in their nonaffected siblings whilst for controls enhancements were only found for accuracy. Since incentives were given predominantly for accuracy, participants optimized their response strategies accordingly in order to get more payback. Consistently for all four performance parameters, the impact of incentives followed a linear trend across groups. Thus nonaffected siblings displayed intermediate effects, suggesting that sensitivity to reward on the Go/Nogo task may constitute an endophenotype for ADHD. This complements the conclusion drawn by Andreou et al. 2007 from an overlapping sample – incentives generated stronger effects between groups than manipulations of event-rate – and is in line with recent theories that attribute main ADHD symptoms to deficits in a reinforcement system partly due to deficient fronto-striatal dopaminergic circuits (Luman et al., 2005; Sagvolden et al., 2005; Tripp & Wickens, 2008).

Although the incentive condition was always administered last, differential effects of incentives are not explainable by means of training or fatigue: there would have to be a stronger training-effect or less fatigue in ADHD compared to other groups analysed in order to support this alternative explanation - which is generally not supported by the literature (Heinrich *et al.*, 2001; van der Meere et al., 1995a; Willcutt *et al.*, 2005).

Effects of gender and age

In this study based on participants with ADHD who had been referred to an outpatient service, females were outnumbered. However, since the sample size was large, effects of gender could be disentangled from effects of ADHD or familiality. We found generally that females showed a response-style shifted towards accuracy, which was similar in all three groups. However, in this study only additive effects of gender were found, and thus the conclusions drawn remain applicable to both genders. This was supported for the boys-only subsample by additional analyses with nonparametric tests.

As expected, younger childern showed generally poorer performance. Their RT were slower and the accuracy reduced. Moreover, both effects of poorer performance due to slow event-rate as well as enhanced performance due to incentives were more pronounced in younger children. But no interactions of age by group were found. Thus, for the broad age-range assessed, we can confirm the relevance of cognitive-energetic and motivational factors on performance.

Limitations

Since this was a multi-centre, multi-country project with the benefits of a large sample-size, some heterogeneity in samples and procedures can not be avoided. However, the researchers were well trained on instruments used and a maximal compatibility of equipment and diagnostic procedure was ensured. Nevertheless, ADHD should be regarded as a disorder with heterogeneous underlying neuropsychological and neurophysiological strengths and difficulties.

Conclusion

It is a well established finding that children with ADHD exhibit poor performance in tasks involving executive functions. Furthermore, it is even likely that these deficits form endophenotypes. However, there is some evidence that different event-rates and the presence/absence of immediate incentives are performance modulators for children. With this study, we could replicate deficits in some executive functions such as sustained attention, response control and performance variability as endophenotypes for ADHD, reflected particularly by the performance parameters response variability and accuracy. Further, for the first time we could show the moderating effects of incentives, but not of event-rate, as an endophenotypic function for ADHD. Thus, motivationally driven behaviour seems to be familial and may play an important role with regard to etiologic pathways as well as approaches to treatment in ADHD. Moreover, these potential endophenotypes are not confounded by influences of gender and age, which may have additional impact on molecular genetic studies.

Key Points

- ADHD is a common and highly heritable child psychiatric disorder, but developmental pathways from genes and environmental factors to behaviour are poorly understood. To search for neuropsychological intermediate phenotypes (endophenotypes) may be warranted to close the gap.
- In ADHD, good candidates for endophenotypes may be the known parameters of executive functions, which may also reflect deficits in motivation or state regulation.

- In this study using a Go/Nogo task controlled for event-rates and incentives, deficits in sustained attention, response control and performance variability could be confirmed as gender-independent endophenotypes of ADHD. Moreover, a motivational dysfunction in ADHD was found to be familially driven.
- These findings extend the view on ADHD and highlight that familiality and the role of incentives need to be considered in further research on and clinical practice of ADHD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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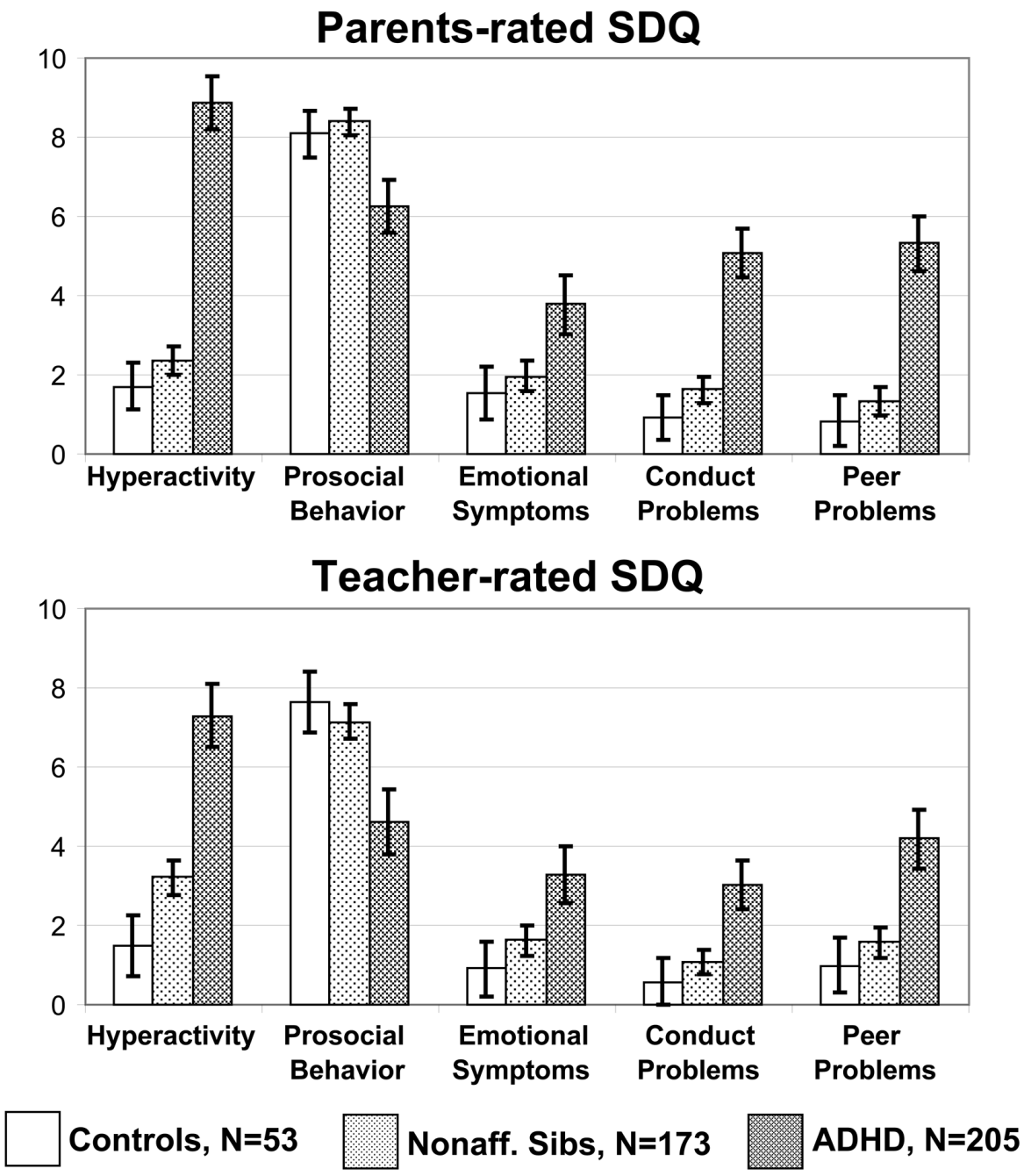

Figure 1. Sample Description

Estimated marginal means as well as confidence intervals at p=.05 for Parent- and Teacher-rated SDQ.

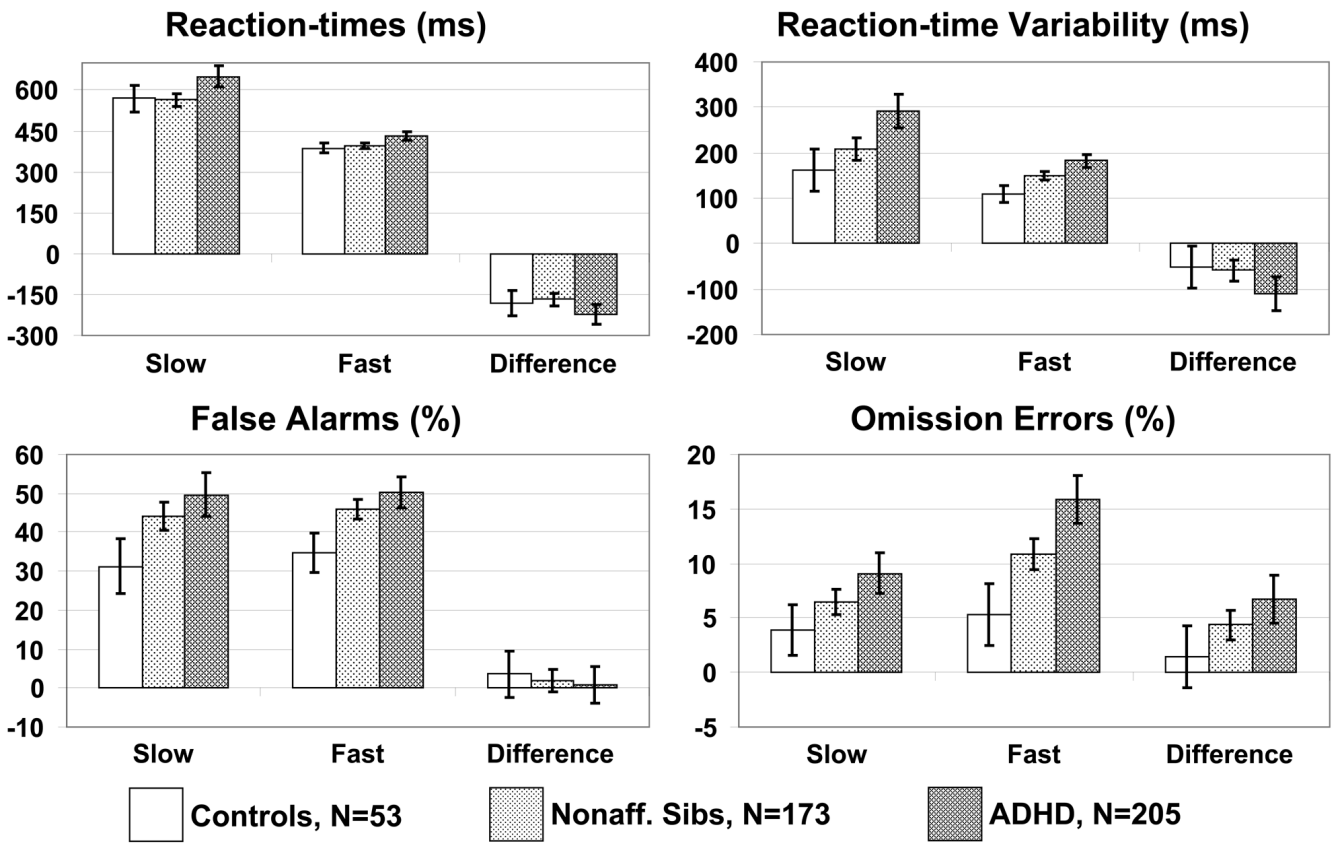

Figure 2. Behavioural Data of Slow vs. Fast Event-Rate

Estimated marginal means with age taken as covariate as well as confidence intervals at p=. 05 for Slow and Fast conditions.

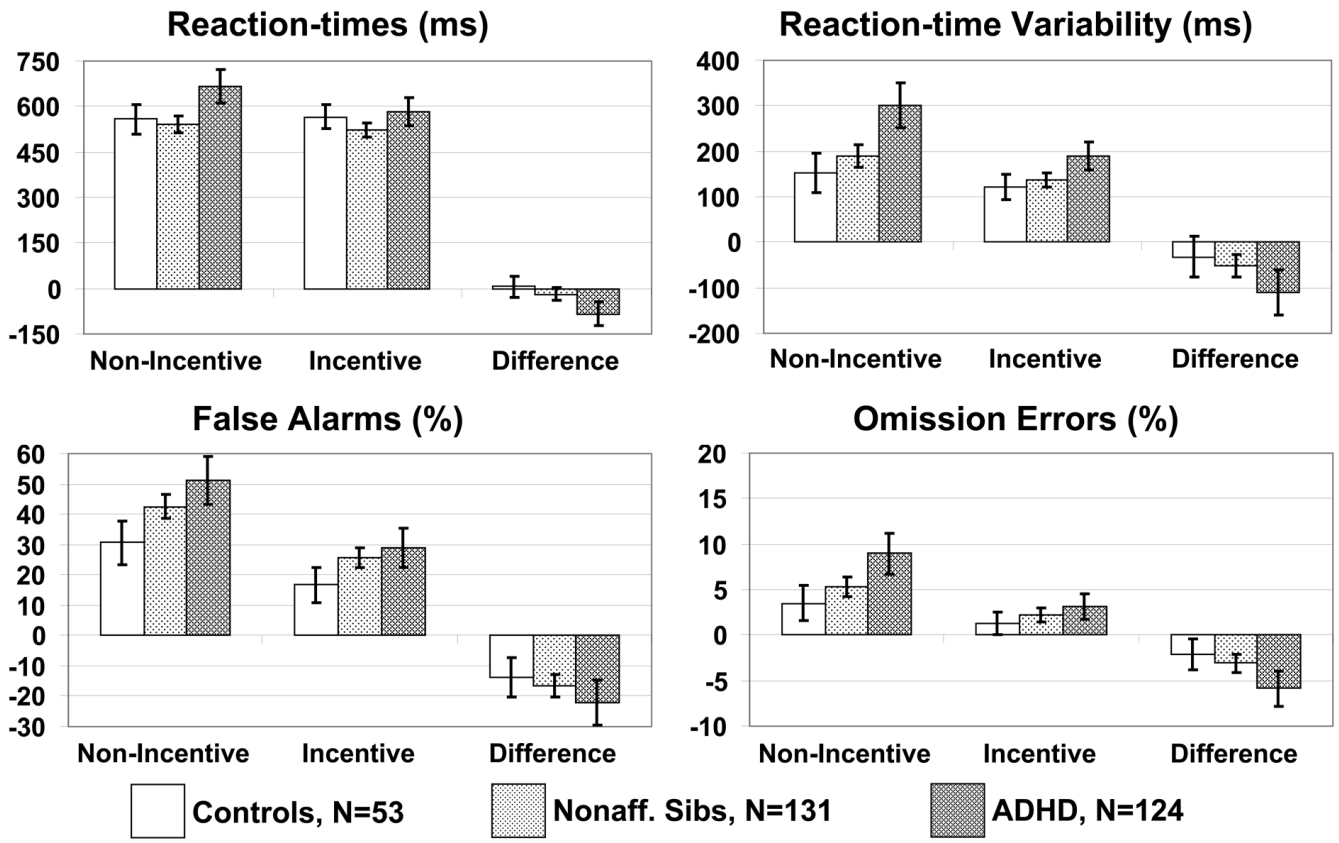

Figure 3. Behavioural Data of Non-Incentive vs. Incentive Condition, both with Slow Event-Rate

Estimated marginal means with age taken as covariate as well as confidence intervals at p=. 05 for the Non-Incentive and Incentive Slow conditions.