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ORIGINAL PAPER

Neural correlates (ERP/fMRI) of voluntary selection in adult ADHD patients

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Abstract Deficits in executive functions, e.g. voluntary selection, are considered central to the attention-deficit/hyperactivity disorder (ADHD). The aim of this simultaneous EEG/fMRI study was to examine associated neural correlates in ADHD patients. Patients with ADHD and healthy subjects performed an adapted go/nogo task including a voluntary selection condition allowing participants to freely decide, whether to press the response button. Electrophysiologically, response inhibition and voluntary selection led to fronto-central responses. The fMRI data revealed increased medial/lateral frontal and parietal activity during the voluntary selection task. Frontal brain responses were reduced in ADHD patients compared to controls during free responses, whereas parietal brain functions seemed to be unaffected. These results may indicate that selection processes are related to dysfunctions, predominantly in frontal brain regions in ADHD patients.

Keywords Voluntary selection · ADHD · EEG–fMRI

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Introduction

Adult attention-deficit/hyperactivity disorder (ADHD) has become the focus of widespread clinical attention in the past few years. While ADHD starts in childhood, about one-third of the patients present with persisting symptoms in adulthood [46, 50]. ADHD is associated with significant impairments in various areas of life, e.g. work performance [45], leading to an impaired quality of life. Deficits in executive functions, like cognitive control, are considered central to ADHD. Cognitive control refers to the ability to orchestrate, direct and adaptively modulate cognitive processes in accordance with internal goals and intentions and with external demands [29].

ADHD has been described as a disorder of executive functioning [3, 33, 73]. A variety of deficits in executive functioning, including deficits in behavioural inhibition processes as well as decision-making, seem to be affected [34, 59, 73, 83]. ADHD-related deficits in executive functions have been addressed in numerous neuropsychological, electrophysiological and functional neuroimaging studies [1, 14, 23, 36, 70, 72, 77, 78]. Studies focusing on neurobiological correlates of cognitive anomalies in ADHD patients provided some evidence for fronto-striatal hyper- [71, 80] and hypoperfusion [11, 84, 85]. Other studies demonstrated the involvement of a more diffuse network of brain regions in ADHD patients compared to healthy subjects [12, 20, 27, 78]. These results probably indicate altered brain functions, e.g. compensatory mechanisms in subjects with ADHD compared to healthy subjects [27]. With respect to response inhibition, patients with ADHD showed impaired inhibitory control [38, 48, 60, 70] and a reduced P3 [6, 26]. The reduced P3-amplitude was associated with a significantly reduced activation of the anterior cingulate cortex [26]. A dysfunction in the cognitive part of the ACC

was also demonstrated during functional MRI studies [11]. Moreover, there are reports of enhanced BOLD-responses during inhibition in the VLPFC, as well as in frontopolar regions [71].

Impulsivity and behavioural inhibition are features under cognitive control and are often addressed using so called *go/nogo* tasks [25, 42, 82]. In the *go/nogo* paradigm, the subject is required to perform speeded reactions on *go* trials and to withhold behavioural responses to another stimulus on *nogo* trials. Electrophysiological studies demonstrated fronto-central activity (N2, P3) associated with the behavioural inhibition [5, 10, 25]. Functional MRI studies, too, revealed increased inhibition-associated BOLD-responses, especially in medial and lateral frontal brain areas, including the middle and inferior frontal gyrus, the anterior insula cortex [8, 68, 78, 82], the anterior cingulate cortex (ACC) [9, 23, 32] and pre-motor as well as supplementary motor areas (SMA) [13, 32]. In addition, parietal brain regions seemed to be involved [13, 32, 82].

Another important ability to control cognitive processes are 'willed actions': actions are called 'willed' if we consciously pay attention to their selection [30] and if we can choose between several response alternatives [19, 30, 52, 61]. Neuroimaging, electrophysiological and lesion studies have shown that frontal areas play an important role in voluntary action selection [65, 69, 79]. This was demonstrated, for example, for the pre-supplementary motor area (pre-SMA)/SMA, the ACC and the dorsolateral prefrontal cortex (DLPFC) [19, 28, 30, 37, 41, 52, 81] as well as the superior parietal lobule and the posterior part of the intraparietal sulcus [28]. The functional specialisation of these regions is unclear: some studies suggest rostral pre-SMA activations to be conflict-related, whereas the generation of volitional plans seemed to engage a more caudal region of the pre-SMA [57]. By contrast, other studies assume the pre-SMA to be involved in the voluntary generation of action, whereas response conflict seems to be associated with the ACC [51]. DLPFC activation increases with increased working memory capacities which are required, at least to some extent, in most selection tasks. Regarding electrophysiological analysis, the N2 potential is related to the process of response selection and is meant to influence subsequent processing stages reflected in the P3 [31].

Many decisions we make rely on the experience of rewards and losses [33]. Hence, deficits in decision making are suggested to be influenced by an impaired reinforcement learning capacity. Contrary to earlier studies, voluntary selection processes are unrelated to gain/loss consequences in the present study.

Altogether, voluntary responses as well as underlying neural responses have not yet been explored extensively in ADHD patients. The aim of the present study was to examine *voluntary selection* between response alternatives and their neural basis in adults with ADHD. The *go/nogo/voluntary selection paradigm* allowed us to address several questions: (1) are medial frontal areas of importance when subjects can choose between response alternatives? (voluntary selection) (e.g. [28]), and (2) can voluntary responses as well as related ERPs and BOLD responses of ADHD patients be distinguish from those of healthy controls? Neural correlates of voluntary selection are to be separated from those during forced responses. Hence, behavioural data as well as associated electrophysiological responses (event-related potentials) and haemodynamic responses (fMRI) were examined. We hypothesised that ADHD patients would show slower responses during the voluntary selection task compared to healthy controls, indicating deficient decision making processes. These behavioural variations could be related to functional deficits, especially in (medial) frontal brain regions.

Thereby, the combination of EEG and functional MRI allows for high-spatial and temporal acquisition of mental processes and may contribute to a more comprehensive understanding of neural correlates of perception and cognition [17, 18, 24, 55, 56]. In the present study, event-related potentials (ERPs) and functional MRI responses were acquired simultaneously. The acquisition of these responses allows the combination of high temporal resolutions of ERPs with high spatial resolutions of BOLD responses. Furthermore, differences in the participant's mood, vigilance and familiarity with the task, for example, have proved to be crucial for cognitive processes as well as underlying brain activations [17, 53, 54] which means that cognitive processes are not identical even if repeated several times. However, simultaneous EEG-fMRI recordings share the advantage of an identical environment, identical conditions of stimulation and subject state, e.g. time of the day, time spent on the task, level of arousal. Therefore, this method is advantageous for distinct samples like psychiatric patients, avoiding multiple and lengthy sessions and providing comprehensive multimodal information [54].

Methods

Subjects

Eight adult patients (seven men, one woman; aged between 26 and 47 years; mean age 38.3 ± 7.82) with ADHD were examined in a simultaneous EEG and functional MRI experiment. All patients included in the study were outpatients contacting the health care centre because of pronounced cognitive deficits, including attentional impairments and deficient planning abilities. In order to be diagnosed with ADHD, subjects had to (1) meet six of nine *DSM-IV* criteria for inattention and hyperactivity/

impulsivity for a diagnosis in childhood, and at least five of nine criteria in adulthood, (2). They had to describe persistent ADHD symptoms from childhood to adulthood (self-report), and (3) experience a moderate-to-severe level of impairments attributable to the ADHD symptoms. Detailed medical and psychiatric histories were collected by a psychiatrist. In addition, current neuropsychological functioning (intelligence, attention, executive functions/planning, memory) of patients was considered as well as their attention capacity in the past (based on school reports). The Conners' Adult ADHD Rating Scales (CAARS; self-report) [16] and the Wender Utah Rating Scale (Wurs; self-report) [64] were used to assess past and persisting symptoms of ADHD (Tables 1, 2). Patients with comorbid psychiatric and/or neurological diagnoses were not included into the study. Patients had to be free of any psychopharmacological drug treatment. One adult patient had taken atomoxetine in childhood; the medication had been cancelled after a few weeks because of adverse effects. All other patients were drug-naïve. Exclusion criteria included neurological diseases (e.g. head injury) as well as comorbid psychiatric disorders. In addition, usual exclusion criteria for MRI (e.g. metal implants, pregnancy) were considered for both groups (patients, healthy subjects). None of the patients reported the use of illegal substances in the past.

The results of the ADHD patients were compared to those of age- and gender-matched subjects (seven men, one woman; aged between 25 and 45 years; mean age 37.8 ± 6.61) without any neurologic or psychiatric diagnoses (standardised questionnaire). Healthy subjects did not differ significantly from ADHD patients regarding verbal intelligence (healthy subjects: IQ = 119.6 ± 7.84; patients: IQ = 118.7 ± 9.66; $p > 0.05$) and years of education (healthy subjects: mean = 15.9 ± 3.12; patients: mean = 15.5 ± 3.59; $p > 0.05$). All patients and healthy subjects had finished secondary school and had started and/or completed their academic studies or a school providing vocational education. Written informed consent was obtained from each participant after procedures had been fully explained. The study was approved by the local ethics committee. The investigation was carried out in accordance with the Declaration of Helsinki. Each healthy volunteer was paid €25 for participating in the study.

Table 1 Clinical characteristics of ADHD pathology and cognitive abilities

	ADHD patients	
	T	SD
Conners' adult ADHD rating scales (CAARS)		
Inattention/memory problems	58.1	12.26
Hyperactivity/restlessness	71.0	5.6
Impulsivity/emotional lability	62.6	4.69
Problems with self-concept	60.4	9.34
ADHD index	73.6	3.16
Wender Utah Rating Scale (Wurs)	58.1	12.26

T *T*-score, *SD* standard deviation

Procedure, paradigm and analysis of behavioural data

Participants were scanned in one measurement session of approx. 25 min and positioned comfortably on the scanner bed with their heads cushioned tightly in place to reduce head movement. Auditory stimuli were generated on a PC outside the MR environment using the BrainStim software package (Brain Products, Munich) and conducted via a pair of plastic tubes into a set of headphones placed over the subjects' ears [55, 56]. Participants kept their right index finger mounted on the button of the response box while lying inside the scanner.

Subjects performed an attention task where the auditory stimuli consisted of sinusoidal tones (duration: 50 ms, pressure level: 100 dB) of three differential pitches delivered binaurally via headphones. The tones were presented in pairs at intervals of 1000 ms; the subsequent trial was presented 2000 ms after the second tone.

Table 2 Clinical characteristics of cognitive abilities

	Cognitive abilities						
	Basal attention	Response inhibition	Working memory	Divided attention	Flexibility	Planning/ categorise	Verbal memory
Pat01	⇓	⇓	⇓			ns	ns
Pat02	ns	⇓	⇓		⇓	ns	ns
Pat03	ns	ns	ns	⇓	⇓	ns	ns
Pat04	ns	⇓	⇓	⇓	⇓	ns	⇓
Pat05	⇓	⇓	⇓	⇓			ns
Pat06	ns	ns	⇓	⇓	⇓	ns	ns
Pat07	ns	ns	⇓	⇓		⇓	ns
Pat08	ns	ns	⇓	⇓	ns	ns	ns

ns within normal ranges, ⇓ below average; *planning/ categorise* planning/ categorisation (Tower of London; Halstead category test); *attention test battery [TAP]* basal attention, response inhibition, flexibility, divided attention, working memory

The tone with the middle frequency (1000 Hz) served as cue indicating that a button press was required when it was directly followed by the high-frequency tone (1300 Hz; *go condition*). The subject's objective was to press a button with their right index finger for the *go condition*. Subjects were instructed to respond as quickly as possible after the stimuli were presented, while minimising errors. The prepared behavioural response was to be inhibited if the cue was followed by the tone with a low frequency (800 Hz; *nogo condition*). In the *voluntary selection condition,* the cue was followed by the tone with a same frequency (1000 Hz; *selection*). In the *voluntary selection condition*, participants were instructed to freely decide whether to press the response button or not. After completion of the experiment, the *voluntary selection* trials were classified more precisely according to the individual response of each participant and each point in time: *voluntary selection* trials which were followed by a button press were labelled *selection+* , trials without button press were labelled *selection–*. Participants were asked to decide at each trial of the *voluntary selection* condition separately if they wanted to respond or not. Subjects were told that the ratio *selection+/selection–* did not matter as long as it was approximately equally often and in random order. In addition, subjects were asked not to count how often they pressed the button and to not alternate between button press and not press. Subjects who responded in each trial of the voluntary selection condition or did not respond at all during the *voluntary selection* condition were not included in the study, because there was no guarantee that they had fully understood the instructions; these data were not analysed. In addition, the paradigm included two passive listening tasks which served as control conditions. During the control conditions, the tone with the low frequency was presented first indicating that no behavioural response was necessary regardless of which tone was presented next (*control conditions*: 800–1000 Hz; 800–1200 Hz). All conditions were presented in pseudo-randomised order. The go condition was presented 160 times; the other conditions were presented 80 times with an interstimulus interval of 3 s. Prior to the EEG-fMRI session, all subjects received a practice block of at least 10 min in order to assure that the instructions were understood fully.

Reaction times (RTs), errors of omission and errors of commission were recorded. Any response delayed by more than 1000 ms after the stimulus was counted as error during the *go* condition. In addition, responses faster than 50 ms were suggested anticipatory responses and were also counted as error. The mean RTs for each condition (*go*, *voluntary selection*) and for each subject were calculated separately. The RTs and error rates were tested with a repeated-measurement ANOVA.

EEG acquisition and data analysis

Event-related potentials were recorded during the acquisition of functional MRI images by 61 Ag/AgCl electrodes placed on the scalp according to the international 10-10 system, using an electrode cap set (Easycap, Germany). During the acquisition, all electrodes referred to Cz. Eye movements were recorded from a channel placed beneath the right eye. The ECG was recorded with three electrodes placed on the back of the participants. EEG was continuously recorded and digitised at 5000 Hz without any filtering during acquisition. Impedances were usually maintained below 10 kΩ. EEGs were acquired with an amplifier designed for inside scanner recordings (Brain Products, Munich). Participants were asked to stay calm and keep their eyes closed during the task. Eye movements and eye-blinks as well as cardioballistic artefacts were excluded using a spatial filter algorithm. Common to spatial filter techniques is the decomposition of the EEG into components which ideally model either artefact or brain activity [39]. A suitable decomposition is achieved when artefact activity can be reconstructed as the product of artefact topographies and waveforms. We used the '*surrogate*' algorithm which is implemented in the BESA software package (MEGIS Software GmbH, Graefelfing, Germany): brain activity is modelled using a dipole configuration with dipoles placed at strategic positions of the brain. This method has already been used for the removal of cardioballistic artefacts [43, 74]. Further analyses were done with Analyzer Software (Brain Products, Munich). The data were re-referenced to an average reference. The EEG data were filtered with a 20-Hz low-pass filter (slope 48 dB/oct) and segmented into 750 ms epochs time-locked to the onset of the second stimulus of each pair of tones, separately for the different conditions (*voluntary selection*, *go*, *nogo*, *control*). The sampling epoch commenced 150 ms before the presentation of the second tone that indicated which task was to be performed. The pre-stimulus interval was used for baseline correction. Epochs containing artefacts (amplitude higher than ±90 μV) were rejected. The artefact detection was done on Fz, F3, F4, FCz, Cz, C3, C4 and Pz. Trials with incorrect responses (button press after the *nogo* or *control* tasks; no response after the *go* task) were rejected prior to averaging. The ERPs of subjects with less than 30 trials remaining after artefact rejection were excluded from the analyses (three subjects both, for the *voluntary selection* task with button press and the *voluntary selection* task without button press). The N2 and P3 ERPs were examined at the midline fronto-centro-parietal scalp electrodes (Fz, FCz, Cz, Pz). NoGo-related electrophysiological variations in these locations were determined a priori from previous studies [5, 10, 25, 42, 43]. The N1 was defined as the relative

minimum of the ERP at electrode in the search window of 70–130 ms. The N2 was defined as the largest relative minimum of the ERP in the search window of 170–230 ms. The P3 was defined as the largest relative maximum of the ERP 230–550 ms after the presentation of the respective task. To test the significance of each effect, repeated measurements MANOVAs were run on the maximum ERP-amplitude in each search window (N1, N2, P3) with two repeated-measure factors of *task* (*voluntary selection*, *nogo*, *go*, *control*) and *electrode position* (Fz, FCz, Cz, Pz) and one between subject factor *group* (ADHD patients, healthy subjects). In the case of a significant Mauchly-test the Greenhouse–Geisser correction was used. In addition, post hoc *t*-tests were employed. Based on $4 \times 4 \times 2$ task conditions, 32 different tests were performed. Therefore, using Bonferroni-correction, all tests were performed with a two-sided $p < 0.0016$; *p*-values smaller than 0.0032 were marked as trend. Furthermore, the ERP-amplitudes (N1, N2, P3) of *selection+* were compared to the *selection–* responses using MANOVAs with repeated measurements. Post hoc *t*-tests were Bonferroni-corrected with a two-sided $p < 0.003125$ (trend level $p < 0.00625$).

Image acquisition and analysis of MRI data

Imaging was performed using a 1.5 T Siemens Sonata MR scanner at the Institute of Clinical Radiology, University of Munich. High-resolution anatomical data sets were collected using 3D T1-weighted sequences. The function data were adapted on the anatomical data set. During the functional imaging session, ten T2*-weighted images were obtained with gradient echo EPI sequence in the same position as the 3D data set (volume repetition time TR = 3 s; echo time TE = 53 ms; matrix: 64×64; FOV: 192×192; slice thickness: 8 mm; interslice-gap: 0.4 mm; interleaved slice acquisition). Data were acquired in temporal synchrony to the task.

An interleaved design was used: the tones were presented during the intervals between the MR acquisitions in order to reduce the influence of scanner noise on stimulus presentation and to diminish MR-provoked artefacts on the EEG. 485 image volumes (160 *go* condition; 80 *nogo* condition; 80 *voluntary selection* condition; 160 *control* conditions; 5 baseline at the beginning) were acquired in total.

Data analysis and statistical analysis were carried out using the BrainVoyager Software package version 4.96 (Brain Innovation, Maastricht, Netherlands). The first five volumes were discarded in order to allow for T1 equilibrium effects. The remaining images were realigned and spatially smoothed using an 8-mm full-width-half-maximum (FWHM) Gaussian kernel. The preprocessing of the functional images also included slice scan time correction. The functional images were transferred to a standard Talairach brain.

Statistical analysis was carried out using a general linear model approach. Each condition (*voluntary selection, nogo*, *go, control*) was modelled separately after convolution with a canonical hemodynamic response. Individual's contrast images were used in the subsequent analysis in order to derive statistical maps. For group analysis, a second level fixed effects analysis (*selection+*, *selection–*, *nogo*, *go*, *control*) was computed. If not otherwise specified, selection specific BOLD responses were demonstrated comparing voluntary behaviour (*selection+*, *selection–*) with forced behaviour (*go*, *nogo*), thresholded at $p < 0.01$ corrected for multiple comparisons (Bonferroni correction; confidence range *T*: 5.2–8). For visualisation, regions with significant activations were overlayed on a talairachised T1-weighted image of a single subject. Comparisons were made using a random effects analysis and fixed effects analysis, respectively. A fixed-effects analysis can support inference about the group of measurements (subjects, etc.) you actually have—the actual subject pool you looked at. By contrast, a random-effects analysis allows you to infer something about the population from which you drew the sample.

In order to directly compare BOLD responses with behavioural data and ERP amplitudes, a region of interest (ROI) analysis was included. For that purpose, the anatomical ROI definitions of BrainVoyager 2000 for the cingulate gyrus, the middle frontal gyrus, the superior frontal gyrus, the medial frontal gyrus, the supramarginal gyrus, the postcentral gyrus and the precentral gyrus were used. For each subject, the average *T*-value of the activated voxels [*T*-score: 2.6–8; $p < 0.01$ (uncorrected for multiple comparisons)] was determined separately for *selection+*, *selection–*, *nogo* and *go.* Comparisons were done with the Kendall tau coefficient.

Statistics

Statistics were obtained using the routines in the SPSS 14.0.1 programme. The significance level was 0.05, *p*-values between 0.05 and 0.1 were marked as a trend. Correlations were calculated between *go*-associated behavioural performance (reaction time; percentage of responses) and accordant ERP-amplitudes in Fz, FCz, Cz and Pz (Kendall tau coefficient). In addition, behavioural responses during the *voluntary selection* condition were related to the respective electrophysiological responses (*selection+* task). Furthermore, the average *T*-value of each ROI was correlated with behavioural data in the *go* and *selection+* task. ROI information (frontal and parietal brain regions) was also related to P3-amplitudes in Fz, FCz, Cz and Pz during the *voluntary selection* condition. In

addition, BOLD responses of frontal brain regions (ACC, middle frontal gyrus, superior frontal gyrus, medial frontal gyrus) were associated with the N2 amplitudes in Fz, FCz and Cz.

Results

Behavioural results

Behavioural data are shown in Table 3. The group averages for the mean response times were significantly longer in *voluntary selection* trials than in *go* trials [$F(1,14) = 60.007$; $p < 0.001$]. Responses did not differ significantly between patients and the control group [$F(1,14) = .360$; $p = 0.558$]. In addition, the interaction effect (condition × group) was not significant [$F(1,14) = 1.611$; $p = 0.225$].

The percentage of responses was significantly increased in the *go* compared to the *voluntary selection* [$F(1,14) = 179.103$; $p < 0.001$]. Also, differences between patients and healthy subjects [$F(1,14) = 4.938$; $p = 0.043$] as well as the interaction effect [$F(1,14) = 5.737$; $p = 0.031$] turned out to be significant: the response rate was higher in ADHD patients compared to healthy subjects during the *voluntary selection* condition.

ERP results

Comparison of go, nogo, voluntary selection and control condition

Results are shown in Fig. 1. Regarding the N1-amplitude, the main effect of electrode position (Fz, FCz, Cz, Pz) [$F(1.678, 23.489) = 35.503$; $p < 0.001$] and the interaction between condition (*go*, *nogo*, *selection*, *control*) and electrode position [$F(4.162, 58.271) = 3.700$; $p = 0.009$] turned out to be significant. The differences between conditions [$F(3, 42) = 1.306$; $p = 0.285$] and between groups (ADHD patients, healthy subjects) [$F(1, 14) = 1.565$; $p = 0.231$], as well as interaction effects [condition × group: $F(3, 42) = 0.864$; $p = 0.467$; electrode position × group: $F(1.678, 23.489) = 1.258$; $p = 0.297$; condition × electrode position × group: $F(4.162, 58.271) = 1.511$; $p = 0.209$] were not significant.

The N2-amplitudes differed significantly between conditions [$F(3, 42) = 7.693$; $p < 0.001$] and between electrode positions [$F(1.631, 22.833) = 6.146$; $p = 0.010$]. Post hoc tests revealed that the N2 was less pronounced in *go* compared to *nogo* ($p = 0.011$), *voluntary selection* ($p = 0.002$) and *control* ($p = 0.005$). In addition, the N2 was smaller in Cz compared to Fz ($p = 0.001$), FCz ($p = 0.046$), and Pz ($p = 0.018$). The interaction effect of condition × electrode position was also significant [$F(3.296, 46.137) = 3.243$; $p = 0.027$]. Differences between groups failed to differ significantly [$F(1, 14) = 0.193$; $p = 0.668$]. Furthermore, the N2 results regarding the interaction between condition and group [$F(3, 42) = 0.672$; $p = 0.574$], electrode position and group [$F(1.631, 22.833) = 0.057$; $p = 0.914$] as well as electrode position, condition and group [$F(3.296, 46.137) = 1.546$; $p = 0.212$] were not significant.

Regarding P3-amplitudes, significant differences were demonstrated between conditions [$F(1.893, 26.503) = 22.823$; $p < 0.001$], between electrode positions [$F(3, 42) = 7.622$; $p < 0.001$] as well as the interaction between condition and electrode position [$F(3.050, 42.697) = 4.488$; $p = 0.008$]. Post hoc tests revealed an increased P3 amplitude in *nogo* compared to *go* ($p < 0.001$), *voluntary selection* ($p < 0.001$), and *control* ($p < 0.001$). The P3 amplitudes were smaller in the *control* task than *go* ($p = 0.016$), *nogo* ($p < 0.001$), and *voluntary selection* ($p = 0.040$). Moreover, the P3 amplitudes were decreased in Fz compared to FCz ($p = 0.002$), and Cz ($p = 0.002$). The main effect of group was not significant [$F(1, 14) = 0.758$; $p = 0.399$]. Furthermore, none of the interaction effects turned out to be significant [condition × group: $F(1.893, 26.503) = 0.239$; $p = 0.777$; electrode position × group: $F(3, 42) = 0.325$; $p = 0.807$; condition × electrode position × group: $F(3.050, 42.697) = 1.418$; $p = 0.250$].

Table 3 Behavioural data of ADHD patients and healthy controls

	ADHD patients		Control group	
	M	SD	*M*	SD
Reaction times (ms)				
go	419.3	85.21	424.2	87.49
selection+	730.5	212.4	647.9	161.53
Number of responses (%)				
go	97.2	2.4	98.1	1.16
selection+	66.7	8.44	54.4	12.23

M mean value, *SD* standard deviation, *ms* milliseconds, % percentage

Functional MRI results

In healthy subjects, increased BOLD responses were demonstrated during voluntary behaviour *(selection+*, *selection–)* compared to behaviour that was determined by the instruction (*go*, *nogo*), especially in medial frontal brain regions including the superior and medial frontal gyrus (BA 6/8) as well as lateral frontal regions (middle frontal gyrus, BA 6/8; left and right). Furthermore, the inferior frontal lobe (BA 40; left > right) was affected. The results are summarised in Table 4 and Fig. 2.

In ADHD patients the following brain regions proved to be involved for voluntary responses compared to

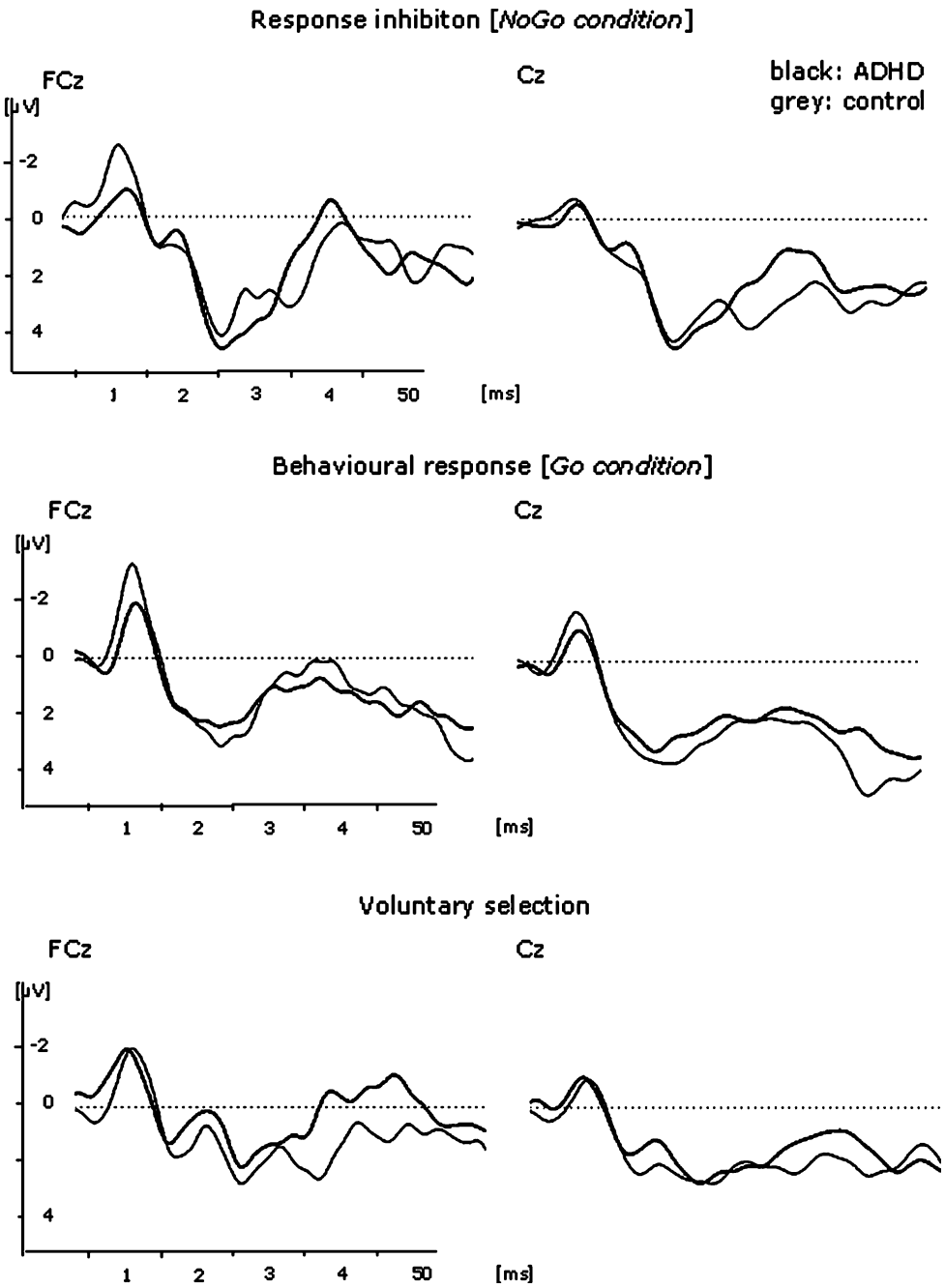

Fig. 1 Response, inhibition- and selection-associated ERP waveforms of ADHD patients and healthy controls at fronto-central sites. (*ms* milisecond, μV microvolt)

responses, that were determined by the instruction: superior frontal gyrus (BA 6), left middle frontal gyrus (BA 9) and left inferior parietal lobe (BA 40; see also Table 5, Fig. 2).

The comparison of BOLD responses of healthy controls and ADHD patients revealed no significant results when a random effects analysis was calculated. Using a fixed effects analysis (thresholded at $p < 0.001$ uncorrected for multiple comparisons; *T*-range: 3.3–8; cluster size >10 voxel), we found enhanced haemodynamic responses in healthy controls, especially in medial frontal regions [medial frontal gyrus (BA 9/10) and superior frontal gyrus (BA 6/8)]. Apart from that, differences were demonstrated in lateral frontal brain regions: left superior frontal gyrus (BA 8), left and right middle frontal gyrus (BA 6/10); brain responses of healthy subjects were more pronounced than those of ADHD patients (Table 6; Fig. 3).

Correlations between behavioural data and ERPs

In healthy subjects, fast reactions in *selection+* were related to an increased N2-amplitude in Fz ($CC = 0.714$, $p = 0.013$) and an increased P3 amplitude in Pz ($CC = -0.571$, $p = 0.048$). The association between reaction time during *selection+* and the P3 amplitude in Cz reached trend

Table 4 Brain regions associated with voluntary responses compared to behaviour that was determined by the task instruction [(*selection*– + *selection*+) – (*go* + *nogo*)] in healthy controls

Cerebral region	BA	Side	Avg *t*-score	Max *t*-score	Size	Centre of mass		
						x	*y*	*z*
Frontal lobe								
Superior/medial frontal gyrus	6/8	R	6.363	8.688	8,917	1	19	54
Middle frontal gyrus	8	L	5.773	7.017	2,767	−44	17	45
	6/8	R	5.508	6.141	712	51	15	45
Parietal lobe								
Inferior parietal lobe	40	L	5.943	7.541	1,644	−43	−57	44
	40	R	5.300	5.533	114	49	−48	45

Cluster foci of highest *t*-value are reported for activation seen during *voluntary selection* in healthy controls [(*selection*− + *selection*+) – (*go* + *nogo*)] [fixed effects analysis, $p < 0.01$ corrected (Bonferroni) for multiple comparisons; *T*-score: 5.2–8; cluster size >10 voxel]. Coordinates are in Talairach space. *BA* Brodmann's area; *avg* average; *max* maximum; *R* right hemisphere; *L* left hemisphere; *Size* no. of activated voxels

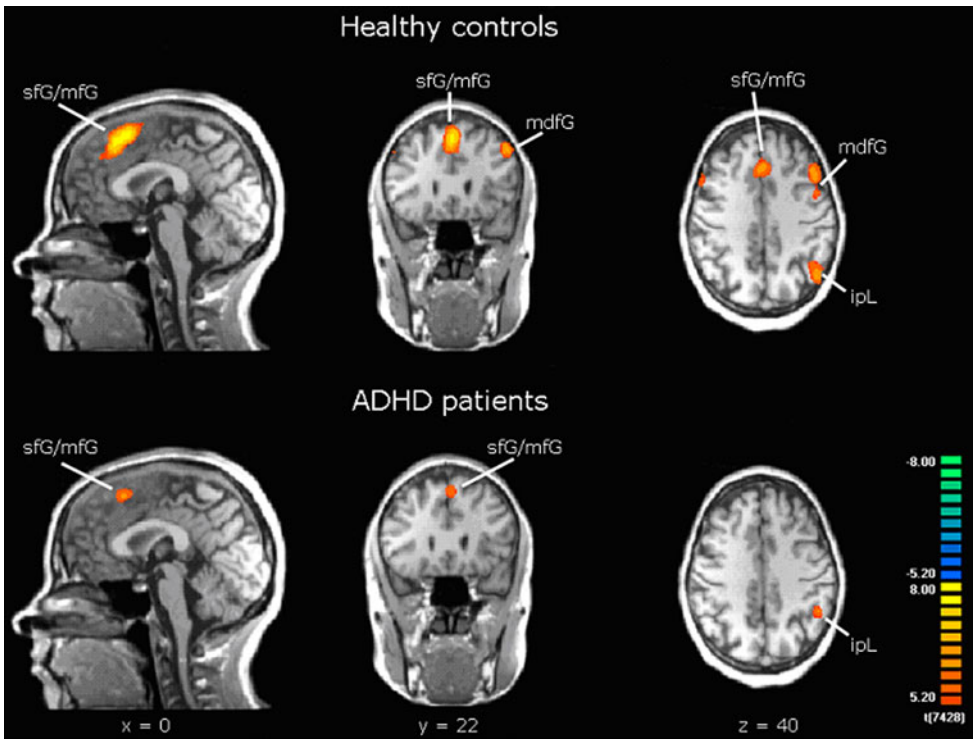

Fig. 2 Selection-related functional MRI responses [(*selection*– + *selection*+) – (*go* + *nogo*)] in healthy controls and ADHD patients [fixed effects analysis thresholded at $p < 0.01$ corrected for multiple comparisons (Bonferroni); confidence range *T*-score: 5.2–8; *xyz*: 0 22 40] (*sfG* superior frontal gyrus, *mfG* medial frontal gyrus, *mdfG* middle frontal gyrus, *ipL* inferior parietal lobe)

level (CC = −0.500, $p = 0.083$). We did not find any significant association between reaction times and event-related potentials during the *selection*− condition. There were no significant associations between behavioural responses and ERP-responses in ADHD patients.

Correlations between behavioural data and ROIs

In healthy subjects, fast voluntary responses (*selection*+) were associated with increased responses of the cingulate gyrus (CC = −0.714, $p = 0.013$). Apart from that, none of the associations between the behavioural responses and BOLD responses (middle/medial/superior frontal gyrus, supramarginal gyrus, pre-/postcentral gyrus) reached the significance level.

Selection+ responses of ADHD patients were related to enhanced activations in the superior frontal gyrus (CC = −0.618, $p = 0.034$). The relation between response time and BOLD response in the medial frontal gyrus reached trend level (CC = −0.546, $p = 0.061$). We did not find

Table 5 Brain regions related to voluntary behaviour compared to behaviour that was determined by the task instruction [(*selection*– + *selection*+) – (*go* + *nogo*)] in ADHD patients

Cerebral region	BA	Side	Avg *t*-score	Max *t*-score	Size	Centre of mass		
						x	*y*	*z*
Frontal lobe								
Superior frontal gyrus	6	L	5.658	6.413	896	−1	19	55
Middle frontal gyrus	9	L	5.341	5.640	11	−45	11	34
Parietal lobe								
Inferior parietal lobe	40	L	5.519	6.230	474	−46	−44	41

Cluster foci of highest *t*-value are reported for activation seen during *voluntary selection* in ADHD patients [(*selection*– + *selection*+) – (*go* + *nogo*)] [fixed effects analysis, $p < 0.01$ corrected (Bonferroni) for multiple comparisons; *T*-score: 5.2–8; cluster size >10 voxel]. Coordinates are in Talairach space. *BA* Brodmann's area; *avg* average; *max* maximum; *R* right hemisphere; *L* left hemisphere; *Size* no. of activated voxels

Table 6 Increased selection-specific BOLD responses [(*selection*– + *selection*+) – (*go* + *nogo*)] in healthy controls compared to ADHD patients

Cerebral region	BA	Side	Avg *t*-score	Max *t*-score	Size	Center of mass		
						x	*y*	*z*
Frontal lobe								
Medial frontal gyrus	9		3.531	4.016	899	0	40	27
	10	R	3.367	3.489	75	4	59	8
Superior frontal gyrus	8	R	3.610	4.251	1,110	16	41	53
	8	L	3.494	3.919	384	−41	19	47
	6	L	3.424	3.573	87	−8	8	61
	6	R	3.401	3.614	85	8	15	59
Middle frontal gyrus	6	L	3.643	4.357	627	−47	8	50
	10	R	3.425	3.687	57	−36	39	22

Cluster foci of highest *t*-value are reported for activation seen during *voluntary selection* in healthy controls compared to ADHD patients [(*selection*– + *selection*+) – (*go* + *nogo*)] [fixed effects analysis, $p < 0.001$ uncorrected for multiple comparisons; *T*-score: 3.3–8; cluster size >10 voxel]. Coordinates are in Talairach space. *BA* Brodmann's area; *avg* average; *max* maximum; *R* right hemisphere; *L* left hemisphere; *Size* no. of activated voxels

any significant association between reaction times and BOLD responses in frontal and parietal brain regions during the *selection*− condition.

Correlations between ERPs and ROIs

P3 amplitudes in Fz of healthy subjects during voluntary button presses (*selection*+) were related to neural responses in the middle frontal gyrus (CC = −0.714, $p = 0.013$) and superior frontal gyrus (CC = −0.643, $p = 0.026$). In addition, during enhanced N2 amplitudes in Fz were associated with increased BOLD responses of the cingulate cortex (CC = −0.714, $p = 0.013$). ADHD patients showed associations between responses in the middle frontal gyrus and Fz (CC = 0.571, $p = 0.048$) as well as FCz (CC = 0.643, $p = 0.026$). There were no significant correlations between the electrophysiological responses in Cz and/or Pz and BOLD responses.

In addition, there were no significant associations between P3 and N2 amplitudes of healthy controls and ROIs during *selection*−. In patients, the P3 amplitude at FCz correlated with cingulate responses (CC = 0.645, $p = 0.034$): the P3 amplitude in Pz was associated with responses in the supramarginal gyrus (CC = 0.571, $p = 0.048$), postcentral gyrus (CC = 0.725, $p = 0.017$) and superior frontal gyrus (CC = 0.571, $p = 0.048$).

Discussion

In the present study, we examined voluntary selection processes and their neural correlates in ADHD patients and healthy subjects. These results were compared to neural correlates of responses determined by the task instruction (*go*, *nogo*). Hence, event-related potentials and functional MRI data were acquired simultaneously in order to reliably

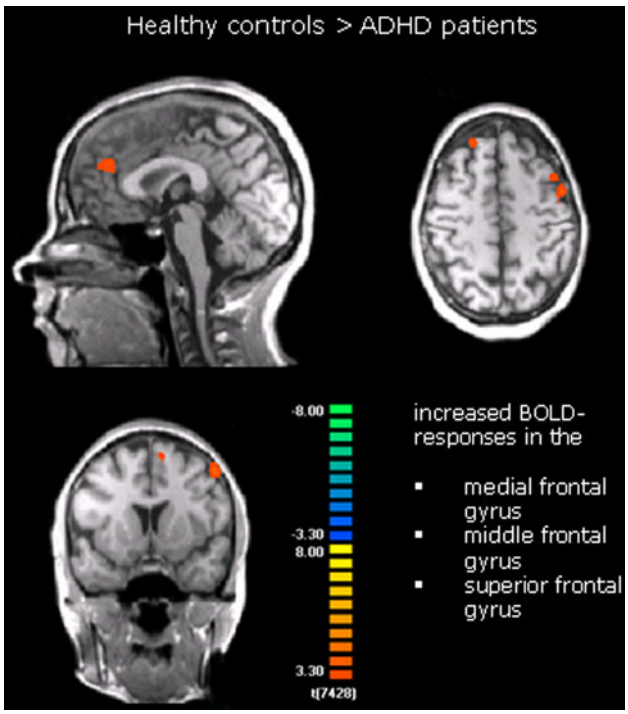

Fig. 3 Selection-related functional MRI responses [(*selection*– + *selection*+) – (*go* + *nogo*)] in healthy controls minus ADHD patients (fixed effects analysis thresholded at $p < 0.001$ uncorrected for multiple comparisons; confidence range *T*-score: 3.3–8; *xyz*: 0 8 46)

examine spatial and temporal aspects of functional variations associated with these decision-making processes.

As expected, the results revealed significantly slower responses in healthy subjects and ADHD patients in the *voluntary selection* task compared to the *go* condition. Similar results were presented earlier [2]. In either group voluntary behavioural responses seemed to be associated predominantly with frontal brain responses, e.g. the medial frontal gyrus and the superior frontal gyrus (BA 6/8). Apart from that, the dorsolateral prefrontal cortex (BA 6/8) and parietal brain regions (BA 40) showed increased responses. In previous studies these brain regions were related to 'willed' action, conflict and decision-making [7, 19, 28, 32, 35, 37, 40, 57, 62]. These results indicate the importance of frontal brain regions as well as the inferior parietal gyrus for voluntary responses. Medial frontal functional responses are consistent with reports from earlier neuroimaging studies about voluntary behaviour [28, 29, 44, 52], e.g. the voluntary selection between two or more motor response alternatives [19, 30, 37, 41]. In accordance with Lau and colleagues [52], we found enhanced responses to internally initiated actions in the pre-SMA (Talairach Coordinate *xyz*: 2 4 54). Apart from the pre-SMA, the rostral cingulate zone proved to be important in the present study. These findings are in line with those of Forstmann et al. [28] who also showed that the rostral cingulate zone is of importance to choices (Talairach Coordinates *xyz*: −5 23 38). Altogether, there are some discrepancies between studies on which medial frontal regions are associated with voluntary responses: the present study demonstrated that both the pre-SMA and the rostral cingulate zone are of importance.

In addition, inferior parietal areas (BA 40) seemed to be essential in voluntary selection tasks [28, 44]. Furthermore, patients with parietal lesions also showed difficulties regarding conscious monitoring of voluntary actions [75]. In summary, parietal brain regions seem to be associated with intentional responses and the generation of movements.

The importance of frontal brain regions for response control was underlined by the electrophysiological results: voluntary decision tasks led to a negative decline in fronto-central brain regions in the control group. These responses were more pronounced than during *go* and the *control condition. Nogo* N2 amplitudes did not differ significantly from those related to voluntary responses. The N2 has been associated with top-down inhibitory processes in order to suppress incorrect response tendencies [25, 47] and also with low-frequency stimuli, regardless of the kind of response requested [4, 22, 58]. Furthermore, the N2 has been linked to response selection [31] and stimulus classification in choice tasks [66, 67], respectively, and it is assumed that it originates from the ACC [31]. Our results match those of former studies: we found a significant association between the N2 amplitude in Fz and BOLD responses of the cingulate cortex in healthy subjects.

Fronto-central selection-related P3 amplitudes, however, were related predominantly to hemodynamic responses in the middle frontal gyrus and superior frontal gyrus. In addition, an association between the fronto-central P3 and the anterior cingulate gyrus was demonstrated in ADHD patients. These results indicate different generators underlying the event-related N2 and P3, at least to some extent. Overall, *selection*-related fronto-central P3 amplitudes were more pronounced than those of the control condition. In addition, P3 amplitudes associated with *go* were also more pronounced than during the *control task,* especially in parietal regions. The highest fronto-central P3 amplitude, however, was demonstrated during the nogo-condition: these amplitudes were significantly increased compared to the other conditions. The results regarding electrophysiological correlates of response inhibition match those of earlier EEG studies: response inhibition was shown to be related to increased fronto-central P3 amplitudes in several studies [5, 10, 42]. P3 potentials related to attention, information processing and context updating are usually located in centro-parietal areas [21, 49, 63]. Selection-associated ERPs could be influenced by attention

as well as inhibitory processes. In addition, there is some evidence that the P3 is also directly associated with selection processes [31].

Patients with ADHD showed difficulties with the *voluntary selection task*: contrary to the specific instruction, to respond and inhibit responses approximately equally often during the selection task, ADHD patients responded by button press in about 67% of trials. The response rate was significantly increased compared to the control group (response rate: 54%). Reaction times did not differ significantly between groups. BOLD responses of ADHD patients and healthy controls were identified in comparable brain areas: during voluntary selection medial and lateral frontal as well as parietal brain regions were prevalent. However, impaired behavioural responses were associated with neuronal dysfunctions: medial and lateral frontal hemodynamic responses in ADHD patients were less pronounced compared with healthy subjects. Frontal dysfunctions were demonstrated in various reports [11, 14, 15, 26, 71, 80, 84, 85]. BOLD responses in parietal brain regions did not differ significantly between groups.

Altogether, these results suggest functional deficits in frontal brain regions during voluntary responses in ADHD patients. These results are in line with earlier reports about functional deficits in frontal brain areas in patients with ADHD.

We did not find any significant differences between ADHD patients and healthy controls regarding the ERPs. These results contradict reports about electrophysiological differences between ADHD patients and healthy subjects, especially during executive functioning [6, 76]. In addition, the correlation between electrophysiological data and BOLD responses was small. Considering former EEG-fMRI studies, we expected these associations to be more pronounced.

One reason for these results might be that the results of ADHS patients are relatively inconsistent regarding the occurrence of ERPs as well as underlying brain regions. Selection-related hemodynamic differences, for example, were shown only in frontal brain regions, whereas posterior regions appeared not to be affected. Given that P3 amplitudes are influenced by frontal and posterior brain regions, it is not surprising that there are no significant differences between groups. In addition, the temporal characteristics of brain regions involved in task execution probably differ between patients. Apart from this, the neural correlates of ADHD patients who suffer predominantly from attention deficits may differ from patients with hyperactivity. Hence, it may require larger groups as well as separate analysis of subgroups in order to demonstrate significant differences.

There are several caveats to our results. The sample size is comparatively small. In addition, subjects of both sexes were examined and their age varied considerably. However, all ADHD patients were unmedicated and were diagnosed in detail including self rating scales, the assessment of neuropsychological functioning and of attention ability in the past (based on school reports). Furthermore, ADHD patients and healthy subjects were precisely matched according to age, intelligence and years of education. Nonetheless, these results should be considered preliminary.

In this study, event-related potentials, functional MRI data and behavioural responses were recorded simultaneously. Up to now, there have been few simultaneous EEG-fMRI studies including psychiatric patients [43], and to our knowledge, the present study is the first simultaneous EEG-fMRI study with ADHD patients. However, the EEG and fMRI results are inconsistent: to a certain extent, we found high associations between electrophysiological data and BOLD responses. However, the N2 amplitudes between patients and controls did not differ significantly, whereas patients demonstrated decreased BOLD responses compared to healthy controls. While comparable P3 amplitudes of healthy subjects and ADHD patients could be attributed to similar BOLD responses in parietal regions, the N2 results remain unclear.

Conclusion

The results may indicate that selection processes are related predominantly to both medial frontal brain regions and parietal areas. Difficulties in decision-making in ADHD patients seem to be associated with frontal deficits, whereas parietal brain functions seemed to be unaffected.

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