Published in final edited form as:

Biol Psychiatry. 2008 October 1; 64(7): 615–625. doi:10.1016/j.biopsych.2007.12.016.

Action Monitoring in boys with ADHD, their Nonaffected Siblings and Normal Controls: Evidence for an Endophenotype

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Abstract

Background—Attention deficit/hyperactivity disorder is a very common and highly heritable child psychiatric disorder associated with dysfunctions in fronto-striatal networks that control attention and response organisation. Aim of this study was to investigate whether features of action monitoring related to dopaminergic functions represent endophenotypes which are brain functions on the pathway from genes and environmental risk factors to behaviour.

Methods—Action monitoring and error processing as indicated by behavioural and electrophysiological parameters during a flanker task were examined in boys with ADHD combined type according to DSM-IV (N=68), their nonaffected siblings (N=18) and healthy controls with no known family history of ADHD (N=22).

Results—Boys with ADHD displayed slower and more variable reaction-times. Error negativity (Ne) was smaller in boys with ADHD compared to healthy controls, while nonaffected siblings displayed intermediate amplitudes following a linear model predicted by genetic concordance. The three groups did not differ on error positivity (Pe). N2 amplitude enhancement due to conflict (incongruent flankers) was reduced in the ADHD group. Nonaffected siblings also displayed intermediate N2 enhancement.

Conclusions—Converging evidence from behavioural and ERP findings suggests that action monitoring and initial error processing, both related to dopaminergically modulated functions of anterior cingulate cortex, might be an endophenotype related to ADHD.

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Financial Disclosures

Dipl.-Psych. Albrecht, Dr. Banaschewski, Dr. Brandeis, Dr. Hasselhorn, Dr. Heinrich, lic. phil Mueller, Dr. Uebel and Dr. Rothenberger reported no direct or indirect financial or personal relationships, interests, and affiliations relevant to the subject matter of the manuscript. Dr. Steinhausen serves on advisory boards for Eli Lilly, Janssen-Cilag and UCB companies.

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Keywords

error negativity; error positivity; N2; action monitoring; ADHD; endophenotype

Introduction

Attention deficit/hyperactivity disorder (ADHD) is a very common child psychiatric disorder. The core symptoms of severe age-inappropriate levels of hyperactivity, impulsivity and inattention affect at least 3–5% of school-aged children (1) independent of cultural background (2), and with an overrepresentation of boys (3). Heritability estimates are high (4), but developmental pathways to the phenotype ADHD are not well understood (5). This potential gap may be filled by the concept of quantitative trait loci (QTL) and endophenotypes. Following this, multiple susceptibility genes may constitute a rather continuous dimension of ADHD symptoms in which an endophenotype is a simple function more proximal to biological foundations in-between on the one hand genetic and environmental risk factors and on the other hand the phenotype (6–8). Theoretically, associations between genes and endophenotype should be larger than between genes and phenotype, qualifying the endophenotype as a better ground for molecular genetic studies (9).

Several cognitive theories ascribe impairments in executive functions or self-regulation associated with dysfunctions in fronto-striatal dopaminergic networks that control attention and response organisation to patients suffering from ADHD (3;10–14). Children with ADHD perform poorly in a wide range of tasks involving executive control. In general, their responses tend to be slower, more variable, and more error prone (11;12;15;16). Specific deficits in adaptation to task demands and error monitoring such as diminished post-error slowing have been reported early on (17;18), but little is known about neural mechanisms in ADHD. Using event-related potentials (ERP), covert neurophysiological correlates of task performance can be tracked with high temporal resolution (19;20).

Action monitoring comes into play when actual requirements interfere with automatisms, or after errors. For instance, in Go-NoGo tasks which require responding to frequent stimuli but to withhold the response to rare ones, the stimulus-locked ERP usually shows a fronto-central negativity peaking around 200 to 400ms after onset of the stimulus (N2), which is larger for the Nogo than for the Go condition. The same effect can be observed for a target primed with incongruent compared to congruent distractors. This N2-enhancement was originally attributed to response inhibition (21–23), but recent studies suggest that it may reflect a more general monitoring process which is also present without need for response inhibition (24;25). Sources of the N2 as evoked by Go-Nogo- and Stroop-Tasks have been localized in the anterior cingulate cortex (ACC) (24;26;27).

While most studies using CPT or Go-Nogo-tasks in children did not find specific differences in N2 between ADHD and controls (16;28;29) some studies did, but effects were explained by comorbidity (30;31) or appeared only within time-on-task effects (32). However, in more demanding tasks such as the Stop-Task, diminished N2 amplitudes or topographic N2 alteration have been reported (33–36).

Error processing is generally accompanied by a negative component (error negativity, Ne) peaking approximately 40–120ms after the erroneous response at fronto-central sites. It is frequently followed by a more parietal positive deflection (error positivity, Pe) within 200 to 500ms after the response (37–39). Ne is described in a variety of tasks (38;40;41), error types (42) and response modalities (43;44). Thus, several hypotheses ascribe Ne a crucial role in error detection and action monitoring such that it may reflect mismatch (37;39) or conflict

(45) between error and required response. Ne is susceptible to dopaminergic manipulations (46), i.e. dopamine agonists enhance (47) and antagonists reduce its amplitude (48;49). Dipole modelling showed a generator of Ne located in the ACC (43;50–53). A number of studies suggest that Ne and N2 may reflect the same process which rely on different aspects of task performance (54;55). Far less research has addressed the subsequent Pe. It is elicited unlike Ne only after full errors of which the subject is aware (44) and seems to mature earlier (56). The rostral ACC generators of Pe suggest that it rather reflects affective error assessment (53).

Clinical studies found Ne to be enhanced in patients with obsessive compulsive disorder (57) or in subjects with obsessive compulsive or anxiety characteristics (58;59) or negative affect (60). Higher sensitivity for punishment also goes along with enhanced Ne while Pe was enhanced in subjects with higher reward sensitivity (61). A reduction of Ne but not Pe was found for patients with schizophrenia (62;63) and borderline personality disorder (64). Parkinson's disease associated with dysfunctions in the dopaminergic system of basal ganglia was also accompanied with reduced Ne (65;66), but unimpaired Pe (67). Moreover, Ne was found to be reduced in patients suffering from Huntington's Disease which goes along with neural cell death in the striatum (68). Thus, there is converging evidence, that Ne is related to striatal dopaminergic modulations, which leads to the hypothesis that it may also be impaired in ADHD (14;69). However, the few studies on ADHD or ADHD-related behaviours yielded mixed results. While Ne was found to be reduced in adult subjects with higher impulsiveness (70) and in children suffering from ADHD (71), other studies with younger ADHD children found no error-specific Ne and similar amplitude reductions for errors and correct responses (72), failed to find a reduction of Ne but instead Pe was reduced (73) or even observed an enhanced Ne in ADHD children (74), which may again in part be explained by heterogeneity of the methods used. In search for ADHD endophenotypes, this study is focused on action-monitoring and error-processing using a simple, nonverbal flanker-task that is highly demanding (75–77). It was hypothesized that control children exhibit higher task performance, i.e. fewer errors, shorter reaction-times and less intra-individual reaction-time variability than children of the ADHD-group. Furthermore, we predict that the effect of congruency on N2 amplitude as well as Ne- and Pe amplitudes were higher in controls compared to ADHD.

In order to differentiate effects from partial overlap of phenotypes, nonaffected siblings of ADHD patients were included in analyses regarding the endophenotype concept. If the parameter in question reflects the phenotype, nonaffected siblings should display the same difference compared to ADHD-patients as unrelated controls did. On the other hand, since nonaffected siblings share half of their genes with ADHD patients, according to the QTL model also susceptibility genes and therefore impairments should be shared to that extent. Hence, the respective parameter should decrease as a linear function of genetic concordance with ADHD across groups (controls 0%, nonaffected siblings 50%, children with ADHD 100%) without a residual component (78–80) and may thus constitute an endophenotype.

Methods and Materials

Subjects

Recruitment of ADHD sib pairs was conducted as part of the International Multi-centre ADHD Gene study (IMAGE (81;82)). For this analysis, European Caucasian subjects, all aged 8 to 15 years with an estimated full-scale IQ above 80 (83;84) and no known child psychiatric disorder that may mimic ADHD were included. They belonged to one of three subgroups:

1. Children with DSM-IV diagnosis of ADHD combined type having at least one biological sibling.

2. Nonaffected siblings of children with DSM-IV diagnosis of ADHD combined type, without any clinical diagnosis of ADHD.
3. Unrelated healthy control-subjects without a clinical diagnosis or a known family history of ADHD.

Children of groups 1 & 2 were recruited by child psychiatry clinics from Goettingen, Germany and Zurich, Switzerland. The control group was recruited from regular schools in Goettingen only. Ethical approval was obtained from local ethical review boards. Detailed information sheets were provided and informed consent from children and parents were obtained. Children taking stimulant treatment were off medication for at least 48h before testing. All children earned small prizes; parents did not receive any financial reward except travel expense reimbursements.

The diagnostic assessment was performed with long versions of Conners' rating scales (85; 86) and Strengths and Difficulties Questionnaires (SDQ (87;88)) for parents and teacher. If T scores on Conners ADHD scales (L, M, N) exceeded 62 and scores on SDQ Hyperactivity scale exceeded the 90th percentile, a semi-structured clinical interview (PACS (89–93)) was applied by trained investigators in order to verify ADHD diagnosis according to DSM-IV and to confine symptoms from other child psychiatric disorders (94;95). To ensure that control subjects were free of susceptibility for ADHD, children with T-scores exceeding 60 on both parent and teacher scales of the Conners total symptoms scale were excluded from that group.

Since female subjects in our ADHD sample were outnumbered and considerably younger, only datasets from 125 males (14 from Zürich and 111 from Göttingen) were analysed here. All had normal or corrected to normal vision and understood task instructions as verified during practice blocks. Due to excessive artefacts in the EEG or too few errors or correct responses, seventeen subjects had to be excluded (three controls, two nonaffected siblings and 12 subjects with ADHD; reflecting comparable exclusion-ratio across groups, $\chi^2_{(2)}=0.41$, $p=.82$).

Groups were matched for age ($F_{(2, 105)}=.1$, $p=.90$) and there was only a trend for different estimated total IQs ($F_{(2, 105)}=2.9$, $p=.06$, see Table 1 for further sample characteristics). In the ADHD-group, PACS interview yielded susceptibility for mood disorder (N=7), tourette's syndrome (N=2), substance abuse (N=1), obsessive compulsive disorder (N=3), anxiety disorder (N=34), oppositional defiant disorder (ODD, N=46) and conduct disorder (CD, N=14).

Procedure

Assessments of children were carried out on two days. The neurophysiological took place before the neuropsychological testing or vice versa, following a randomization scheme. Neurophysiological test-sessions were carried out in video-controlled, noise-shielded and slightly dimmed rooms. Subjects sat on a comfortable seat during electrode attachment and task-performance. The flanker-task was administered after 6 minutes of resting EEG followed by a Continuous Performance Test lasting 11 minutes and, if desired, a short break.

Stimuli and Task

The flanker-task consisted of ten blocks á 40 trials each, modelled after Kopp et al. (75) (Figure 1). Columns of black arrowheads (equilateral triangles with 18 mm edge length at 3 positions with 23mm distance centre to centre) were presented in the centre of a 17" CRT monitor with 800*600 points resolution against light grey background at 120cm viewing-distance. On every trial, a fixation mark in the centre of the screen was replaced by the stimuli. Initially, only flankers (two arrowheads pointing to the same direction above and below the position of the fixation mark) were presented for 100ms, before the target arrowhead also appeared for 150ms

between the flankers. Subjects had to press response buttons with the index-finger of their hand corresponding to the direction indicated by the target. The standard serial mouse used to record responses caused a response-trigger delay of approximately 35 ms which was corrected for in the analyses (96). On congruent trials, flanker and target arrowheads pointed in the same and on incongruent trials into opposite directions. A trial was presented every 1650ms, and total task duration was approximately 13 min. The features congruent vs. incongruent and target pointing to the left vs. right were balanced and randomized.

Written feedback was given at the end of each block. If more than 10% errors on congruent or more than 40% errors on incongruent trials were made, it was instructed to be more accurate. In case of less than 10% errors in the congruent and less than 40% errors in incongruent trials, it was stressed to respond faster; otherwise it was told to go on the same way. Feedback was introduced in order to control for accuracy, which may influence error processing (38;39). Two practice blocks with 24 trials each were administered first.

Electrophysiological recording and processing

For subjects from Göttingen, the electroencephalogram was recorded with Ag/AgCl electrodes and Abralyt 2000 electrode cream from 23 sites according to an extended 10–20 system using a BrainAmp amplifier. The electrooculogram was recorded from two electrodes placed above and below the right eye and at the outer canthi. EEG and EOG were recorded simultaneously using FCz as recording reference at a sampling rate of 500Hz with low and high cutoff filters set to 0.016Hz and 100Hz respectively and a 50Hz notch filter. The ground electrode was placed at the forehead. In Zürich, the EEG was recorded from additional channels using a Neuroscan SynAmps amplifier with reference at Fpz and a ground electrode placed at the forehead. The EOG was recorded from electrodes below the left and right eye. Sampling rate was 500Hz and filter settings were 0.1 to 70 Hz. Impedances were kept below 10 k Ω . Postprocessing ensured full compatibility.

Altogether 24 common sites were analysed here. After downsampling to 256 Hz the EEG was re-referenced to the average and filtered offline with 0.1 – 15 Hz, 24 dB/oct Butterworth filters. Occular artifacts were corrected using the method of Gratton and Coles without raw average subtraction (97). If the amplitude at any EEG-electrode exceeded $\pm 100 \mu\text{V}$, a section -100 to $+800$ ms was excluded from further analyses. Response locked (-500 ms to $+1000$ ms relative to the button press) and stimulus-locked (-200 to $+1825$ ms around target-onset) segments were subsequently checked and averaged. To avoid distortion of ERP topography, no baseline subtraction was applied.

Averages of stimulus-locked waveforms to congruent and incongruent correct responded trials contained at least 40 sweeps, response-locked averages to incongruent trials contained at least 25 sweeps for errors and 40 sweeps for correct responses. Consideration of signal to noise ratios revealed group-differences only for waveforms stimulus-locked to congruent correct responded trials at site Cz ($F_{(2, 105)}=3.2$, $p=.04$) and response-locked to errors in incongruent trials at Pz ($F_{(2, 105)}=4.8$, $p=.01$).

Analyses

Effects of “congruency” (congruent vs. incongruent trials) and “group” (controls vs. nonaffected siblings vs. ADHD) on number of errors, reaction-time of correct responses and reaction-time variability of correct responses (intra-individual standard deviation of reaction times with sum of squares computed separately for each block to exclude potential reaction-time differences between blocks) were assessed using repeated-measure analyses of variance (ANOVAs). Additional univariate ANOVAs were conducted to explore interactions and

further details. If effects reached significance, additional post-hoc tests adjusted for multiple comparisons following Sidak were conducted.

Inspection of the grand average waveforms revealed that both the effect of congruency on N2 components and the error-related negativity (Ne) were maximal at frontocentral electrodes (see Figures 2 and 3). Stimulus-locked N2 peaks scored at FCz 200–400ms after the stimulus-onset of correct responded trials were subject to an ANOVA with factors “congruency”, “site” (Fz, FCz, Cz) and “group”. Violations from sphericity were corrected following Greenhouse-Geisser, ϵ and adjusted p-values are reported along with original degrees-of-freedom. Ne measured at FCz was defined as the most negative peak 0 to 150ms post erroneous response on incongruent trials with respect to the preceding positivity (PNe, –100 to 20ms) in order to obtain a more robust measure of this component (44; 68; 98). Amplitudes and latencies of error negativity were analysed using repeated-measure ANOVAs with factors “peak” (Ne vs. PNe) and “group”. The plateau-like Pe on incongruent error trials maximal at centro-parietal electrodes was analysed using the mean amplitude in time window 200 to 500ms after an error in an ANOVA with factors “site” (Cz, Pz) and “group”. Since Pe may be confounded with stimulus-locked components, the P3 to incongruent error trials was scored 350–650ms after target onset at site Cz and its mean amplitude at Cz and Pz was entered subsequently as a covariate. Both Ne and Pe were specific for errors.

For each dependent variable, contrasts over the three groups were computed to clarify which measures directly reflected genetic concordance with ADHD. Additional correlations between electrophysiological and behavioural parameters were tested for the total sample to clarify functional significance of ERP findings.

All analyses remained stable when subjects from Zürich were excluded. To differentiate effects of comorbid ODD/CD, analyses were subsequently conducted with patients possibly suffering from ODD/CD excluded.

Results

Performance Data

More errors were committed in incongruent than congruent trials ($F_{(1, 105)}=495.2$, $p<.01$, Table 2), which was more pronounced in the group of controls compared to ADHD ($F_{(2, 105)}=3.8$, $p=.03$). Furthermore, groups differed only regarding error-rates of congruent ($F_{(2, 105)}=5.4$, $p=.01$, controls permitted less errors than ADHD), but not incongruent stimuli ($F_{(1, 105)}=.6$, $p=.53$). If subjects with ODD/CD were excluded, the interaction “congruency*group” vanished and only a trend towards group-differences on error-rate for the congruent condition was found ($F_{(2, 59)}=2.5$, $p=.09$).

Reaction times of correct responses were generally slower for incongruent compared to congruent trials ($F_{(1, 105)}=753.9$, $p<.01$). Groups differed in their reaction times ($F_{(2, 105)}=3.8$, $p=.03$), with controls responding faster than individuals with ADHD for both congruent and incongruent correct trials. Nonaffected siblings did not differ in response speed from boys with ADHD nor from controls. Contrasts revealed a linear trend between reaction-times and genetic concordance with ADHD ($F_{(1, 105)}=7.3$, $p<.01$) in absence of a significant residual ($F_{(1, 105)}=0.3$, $p=.58$). With subjects suffering from ODD/CD excluded, the main effect of group was diminished to a trend ($F_{(2, 59)}=2.9$, $p=.06$), but results of trend analyses remained stable.

Although congruent and incongruent correct trials yielded similar intra-individual reaction-time variability ($F_{(1, 105)}=1.4$, $p=.23$), group-differences were found ($F_{(2, 105)}=10.1$, $p<.01$): controls revealed lower RT-variability than boys with ADHD in both conditions (Table 2).

Nonaffected siblings did not differ from controls or ADHD. Contrasts between RT-variability and genetic concordance with ADHD again detected a linear trend ($F_{(1, 105)}=19.1$, $p<.01$) without a residual ($F_{(1, 105)}=1.1$, $p=.31$). These effects persisted if subjects with ODD/CD were excluded.

ERP Data

N2 peaked at about 330ms relative to target-onset (Table 3 and Figure 4). No effects of any independent variable were found on N2 latency (all $F < 1.1$, $p > .35$).

N2 amplitude was enhanced by incongruent compared to congruent items ($F_{(1, 105)}=50.8$, $p<.01$), and was generally higher at Fz and FCz compared to Cz ($F_{(2, 210)}=102.2$, $p<.01$). N2 enhancement was also highest at Fz and FCz ("congruency*site", $F_{(2, 210)}=17.5$, $p<.01$). Furthermore, the N2 congruency effect (i.e. the mean difference of N2 amplitude across sites Fz, FCz, Cz) differed between groups ("congruency*group", $F_{(2, 105)}=4.1$, $p=.02$), being more pronounced in controls compared to ADHD, while nonaffected siblings displayed no differences to both other groups. Contrasts between the N2 congruency effect and genetic concordance with subjects suffering from ADHD showed a linear trend ($F_{(1, 105)}=7.7$, $p<.01$) and no significant residual ($F_{(1, 105)}=0.5$, $p=.47$). The effects persisted when subjects suffering from ODD/CD were excluded.

Mean N2 enhancement across electrodes Fz, FCz and Cz was correlated with faster and less variable reaction-times in both congruent and incongruent trials (all $r \geq .25$, $p<.01$) and lower error-rate in the congruent condition ($r=.34$, $p<.01$), but also with higher congruency effect on error rate (increased error-rate in incongruent compared to congruent trials, $r=-.31$, $p<.01$).

The whole complex of PNe and Ne had a similar mean latency for all groups ($F_{(2, 105)}=.7$, $p=.51$) but was more widespread for controls compared to ADHD ("peak*group", $F_{(2, 105)}=4.7$, $p=.01$, Table 4 and Figure 5).

Ne amplitude measured peak-to-peak was higher in controls compared to ADHD ("peak*group", $F_{(2, 105)}=5.7$, $p<.01$). There was a linear trend ($F_{(1, 105)}=10.9$, $p<.01$), but no significant residual ($F_{(1, 105)}=0.5$, $p=.50$) between genetic concordance with ADHD and Ne amplitude peak-to-peak. Higher peak-to-peak Ne amplitude was correlated similar to N2-enhancement with faster and less variable reaction-times as well as lower error-rate in the congruent condition (all $r \geq .32$, $p<.01$), but also with higher increase in error-rate in incongruent compared to congruent trials ($r=-.26$, $p<.01$). Ne ($r=.33$, $p<.01$), but not Pe were correlated with N2-enhancement. When subjects with ODD/CD were excluded, effects on the peak-to-peak Ne amplitude remained stable.

A strong effect of stimulus-locked P3 amplitude to incongruent error trials on Pe was found ($F_{(1, 104)}=315.0$, $p<.01$, part. $\eta^2=.75$), but no group-differences were detected irrespectively whether P3 amplitude was taken as covariate or not. Higher Pe amplitude was correlated with lower error-rate in both congruent and incongruent conditions and lower RT-variability in both congruent and incongruent conditions (all $r < -.22$, $p<.03$).

Discussion

In this study, we examined neuropsychological and neurophysiological aspects of action monitoring and error processing as candidates for endophenotypes of ADHD. Since nonaffected siblings were contrasted with children suffering from ADHD and unrelated controls, effects that go beyond differences in the phenotype as reflected by increased ADHD prevalence among family members of patients (99–101) can be detected. The adaptive feedback-procedure used in this version of the flanker-task prompted subjects to respond with

similar accuracy, thus confounds with speed-accuracy tradeoff and possible task-induced differences in motivation could be avoided. Therefore groups differed mainly in reaction-time and intra-individual reaction-time variability. As expected (3;11;12;15), boys with ADHD performed worse than unrelated healthy controls. However, ADHD boys' performance deficit did not increase under conflict. Nonaffected siblings of subjects suffering from ADHD – despite sharing the same phenotype with unrelated healthy controls – neither differed from ADHD subjects as controls did nor from controls. There was a reliable linear trend between genetic concordance with children suffering from ADHD and reaction-time as well as RT-variability without significant residuals. This agrees with recent papers concluding that state-regulation as indexed by RT-variability is probably an endophenotype for ADHD (9;92).

Incongruent compared to congruent stimuli yielded the typical N2 amplitude enhancement (24;25) which is correlated with faster and less variable reaction-times in both congruent and incongruent conditions and with reduced error-rates only in the congruent. This is in line with the notion that N2 is an index for a more general monitoring process triggered in this case by incongruent stimuli features. Since the magnitude of diminished accuracy due to incongruent trials is additionally correlated with higher magnitude of N2 enhancement, modulations in N2 amplitude do not reflect activity of response-inhibitory processes which should control for conflicting impact and should thus lead to an inverse correlation.

N2-enhancement was found to be higher in unrelated controls, but not in nonaffected siblings compared to boys with ADHD. It followed a pure linear trend for genetic concordance with ADHD over groups, which indicates that conflict-monitoring as indexed by N2-enhancement might be a specific biological basis for behavioural endophenotypes like RT-SD as described above.

Furthermore, this flanker-task evoked clear fronto-central error negativity in children. We found reduced Ne amplitude in ADHD compared to unrelated controls which may reflect impairments in fronto-striatal networks as advocated by several cognitive theories of ADHD (11–13). This finding is also in agreement with other clinical studies (70;71), but not with selective Pe reduction in a Go-NoGo task (73), or with unexpected Ne enhancement in a simple discrimination task presumably reflecting compensatory processes (74). There was also a linear relation between genetic concordance and Ne amplitude, and nonaffected siblings did not differ from both other groups but had intermediate scores, which again points out that Ne might index an endophenotype (6). Since both N2 and Ne are highly correlated and share sources in ACC, a common dopaminergic dysfunction may underlie these findings. Thus, it might be fruitful to search for associations between the reported endophenotypes and risk alleles related to dopaminergic pathways (102).

No such relations were found for Pe, which did not differ between groups irrespectively whether amplitude of potentially confounded stimulus-locked P3 was controlled for or not. This is similar to what was reported in a study with patients suffering from Parkinson's Disease (67), which supports the notion, that Pe unlike Ne does not depend on the dopaminergic system.

The findings reported may be compromised by confounding comorbid disorders. Concerning mood disorders, anxiety and obsessive compulsive disorder, an effect of Ne enhancement is widely reported (57–59) which would have diminished the effect of ADHD. On the other hand, comorbid oppositional defiant or conduct disorder might have led to reduced Ne (31), but effects remain stable even when subjects possibly suffering from that were excluded. Another limitation of this study is, that we administered the clinical interview only if susceptibility for ADHD was given, thus cases of potentially comorbid ODD/CD may not have been detected in controls and nonaffected siblings. However, SDQ scores of Conduct Problems did not

differentiate these groups. Thus, we think that results reported are not compromised by comorbidities.

Group differences in ERP parameters may origin due to differences in data quality. Thus we analysed signal to noise ratios for each examined waveform. It turned out, that differences in SNR emerged only for waveforms in which no significant group-differences were found, and therefore rejections of the Null-hypotheses are not compromised by data quality.

Acknowledgements

The authors thank all children and their families for participation. Christa Dahlmann, Renate Kolle and Antonia Seitz conducted the ERP-recordings; Renate Drechsler, Anke Fillmer-Otte, Anne Reiners and Nicola Woestmann performed IQ-testings and conducted further neuropsychological testings. Daniel Brandeis received support from the Swiss National Science Foundation grant 32-109591. Recruitment of ADHD sib pairs was supported by NIMH-grant R01MH062873 to Steve Faraone.

Abbreviations

ACC	anterior cingulate cortex
ADHD	Attention deficit/Hyperactivity Disorder
ERP	event related potential
Ne	error negativity or error related negativity
Pe	error positivity

References

1. American-Psychiatric-Association. Diagnostic and statistical manual of mental disorders. 4. Washington: American Psychiatric Association; 1994.
2. Rohde LA, Szobot C, Polanczyk G, Schmitz M, Martins S, Tramontina S. Attention-deficit/hyperactivity disorder in a diverse culture: do research and clinical findings support the notion of a cultural construct for the disorder? *Biol Psychiatry* 2005;57:1436–41. [PubMed: 15950018]
3. Tannock R. Attention deficit hyperactivity disorder: advances in cognitive, neurobiological, and genetic research. *J Child Psychol Psychiatry* 1998;39:65–99. [PubMed: 9534087]
4. Faraone SV, Perlis RH, Doyle AE, Smoller JW, Goralnick JJ, Holmgren MA, et al. Molecular genetics of attention-deficit/hyperactivity disorder. *Biol Psychiatry* 2005;57:1313–23. [PubMed: 15950004]
5. Banaschewski T, Hollis C, Oosterlaan J, Roeyers H, Rubia K, Willcutt E, et al. Towards an understanding of unique and shared pathways in the psychopathophysiology of ADHD. *Dev Sci* 2005;8:132–40. [PubMed: 15720371]
6. Gottesman II, Gould TD. The endophenotype concept in psychiatry: etymology and strategic intentions. *Am J Psychiatry* 2003;160:636–45. [PubMed: 12668349]
7. Gould TD, Gottesman II. Psychiatric endophenotypes and the development of valid animal models. *Genes Brain Behav* 2006;5:113–9. [PubMed: 16507002]
8. Kuntsi J, Andreou P, Ma J, Borger NA, van der Meere JJ. Testing assumptions for endophenotype studies in ADHD: reliability and validity of tasks in a general population sample. *BMC Psychiatry* 2005;5:40. [PubMed: 16262903]
9. Doyle AE, Willcutt EG, Seidman LJ, Biederman J, Chouinard VA, Silva J, et al. Attention-deficit/hyperactivity disorder endophenotypes. *Biol Psychiatry* 2005;57:1324–35. [PubMed: 15950005]

10. Biederman J. Attention-deficit/hyperactivity disorder: a selective overview. *Biol Psychiatry* 2005;57:1215–20. [PubMed: 15949990]
11. Barkley RA. Behavioral inhibition, sustained attention, and executive functions: constructing a unifying theory of ADHD. *Psychol Bull* 1997;121:65–94. [PubMed: 9000892]
12. Pennington BF, Ozonoff S. Executive functions and developmental psychopathology. *J Child Psychol Psychiatry* 1996;37:51–87. [PubMed: 8655658]
13. Sergeant J. The cognitive-energetic model: an empirical approach to attention-deficit hyperactivity disorder. *Neurosci Biobehav Rev* 2000;24:7–12. [PubMed: 10654654]
14. Castellanos FX, Giedd JN, Marsh WL, Hamburger SD, Vaituzis AC, Dickstein DP, et al. Quantitative brain magnetic resonance imaging in attention-deficit hyperactivity disorder. *Arch Gen Psychiatry* 1996;53:607–16. [PubMed: 8660127]
15. Oosterlaan J, Logan GD, Sergeant JA. Response inhibition in AD/HD, CD, comorbid AD/HD + CD, anxious, and control children: a meta-analysis of studies with the stop task. *J Child Psychol Psychiatry* 1998;39:411–25. [PubMed: 9670096]
16. Banaschewski T, Brandeis D, Heinrich H, Albrecht B, Brunner E, Rothenberger A. Questioning inhibitory control as the specific deficit of ADHD—evidence from brain electrical activity. *J Neural Transm* 2004;111:841–64. [PubMed: 15206002]
17. Schachar RJ, Chen S, Logan GD, Ornstein TJ, Crosbie J, Ickowicz A, et al. Evidence for an error monitoring deficit in attention deficit hyperactivity disorder. *J Abnorm Child Psychol* 2004;32:285–93. [PubMed: 15228177]
18. Sergeant JA, van der Meere J. What happens after a hyperactive child commits an error? *Psychiatry Res* 1988;24:157–64. [PubMed: 3406236]
19. Picton TW, Bentin S, Berg P, Donchin E, Hillyard SA, Johnson R Jr, et al. Guidelines for using human event-related potentials to study cognition: recording standards and publication criteria. *Psychophysiology* 2000;37:127–52. [PubMed: 10731765]
20. Banaschewski T, Brandeis D. Annotation: What electrical brain activity tells us about brain function that other techniques cannot tell us – a child psychiatric perspective. *J Child Psychol Psychiatry*. 2006early online published
21. Kok A. Effects of degradation of visual stimuli on components of the event related potential (ERP) in Go/nogo reaction tasks. *Biol Psychol* 1986;23:21–38. [PubMed: 3790646]
22. Kok A. Varieties of inhibition: manifestations in cognition, event-related potentials and aging. *Acta Psychol (Amst)* 1999;101:129–58. [PubMed: 10344183]
23. Falkenstein M, Hoormann J, Hohnsbein J. ERP components in Go/Nogo tasks and their relation to inhibition. *Acta Psychol (Amst)* 1999;101:267–91. [PubMed: 10344188]
24. Nieuwenhuis S, Yeung N, van den Wildenberg W, Ridderinkhof KR. Electrophysiological correlates of anterior cingulate function in a go/no-go task: effects of response conflict and trial type frequency. *Cogn Affect Behav Neurosci* 2003;3:17–26. [PubMed: 12822595]
25. Donkers FC, van Boxtel GJ. The N2 in go/no-go tasks reflects conflict monitoring not response inhibition. *Brain Cogn* 2004;56:165–76. [PubMed: 15518933]
26. Liotti M, Woldorff MG, Perez R, Mayberg HS. An ERP study of the temporal course of the Stroop color-word interference effect. *Neuropsychologia* 2000;38:701–11. [PubMed: 10689046]
27. Bekker EM, Kenemans JL, Verbaten MN. Source analysis of the N2 in a cued Go/NoGo task. *Brain Res Cogn Brain Res* 2005;22:221–31. [PubMed: 15653295]
28. Overtom CC, Verbaten MN, Kemner C, Kenemans JL, van Engeland H, Buitelaar JK, et al. Associations between event-related potentials and measures of attention and inhibition in the Continuous Performance Task in children with ADHD and normal controls. *J Am Acad Child Adolesc Psychiatry* 1998;37:977–85. [PubMed: 9735617]
29. Fallgatter AJ, Ehlis AC, Seifert J, Strik WK, Scheuerpflug P, Zillesen KE, et al. Altered response control and anterior cingulate function in attention-deficit/hyperactivity disorder boys. *Clin Neurophysiol* 2004;115:973–81. [PubMed: 15003781]
30. Lawrence CA, Barry RJ, Clarke AR, Johnstone SJ, McCarthy R, Selikowitz M, et al. Methylphenidate effects in attention deficit/hyperactivity disorder: electrodermal and ERP measures during a continuous performance task. *Psychopharmacology (Berl)* 2005;183:81–91. [PubMed: 16160877]

31. Wiersema R, van der Meere J, Roeyers H, Van Coster R, Baeyens D. Event rate and event-related potentials in ADHD. *J Child Psychol Psychiatry* 2006;47:560–7. [PubMed: 16712632]
32. Yong-Liang G, Robaey P, Karayanidis F, Bourassa M, Pelletier G, Geoffroy G. ERPs and behavioral inhibition in a Go/No-go task in children with attention-deficit hyperactivity disorder. *Brain Cogn* 2000;43:215–20. [PubMed: 10857697]
33. Brandeis D, van Leeuwen TH, Rubia K, Vitacco D, Steger J, Pascual-Marqui RD, et al. Neuroelectric mapping reveals precursor of stop failures in children with attention deficits. *Behav Brain Res* 1998;94:111–25. [PubMed: 9708844]
34. Pliszka SR, Liotti M, Woldorff MG. Inhibitory control in children with attention-deficit/hyperactivity disorder: event-related potentials identify the processing component and timing of an impaired right-frontal response-inhibition mechanism. *Biol Psychiatry* 2000;48:238–46. [PubMed: 10924667]
35. Dimoska A, Johnstone SJ, Barry RJ, Clarke AR. Inhibitory motor control in children with attention-deficit/hyperactivity disorder: event-related potentials in the stop-signal paradigm. *Biol Psychiatry* 2003;54:1345–54. [PubMed: 14675798]
36. Albrecht B, Banaschewski T, Brandeis D, Heinrich H, Rothenberger A. Response inhibition deficits in externalizing child psychiatric disorders: An ERP-study with the Stop-task. *Behav Brain Funct* 2005;1:22. [PubMed: 16336676]
37. Falkenstein, M.; Hohnsbein, J.; Hoormann, J. Effects of errors in choice reaction tasks on the ERP under focused and divided attention. In: Brunia, CHM.; Gaillard, AWK.; Kok, A., editors. *Psychophysiological Brain research*. Tilburg: Tilburg University Press; 1990. p. 192–195.
38. Falkenstein M, Hoormann J, Christ S, Hohnsbein J. ERP components on reaction errors and their functional significance: a tutorial. *Biol Psychol* 2000;51:87–107. [PubMed: 10686361]
39. Gehring WJ, Goss B, Coles MG, Meyer DE, Donchin E. A neural system for error detection and compensation. *Psychol Sci* 1993;4:385–390.
40. Hogan AM, Vargha-Khadem F, Kirkham FJ, Baldeweg T. Maturation of action monitoring from adolescence to adulthood: an ERP study. *Dev Sci* 2005;8:525–34. [PubMed: 16246244]
41. Band GP, Kok A. Age effects on response monitoring in a mental-rotation task. *Biol Psychol* 2000;51:201–21. [PubMed: 10686366]
42. Scheffers MK, Coles MG, Bernstein P, Gehring WJ, Donchin E. Event-related brain potentials and error-related processing: an analysis of incorrect responses to go and no-go stimuli. *Psychophysiology* 1996;33:42–53. [PubMed: 8570794]
43. Holroyd CB, Dien J, Coles MG. Error-related scalp potentials elicited by hand and foot movements: evidence for an output-independent error-processing system in humans. *Neurosci Lett* 1998;242:65–8. [PubMed: 9533395]
44. Nieuwenhuis S, Ridderinkhof KR, Blom J, Band GP, Kok A. Error-related brain potentials are differentially related to awareness of response errors: evidence from an antisaccade task. *Psychophysiology* 2001;38:752–60. [PubMed: 11577898]
45. Carter CS, Braver TS, Barch DM, Botvinick MM, Noll D, Cohen JD. Anterior cingulate cortex, error detection, and the online monitoring of performance. *Science* 1998;280:747–9. [PubMed: 9563953]
46. Holroyd CB, Coles MG. The neural basis of human error processing: reinforcement learning, dopamine, and the error-related negativity. *Psychol Rev* 2002;109:679–709. [PubMed: 12374324]
47. de Bruijn ER, Hulstijn W, Verkes RJ, Ruigt GS, Sabbe BG. Drug-induced stimulation and suppression of action monitoring in healthy volunteers. *Psychopharmacology (Berl)* 2004;177:151–60. [PubMed: 15578258]
48. de Bruijn ER, Sabbe BG, Hulstijn W, Ruigt GS, Verkes RJ. Effects of antipsychotic and antidepressant drugs on action monitoring in healthy volunteers. *Brain Res* 2006;1105:122–9. [PubMed: 16499887]
49. Zirnheld PJ, Carroll CA, Kieffaber PD, O'Donnell BF, Shekhar A, Hetrick WP. Haloperidol impairs learning and error-related negativity in humans. *J Cogn Neurosci* 2004;16:1098–112. [PubMed: 15298795]
50. Dehaene, s; Posner, MI.; Tucker, DM. Localization of a neural system for error detection and compensation. *Psychol Sci* 1994;5.
51. Ullsperger M, von Cramon DY. Subprocesses of performance monitoring: a dissociation of error processing and response competition revealed by event-related fMRI and ERPs. *Neuroimage* 2001;14:1387–401. [PubMed: 11707094]

52. Herrmann MJ, Rommner J, Ehrlis AC, Heidrich A, Fallgatter AJ. Source localization (LORETA) of the error-related-negativity (ERN/Ne) and positivity (Pe). *Brain Res Cogn Brain Res* 2004;20:294–9. [PubMed: 15183400]
53. Van Veen V, Carter CS. The timing of action-monitoring processes in the anterior cingulate cortex. *J Cogn Neurosci* 2002;14:593–602. [PubMed: 12126500]
54. Yeung N, Cohen JD. The impact of cognitive deficits on conflict monitoring. Predictable dissociations between the error-related negativity and N2. *Psychol Sci* 2006;17:164–71. [PubMed: 16466425]
55. Ridderinkhof KR, de Vlugt Y, Bramlage A, Spaan M, Elton M, Snel J, et al. Alcohol consumption impairs detection of performance errors in mediofrontal cortex. *Science* 2002;298:2209–11. [PubMed: 12424384]
56. Davies PL, Segalowitz SJ, Gavin WJ. Development of response-monitoring ERPs in 7- to 25-year-olds. *Dev Neuropsychol* 2004;25:355–76. [PubMed: 15148003]
57. Gehring WJ, Himle J, Nisenson LG. Action-monitoring dysfunction in obsessive-compulsive disorder. *Psychol Sci* 2000;11:1–6. [PubMed: 11228836]
58. Hajcak G, Simons RF. Error-related brain activity in obsessive-compulsive undergraduates. *Psychiatry Res* 2002;110:63–72. [PubMed: 12007594]
59. Hajcak G, McDonald N, Simons RF. Anxiety and error-related brain activity. *Biol Psychol* 2003;64:77–90. [PubMed: 14602356]
60. Hajcak G, McDonald N, Simons RF. Error-related psychophysiology and negative affect. *Brain Cogn* 2004;56:189–97. [PubMed: 15518935]
61. Boksem MA, Tops M, Wester AE, Meijman TF, Lorist MM. Error-related ERP components and individual differences in punishment and reward sensitivity. *Brain Res* 2006;1101:92–101. [PubMed: 16784728]
62. Morris SE, Yee CM, Nuechterlein KH. Electrophysiological analysis of error monitoring in schizophrenia. *J Abnorm Psychol* 2006;115:239–50. [PubMed: 16737389]
63. Kim MS, Kang SS, Shin KS, Yoo SY, Kim YY, Kwon JS. Neuropsychological correlates of error negativity and positivity in schizophrenia patients. *Psychiatry Clin Neurosci* 2006;60:303–11. [PubMed: 16732746]
64. Ruchow M, Walter H, Buchheim A, Martius P, Spitzer M, Kachele H, et al. Electrophysiological correlates of error processing in borderline personality disorder. *Biol Psychol* 2006;72:133–40. [PubMed: 16288950]
65. Falkenstein M, Hielscher H, Dziobek I, Schwarzenau P, Hoormann J, Sunderman B, et al. Action monitoring, error detection, and the basal ganglia: an ERP study. *Neuroreport* 2001;12:157–61. [PubMed: 11201078]
66. Ito J, Kitagawa J. Performance monitoring and error processing during a lexical decision task in patients with Parkinson's disease. *J Geriatr Psychiatry Neurol* 2006;19:46–54. [PubMed: 16449761]
67. Falkenstein M, Willemsen R, Hohnsbein J, Hielscher H. Error Processing in Parkinson's Disease: The Error Positivity. *Journal of Psychophysiology* 2005;19:305–310.
68. Beste C, Saft C, Andrich J, Gold R, Falkenstein M. Error processing in Huntington's disease. *PLoS ONE* 2006;1:e86. [PubMed: 17183717]
69. Castellanos FX, Tannock R. Neuroscience of attention-deficit/hyperactivity disorder: the search for endophenotypes. *Nat Rev Neurosci* 2002;3:617–28. [PubMed: 12154363]
70. Potts GF, George MR, Martin LE, Barratt ES. Reduced punishment sensitivity in neural systems of behavior monitoring in impulsive individuals. *Neurosci Lett* 2006;397:130–4. [PubMed: 16378683]
71. Liotti M, Pliszka SR, Perez R, Kothmann D, Woldorff MG. Abnormal brain activity related to performance monitoring and error detection in children with ADHD. *Cortex* 2005;41:377–88. [PubMed: 15871602]
72. van Meel CS, Heslenfeld DJ, Oosterlaan J, Sergeant JA. Adaptive control deficits in attention-deficit/hyperactivity disorder (ADHD): The role of error processing. *Psychiatry Res*. 2007
73. Wiersma JR, van der Meere JJ, Roeyers H. ERP correlates of impaired error monitoring in children with ADHD. *J Neural Transm* 2005;112:1417–30. [PubMed: 15726277]
74. Burgo-Murphy A, Klorman R, Shaywitz SE, Fletcher JM, Marchione KE, Holahan J, et al. Error-related event-related potentials in children with attention-deficit hyperactivity disorder, oppositional

defiant disorder, reading disorder, and math disorder. *Biol Psychol* 2007;75:75–86. [PubMed: 17257731]

75. Kopp B, Rist F, Mattler U. N200 in the flanker task as a neurobehavioral tool for investigating executive control. *Psychophysiology* 1996;33:282–94. [PubMed: 8936397]
76. Eriksen BA, Eriksen CW. Effects of noise letters upon the identification of a target letter in a nonsearch task. *Perception & Psychophysics* 1974;16:143–149.
77. Eriksen CW, Schultz DW. Information processing in visual search: a continuous flow conception and experimental results. *Percept Psychophys* 1979;25:249–63. [PubMed: 461085]
78. Hager W. On testing a priori hypotheses about quantitative and qualitative trends. *Methods of Psychological Research Online* 1996;1:1–23.
79. Mintz J. A Correlational Method for the Investigation of Systematic Trends in Serial Data. *Educational and Psychological Measurement* 1970;30:575–578.
80. Slaats-Willemse D, Swaab-Barneveld H, de Sonneville L, van der Meulen E, Buitelaar J. Deficient response inhibition as a cognitive endophenotype of ADHD. *J Am Acad Child Adolesc Psychiatry* 2003;42:1242–8. [PubMed: 14560175]
81. Kuntsi J, Neale BM, Chen W, Faraone SV, Asherson P. The IMAGE project: methodological issues for the molecular genetic analysis of ADHD. *Behav Brain Funct* 2006;2:27. [PubMed: 16887023]
82. Asherson P. Attention-Deficit Hyperactivity Disorder in the post-genomic era. *Eur Child Adolesc Psychiatry* 2004;13(Suppl 1):I50–70. [PubMed: 15322957]
83. Tewes, U.; Rossmann, P.; Schallenger, U. Hamburg-Wechsler-Intelligenztest für Kinder III. Bern: Hans Huber; 1999.
84. Sattler, JM. Assessment of Children: Wisc-III and Wppsi-R Supplement. San Diego: Jerome M. Sattler; 1992.
85. Conners CK, Sitarenios G, Parker JD, Epstein JN. The revised Conners' Parent Rating Scale (CPRS-R): factor structure, reliability, and criterion validity. *J Abnorm Child Psychol* 1998;26:257–68. [PubMed: 9700518]
86. Conners CK, Sitarenios G, Parker JD, Epstein JN. Revision and restandardization of the Conners Teacher Rating Scale (CTRS-R): factor structure, reliability, and criterion validity. *J Abnorm Child Psychol* 1998;26:279–91. [PubMed: 9700520]
87. Goodman R. The Strengths and Difficulties Questionnaire: a research note. *J Child Psychol Psychiatry* 1997;38:581–6. [PubMed: 9255702]
88. Woerner W, Fleitlich-Bilyk B, Martinussen R, Fletcher J, Cucchiaro G, Dalgalarondo P, et al. The Strengths and Difficulties Questionnaire overseas: evaluations and applications of the SDQ beyond Europe. *Eur Child Adolesc Psychiatry* 2004;13(Suppl 2):II47–54. [PubMed: 15243786]
89. Taylor E, Everitt B, Thorley G, Schachar R, Rutter M, Wieselberg M. Conduct disorder and hyperactivity: II. A cluster analytic approach to the identification of a behavioural syndrome. *Br J Psychiatry* 1986;149:768–77. [PubMed: 3790876]
90. Taylor E, Schachar R, Thorley G, Wieselberg HM, Everitt B, Rutter M. Which boys respond to stimulant medication? A controlled trial of methylphenidate in boys with disruptive behaviour. *Psychol Med* 1987;17:121–43. [PubMed: 3554290]
91. Taylor E, Schachar R, Thorley G, Wieselberg M. Conduct disorder and hyperactivity: I. Separation of hyperactivity and antisocial conduct in British child psychiatric patients. *Br J Psychiatry* 1986;149:760–7. [PubMed: 3790875]
92. Uebel H, Albrecht B, Asherson P, Boerger N, Butler L, Chen W, et al. Reaction-time variability and false alarms as endophenotypes in a Go/No-Go task with ADHD children, their nonaffected siblings and unrelated healthy controls. 2007in preparation
93. Andreou P, Chen W, Christiansen H, Gabriels I, Heise A, Meidad S, et al. Reaction time performance in ADHD: improvement under fast-incentive condition and familial effects. 2007in preparation
94. Brookes K, Xu X, Chen W, Zhou K, Neale B, Lowe N, et al. 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* 2006;11:934–53. [PubMed: 16894395]
95. Rommelse NN, Oosterlaan J, Buitelaar J, Faraone SV, Sergeant JA. Time Reproduction in Children With ADHD and Their Nonaffected Siblings. *J Am Acad Child Adolesc Psychiatry* 2007;46:582–590. [PubMed: 17450049]

96. Chambers CD, Brown M. Timing accuracy under microsoft windows revealed through external chronometry. *Behav Res Methods Instrum Comput* 2003;35:96–108. [PubMed: 12723784]
97. Gratton G, Coles MG, Donchin E. A new method for off-line removal of ocular artifact. *Electroencephalogr Clin Neurophysiol* 1983;55:468–84. [PubMed: 6187540]
98. Falkenstein M, Hoormann J, Hohnsbein J. Changes of error-related ERPs with age. *Exp Brain Res* 2001;138:258–62. [PubMed: 11417467]
99. Biederman J, Faraone SV, Keenan K, Knee D, Tsuang MT. Family-genetic and psychosocial risk factors in DSM-III attention deficit disorder. *J Am Acad Child Adolesc Psychiatry* 1990;29:526–33. [PubMed: 2387786]
100. Biederman J, Faraone SV, Keenan K, Benjamin J, Krifcher B, Moore C, et al. Further evidence for family-genetic risk factors in attention deficit hyperactivity disorder. Patterns of comorbidity in probands and relatives psychiatrically and pediatrically referred samples. *Arch Gen Psychiatry* 1992;49:728–38. [PubMed: 1514878]
101. Faraone SV, Biederman J, Mick E, Williamson S, Wilens T, Spencer T, et al. Family study of girls with attention deficit hyperactivity disorder. *Am J Psychiatry* 2000;157:1077–83. [PubMed: 10873914]
102. Asherson P, Kuntsi J, Taylor E. Unravelling the complexity of attention-deficit hyperactivity disorder: a behavioural genomic approach. *Br J Psychiatry* 2005;187:103–5. [PubMed: 16055819]

Figure 1. Task description

Flanker arrowheads (red) preceded the presentation of the central target and flanker arrowheads (green) by 100ms. Conditions were congruent or incongruent and responses were required either to the left or right.

Figure 2. Stimulus-locked curves

For both congruent and incongruent correct responded trials a N2 is apparent at a latency of 330ms after the onset of the target. N2 amplitude is enhanced in incongruent trials.

Figure 3. Response-locked curves to correct responses and errors in incongruent trials
 Response-locked grand average waves of controls (black), nonaffected siblings (red) and boys with ADHD (green). The Ne peaked for all groups at around 60–80ms after the erroneous response (red curve) and was followed by an adjacent more posterior located error positivity (Pe). Both deflections were not present in curves evoked by correct responses.

Figure 4. Stimulus-locked N2 to congruent and incongruent correct responded trials
 Response-locked grand average waves of controls (black), nonaffected siblings (red) and ADHD boys (green) with spline-interpolated maps of N2 evoked by correct congruent (left) and incongruent (right) trials at the respective group mean latency.

Figure 5. Response-locked error-related components

Response-locked grand average waves of controls (black), nonaffected siblings (red) and ADHD boys (green) with spline-interpolated maps of Ne at the respective group mean latency (left side) and Pe mean activity 200–500ms post error response (right side). The response-locked Ne has its maximum at FCz (even more prominent when measured peak-to-peak), while Pe was maximal at centro-parietal electrodes.

Table 1

Sample description

Measure	Controls (C) N = 22 Mean (SD)	Nonaffected siblings (S) N = 18 Mean (SD)	ADHD (A) N = 68 Mean (SD)	F _(2, 105)	ANOVA Post-hoc-Tests
Age (in months)	134.1 (20.6)	137.0 (26.5)	135.9 (19.0)	0.1	-
Proated-IQ	110.3 (11.5)	109.3 (12.7)	104.4 (10.8)	2.9 ⁺	-
SDQ ^b					
Parents ^c					
Hyperactivity	2.3 (1.8)	2.9 (2.4)	8.3 (1.5)	135.1 ^{**}	C < A ^{**} , S < A ^{**}
Prosocial Behavior	7.8 (1.7)	6.7 (2.1)	6.5 (2.2)	3.0 [*]	C < A ^{**} , S < A [*]
Emotional Symptoms	1.7 (1.7)	2.5 (3.3)	4.4 (2.6)	10.4 ^{**}	C < A ^{**} , S < A ^{**}
Conduct Problems	1.1 (1.3)	2.8 (2.3)	5.1 (2.1)	35.6 ^{**}	C < A ^{**} , S < A ^{**}
Peer Problems	1.0 (1.4)	2.2 (2.3)	4.4 (2.5)	18.8 ^{**}	C < A ^{**} , S < A ^{**}
Teacher ^d					
Hyperactivity	2.2 (2.8)	4.1 (3.1)	8.3 (1.7)	70.3 ^{**}	C < A ^{**} , S < A ^{**} , C < S [*]
Prosocial Behavior	6.8 (1.8)	6.8 (1.7)	5.3 (2.9)	4.1 [*]	C < A ⁺
Emotional Symptoms	1.2 (1.8)	2.3 (2.7)	3.4 (2.6)	6.3 ^{**}	C < A [*]
Conduct Problems	0.8 (2.1)	2.2 (2.0)	3.5 (2.1)	12.6 ^{**}	C < A ^{**} , S < A ⁺
Peer Problems	0.8 (1.5)	1.8 (2.0)	3.9 (2.6)	15.0 ^{**}	C < A ^{**} , S < A ^{**}

⁺ $\alpha < .1$

^{*} $\alpha < .05$

^{**} $\alpha < .01$

^b Strengths and difficulties Questionnaire

^c not available for 1 subjects, df=2, 104

^d not available for 4 subjects, df=2, 101

Table 2

Performance Data

Measure	Controls (C) N = 22 Mean (SD)	Nonaffected siblings (S) N = 18 Mean (SD)	ADHD (A) N = 68 Mean (SD)	F _(2, 105)	ANOVA group Sidak-Tests	congruency	repeated measure ANOVA group	conflict * group
Error-rate (%)								
congruent trials	4.5 (5.7)	5.4 (4.6)	8.5 (5.6)	5.4**	C < A*	F _(1, 105) = 495.2** part. η^2 = .83** con < incon	F _(2, 105) = 0.6 part. η^2 < .01 -	F _(2, 105) = 3.8* part. η^2 = .07 C > A
incongruent trials	31.5 (11.6)	29.0 (9.4)	29.2 (7.7)	0.6*	- *			
difference	27.0 (11.8)	23.6 (9.4)	20.7 (8.6)	3.8*	C > A			
Reaction-times of correct responses (ms)								
congruent trials	335 (56.7)	358 (70.0)	386 (79.4)	4.3*	C < A*	F _(1, 105) = 753.9** part. η^2 = .88** con < incon	F _(2, 105) = 3.8* part. η^2 = .07 C < A	F _(2, 105) = 0.2 part. η^2 < .01 -
incongruent trials	433 (71.7)	459 (79.9)	482 (86.8)	3.1*	C < A*			
difference	98 (33.2)	101 (34.2)	96 (30.2)	0.2	-			
Reaction-time variability of correct responses (ms)								
congruent trials	91 (39.6)	129 (75.9)	161 (68.7)	9.9**	C < A**	F _(1, 105) = 1.4 part. η^2 = .01 -	F _(2, 105) = 10.1** part. η^2 = .16 C < A	F _(2, 105) = 0.4 part. η^2 < .01 -
incongruent trials	94 (42.1)	132 (81.0)	170 (81.7)	9.0**	C < A**			
difference	3 (19.1)	3 (25.4)	9 (42.4)	0.4	-			

+ p < 0.1

* p < .05

** p < .01

Table 3
Stimulus-locked effects of conflict on electrophysiological parameters

Measure	Controls (C) N = 22 Mean (SD)	Nonaffected siblings (S) N = 18 Mean (SD)	ADHD (A) N = 68 Mean (SD)	ANOVA
Stimulus-locked N200 Latency at FCz (ms)				
incongruent correct	329 (34)	335 (30)	338 (27)	congruency: $F_{(1, 105)}=0.5$, part. $\eta^2<.01$ congr. * group: $F_{(2, 105)}=0.1$, part. $\eta^2<.01$ group: $F_{(2, 105)}=1.0$, part. $\eta^2=.02$
congruent correct	328 (29)	331 (23)	337 (33)	
difference	1 (26)	5 (25)	1 (29)	
Stimulus-locked N200 Amplitude (μV)				
congruent correct				
Fz	-4.5 (3.5)	-4.1 (3.8)	-4.5 (2.9)	congruency: $F_{(1, 105)}=50.8^{***}$, part. $\eta^2=.33$ (incongr.<congr.) congr. * group: $F_{(2, 105)}=4.1^*$, part. $\eta^2=.07$ (C<A) congr. group: $F_{(2, 105)}=102.2^{***}$, $\epsilon=.60$, part. $\eta^2=.49$ (Fz<Cz) site: $F_{(2, 210)}=17.5^{***}$, $\epsilon=.66$, part. $\eta^2=.14$ (Fz<Cz) FCz<Cz)
FCz	-3.8 (2.5)	-3.3 (3.2)	-3.7 (3.4)	
Cz	-.3 (3.3)	.5 (2.9)	-.3 (3.8)	
incongruent correct				
Fz	-7.0 (3.7)	-6.4 (3.1)	-6.1 (3.7)	congr. * site group: $F_{(4, 210)}=1.2$, part. $\eta^2=.02$ congr. site group: $F_{(2, 105)}=0.9$, part. $\eta^2=.02$ FCz<Cz)
FCz	-7.5 (4.2)	-5.6 (3.4)	-5.2 (3.8)	
Cz	-2.0 (3.7)	-.3 (4.1)	-.4 (3.9)	

+ p < 0.1

* p < .05

** p < .01

Table 4
Response-locked electrophysiological data of error processing

Measure	Controls (C) N = 22 Mean (SD)	Nonaffected siblings (S) N = 18 Mean (SD)	ADHD (A) N = 68 Mean (SD)	F _(2, 105)	ANOVA group Sidak-Tests ^a	peak	repeated measure ANOVA group	peak * group
Error Negativity Latency at FCz (ms)								
PNe	-31 (29)	-30 (27)	-27.0 (29)	.2	-	F _(1, 105) =912.0 ^{**} part. η^2 =90 ^{**} Ne < PNe	F _(2, 105) =0.7 part. η^2 =0.01	F _(2, 105) =4.7 [*] part. η^2 <.08 ^{**} C > A
Ne	78 (29)	62 (25)	61 (32)	2.8 ⁺	C > A ⁺ C > A ^{**}			
Peak-to-Peak	109 (21)	92 (22)	88 (31)	4.7 ^{**}				
Error Negativity Amplitude at FCz (μ V)								
PNe	1.8 (3.6)	1.4 (3.6)	.8 (3.3)	.7	-	F _(1, 105) =305.3 ^{**} part. η^2 =74 ^{**} Ne < PNe ^{**}	F _(2, 105) =0.4 part. η^2 <.01	F _(2, 105) =5.7 ^{**} part. η^2 =.10 ^{**} C < A ^{**}
Ne	-8.1 (3.4)	-6.9 (4.8)	-5.7 (4.3)	2.8 ⁺	C < A ⁺ C < A ^{**}			
Peak-to-Peak Ne	-9.9 (4.2)	-8.3 (4.0)	-6.6 (4.2)	5.7 ^{**}				
Error Positivity Mean Amplitude (μ V)								
Cz	9.1 (4.1)	7.2 (3.8)	8.0 (4.4)	1.0	-	F _(1, 105) =3.2 ⁺ part. η^2 =0.03	F _(2, 105) =1.3 part. η^2 =0.03	F _(2, 105) =0.1 part. η^2 <.01
Pz	9.8 (4.0)	8.2 (2.8)	8.6 (4.0)	1.1	-			
mean	9.5 (3.8)	7.7 (3.0)	8.3 (3.7)	1.3	-			

⁺ p < 0.1
* p < .05
** p < .01