Disentangling Deficits in Adults With Attention-Deficit/Hyperactivity Disorder

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Context: A lack of inhibitory control has been suggested to be the core deficit in attention-deficit/hyperactivity disorder (ADHD), especially in adults. This means that a primary deficit in inhibition mediates a cascade of secondary deficits in other executive functions, such as attention. Impaired stopping has been claimed to support the inhibition hypothesis. However, executive functions such as inhibition and attention are hard to disentangle.

Objective: To use event-related potentials in adult patients with ADHD to show that impaired stopping is associated with abnormalities of attention.

Design: The stop signal task was presented to 24 adults with ADHD combined subtype and 24 controls. Stop event-related potentials are distorted by overlap from event-related potentials to other stimuli in close temporal proximity, but we applied a method (Adjar level 2) to effectively remove this overlap.

Results: In line with an inhibitory control deficit, the stop signal reaction time was longer in adults with ADHD ($F_{1,44}=7.12, P<.01$) whereas there was no significant difference for go stimulus reaction time. Overlap-free stop event-related potentials revealed smaller stop P3s in adults with ADHD ($F_{1,44}=4.20, P<.05$). In children with ADHD, this has been interpreted to reflect deficient inhibitory control. However, controls were also found to have larger early responses in the auditory cortex (N1) when stop signals resulted in successful stops, relative to failed stops, signifying increased attention ($F_{1,23}=11.88, P<.01$). This difference was completely absent in adults with ADHD.

Conclusions: Disturbed attentional processing of the stop signal contributed to impaired stopping in adults with ADHD. This finding may have implications for treatment.

Arch Gen Psychiatry. 2005;62:1129-1136
The efficacy of Adjar in the stop signal task. After correction, successful stops were associated with a larger positivity over frontal areas as from 140-milliseconds post–stop signal. Successful stops were associated with a larger negativity at about 100 milliseconds post-correction. In our opinion, the only method that validly addresses overlap problems is the Adjacent Response filter method (Adjar level 2) developed by Woldorff. In a previous study with healthy subjects, we demonstrated the efficacy of Adjar in the stop signal task. After correction, successful stops were associated with a larger positivity over frontal areas as from 140-milliseconds post–stop signal than failed stops. This stop P3 has been reported before and has been interpreted to reflect response inhibition.

Even with the overlap problem being resolved for the stop P3, the interpretation in terms of inhibition remains somewhat arbitrary. A completely new finding after Adjar correction was that successful stops were associated with a larger negative peak at about 100 milliseconds post-stimulus. This N1 almost certainly originates in auditory cortex and is very sensitive to selective attention. More generally, it reflects the trial-to-trial varying impact a stimulus has in auditory cortex, which is an essential ingredient of the amount of attention that is switched to the stimulus on its presentation. This prompts the intriguing possibility that impaired stopping at least partly depends on the inability to switch attention to the stop signal.

In the present study, Adjar-corrected stop signal ERPs obtained from adults with ADHD (n=24) were compared with those obtained from matched controls (n=24). Three hypotheses were tested. First, in the present sample of controls, successful stops are associated with larger N1s and stop P3s than failed stops. Second, the stop P3 effect is reduced in adults with ADHD, suggesting a deficient inhibitory mechanism. Third, the N1 effect is reduced in the ADHD group, suggesting that deficient attention switching to the stop signal is the precursor of deficient inhibitory control.

**METHODS**

**SUBJECTS**

Twenty-four outpatient adults with ADHD diagnosed with the combined subtype (mean ± SD age, 34.3 ± 11.68 years; range, 18-57 years; 12 men; 3 left-handed) were matched on age and gender with 24 controls (mean ± SD age, 34.9 years; range, 18-57 years; 12 men; 1 left-handed). The vocabulary and block design subtests of the Wechsler Adult Intelligence Scale III were administered to ensure comparable IQ across groups (mean ± SD age-scaled scores were 10.3 ± 3.6 and 10.0 ± 3.0 for adults with ADHD and 11.1 ± 3.2 and 10.5 ± 3.9 for controls, respectively; F1,46=0.79, P =.38, and F1,46=0.21, P =.65). All subjects claimed to have normal hearing and normal or corrected-to-normal vision. Prior to participation, the use of psychoactive medication (at least 6 times the half-life concerned); drugs (at least 3 weeks); alcohol (at least 24 hours); and nicotine, caffeine, and cacao (at least 12 hours) was prohibited. All subjects signed informed-consent forms. The ethics committee of the Utrecht University Medical Center (Utrecht, the Netherlands) approved this study.

**RECRUITMENT AND SCREENING**

Patients were recruited when first seeking clinical help and had no former experience with psychostimulant medication, which is common among newly referred patients with ADHD in the Netherlands. Controls were recruited with advertisements in local newspapers and received €90.00 each for their participation. All subjects were first screened with a telephone interview addressing past and current ADHD symptoms; psychiatric, neurological, and medical disorders; physical impairments; use of medication; and substance abuse. Then, subjects filled out translated versions of the Brown ADD Scale, the Conners’ Adult ADHD Rating Scales, and the DSM-IV ADHD-rating scale for current and past ADHD symptoms. Finally, we administered 2 structured interviews: a translated version of the Diagnostic Interview Schedule assessing ADHD symptoms (DIS-L) and the computerized Comorbid International Diagnostic Interview, assessing comorbid DSM-IV disorders. In contrast with controls, patients scored above ADHD cut-off values on both self-report questionnaires (details described elsewhere and the DIS-L).

**EXCLUSION**

Subjects who reported clinically unstable conditions (ie, suicidal behaviors, psychosis, mania, or physical aggression), organic brain disorder, epilepsy, or past concussions were excluded.

Regarding controls, subjects were additionally excluded if they were currently suspected of having ADHD, other psychiatric disorders, or substance abuse; if they were diagnosed with a developmental disorder in childhood; or if they reported ADHD among relatives. This decision was based on the telephone interview, the self-report questionnaires, and the DIS-L.

Regarding the ADHD group, patients were additionally excluded if an experienced physician stated that the severity of a...
A psychiatrist who specializes in adult ADHD supervised each diagnostic evaluation performed by an experienced physician. If needed, they met the patient together (n=2). Only if both agreed was the patient allowed to participate. To be diagnosed with ADHD, subjects must have (1) met 6 of 9 DSM-IV criteria for inattention and hyperactivity/impulsivity for a diagnosis in childhood and at least 5 of 9 criteria in adulthood. If (2) described persistent ADHD symptoms from childhood to adulthood, and (3) experienced a moderate to severe level of impairment attributable to the ADHD symptoms. Current and childhood symptoms were evaluated with a semistructured diagnostic interview for ADHD and comorbid disorders (the SGIK) and the DIS-L. Other childhood disruptive disorders were assessed with a translated version of the structured diagnostic interview for retrospective diagnosis of ADHD and other disruptive disorders, the sections N (oppositional defiant disorder), O (conduct disorder), and P (antisocial personality disorder) of the DIS-IV. If possible, school reports were examined, and 17 parents (70.8%) or 7 siblings (29.2%) were interviewed with a semistructured interview on childhood ADHD symptoms. Twenty-one (87.5%) partners attended all interviews with the patients and were asked for their opinions on the presence, severity, and duration of current ADHD symptoms as well as the level of dysfunction caused by these symptoms. Finally, the physician filled out the DSM-IV rating scale and based the diagnosis of childhood-onset and current ADHD on all of this information.

**TASKS AND PROCEDURES**

The use of drugs (amphetamine, barbiturates, benzodiazepines, cocaine, morphine, and tetrahydrocannabinol) was tested with a urinal drug-detection device (Instant-View Drug Screen; Rapid Detect, Poteau, Okla), and the use of alcohol was tested with a breath device (Alcotest; Dräger Medical, Lübeck, Germany). A practice block consisting of the stop signal task was presented without tones. We stressed the speed of responding so that the subjects would not develop waiting strategies. If reaction times increased more than 10% compared with the practice block without tones, subjects were urged to speed up their responses.

**ELECTROPHYSIOLOGICAL RECORDINGS**

Electroencephalographic data were recorded using an elastic cap with 62 tin electrodes arranged according to the International 10-10 system. Tin electrodes were also used for bipolar recording of the vertical electro-oculogram from above and below the left eye and the horizontal electro-oculogram from the outer canthi of each eye. Electroencephalographic signals were referenced to the left mastoid. The AFz electrode functioned as ground. Impedances were kept below 5 kΩ. Data acquisition was continuous with a sampling rate of 1000 Hz. Signals were cut off below 0.05 Hz and above 30 Hz. Offline, signals were down-sampled to 250 Hz and cut off above 30 Hz.

**DATA ANALYSIS**

Performance measures were calculated separately for each subject and each block. Mean RTs were computed out of a response window of 150 to 1250 milliseconds poststimulus. Furthermore, we calculated the SSRT, the corrected percentage of successful inhibitions, and the mean SOA. All measures were averaged across blocks (individual data) and subjects (grand-average data).

We computed ERPs separately for successful stops and failed stops from −100 to 1352 milliseconds relative to the onset of the S1 (go stimulus) and S2 (stop stimulus). The 100 milliseconds preceding S1 served as a baseline. Trials with artifacts or analogue-to-digital–converter saturation were rejected from further analysis (discarded stop trials, 6.28% for controls and 7.35% for subjects with ADHD). Ocular artifacts were estimated and subtracted by time domain regression. Data were merged across 6 experimental blocks. Stopped ERPs were filtered with Adjar level 2 in the interval from −100 to 700 milliseconds. Subsequently, a 100-millisecond pre-S2 baseline was applied.

**TOPOGRAPHICAL MAPPING AND SOURCE ANALYSIS**

We used BESA 2.2 (MEGIS Software GmbH, Graefeling, Germany) to derive maps and source models for the grand-average, average-referenced ERPs elicited by successful and failed stops. Models were derived for each group and each trial type (successful and failed stops) separately. The N1 was analyzed at the first negative peak after 80 milliseconds at FCz. The stop P3 was analyzed at the first positive peak after 130 milliseconds at Cz. The default 3-shell head model was used to model intracranial generators as a single bilateral dipole source. Digitized elec-
trode locations were projected on a least-square-fitted sphere, which was rotated with respect to mastoid and nasion locations. The resulting coordinates were averaged across subjects within each group. These averaged coordinates were used as a representation of recording sites. Each dipole was characterized by 7 parameters: 3 for location, 3 for orientation, and 1 for strength or dipole moment. To limit the number of parameters to be estimated, we applied symmetry constraints with respect to location and orientation to each bilateral dipole pair. The possibility of interacting dipoles was reduced by preferring solutions with relatively low dipole moments with the aid of an “energy” constraint (weighted 20% in the compound cost function, as opposed to 80% for the residual variance). We found the optimal set of parameters in an iterative manner by searching for a minimum in the compound cost function. Reported dipole solutions were stable across randomly varying starting positions.

STATISTICAL ANALYSIS

All dependent measures were subjected to repeated measures of variances (Wilks λ) containing the between-factor group (ADHD vs control) and the within-factor trial type (successful vs failed stops) with a critical α level of .05. Sample wise testing (5 milliseconds) of ERP amplitudes was restricted to leads and time windows for which the effects were expected to be largest, a choice based on a previous study.24 The N1 was analyzed from 80 to 124 milliseconds at FCz, and the stop P3 was analyzed from 136 to 352 milliseconds at Cz. Because this analysis involved many tests, the probability of making type I errors was minimized by considering effects significant only if they extended over at least 5 time points.41

RESULTS

PERFORMANCE

Performance data have been described in detail elsewhere.11 Briefly, SSRT was longer in patients with ADHD (mean ± SD, 185.2 ± 38.9 milliseconds for controls and 237.3 ± 87.2 milliseconds for adults with ADHD: F1,46 = 7.12, P < .01) whereas there was no significant difference regarding RT (mean ± SD, 463.3 ± 68.8 milliseconds for controls and 467.9 ± 87.6 milliseconds for adults with ADHD: F1,46 = 0.04, P = .84). We adjusted the SOA individually (mean ± SD, 267.6 ± 38.4 milliseconds for controls and 230.3 ± 78.1 milliseconds for adults with ADHD: F1,46 = 3.51, P = .07) to yield a probability of successful stops of around 50% in both groups26 (46.4 ± 6.3% for controls and 42.8 ± 10.6% for adults with ADHD: F1,46 = 2.08, P = .16).

EVENT-RELATED POTENTIALS

Figure 1 displays ERPs elicited by stop signals associated with successful and failed stops at FCz and Cz. As for the N1, stop signals elicited a pronounced negative peak around 100 milliseconds latency. At FCz, the N1 was larger for successful than for failed stops, but only for the control group (interaction with group, 92-124 milliseconds: F1,46 = 4.77, P < .05). At Cz, the stop P3 was smaller for the ADHD group. However, we did not find the expected interaction with group. Closer inspection revealed that the distribution across individuals of trial-type differences in amplitude deviated from normality in the ADHD group. Removal of 1 outlier (and the matched counterpart) yielded an interaction with group (140-352 milliseconds: F1,46 = 4.21, P < .05). Especially the difference waves in Figure 2 suggest that the stop P3 was smaller for the ADHD group. However, we did not find the expected interaction with group. Closer inspection revealed that the distribution across individuals of trial-type differences in amplitude deviated from normality in the ADHD group. Removal of 1 outlier (and the matched counterpart) yielded an interaction with group (172-200 milliseconds: F1,46 = 4.20, P < .05), indicating smaller stop P3s in adults with ADHD (see also

![Figure 1](image-url)
However, Figure 1 suggests that the interaction with group reflects longer latencies rather than smaller amplitudes of the stop P3 in the ADHD group, which would be consistent with the increase in SSRT. This alternative interpretation was only partly confirmed: sample-wise testing for each group separately yielded an effect of trial type in the interval of 140 to 300 milliseconds for the control group (F1,22=11.29, p<.01) and in the interval of 152 to 352 milliseconds for the ADHD group (F1,22=15.83, p<.01).

To confirm the contribution of auditory cortex to the N1, we conducted coarse source localization using BESA 2.2.42 Figure 3 shows that the resulting source models and associated scalp topographies are consistent with generators in auditory cortex.42 Analogous source modeling for the stop P3 suggested bilateral dipole pairs in more medial frontocentral regions (Figure 3). Importantly, statistical analysis using the latency-of-best-fit method to estimate individual source models43 confirmed that the locations of stop P3 sources were more medial than those of N1 sources (F1,46=52.55, p<.01; after removal of the outlier mentioned earlier in the article, F1,44=48.47, p<.01).

Post hoc correlations between the difference in N1 as well as P3 amplitude (successful minus failed) and SSRT were assessed. No significant correlations were found. This might be due to uncontrolled sources of variance, such as interindividual variability in N1 and P3 effects reflecting global neurophysiological differences, or to an indirect relation between SSRT and successful vs failed stopping. Furthermore, the amplitude measures were not found to correlate with self-report scales reflecting attention and impulsivity, respectively. This might additionally be due to conceptualization differences between experimental and clinical measures or to low validity of self-report scales.

**Table. Mean Event-Related Potential Amplitudes for ADHD and Control Groups**

<table>
<thead>
<tr>
<th>ERP</th>
<th>ADHD</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>N1 (92-124 ms at FCz)</td>
<td>−9.25 ± 5.14</td>
<td>−9.06 ± 4.43</td>
</tr>
<tr>
<td>Stop P3 (n = 24; 172-200 ms at Cz)</td>
<td>5.45 ± 3.74</td>
<td>2.87 ± 3.86</td>
</tr>
<tr>
<td>Stop P3 (n = 23; 172-200 ms at Cz)</td>
<td>5.28 ± 3.73</td>
<td>3.22 ± 3.52</td>
</tr>
</tbody>
</table>

Abbreviation: ADHD, attention-deficit/hyperactivity disorder.

*All values are means and standard deviations in µV, calculated in the interval for which significant differences between the ADHD and control groups were found.

The present study revealed that successfully stopping an ongoing response process is associated with a sequence of cortical activations elicited by the stop signal. Successful stops were associated with enhanced short-latency (100 milliseconds) activation in sensory cortex, followed by a longer-latency (as from 140 milliseconds) enhancement of activity in more medial frontocentral areas. These N1 and stop P3 effects were smaller in adults with ADHD, who also manifested impaired stopping as reflected in the behavioral index of stopping speed, the SSRT.

Our first hypothesis, that successful stops are associated with larger N1s and stop P3s than failed stops in the control group, was confirmed. Around 100 milliseconds,
stop signals elicited a negative deflection over frontocentral scalp sites. In the control group, successful stops were associated with a larger N1 than failed stops. Similar results were found in a previous study with healthy subjects after overlap removal with Adjar level 2. Because the N1 has been shown to be very sensitive to manipulations of selective attention to auditory stimuli, these findings imply that whether an auditory stop signal results in a successful or a failed stop at least partly depends on the amount of attention that is paid or switched to the stop signal. Further analysis of overlap-free stop ERPs revealed larger positive amplitudes for successful than for failed stops over central scalp sites as from 140 milliseconds. This stop P3 has previously been claimed to reflect response inhibition. Replication after overlap removal excludes the possibility that this effect merely reflects differences in motor-related potentials (see the introduction).

Coarse source localization of the N1 yielded models consistent with generators in auditory cortex. The stop P3 was modeled in more medial regions. This is in line with source models reported for the no-go P3 elicited in go/no-go tasks and might reflect a generator in anterior cingulate cortex, which is thought to be involved in response inhibition, either directly or by the detection of conflict that signals other brain areas to exert inhibitory control. Previous source localization of the stop P3 revealed generators in more posterior regions. These probably reflect overlapping activity related to the processing of the go stimulus, underlining the importance of applying Adjar level 2 to validly isolate cortical processing of the stop signal. It should be noted that dipoles reflect an oversimplification of actually activated brain areas. Previous studies using functional magnetic resonance imaging have suggested right lateralized frontostriatal involvement in response inhibition.

Consistent with earlier findings in children, the stop P3 effect was smaller in adults with ADHD. Previous results indicating smaller N2s to stop signals or smaller N1s to go stimuli (not reported) could not be replicated. The reduced stop P3 can be interpreted by assum-
ing that, although individuals with ADHD can generate an inhibitory response to stop signals with a probability similar to that found for controls (around 50%), if stimulus conditions are appropriately adjusted, stopping was less efficient or the activation of the inhibition system was weaker in individuals with ADHD, as was also indicated by the increase in SSRT. Because the difference in onset of the stop P3 effect (140 milliseconds for controls, 152 milliseconds for ADHD) was smaller than the difference in SSRT (185 milliseconds for controls, 237 milliseconds for ADHD), which is thought to reflect the finishing time of the internal stop response, this component might not be directly related to inhibition of ongoing responses. Furthermore, it should be noted that because of the transmission delay, inhibitory processes reflected in the stop P3 are not likely to exert an effect on behavioral measures until around 100 milliseconds after its onset. Therefore, at least on some part of the trials, processes other than those reflected in the stop P3 are associated with (impaired) response inhibition.

The increase in N1 amplitude for successful stops relative to failed stops was absent in adults with ADHD. Given that the difference in N1 for successful vs failed stops reflects attentional modulation of auditory-cortex activation elicited by the stop signal, it can be concluded that such attentional modulation is absent in adult ADHD. A number of reports on children with ADHD have revealed significantly reduced enhancement of auditory-cortex activation by stimuli that are deemed relevant by task. The present lack of N1 modulation, however, must reflect a more subtle mechanism. Internally generated trial-to-trial variation in N1 amplitude reflects fluctuations in the impact that stop signals have in auditory cortex, or, in other words, the amount of attention that is switched to the stimulus on its presentation. In healthy controls, these varying amounts of attention are directly related to the probability that subsequent stopping is successful. In adults with ADHD, this link between attention and stopping is lacking. Stated differently, no matter what the impact of the stop signal is in auditory cortex, it does not determine the probability of subsequent stopping; only a weakly activated inhibitory mechanism (reflected in a smaller stop P3 effect) was used for stopping. Because attention to go stimuli was unimpaired (there was no group effect on RT), the attentional deficit in adults with ADHD seems specifically related to the inability to switch attention to the stop signal. Accordingly, task-set switching deficits have been demonstrated in children with ADHD. The present study reveals that in adults with ADHD, at least on part of the trials, deficits in attentional switching might be the precursor of deficient inhibitory control, which is reflected in a disproportional elongation in SSRT (relative to RT).

One could argue that in controls, failed stopping was related to failed attention as well as failed inhibition whereas in adults with ADHD, failed stopping was related to failed inhibition only. However, the mean amplitudes provided in the Table suggest that the N1 associated with failed stops in the control group was comparable with the N1 associated with both successful and failed stops in the ADHD group (difference, 0.58 and 0.39 µV, respectively), whereas the N1 associated with successful stops in the control group was enlarged (difference, 1.42 and 1.61 µV, respectively). Following this line of reasoning, enhanced attention contributes to better stopping in controls, but not in ADHD.

A possible limitation of this study is the inclusion of patients with comorbid disorders. Because at least 75% of adults with ADHD suffer from additional DSM-IV disorders, isolating ADHD is difficult and might not yield a representative sample. The nonsystematic presence of comorbidity is expected to increase error variance, which would reduce the likelihood of finding significant group effects. Furthermore, comorbidity mainly consisted of depression and anxiety. As for depression, symptoms were mild or currently absent. As for anxiety, in children, SSRTs have been found to be comparable with those measured in controls.

In sum, the increase in SSRT found in patients with ADHD has often been interpreted to support a core deficit in inhibitory control rather than in attention. However, behavioral measures used as indices of executive functions merely reflect the compound contribution of different underlying subfunctions, which are hard to distinguish. Event-related potentials enable the disentangling of the relative contribution of inhibitory and attentional deficits eventuating in an increased SSRT. The present ERP study revealed that although general attention to task stimuli seemed undisturbed in adults with ADHD (no effect on RT), impaired stopping may still be related to deficiencies in other aspects of attention, in particular the ability to switch attention to the stop signal. This throws doubt on response inhibition as the primary deficit in ADHD and may have important implications for treatment.

Submitted for Publication: December 8, 2004; final revision received March 14, 2005; accepted March 25, 2005.

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Funding/Support: This study was funded by grant 425-20-205 from the Netherlands Organization for Scientific Research, the Hague. Carin C.E. Overtoom, PhD, was supported by a Grotius grant from the University of Amsterdam, Amsterdam, the Netherlands.

Acknowledgment: We thank Ineke de Noord and Carla Oostenbach for assisting in patient recruitment and screening.

REFERENCES

6. Sergeant JA, Oosterlaan J, Van der Meere J. Information processing and energetic factors in attention-deficit hyperactivity disorder. In: Quay HC, Hogan AE,