The following Report provides the close-out summary for the 2-year OTKA Project NN 103325, entitled

„Neurobiological Basis of Adult Attention-deficit Hyperactivity Disorder (ADHD): a functional MRI and High-density Event Related Brain Potential (ERP) Investigation."

Study Period: 24 months.

Progress Report for 2nd year and Close-out Summary

Project's Objective (as stated in the original submission)

The principal goal of the current study is to identify specific neurobiological markers that are related to basic clinical and neuropsychological impairments in ADHD and thereby gain insight in the neurobiological background of this condition. In order to achieve this, the current project focuses not only on the prefrontal cortex per se but on its interconnected neural circuitry with other brain structures relevant to ADHD. Based on Durston's proposition (Durston et al., 2010), we specifically investigate three major interacting networks, including the dorsal frontostriatal (linked with cognitive control), orbitofronto-striatal (linked with reward processing and deficient emotional self-regulation and impulsivity), and fronto-cerebellar networks (linked with timing). We hypothesize that neurobiological dysfunction in any of these circuits could lead to symptoms of ADHD, as behavioral control could be disturbed by: 1) deficits in the prefrontal cortex itself; or 2) problems in the circuits relaying information to the prefrontal cortex, leading to reduced signaling for control.

Implementation of experimental paradigms for EEG and fMRI sessions

The project we report here relied on complex stimulus task conditions to probe the basic neural circuits associated with cognitive control and timing, as well as with reward processing and deficient emotional self-regulation in ADHD.

The respective paradigms, along with their implementation had been described in prior Progress Report. In brief, participants were subjected to various Go/No-Go task conditions, which required behavioral adjustment and inhibition. We hypothesized that behavioral inhibition is compromised in ADHD, especially in the presence of emotionally arousing stimuli. For the emotional Go/No-Go task we used pictures from the International Affective Picture System (IAPS). Using this system, emotionally neutral, positive, and negative pictures are presented in random sequence in a Go/No-Go trial. Participants were asked to respond as quickly and accurately as possible to every stimulus presentation, but withhold response to the second instance of any stimulus that is repeated.

Since in addition to deficits in attention, executive, affective processing and behavior inhibition functions, ADHD is accompanied by problems with social interactions, we also added a set biological motion stimuli to the affective stimuli. Biological motion - i.e., the motion of other people or animals – is an important source for social information processing; its evaluation helps in understanding other people feelings and intentions. Thus, it is crucial component of social interactions.

Overall, the design-specified experimental paradigms were implemented, as planned.

Project Infrastucture

Hardware and software conditions for conducting electrophysiological and fMRI investigation were established during the initial phase of the project. In terms of infrastructural

achievements, we expanded our high-density EEG system from 128-channels to 256-channels and obtain such high-density recordings in a subset of the data. Expansion of the amplifier system was accomplished in a backward-compatible way, therefore we were able to pool data across the study.

To analyze the large volumes of electrophysiological data, we also expanded our signal processing capabilities; we now apply built-in and self-developed functions as well as the freeware EEGLAB toolbox (Delorme and Makeig, 2004) in the Matlab (MathWorks, Natick, MA) development environment for off-line data analyses, that helps to further automate the preprocessing steps, which include the following: Continuous EEG data are visually inspected; non-stereotype artifacts that would significantly affect the quality of the ICA (Independent Component Analysis) decomposition (see (Mognon, 2011)) are removed. EEG is re-referenced to the common average potential and filtered off-line between 0.1 and 75 Hz using zero-phase shiftforward and reverse IIR Butterworth filter. The signal is filtered using the 48-52Hz Parks-McClellan stop-band Notch filter implemented in the ERPLAB (Lopez-Calderon and Luck, 2014).

To avoid potential artifacts, we perform ICA decomposition (*CUDAICA; (Raimondo et al., 2012)*) individually on the epoched data and artefact-related components identified automatically by ADJUST (Mognon, 2011) are removed. The ERPs for statistical analysis were reconstructed without these components. To handle the large amounts of data, we increased our computer storage and data back-up capabilities. To increase processing speed and efficiency we expanded our computer equipment..

Altogether, these infrastructural accomplishments allowed for a successful completion of the project.

Patient recruitment

Based on the protocol specified Inclusion/Exclusion Criteria, subjects were recruited by the clinical team as planned. The number of subjects available for analyses for some of the modalities varies due to missing data, technical difficulties encountered in some cases during the recording sessions for EEG and fMRI. Replacements for missing data was performed; as a results, for most of the analyses and for most of the experimental task conditions the sample size varied around n=30. (For the analysis of 256-channel EEGs, data from a total of 22 patients are available, since the 256-channel recordings were initially not available in the study.)

In sum, patient enrollment was completed for the study, as planned.

Data collection

Data were collected in the following domains:
- basic background and clinical characteristics;
- neuropsychological and psychopathological testing;
- neurophysiological data using the high-density BioSemi recording system;
- fMRI recordings; and
- behavioral measurements (conducted in both the EEG and fMRI sessions).

EEG-recordings

EEGs were obtained at the Department of Psychiatry and Psychotherapy, Semmelweis University. Recording sessions took place as planned, lasting approximately 1 hour. Briefly, high-density electroencephalograms were recorded using the BioSemi Amplifier System (BioSemi, the Netherlands). Four-minute-long resting EEGs were registered in a comfortable seated position with eyes open. Event-related brain potentials (ERPs) were acquired while the participants subjected to the above described task conditions.

fMRI sessions

All fMRI sessions took place at Semmelweis University using a 3T Philips Achieva system, available at the MR Research Center. Clinical as well as MR personnel participated the sessions. They ran the session according to the study protocol based on the task conditions, and made adjustments, if necessary, in case unforeseen technical difficulties arose during the session. MR personnel also supervised the data acquisition in real time, and examined the stored records' integrity at the end of the sessions. The sessions lasted about 1-hour.

The data collection in the project has been completed.

Data processing

Behavioral data

Raw behavioral data were extracted from the Presentation log files prepared during the EEG and fMRI recording sessions. They were then converted into a SAS database, and computer programs in SAS language were written to yield derived behavioral variables including omission and commission errors, reaction times and post-error slowing. Descriptive results and inferential statistics are provided in the manuscripts submitted for publication. Overall, we found major group differences in the emotional Go/No-Go tasks: patients in the ADHD group made a substantially higher proportion of false alarms than healthy controls. The extent of the difference is larger than in previous studies; it suggests that the emotional response inhibition task may prove a particularly sensitive behavioral probe for adult patients with ADHD. The analysis of behavioral data has been completed.

Electrophysiological data

We conducted a manual review of all electrophysiological data, which included marking of epochs containing artifacts for potential removal as well as exclusion of individual recording channels with artifacts. This process, performed using the EMSE source signal imaging software, yielded an output file that was converted to SAS for a relational database. During the second year of the project, we also expanded the data processing capabilities by adding a MATLAB (EEGLAB)-based processing automation, as described at the section on Project Infrastructure. The data analyses have been completed. Results are provided in the summary below, and are available in attached manuscripts submitted for publication, and in abstracts of conference presentations.

MR data

fMRI data from the project were processed using standard steps including motion correction, smoothing, and conversion to relative signal change in each group. They were then deconvolved with a hemodynamic response function for BOLD images. Group differences in activation were examined using fixed and random effects general linear model. Significant clusters of activation are identified based on a correction for multiple comparisons.

The data processing is completed. Manuscripts are under preparation for publication.

Presentation of the Results:
Summary of the Project's Main Findings

The summary provided herein is based on papers submitted for publications and on conference proceedings at major international and national conferences. Throughout our summary, for each subsection we will provide references [in square brackets] to manuscripts submitted for publication and to conference presentations and abstracts that would give additional details of the findings. A listing of these references is also provided.

Neural Correlates of Impairments in Conflict Monitoring in ADHD [1]

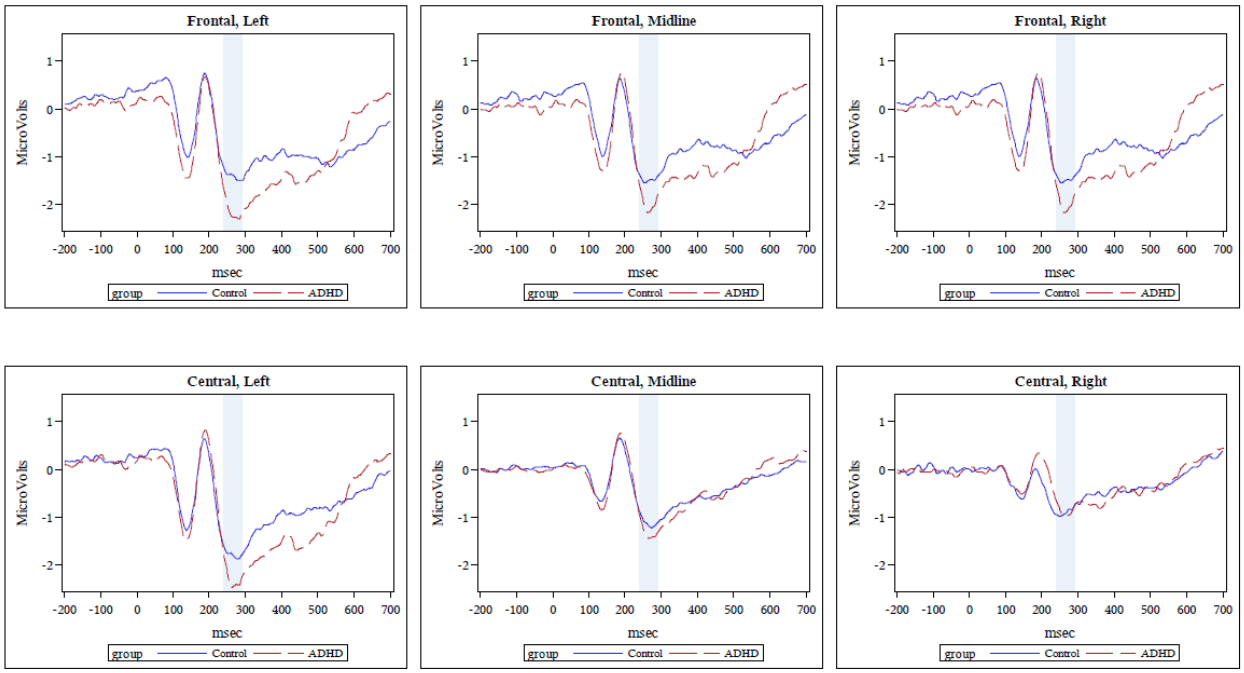
We investigated deficits in cognitive control and conflicts n information processing, since major symptoms evidenced by ADHD patients have been linked to such deficits. Because in cognitive control tasks the N2 ERP component has been linked to response selection and conflict monitoring, we focused on N2. N2 is a negative deflection at 200-300ms post-stimulus, occurring mainly in anterior scalp areas. In GoNoGo paradigms, N2 is detectable both after Go and NoGo stimuli (Donkers and van Boxtel, 2004).

Unlike previous ERP studies that focused on ERPs following incorrect responses in ADHD, we investigated the N2, which reflects conflict monitoring before a correct (not just an incorrect) response. Figure 1 below illustrates the task paradigm and the procedure. Subjects were asked to push a button as soon as possible upon appearance of the letters (Go trials); they were, however, asked to withhold response in case a letter was repeated (NoGo trials). 256 stimuli were presented, with a ratio of 10% for the Nogo trials. Interstimulus time varied randomly (+10%).

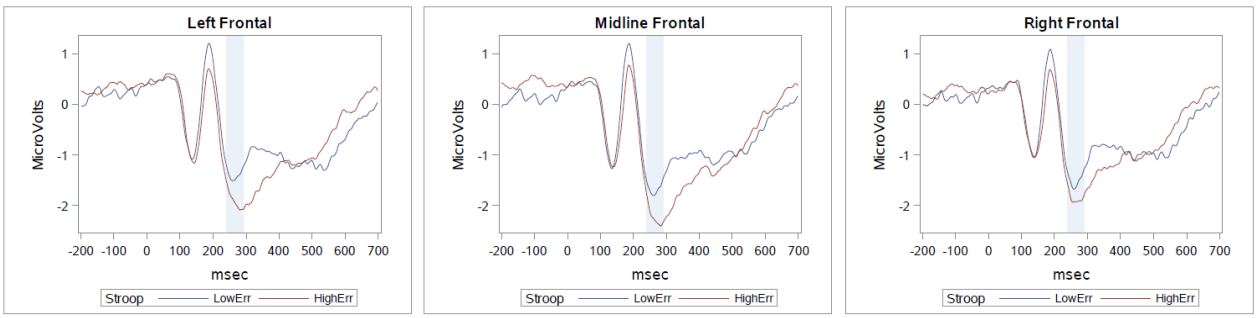
Table 1 below provides basic descriptive data for the study population. Patient sample included subjects who met DSM-IV criteria for ADHD. Controls were matched individually to patients based on gender, level of education and age (±5 yrs). Patients met criteria for ADHD combined subtype.

	Healthy Control (n=29)		ADHD# (n=33)	
	mean	SD	mean	SD
Age (years)	32.9	12.8	31.6	12.1
Education (years)	15.4	2.1	15.1	2.7
Male (%)	72.4%	-	75.7%	-
Conners Adult ADHD Rating Scale				
Inattention/Memory Problem	-	-	24.3	6.3
Hyperactivity/Restlesness	-	-	19.9	7.1
Impulsivity/Emot. Lability	-	-	18.4	7.0
Problems with Self-Concept	-	-	10.6	5.0
Stroop task (Incongruent errors)	0.8	1.0	1.7	2.2

The analysis showed statistically significant group differences in all frontal areas whereas no significant difference was found for any of the central areas. The differences remained significant after adjustment for medication status. ERP waveforms for each of the frontal and central areas are shown in Figure 2 below. The average ERP waveforms across frontal and central regions broken down by study group in the figure. Stimuli were presented at time (msec) = 0. Component time window for N2 is indicated by the shaded area.



The analyses also indicated that the alteration of the N2 ERP component varied with the number of errors made on the Stroop incongruency task. Figure 3 below shows observed average ERP waveforms in the ADHD group for subgroups patients with low and high number of Stroop errors, based on median split (median=1). Stimuli were presented at time (msec) = 0. Component time window for N2 is indicated by the shaded area.



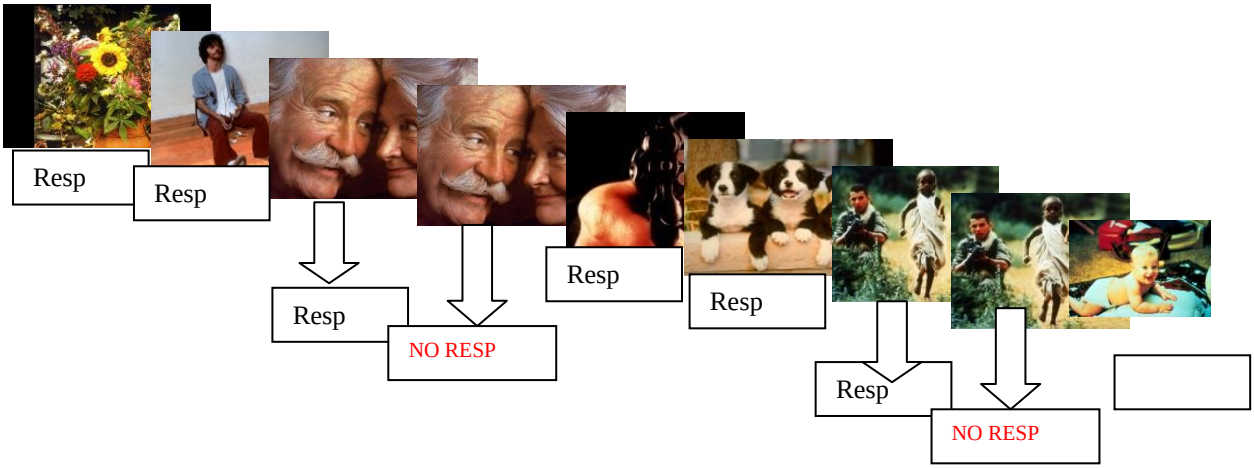
In sum, we identified an enhancement of the ERP N2 amplitude among ADHD patients compared to controls. We also found that the N2 enhancement in the ADHD group was related to the performance on a key measure of attention allocation and executive functions (Stroop incongruency task). The extent of N2 enhancement increased with Stroop errors: the larger the amplitude, the higher the number of errors. Moreover, the ERP changes were region-specific, occurring in frontal areas. The higher N2 may indicate an excessive activation, which could be a reflection of an abnormality in conflict monitoring, a hypothesized mechanism that would underlie a hyperactive action-monitoring in ADHD in tasks involving errors(Silk et al., 2005;Sowell et al., 2003).

Response Inhibition in ADHD: The Influence of Emotional Valence on the P300 Brain Potential [2]

The results summarized here are based on the emotional Go/No-Go (response inhibition) paradigm mentioned above. Briefly, the rationale for this paradigm comes from empirical data

suggesting that disturbances in emotional processing in ADHD may interfere with executive functioning, lead to problems in behavioral inhibition and impulsivity, and account for impairments in life functioning (Barkley, 2010). In normal individuals, brain activations in certain areas (e.g., prefrontal cortex and ACC) during arousal (e.g., through evocative emotional stimuli) constrain the impulsive expression of emotional behavior. While deficits in these brain regions in ADHD are thought to lead to vulnerability to impulsive behavior and to lack of behavioral inhibition, the underlying neurobiological mechanisms are unknown.

For this paradigm, we investigated the P300 ERP component, an electrophysiological measure of response inhibition (Polich, 2007;Nash et al., 2013), using 478 pictures from the International Affective Picture System (IAPS). The emotional valence in these pictures has been rated on a scale from 1 (negative) to 9 (positive). Emotionally neutral, positive, and negative stimuli were randomly presented with a probability of 0.45, 0.275, and 0.275, respectively. Images were presented centrally every 1000ms for 800ms with an inter-stimulus-interval of 200ms. Task and procedure are shown below in Figure 4 (below). Specifically, on this Go/NoGo Task, subjects have to respond quickly to Go stimuli, while withholding responses to the second presentation of any stimulus repeated twice in a row (NoGo stimuli). The probability of Go and NoGo trials was 0.85 and 0.15, respectively.



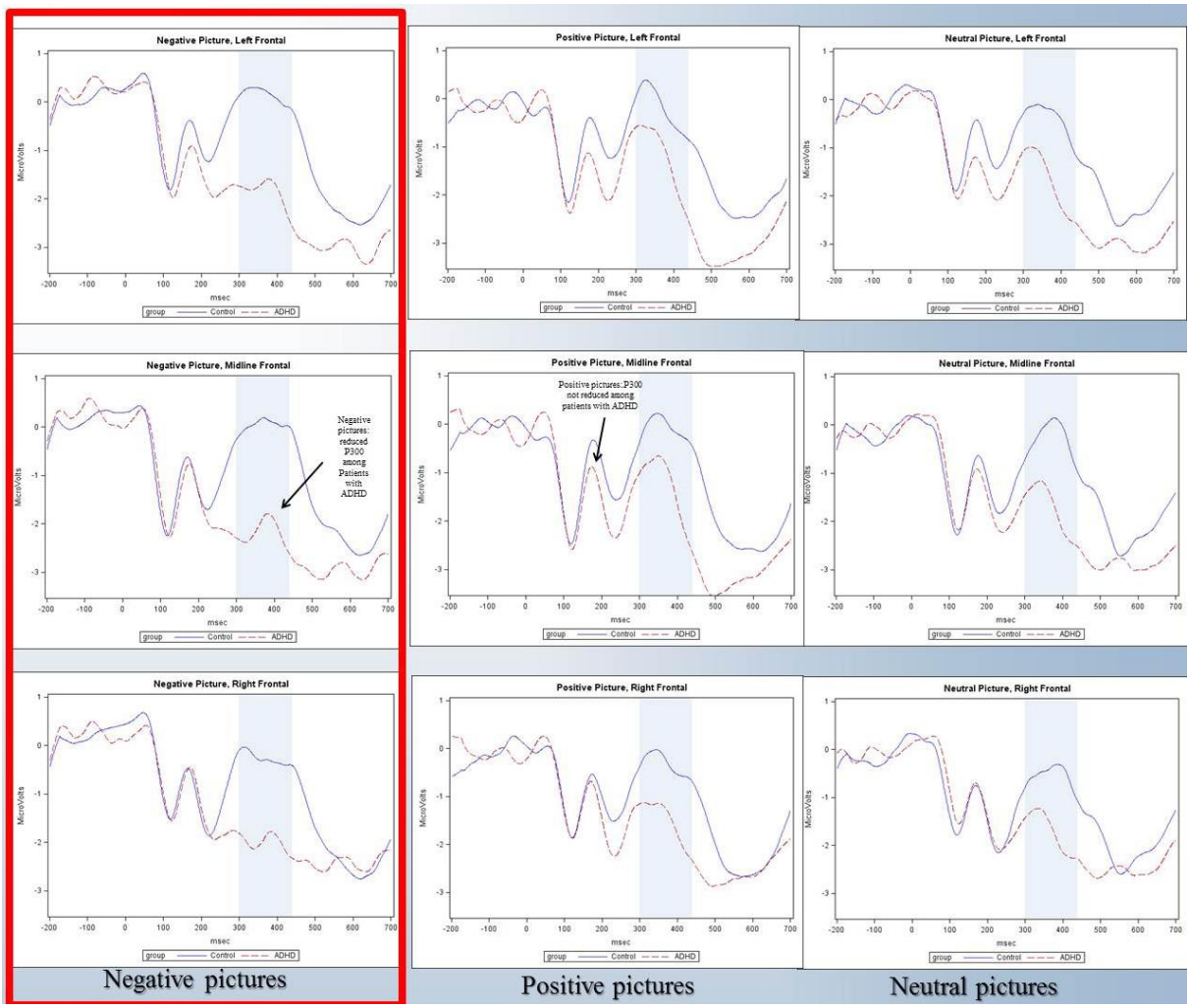
Our specific aim was to investigate whether patients with ADHD evidence deficits in processing emotionally-valenced inputs, and to delineate the neurobiological correlates of these deficits.

Table 2 below provides basic descriptive data for the study population, which was the same as in the analyses detailed above.

	Healthy Control (n=29)		ADHD[A] (n=33)	
	mean	SD	mean	SD
Age (years)	32.9	12.8	31.6	12.1
Education (years)	15.4	2.1	15.1	2.7
Male (%)	72.4%	-	75.7%	-
CAARS Total	47.5	23.5	119.3	24.2
SCL-90	21.2	22.9	75.7	63.1

We identified significant group differences for P300 for negative pictures in frontal areas of interest (midline, and parasagittal left and right). The differences remained significant after

adjustment for medication status. Results were similar for the midline central area. For the rest of the scalp areas, the group difference did not reach significance. Figure 5 below displays the average ERP waveforms for the midline and the parasagittal left and right frontal areas. The Component time window for P300 is indicated by the shaded area.



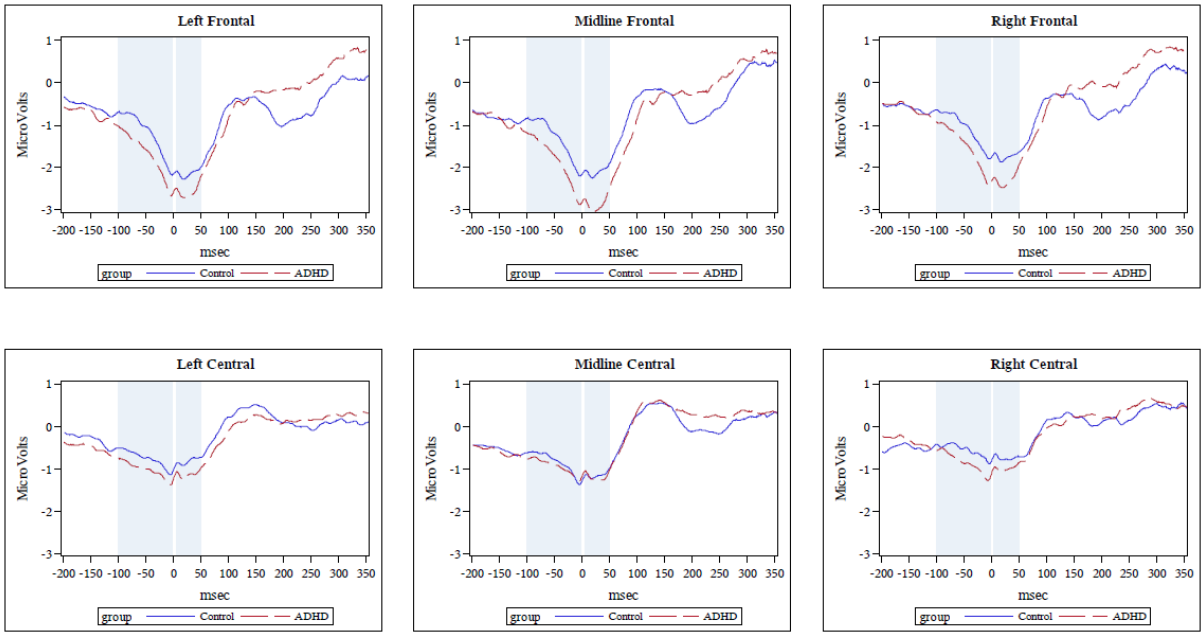
Overall, with regard to frontal NoGo P300, healthy controls were able to overcome the intrusion of negative emotion, and showed the same waveform when presented with negative as they showed with positive or neutral stimuli. By contrast, while ADHD subjects did not differ from controls regarding positive and neutral inputs; they exhibited a pronounced P300 reduction for negative pictures. Thus, our findings are consistent with the view that disturbances in emotional processing in ADHD may interfere with executive functioning and impair response inhibition, and suggest that reduced P300 may constitute a neurobiological correlate of a deficit in dysregulation in cognitive control by emotional inputs.

<u>Altered Response-Preparation in Patients with Adult ADHD [3]</u>

Neurodevelopmental theory posits that aberrations in early-developing bottom-up processes, such as stimulus-driven response preparation, play a critical role in the onset of ADHD, and remain stable over time despite symptom remission (Halperin and Schulz, 2006). Such aberrations may be manifested as premature or impulsive response style with being too quick

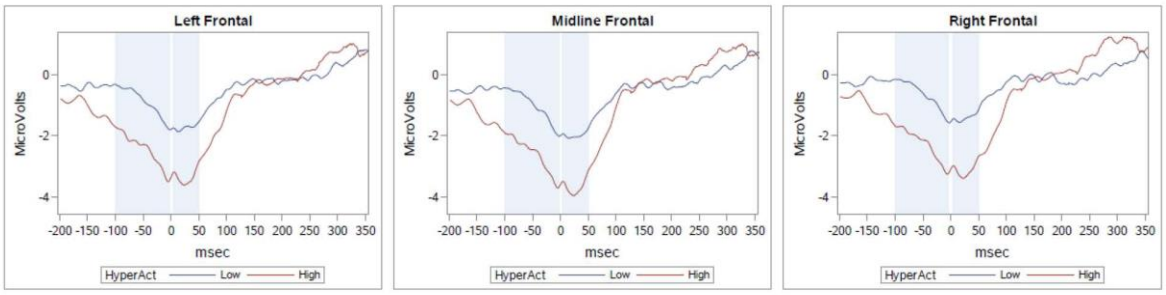
to respond ('acting at the spur of the moment'); a failure to stop or postpone response or action; poor ability to plan; and problems with adaptive adjustments (Botvinick et al., 2004). The neurobiological underpinning of these aberrations, however, remains unclear. We investigated the neurophysiological foundation of response-preparation and response-preceding brain activity in adult ADHD.

In the analyses described here, response-locked ERPs prior and following motor response (RPA and PRA, respectively) were used to probe response-preceding brain activity and subsequent adaptive processes. Our results showed that compared to controls, patients with ADHD showed marked enhancement of the response-locked RPA and PRA components in the frontal areas. Figure 6 below illustrates group difference in response-locked ERPs. The grand mean of response-locked average ERPs for the ADHD group are shown in red (dashed line) and for the control groups in blue (solid line). Time windows of interest, shown as subsequent shaded areas, were -100-0ms prior motor response for response-preceding activity (RPA) and 1-50ms after motor response for post-response activity (PRA).



These changes in ADHD were associated with poor performance on the Stroop incongruency-task: the greater the enhancement, the higher the number of errors. Moreover, the ERP-enhancement showed association with the severity on core psychopathological measures of ADHD, including hyperactivity and impulsivity; and with a marker of inefficient response-preparation: heightened response-variability.

Figure 7 below demonstrates the difference in response-locked ERPs in patients who displayed high vs. low severity on the CAARS Hyperactivity factor. Specifically, grand mean of response-locked average ERPs for patients with low (in blue, solid line) and high severity on the CAARS Hyperactivity factor (in red, dashed line) are shown. Patients who scored below the mid-point (score=18) of the theoretical range of the Hyperactivity factor (range: 0-36) were classified in the "low hyperactivity" group (n=16); those whose score reached or exceeded the midpoint (>18) were classified in the "high hyperactivity" group (n=17).



In sum, patients with ADHD demonstrate marked neurophysiological alterations in response-preparation and response-preceding brain activity, suggestive of excessive activation of prefrontal neural circuits that underlie conflict-monitoring and response-preparation. Given the correlation with neuropsychological and psychopathological measures, these changes may constitute a key pathway leading to some of the core symptoms of ADHD, including premature and impaired response-preparation during stimulus-driven actions, and motor-hyperactivity.

Electrophysiological Indices of Aberrant Error-Processing in Adults with ADHD: A New Region of Interest [4]

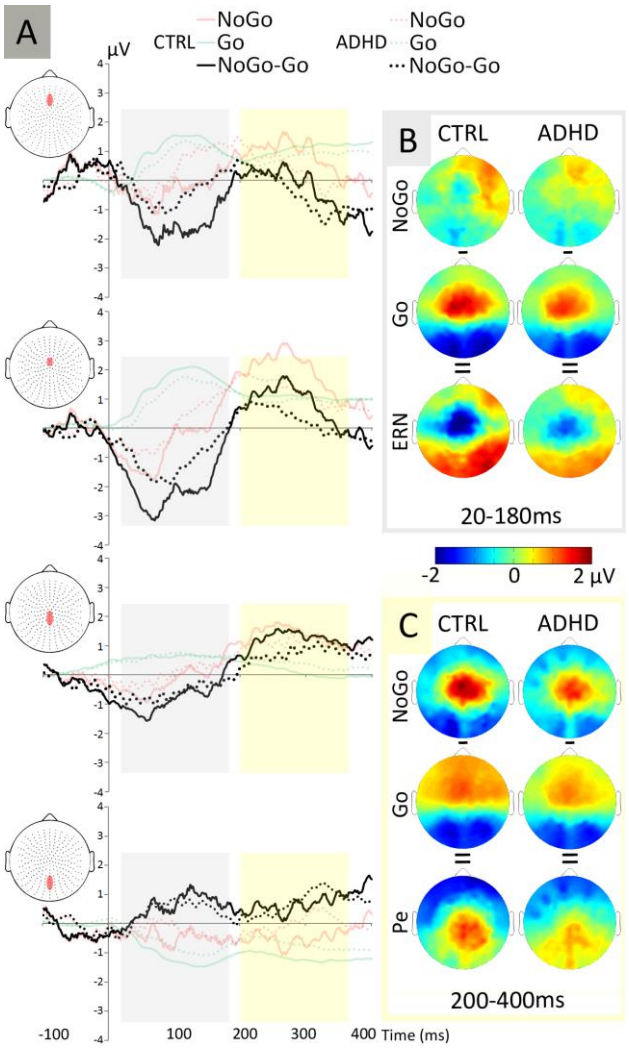
The aim of the analyses described here was to investigate the neurobiological basis of abnormal error-processing and adaptive adjustments in ADHD. Deficits in error-processing and adaptive adjustments have been implicated in core symptoms of Attention Deficit Hyperactivity Disorder (ADHD) (Wiersema et al., 2009;Geburek et al., 2013), but the neurobiological basis of these deficits is poorly understood. Response-locked event-related potentials (ERPs) elicited by erroneous responses, and in particular the error-related negativity and positivity (ERN and Pe), are considered as principal biomarkers of error-processing (van Veen and Carter, 2002). ERN reflects an initial automatic brain response after an error. ERN is followed by a positive wave, the Pe, which is related to the conscious recognition and motivational significance of the error (Overbeek T.J.M, 2005;Falkenstein et al., 2000;Nieuwenhuis et al., 2001).

To date, error-processing in adult ADHD, as indexed by the ERN and Pe, has received limited attention (Geburek et al., 2013). Most individual studies remained inconclusive, with only 2 of 7 studies yielding a significant finding. However, two key limitations must be kept in mind regarding these data. *First*, former studies investigated a limited set of specific scalp regions of interest (ROIs) (typically the Fz, Cz and Pz channels). This research strategy ignores evidence indicating that the brain's error-processing network is highly functionally coupled with other widespread neural networks. Since erroneous outcomes represent salient events, a recently described network, the Salience Network (SN) system is of particular importance (Harsay et al., 2012). It encompasses several major cortical areas including the dorsal anterior cingulate cortex(dACC), the left and anterior right insula, along with the adjacent inferior frontal gyri; and the temporo-parietal cortices, including the temporo-parietal junction (TPJ) in a right-lateralized fashion (Seeley et al., 2007). Emerging evidence indicates that errors are associated with robust SN activation, signaling the need for behavioral adaptation (Carter et al., 1998;Holroyd et al., 2004). *Second*, previous studies did not recognize that deficits in error-processing may have a differential association with core clinical symptoms.

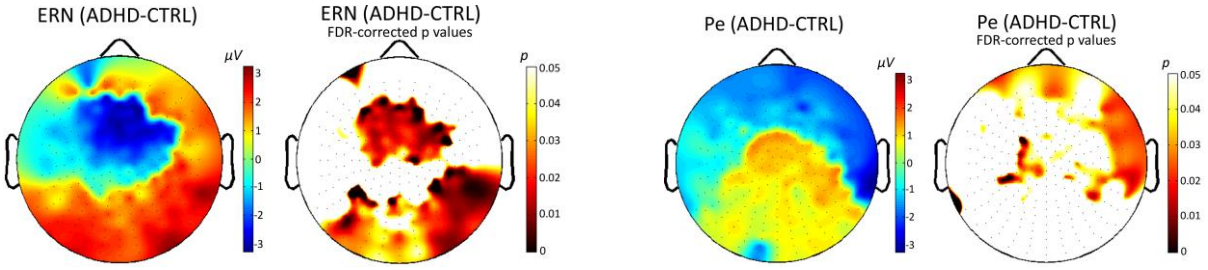
We aimed to investigate the neurobiological underpinnings of the deficits in error-processing and adaptive adjustments in ADHD with a twofold objective. First, we wanted to examine

whether patients with ADHD differ from healthy controls in electrophysiological indices of error-processing, including the ERN and Pe. We exploited information from a high-density, 256-electrode sensor-array, investigating whether differences are observable beyond the traditional ROIs, particularly to those that are expected to be involved in adaptive adjustments, such as the SN system. Second, we also wanted to investigate whether alterations in post-error brain activity in ADHD are related to core psychopathology of ADHD. We expected that uncovering associations could provide important insights into why patients with ADHD are unable to detect or utilize error-related information. We obtained event-related potentials(ERPs) during a Go/NoGo task from 22 adult-ADHD patients and 29 matched healthy controls.

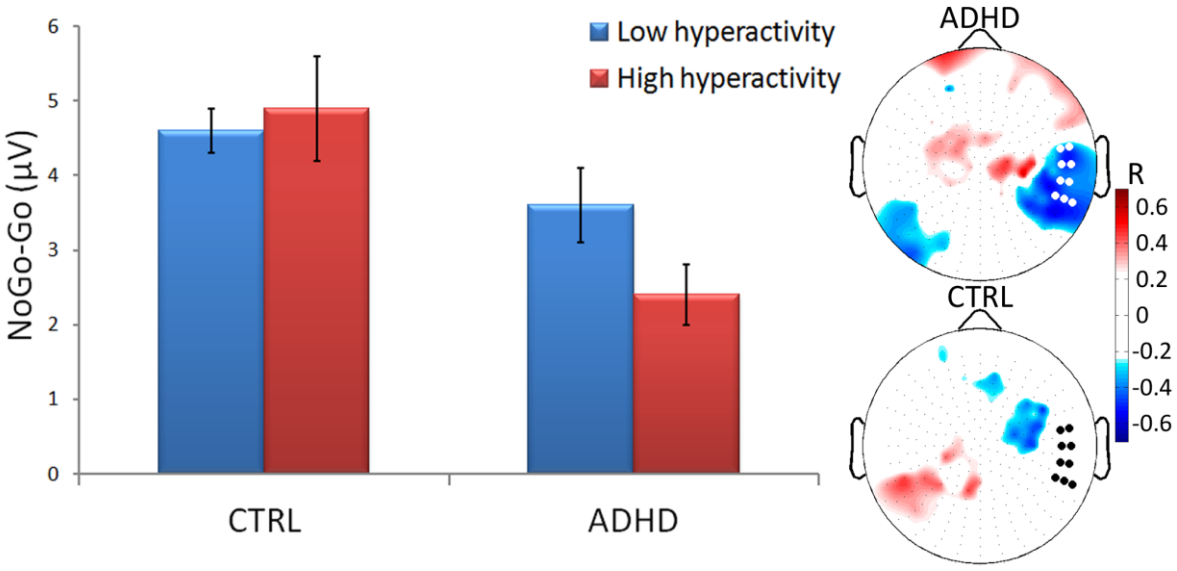
Figure 8 (below) shows response-locked ERP-s in four scalp regions of interest typically used in studies of error-related ERP activity. Time-windows for the two error-related ERP components, ERP and Pe are shaded. Panel A shows the response-locked ERPs separately for both groups for the NoGo condition (commission error-responses) and the Go condition (correct responses). The difference between the error (false alarms) and correct responses (actual signal detection) is also shown. Panels B and C display for both groups the topographical-maps of the ERN and Pe responses based on the full set of the 256 individual channels for the two conditions (NoGo, Go); and for their difference (NoGo - Go).



Our results indicate that in ADHD patients the error-related activity in the ERN and Pe time-windows was significantly reduced, and the reduction was associated with core psychopathological symptoms. The ERP-attenuation was prominent not only at traditional ROI-electrodes but across many other brain areas, with a distinctive subset of group-differences and symptom-correlations manifested at temporo-parietal sites, with a right-lateralization. To illustrate the groups differences, Figure 9 below shows the scalp map of the ADHD vs. Control group difference in terms of raw amplitude (uV) values and False Discovery Rate (FDR) Corrected Type I error probabilities. The left and right two panels pertain to ERN and Pe, respectively.



Furthermore, we found that the group differences I error-related activity showed a correlation with clinical symptoms. To illustrate this finding, Figure 10 displays Pe amplitude values in the right temporal region for high and low values of hyperactivity as measured on the CAARS scale (see bargraphs on the left). Low and high values were defined as 12 and 24 points, which respectively represent a value 1 point below or above the middle of the theoretical range of the item scores for each of the constituting items (12) of the subscale. Right: topographical map of the Pearson-correlations between the amplitude changes and symptom severity across the entire scalp.



Together, these neurobiological alterations – which may underlie reduced detection, reduced awareness and deficient evaluation of salience of error signals - form a non-reflective, "error-blind" pattern of responding that results in a hyperactive and impulsive style, including premature responding rather than slowing down and reflecting. These deficits may underlie an inability to utilize feedback information, with a failure in self-regulation and disinhibited

behavior associated with ADHD. In sum, these findings allow us to see how basic deficiencies in error-processing are manifested at the neurophysiological level in ADHD, and provide a greater understanding of the neurobiological basis of the core symptoms of the disorder. The neural patterns may be the result of altered interactions between a dorsal midline error-processing brain network involved in "error-processing proper" and a right lateralized temporo-parietal salience network, which is involved in the evaluation of significance of the error-signals, and has not been identified before.

fMRI: Summary of Methods and Findings

The scans were acquired in the MR Research Center of the University, on a 3T Philips Achieva Scanner (Philips Medical Systems, Best, The Netherlands) using an 8-channel receive-only head coil. All subjects were undergoing a high resolution 3D T1 anatomical spin echo images (TR = 9.7 ms, TE= in-phase 4.6 ms, Flip angle =8, FOV = 240, 240, 180, slice thickness = 1mm) and 3 times the functional sequences. All echo planar imagining (EPI) images were collected (repetition time [TR] = 2000 ms, echo time [TE] = 35ms). Slice thickness was 3.5 mm and 34 slices were collected, without gaps, to provide total brain coverage. The field of view (FOV) was 240, 119, 240 mm. During the EPI acquisition the stimuli was presented with Presentation (Neurobehavioral Systems, Inc., Berkeley CA, US). Synchronisation with the scanner and response collection during the tasks were ensured with Nordic hardware (NordicNeuroLab AS, Bergen, Norway). The same task was presented as during the EEG.

Processing

Pre-processing of the images was started with MRIcron software (Chris Rorden), the conversion to NIfTI format with the dcm2nii tool. Further steps of the pre-processing and the analyses of the pre-processed images was done with Matlab 2013a (Mathworks Inc.) and the SPM 8 software package (Wellcome Trust Centre for Neuroimaging, UCL, London). Standard pre-processing steps were performed, after realignment and spatial normalization to standard space, smoothing was done with a Gaussian kernel of 10mm. Before smoothing the coregistration of the anatomical images was done and motion correction parameters were estimated. Parametric statistical models were assumed at each voxel on the smoothed data, using the General Linear Model (GLM). During second level analyses T-test was used to calculate inter-group differences.

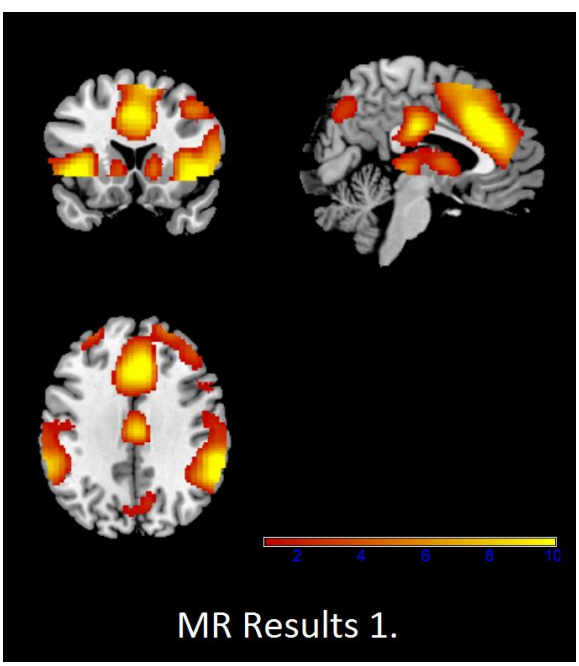
Findings

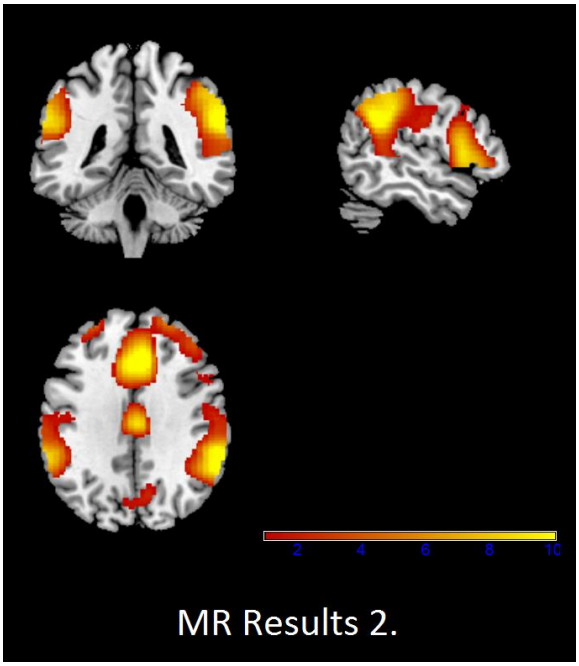
Both groups showed significant (FWE<0.05) activations in the following regions of the brain, for the following contrasts:

1. contrast - NoGo Error vs. Go
    - L and R anterior cingulum (with R dominance)
    - L and R superior parietal and supramarginal gyrus (with R dominance)
    - L and R frontal lobe (also R dominance)
    - L and R anterior insula
    - L and R basal ganglia
2. contrast – NoGo Correct vs. Go
    - similar activation pattern as above, with more visible dominance
3. contrast – NoGo Error vs NoGo Correct

- similar activation pattern as above, without the activation in the superior parietal and supramarginal gyra. Basal ganglia activation is concentrated on the putamen.

Thus, similar to ERP findings shown in Figure 8, we found a pattern of similar error-related activations in both study groups. Figure 11 (below) shows the fMRI activations based on the control group. Specifically, the figure shows the contrast between the NoGo Error vs. Go conditions. As shown by the figure, there is significant (FWE<0.05) activation in the left and right anterior cingulum (with dominance of the right side); in both sides in superior parietal and supramarginal gyrus (again with dominance of the right side); in both sides of the frontal lobe (also right side dominance); and in both anterior insula. The basal ganglia are activated on each side as well.





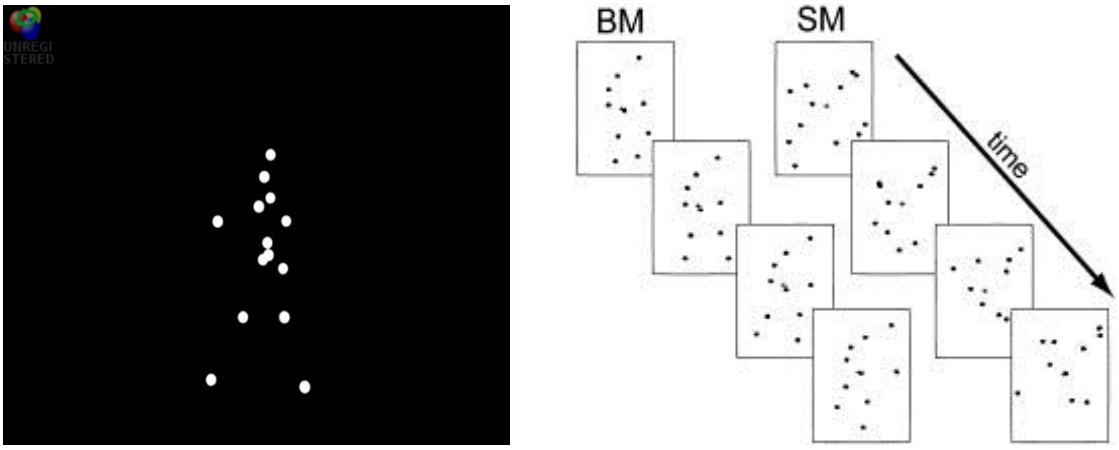
With regard to the ERP data, the extent of error-related enhancement of the amplitudes was markedly attenuated. With regard to the fMRI data we have not been able to identify significant group differences in error-related activation using the traditional fMRI approaches. However, this may be attributable to the poor time resolution of the traditional fMRI approaches, as compared to the ERP approach. We are in the process of implementing novel approaches for the analyses of these data in order to increase the time resolution (e.g., approaches based on window segmentations. In sum, at the time of the current submission, the fMRI analyses for the group differences are ongoing.

Biological Motion Processing [5]

Biological motion - i.e., the motion of other people or animals – is an important source for social information processing; its evaluation helps in understanding other people feelings and intentions. Thus, it is crucial component of social interactions (Pavlova, 2012). Because ADHD is accompanied by impairments in social interactions, we also added a set biological motion stimuli to the affective stimuli we used in our project.

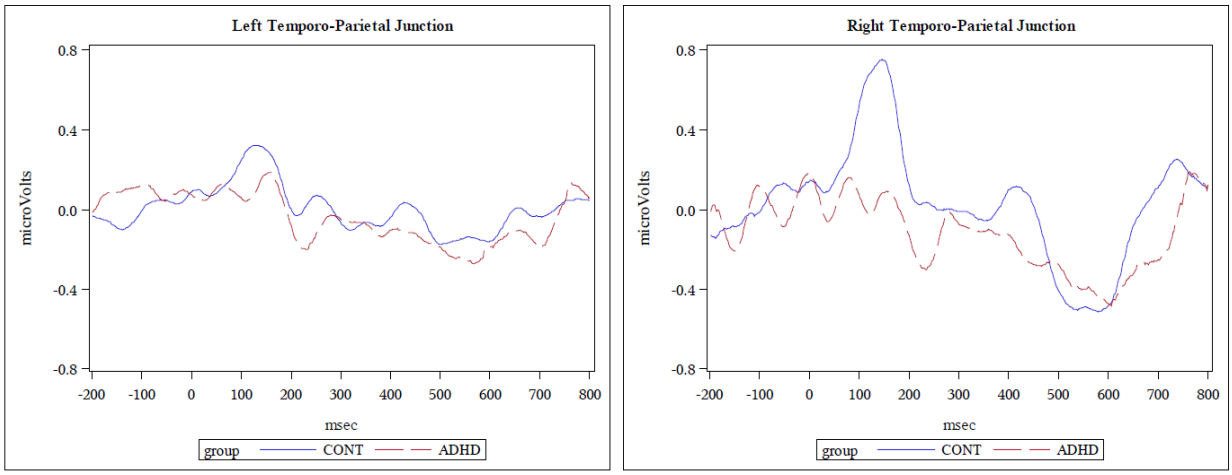
Our aim was to investigate the neurobiological processes that underlie biological motion processing in adult ADHD subjects as compared to controls. Biological motion stimuli were

generated using Point Light Displays (PLDs), which represent standard human motions (e.g., jumping, walking). For a control condition we used scrambled motion (SM) stimuli, which displayed PLDs in an incoherent, random motion. Figure 12 below provides a schematic illustration of the stimuli and stimulus sequence we used in the study. The presentation of stimuli was performed at 1500 msec interstimulus interval, in a pseudo-random order (e.g., BM, SM, BM, BM, SM..). Biological motion stimuli were presented both in an unattended and an attended condition during the study.



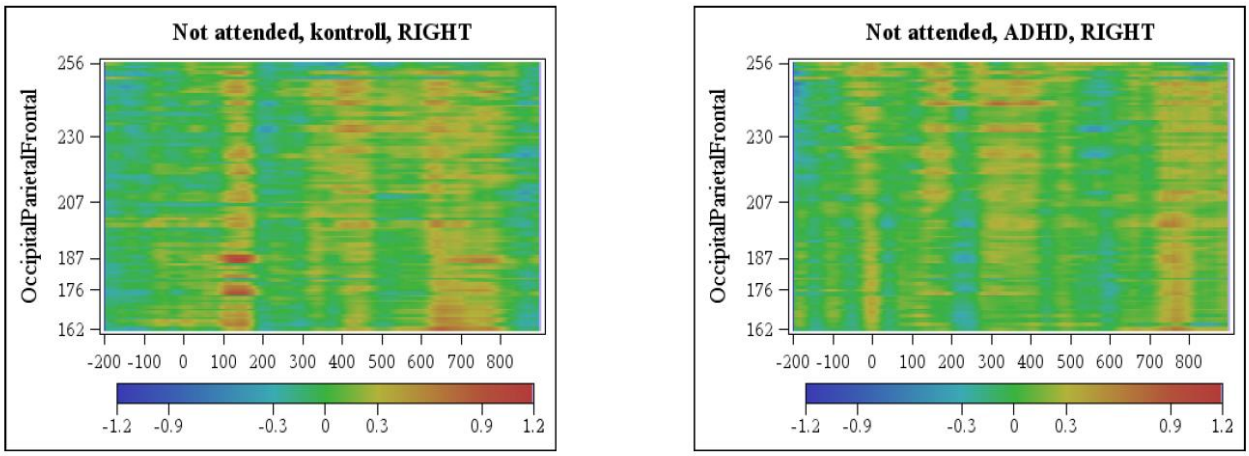
For regions of interest (ROIs) we investigated brain areas that have been linked to the processing of biological motion stimuli in healthy individuals, including the visual cortex (extrastriatal and parietal areas, posterior temporal sulcus [PTS]) and temporo-parietal junction [TPJ].

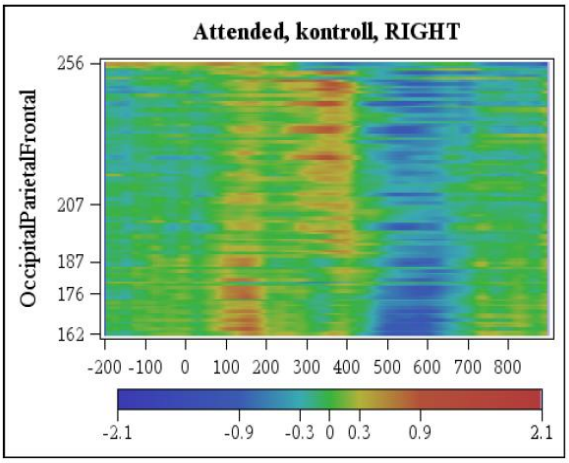
Figure 13 below shows the difference waveforms computed between BM and SM in the scalp regions above the left and right temporo-parietal junction,TPJ. The deviation of the difference-waveform from the 0 microvolt value indicates ERP activity specific to BM as compared to SM. Based on data from the literature, TPJ is one of the major areas responsible for the processing of biological motion (Carter and Huettel, 2013). Our results show that both groups evidence a statistically significant enhancement of the ERP activity at late time window (500-600 msec). However, at an earlier time window (100-200 msec), there is significant BM-specific difference in the control group, while no such difference is observable among patients with ADHD. As shown by the figure, the differences are manifested with a right lateralization, as expected on the basis of prior literature about the right-lateralization BM processing in healthy individuals.

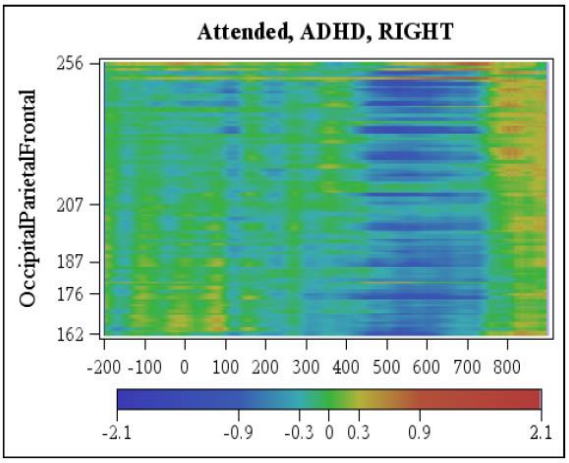


Our findings in the context of scalp topography, based on data from the 256 recording electrodes, are shown in below in Figure 14. We note that this figure was prepared as part of a Dissertation Project [6] for earning an MD degree from Semmelweis Univestity by Máté Baradits, a 6-year student who joined in the analyses of the project. Specifically, the figure presents BM-SM amplitude differences in the form of heat maps, broken down by laterality and condition. As shown by the figure, in control subjects BM motion elicits a robust activation in the right occipital and temporo-parietal regions, no such activation is observable in the ADHD group.

It is noteworthy that in addition to the ERP alteration of the processing of BM stimuli, we found significant group differences in terms the processing of SM stimuli.







Overall, our results reveal an impairment of biological motion processing in adult ADHD, which may contribute to social cognition problems described in patients with ADHD. The impairment that we observed at the more basic level of motion processing may be related to motor-coordination and sensorimotor synchronization problems described in ADHD(Noreika et al., 2013). It is also in line with the high prevalence of motor development disorders that co-occurring with ADHD (i.e., developmental coordination disorder) (Piek and Dyck, 2004).

References for the project's results used for the summary

[1] Kakuszi,B., Papp,S., Tombor,L., Balogh,L., Bitter,I. and Czobor,P. Neural Correlates of Impairments in Conflict Monitoring in ADHD: An Event Related Potential Study. 22nd European Congress of Psyciatry EPA 2014 Munich. 2014

[2] Czobor,P., Kakuszi,B., Tombor,L., Papp,S., Balogh,L. and Bitter,I. Response Inhibition in ADHD: The Influence of Emotional Valence on the P300 Brain Potential. 22nd European Congress of Psyciatry EPA 2014 Munich. 2014.

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A full text version of the above references are appended at the end of text report (please see Appendix 1).

Future publications and planned continuation

Currently we are in the process of preparing additional manuscripts for further publications. These will include (but not be restricted to) our findings discussed above with regard to „Response Inhibition in ADHD: The Influence of Emotional Valence on the P300 Brain Potential"; "Biological Motion Processing"; and to fMRI findings with regard to group differences in Go/No-Go and error-related activations. Two project participants are in the process of preparing their Ph.D. dissertations. Based on the analyses of the data obtained in the project, they have prepared one manuscipt each, and the manuscipts are submitted to internal revisions for submission for publication. The first manuscript includes international project collaborators as co-authors as they are focusing on the fMRI part of the project, which was conducted in collaboration with University of Utrecht researchers (title: Attention-Deficit/Hyperactivity Disorder in Adults: An fMRI-Study. Authors: S. Papp, L. Tombor, D. Bos, Á. Szabó, L.R. Kozák, J. van Belle, B. Kakuszi, G Rudas, P. Czobor, I. Bitter, S. Durston). The second manuscript summarizes the Quantitative EEG findings from the project based on the analyses of the spontaneous resting-EEG recordings that took place before the stimulus sessions in the project (title Quantitative, High-density EEG Findings in Adult Attention Deficit/Hyperactivity Disorder; Authors: L. Tombor, S. Papp, B. Kakuszi, L. Balogh, V. Simon, I. Bitter, P. Czobor). In addition to the intended publications, we are planning to attend upcoming scientic meetings. This will provide us with the opportunity to present additional results of the project, and exchange ideas about potential future continuation of the research.

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Appendix 1 (see below)

Neural Correlates of Impairments in Conflict Monitoring in ADHD: An Event Related Potential Study

B. Kakuszi[1], S. Papp[1], L. Tombor[1], L. Balogh[1], I. Bitter[1], P. Czobor[1,2].

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[2]*Nathan Kline Institute for Psychiatric Research, Orangeburg, NY*

BACKGROUND

Major symptoms evidenced by ADHD patients have been linked to deficiencies in cognitive control, especially when conflicts in information processing occur. Because in cognitive control tasks the N2 ERP component has been linked to response selection and conflict monitoring, we focused on N2. N2 is a negative deflection at 200-300ms post-stimulus, occurring mainly in anterior scalp areas. In GoNoGo paradigms, N2 is detectable both after Go and NoGo stimuli [1].

OBJECTIVE

To define neural correlates of impairments in conflict monitoring in ADHD using ERPs. Unlike previous ERP studies that focused on ERPs following incorrect responses in ADHD, this study investigated the N2, which reflects conflict monitoring before a correct (not just an incorrect) response [1].

METHODS

SAMPLE

Study participants included subjects with the DSM-IV diagnosis of adult ADHD (n=33) and healthy controls (n=29), matched for age, gender and level of education.

EEG RECORDINGS

High-density EEGs were recorded using the BioSemi System with a 128-channel montage (band-pass filter: 0.05-70Hz, sampling: 1024Hz). Data were stored and analyzed offline using the EMSE Suite as well as the SAS Software. Epoch selection was done manually as well as with automatic artifact rejection, applying a threshold of +90 uV, and exclusion of eye-movement artifacts based on horizontal and vertical EOG. Epochs of 900ms duration, including a 200ms pre-stimulus epoch were averaged.

STIMULI AND PROCEDURE

Participants were seated in a dimly lit room, approximately 100cm from the monitor. Stimuli were capital letters, with each letter presented at the central fixation point for 200ms. Task and procedure are shown below in Figure 1.

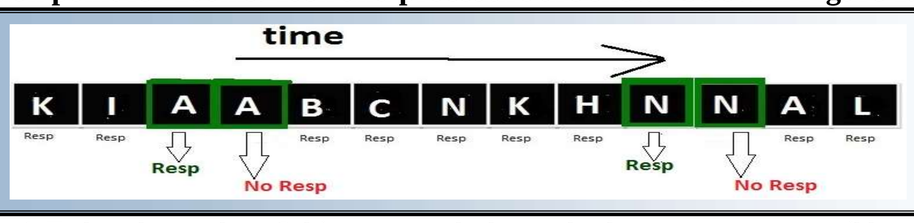

Figure 1. Task and procedure. Subjects were asked to push a button as soon as possible upon appearance of the letters (Go trials); they were, however, asked to withhold response in case a letter was repeated (Nogo trials). 256 stimuli were presented, with a ratio of 10% for the Nogo trials. Interstimulus time varied randomly (+10%).

ERP & CLINICAL VARIABLES

ERP Variables and Brain Regions of Interest

- N2 component time window covered the following post-stimulus latency range: 240-290ms.
- Based on prior fMRI and ERP source localizations,
  - the frontal areas, including the left, right and midline frontal regions served as the primary focus in this study
  - we also investigated the central scalp areas (left, right, midline), since N2 has often been observed over these areas

Figure 1 displays the definition of the 6 regions of interest that we used for analyses.

Psychopathological Symptom Dimensions based on the Conners Adult ADHD Rating Scale

- Inattention/Memory Problems
- Hyperactivity/Restlessness
- Impulsivity/Emotional Lability
- Problem with Self-Concept.
- Stroop test (to probe executive function and conflict processing).
- SCL-90 t(to characterize severity of psychopathological symptoms)

Basic Demographics and Clinical Variables

DSM-IV variables for adult ADHD
Disease history (age of onset, comorbidities)
Current and past medications

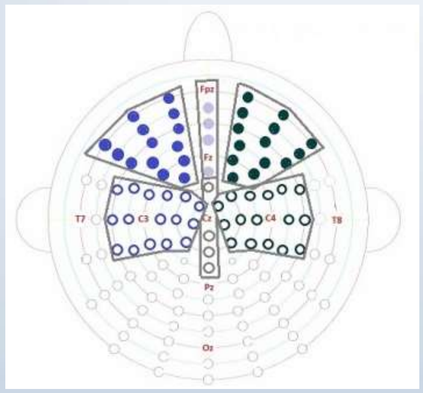

Figure 1. Definition of Six Regions of Interest for N2

STATISTICAL ANALYSES

Analyses were based on the random regression hierarchical linear model (HLM). Amplitude values in the N2 time-window of interest were used as dependent variable. Group and time were the independent variables, with age and gender as covariates. Separate analysis was performed for each brain region, with the Hochberg procedure for multiple testing. For each scalp region with a significant group difference, we conducted further analyses to test whether a measure of executive functions (Stroop incongruent errors) served as a moderator in explaining the N2 alterations in ADHD subjects. In subsidiary analyses, we examined the potential effects of medication.

Acknowledgment: Supported by the Hungarian Scientific Research Fund (OTKA) Grant NN103325

RESULTS

Descriptive Statistics

	Healthy Control (n=29)		ADHD# (n=33)	
	mean	SD	mean	SD
Age (years)	32.9	12.8	31.6	12.1
Education (years)	15.4	2.1	15.1	2.7
Male (%)	72.4%	-	75.7%	-
Conners Adult ADHD Rating Scale				
Inattention/Memory Problem	-	-	24.3	6.3
Hyperactivity/Restlessness	-	-	19.9	7.1
Impulsivity/Emot. Lability	-	-	18.4	7.0
Problems with Self-Concept	-	-	10.6	5.0
Stroop task (Incongruent errors)	0.8	1.0	1.7	2.2

Table 1. Basic descriptive data. Patient sample included subjects who met DSM-IV criteria for ADHD. Controls were matched individually to patients based on gender, level of education and age (±5 yrs). Patients met criteria for ADHD combined subtype.
#: Medication: 14(42.4%) of the patients received some type of psychoactive medication, with 11(78.6%) and 7(21.2%) of these receiving a stimulant medication (methylphenidate) . 3 (1.5%) of the 14 subjects received both medications concomitantly.

ADHD vs. Control: Group Difference in N2 by ROI

HLM analysis showed statistically significant group differences in all frontal areas whereas no significant difference was found for any of the central areas. Statistical test results for each of the frontal regions (left, right and midline) are displayed below in Table 2. The differences remained signficant after adjustment for medication status. ERP waveforms for each of the frontal and central areas are shown in Figure 2.

Left FRONTAL			Right FRONTAL			Midline FRONTAL		
Control μV (SD)	ADHD μV (SD)	Diff. F, p	Control μV (SD)	ADHD μV (SD)	Diff. F, p	Control μV (SD)	ADHD μV (SD)	Diff. F, p
-1.4 (0.2)	-2.1 (0.1)	11.9 .001	-1.5 (0.2)	-2.0 (0.2)	5.0 .029	-1.8 (0.2)	-2.3 (0.2)	5.3 .025

Table 2. Estimated mean (SD) N2 ERP amplitudes (μV) by study group, and test statistics for group difference across frontal areas. Mean ERP amplitudes represent average amplitudes within the specified time window for N2, adjusted for the covariates age and gender.

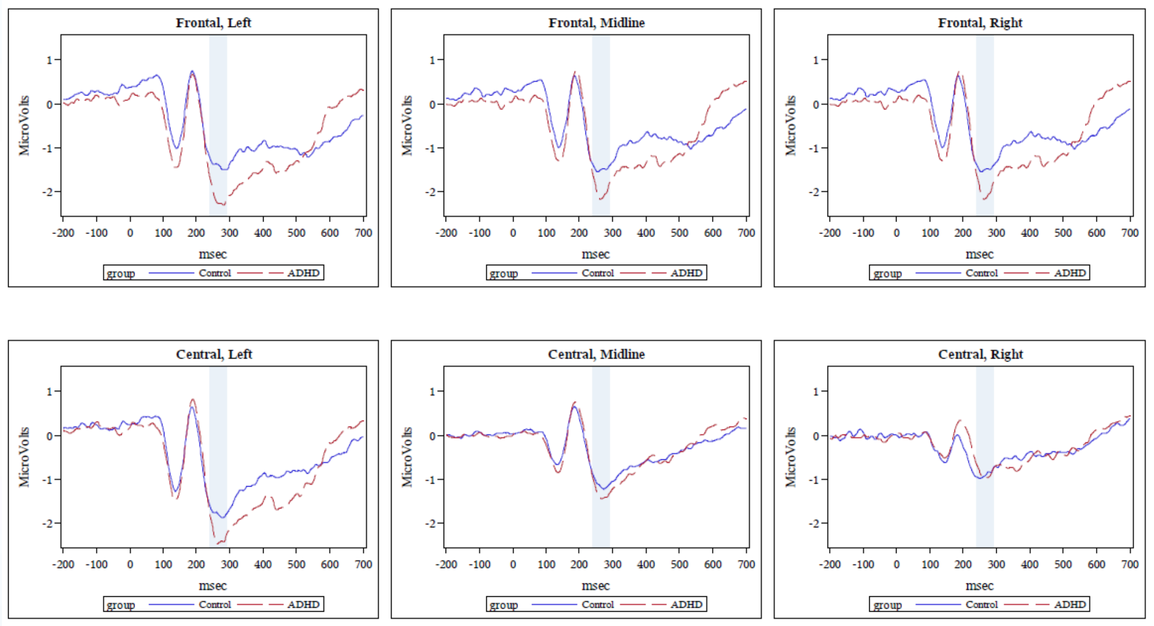

Figure 2. Average ERP waveforms across frontal and central regions broken down by study group. Stimuli were presented at time (msec) = 0. Component time window for N2 is indicated by the shaded area.

N2 in ADHD as a Function of Stroop Errors

Enhancement of the N2 amplitude in the ADHD group showed a significant association in the left frontal area with the number of incongruent errors in the Stroop task (the larger the amplitude, the higher the number of errors). The association on the right side was marginally significant (for results of HLM test see Table 3 below). Figure 3 shows observed average ERP waveforms in the ADHD group for subgroups patients with low and high number of Stroop errors, based on median split (median=1).

Left FRONTAL			Right FRONTAL			Midline FRONTAL		
Low Error μV (SD)	High Error μV (SD)	F, p	Low Error μV (SD)	High Error μV (SD)	F, p	Low Error μV (SD)	High Error μV (SD)	F, p
-1.8 (0.2)	-2.8 (0.3)	8.0 .007	-2.0 (0.2)	-2.2 (0.3)	0.4 .533	-2.1(0.2)	-2.8 (0.3)	3.4 .075

Table 3. HLM test statistics (F, p) for the association of N2 enhancement with the number of incogruent errors in Stroop task in the ADHD group. ERP amplitudes represent average amplitudes within the specified time window for N2 (adjusted for age and gender) for no errors („Low") vs. High number of errors („High error").

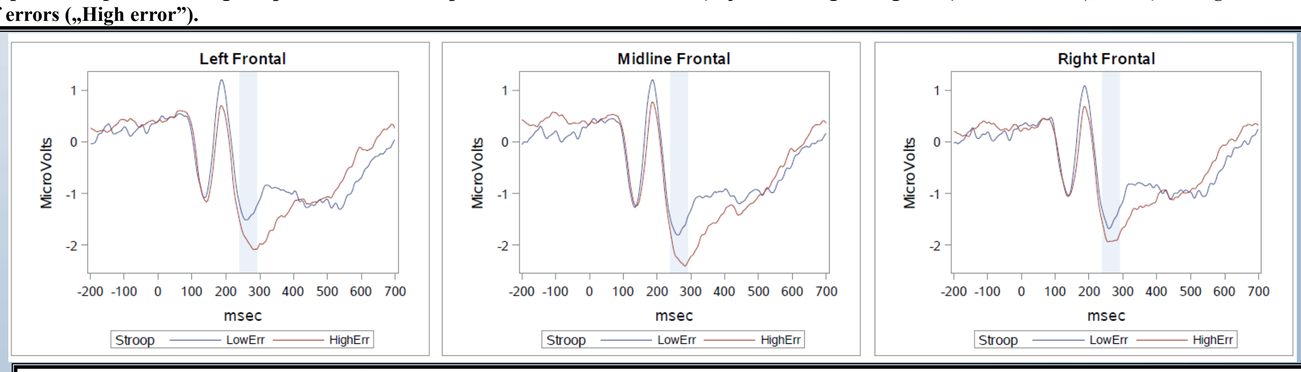

Figure 3. Observed average ERP waveforms in the ADHD group for subgroups patients with low and high number of Stroop errors, based on median split (median=1). Stimuli were presented at time (msec) = 0. Component time window for N2 is indicated by the shaded area.

CONCLUSIONS

We identified an enhancement of the ERP N2 amplitude among ADHD patients compared to controls. We also found that the N2 enhancement in the ADHD group was related to the performance on a key measure of attention allocation and executive functions (Stroop incongruency task). The extent of N2 enhancement increased with Stroop errors: the larger the amplitude, the higher the number of errors. Moreover, the ERP changes were region-specific, occurring in frontal areas. The higher N2 may indicate an excessive activation, which could be a reflection of an abnormality in conflict monitoring, a hypothesized mechanism that would underlie a hyperactive action-monitoring in ADHD in tasks involving errors [2,3]

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Response Inhibition in ADHD: The Influence of Emotional Valence on the P300 Brain Potential

P. Czobor[1,2], B. Kakuszi[1], L. Tombor[1], S. Papp[1], L. Balogh[1], I. Bitter[1]

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[2]*Nathan Kline Institute for Psychiatric Research, Orangeburg, NY*

BACKGROUND

Emerging data suggest that disturbances in emotional processing in ADHD may interfere with executive functioning, lead to problems in behavioral inhibition and impulsivity, and account for impairments in life functioning [1]. In normal individuals, brain activations in certain areas (e.g., prefrontal cortex and ACC) during arousal (e.g., through evocative emotional stimuli) constrain the impulsive expression of emotional behavior. While deficits in these brain regions in ADHD are thought to lead to vulnerability to impulsive behavior and to lack of behavioral inhibition, the underlying neurobiological mechanisms are unknown.

OBJECTIVE

Our aim was to investigate whether patients with ADHD evidence deficits in processing emotionally-valenced inputs, and to delineate the neurobiological correlates of these deficits.

METHODS

STUDY SAMPLE

- **Patients with the DSM-IV diagnosis of adult ADHD (n=33)**
- **Healthy controls (n=29, matched to patients for age, gender and education)**

EEG RECORDINGS

- **High-density EEGs using the BioSemi System (128-channel montage, band-pass filter=0.05-70Hz, sampling=1024Hz).**
- **Data stored and analyzed offline (EMSE Suite, SAS Software).**
- **Epoch selection: manual + automatical (rejection threshold=±90μV + exclusion of eye-movement artifacts based on horizontal and vertical EOG).**
- **Averaging: epochs of 900ms duration (with 200ms pre-stimulus time).**

STIMULI AND PROCEDURE

We used 478 pictures from the International Affective Picture System (IAPS). The emotional valence in these pictures has been rated on a scale from 1 (negative) to 9 (positive). Emotionally neutral, positive, and negative stimuli were randomly presented with a probability of 0.45, 0.275, and 0.275, respectively. Images were presented centrally every 1000ms for 800ms with an inter-stimulus-interval of 200ms. Task and procedure are shown below in Figure 1.

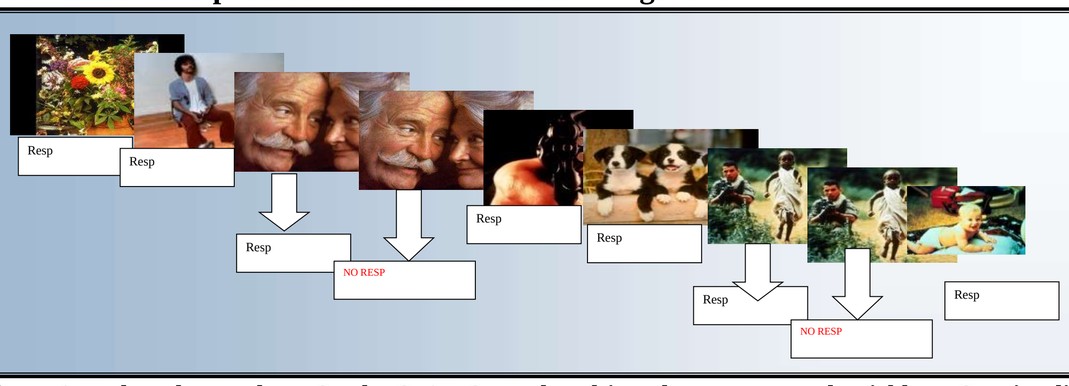

Figure 1. Task and procedure. On the Go/NoGo Task, subjects have to respond quickly to Go stimuli, while withholding responses to the second presentation of any stimulus repeated twice in a row (NoGo stimuli). The probability of Go and NoGo trials was 0.85 and 0.15, respectively.

ERP & CLINICAL VARIABLES

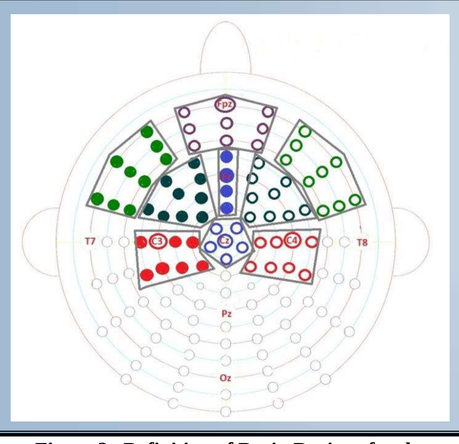

Figure 2. Definition of Brain Regions for the Analyses of P300

ERP Variables and Brain Regions of Interest

- P300 component time window covered the following post-stimulus latency range: 300-440ms [2,3].
- Based on prior literature for NoGo anteriorization of P300 [2,3],
  - the frontal and central areas, including the midline, and left and right parasagittal regions served as the primary focus in this study
  - we also investigated potential effects in the lateral frontal regions

Figure 2 displays the definition of the 6 regions of interest that we used for analyses.

Basic Demographics and Clinical Variables

- DSM-IV variables for adult ADHD
- Disease history (age of onset, comorbidities)
- Current and past medications

Psychopathological Symptoms

- SCL-90 (screening, characterization of severity of psychopathology)
- Conners Adult ADHD Rating Scale (CAARS)

STATISTICAL ANALYSES

- **Random regression hierarchical linear modelling (HLM)**
- **Dependent variable: Amplitude values in the P300 time-window**
- **Independent variables: Group and time Covariates: Age and gender**
- **Separate analysis for each brain area, Hochberg procedure for multiple testing**

Acknowledgment: Supported by the Hungarian Scientific Research Fund (OTKA) Grant NN103325

RESULTS

Descriptive Statistics

	Healthy Control (n=29)		ADHD[A] (n=33)	
	mean	SD	mean	SD
Age (years)	32.9	12.8	31.6	12.1
Education (years)	15.4	2.1	15.1	2.7
Male (%)	72.4%	-	75.7%	-
CAARS Total	47.5	23.5	119.3	24.2
SCL-90	21.2	22.9	75.7	63.1

Table 1. Basic descriptive data. Patients met DSM-IV criteria for ADHD. Controls were matched individually to patients on gender, level of education and age (±5 yrs). Patients represented the ADHD combined subtype.
[A]: Medication: 14(42.4%) patients received psychoactive medication, with 11(78.6%) and 7(21.2%) receiving a stimulant (methylphenidate), respectively. Both medications were received concomitantly by 3 (1.5%) of the 14 subjects.

NoGo P300 is Reduced for Negative Pictures in ADHD but not in Control Subjects

HLM analysis showed significant group differences for P300 for negative pictures in frontal areas of interest (midline, and parasagittal left and right). Statistical test results for each of the frontal regions of interest are displayed below in Table 2. The differences remained significant after adjustment for medication status. Results were similar for the midline central area. For the rest of the scalp areas, the group difference did not reach significance. Figure 3 below displays the average ERP waveforms for the midline and the parasagittal left and right frontal areas.

Picture	Left FRONTAL			Right FRONTAL			Midline FRONTAL		
	Control μV (SD)	ADHD μV (SD)	Diff. F, p	Control μV (SD)	ADHD μV (SD)	Diff. F, p	Control μV (SD)	ADHD μV (SD)	Diff. F, p
Negative	0.1 (0.5)	-1.8 (0.4)	**8.5 .005**	-0.3 (0.5)	-2.0 (0.4)	**6.7 .012**	0.1 (0.5)	-2.1 (0.5)	**8.9 .0042**
Positive	-0.2 (0.5)	-1.1 (0.5)	1.8 .2	-0.6 (0.5)	-1.7 (.5)	2.2 0.14	-0.1 (0.6)	-1.2 (0.5)	2.0 .16
Neutral	-0.4 (0.5)	-1.6 (0.5)	1.7 .09	-0.4 (0.5)	-1.6 (.5)	2.4 0.13	-0.3 (0.6)	-1.6 (0.5)	3.0 .09

Table 2. Estimated mean P300 amplitudes (μV) by study group, and test statistics for group difference across frontal areas. Mean ERP amplitudes represent average amplitudes within the specified time window for P300, adjusted for the covariates age and gender.

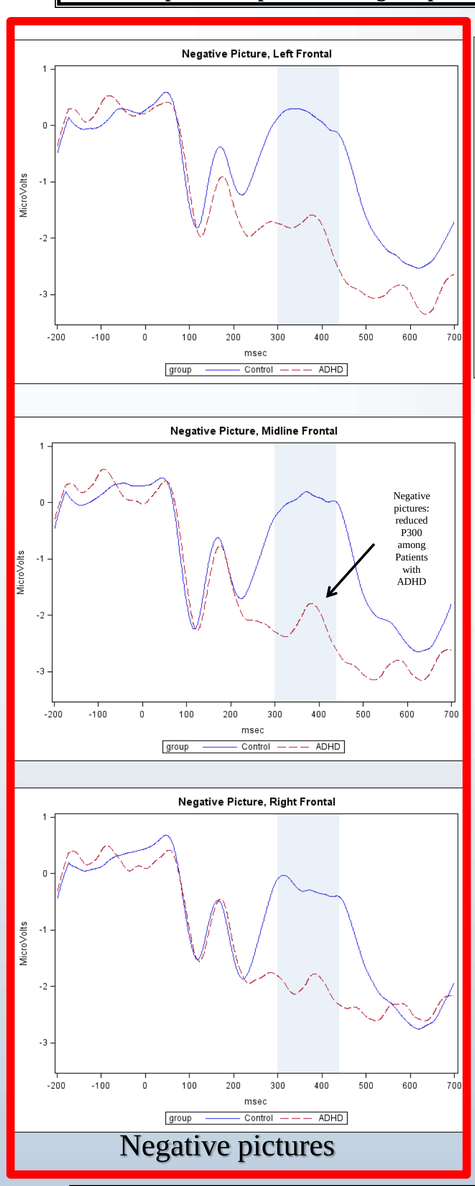

Figure 3. Average ERP waveforms across frontal regions broken down by study group. Stimuli were presented at time (msec) = 0. Component time window for P300 is indicated by the shaded area.

CONCLUSIONS

- **With regard to frontal NoGo P300, HC's were able to overcome the intrusion of negative emotion, and showed the same waveform when presented with negative as they showed with positive or neutral stimuli.**
- **By contrast, while ADHD subjects did not differ from HC's regarding positive and neutral inputs, they exhibited a pronounced P300 reduction for negative pictures.**
- **Thus, our findings are consistent with the view that disturbances in emotional processing in ADHD may interfere with executive functioning and impair response inhibition, and suggest that reduced P300 may consitute a neurobiological correlate of a deficit in dysregulation in cognitive control by emotional inputs.**

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Psychological Medicine

Acting at the Spur of the Moment: An ERP study of Altered Response-Preparation in Patients with Adult ADHD

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	symptoms of ADHD, including premature and impaired response-preparation during stimulus-driven actions, and motor-hyperactivity.

Title:

Acting at the Spur of the Moment: An ERP study of Altered Response-Preparation in Patients with Adult ADHD

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ABSTRACT

Background: Aberrations in early-developing bottom-up processes, such as stimulus-driven response preparation, are thought to play a critical role in the onset of ADHD, and to persist over time despite symptom remission. The neurobiological underpinning of these aberrations, however, remains unclear. We investigated the neurophysiological foundation of response-preparation and response-preceding brain activity in adult ADHD.

Methods: We obtained high-density event-related potentials (ERPs) during a Go/Nogo task from 33 adult ADHD patients and 29 matched healthy controls using a 128-channel BioSemi recording-system. The stimulus-locked N200 served as a probe of response-preparation, while response-locked ERPs prior and following motor response (RPA and PRA, respectively) were used to examine response-preceding brain activity and subsequent adaptive processes.

Results: Compared to controls, patients with ADHD showed marked enhancement of the stimulus-locked N200 and the response-locked RPA and PRA components in the frontal areas. These changes in ADHD were associated with poor performance on the Stroop incongruency-task: the greater the enhancement, the higher the number of errors. Moreover, the ERP-enhancement showed association with the severity on core psychopathological measures of ADHD, including hyperactivity and impulsivity; and with a marker of inefficient response-preparation: heightened response-variability.

Conclusion: Patients with ADHD demonstrate marked neurophysiological alterations in response-preparation and response-preceding brain activity, suggestive of excessive activation of prefrontal neural circuits that underlie conflict-monitoring and response-preparation. Given the correlation with neuropsychological and psychopathological measures, these changes may constitute a key pathway leading to some of the core symptoms of ADHD, including premature and impaired response-preparation during stimulus-driven actions, and motor-hyperactivity.

Key words: ADHD, ERP, N200, response-preparation, response-locked

BACKGROUND

Attention Deficit Hyperactivity Disorder (ADHD) is a neurodevelopmental disorder, which occurs in 3-6% of children, and continues into adulthood at a prevalence of 1.5 to 5% (Simon *et al.* 2009). Individuals with ADHD suffer from difficulties caused by motor hyperactivity, impulsivity and lack of attention. Many researchers believe that these core symptoms of ADHD are due to dysfunction in executive functions, especially to deficits in cognitive control and response preparation. Neurodevelopmental theory posits that aberrations in early-developing bottom-up processes, such as stimulus-driven response preparation, play a critical role in the onset of ADHD, and remain stable over time despite symptom remission (Halperin and Schulz, 2006). Such aberrations may be manifested as premature or impulsive response style with being too quick to respond ('acting at the spur of the moment'); a failure to stop or postpone response or action (Botvinick *et al.* 2004); poor ability to plan; and problems with adaptive adjustments. Despite the fact that these problems have a profound impact on life functioning in ADHD, their neurobiological foundation remains poorly understood.

In this study, we investigated the neurophysiological basis of response preparation and response-preceding brain electrical activity as well as subsequent adaptive processes in adult ADHD using an ERP Go/Nogo paradigm. To this end, we examined response-locked ERPs prior and immediately subsequent to motor response. Moreover, we also investigated the stimulus-locked N200, since in cognitive control tasks it is closely linked to response preparation and conflict monitoring processes (Donkers and van Boxtel, 2004). Under Go/Nogo paradigms, N200 is detectable after both Go and Nogo stimuli (Donkers and van Boxtel, 2004). It is manifested as a negative-going wave that peaks around 200-300ms post-stimulus, and occurs prominently over anterior scalp sites (Donkers and van Boxtel, 2004; Folstein *et al.* 2008).

Previous ERP source localizations pinpointed the anterior cingulate cortex (ACC) as one of the candidate brain structures that serve as a source for both the N200 and the error-related brain activity, including error-related negativity (ERN) and positivity (POSe). Consistent with ACC localization, ERN appears with maximum amplitude in the anterior midline areas, while POSe has a more posterior midline scalp distribution (Bediou *et al.* 2012; Falkenstein *et al.* 2000). Additionally, converging evidence from fMRI literature identified ACC as a key brain structure for error processing and adaptive adjustments (van Veen and Carter, 2002). Based on fMRI evidence, it has been suggested that in addition to ACC, areas of the prefrontal cortex, especially the pre-supplementary motor area (pre-SMA) play a crucial role in cognitive control and adaptive processes. Partially overlapping regions of ACC may feature prominently both in the generation of N200 and ERN (Ullsperger and King, 2010).

Based on the above literature, our specific aim was twofold. *First*, we wanted to investigate response-preceding brain activity in patients with adult ADHD, as compared to healthy controls, using an ERP Go/Nogo paradigm. Specifically, using response-locked averaging, we examined ERP waveforms prior and subsequent to motor response. Since the stimulus-locked N200 has been considered closely linked to response preparation and conflict monitoring, the N200 was also investigated in this study.

Second, we wanted to examine whether alterations in response-preceding brain activity in ADHD are related to potentially important covariates including (a) core psychopathological symptoms, (b) neuropsychological measures of attention allocation and executive functions

(Botvinick *et al.* 2004), and (c) moment-to-moment fluctuations in response time in ADHD patients.

To delineate core psychopathological symptoms, we used the Hyperactivity, Impulsivity and Inattention factors from the Conners' Adult ADHD Rating Scale (CAARS) (Conners, 1999). For a standard measure of attention and executive functions, we adopted the Stroop color-word incongruency task (CWI) (Stroop, 1935) since ADHD patients have been shown to exhibit impaired performance on this task (Badzakova-Trajkov *et al.* 2009), and neural correlates of performance on this task have been examined in ADHD (Banich *et al.* 2009). Specifically, based on an fMRI study applying this task, Banich et al. reported neural dysregulation across several brain regions, including those involved in top-down attentional control, response selection, and inhibition. The dysregulation was most notable in the dorsolateral-prefrontal cortex (DLPFC) and in the medial prefrontal areas (Banich *et al.* 2000; Carter *et al.* 1998).

To index moment-to moment fluctuations, we adopted the Intrasubject Variability (ISV) in response time, which is considered to reflect the markedly inaccurate and inconsistent response style and motor hyperactivity during response preparation under stimulus-driven actions in ADHD(Tamm *et al.* 2012).ISV has been implicated as a marker of response control, (Suskauer *et al.* 2008). During motor task performance, increased ISV may reflect reduced efficiency of response preparation (Rubia *et al.* 2007). Large ISV has been reported in children and adults with ADHD across various tasks (Bellgrove *et al.* 2005; Castellanos *et al.* 2005; Castellanos and Tannock, 2002; Halperin and Schulz, 2006; Johnson *et al.* 2008). The consistency of these findings suggests that increased ISV may be a defining feature of the ADHD syndrome (Castellanos and Tannock, 2002; Klein *et al.* 2006; Suskauer *et al.* 2008). Neural correlates of large ISV have been investigated during a simplified Go/Nogo task in children in two fMRI studies. In the first study (Simmonds *et al.* 2007), large ISV in typically developing children was associated with an enhanced activation of prefrontal circuits, involving the superior and middle frontal gyri. In the second study, an abnormal pattern of activation was reported in children with ADHD, particularly in those with large ISV (Suskauer *et al.* 2008). While increased ISV has also been reported in adult ADHD subjects (Kuntsi and Klein, 2012), the neurobiological correlates of this finding in adults have not been examined.

METHODS

Study sample

Sixty two subjects participated in the study: 33 ADHD patients and 29 controls. Controls were individually matched to patients on age ($\pm$5 years), gender and level of education. Lack of history of psychiatric disease was required for the inclusion in the control group. The 90-item Symptom CheckList (SCL-90R) (Derogatis and Cleary, 1977) was used to select controls with no current psychiatric comorbidity. Patients were diagnosed according to the DSM-IV criteria. Diagnosis was confirmed via semi-structured interview by the treating physician. No neurological illness in prior history was allowed for subjects selected for the study. All ADHD patients included in this study represented the combined subtype.

Measures

The Conners' Adult ADHD Rating Scale (66-item version) was used to delineate ADHD symptom severity across core psychopathological domains of ADHD: Inattention, Hyperactivity, Impulsivity and Problems with Self-Concept (Conners, 1999; Erhardt *et al.* 1999). The Adult Self-Report Scale (ASRS) symptom Checklist (Adler *et al.* 2006) was used to delineate ADHD symptoms and to establish ADHD subtype. The Stroop CWI task (Stroop, 1935) was applied to characterize executive functions and conflict processing. The total score on the SCL-90R was used to describe the severity on general domains of psychopathology.

Stimuli and procedure

Participants were seated in a dimly lit room, approximately 100cm from the monitor. A central fixation was required throughout the stimulus session. Stimuli comprised capital letters, and each letter was presented at the central fixation point for 200ms. Subjects were asked to push a button as soon as possible upon the appearance of the letters; they were, however, asked to withhold response in case a letter was repeated twice (Nogo trials). A total of 256 stimuli were shown, with a ratio of 10% for the stimuli. The mean interstimulus time (1500msec) varied randomly, with a jitter of $\pm$10%.

EEG recording and pre-processing

EEG was acquired through a 128-channel active electrode system at a digitization rate of 1024Hz, with a band-pass of 0.5-70Hz using the BioSemi recording system with average reference. Data were stored and analyzed subsequently using the Electromagnetic Source Signal Imaging (EMSE) Suite as well as the Statistical Analysis System (SAS9.3) software. Epoch selection for the analyses was conducted manually as well as applying automatic artifact rejection criteria, including an absolute threshold of $\pm$90µV, and exclusion of eye-movement artifacts based on horizontal and vertical EOG. For stimulus- locked ERP, epochs of 900ms duration, including a 200ms pre-stimulus duration were investigated. For response-locked ERP, epochs of 550ms duration, including a 200ms pre-stimulus duration were investigated.

Statistical analyses

Based on the fMRI and ERP source localizations, the frontal brain areas, including the left, right and midline frontal regions served as the primary regions of interest. However, we also investigated central scalp regions (left, right, midline), since they encompass the primary motor areas whose activity is considered to be linked directly to the preparation of motor commands (Cunnington *et al.* 2005). Figure 1a displays the definition of the six regions of interest used for the statistical analyses.

The primary statistical analysis was based on the random regression hierarchical linear model (HLM). Amplitude (voltage) values for each of the pre-specified ERP components of interest were used as dependent variable in the HLM. Group, time (sampling point) and their interaction were used as independent variables; age and gender served as covariates. A separate analysis was performed for each component (N200, reponse -preceding activity [RPA], pos-response activity [PRA]) and for each brain region of interest (i.e., left, right,

midline, both frontal and central). The definition of component time windows were the following: N200=240-290ms after stimulus (Donkers and van Boxtel, 2004; Gavin *et al.* 2011); response-preceding activity (RPA)=-100-0ms prior motor response; and PRA=1-50ms post-response.

The Hochberg-procedure was applied for correction for multiple testing. In each scalp region, for each ERP component which reached significance after correction for multiple testing, we conducted additional analyses to examine whether psychopathological and neuropsychological covariates (i.e., the total score on CAARS Hyperactivity, Impulsivity and Inattention factors, and the number of errors on the Stroop color-word incongruency task) as well as ISV were tested as potential moderators in explaining the significant ERP alterations among patients with ADHD. Thus, the latter analyses were conducted for the ADHD group. In ancillary analyses we examined the potential effects of medication on our principal findings. The alpha level of 0.05 was adopted for statistical significance. The SAS 9.3 version was used for all inferential statistical analyses.

RESULTS

Demographics and basic descriptive characteristics

Basic demographic and clinical characteristics of the study population are provided in Table 1. As shown by the table, the two study groups were similar on basic demographic variables including gender, age and years of education. Approximately three-quarters of the sample consisted of males, with 33 years of age and 12.0 years of education. The ADHD group evidenced significantly higher severity of general psychopathology as measured by the SCL-90R scale. ADHD patients also displayed higher severity on specific symptom dimensions, including the CAARS factors of Inattention, Hyperactivity, Impulsivity and Problems with Self-Concept. In addition, with regard to errors on the Stroop color-word incongruency task, ADHD subjects showed significantly worse performance than healthy controls. All ADHD subjects represented the combined subtype. Twelve (36.4%) of the 33 patients were unmedicated in the ADHD sample. Eleven (33.3%) of the patients received methylphenidate, and 7 (21.2%) received an antidepressant. Three (3.0%) of the 33 patients was receiving methylphenidate and antidepressant concomitantly.

Group Comparisons: Task Performance

Both groups demonstrated a low proportion of omission and commission errors (<3%). In view of the high accuracy, group differences in error rates were not tested statistically. With regard to speed of responding, we compared the two groups in terms reaction time distributions during the Go condition using the median and the interquartile limits (i.e., 25% and 75% percentile points). We found significant group difference with a faster reaction time (RT) (Johnson *et al.* 2007) among ADHD subjects. Specifically, the median RT in the control and ADHD group, respectively, was 459.5ms (interquartile limits: 25%=432.8 and 75%=484.9ms) and 433.1ms (interquartile limits: 25%=388.6 and 75%=477.4ms). Quantile regression indicated that the difference was significant in terms of the median RT (Wald-test statistics=4.46, df=1, p=0.035) and the lower quartile (Wald test statistics=7.27, df=1, p=0.007). Besides faster RTs, larger Intra-individual RT variability was observed in the

ADHD group (median Intra-individual SD=140.1ms) than in the controls (median Intra-individual SD=132.3ms); the difference reached significance (F=6.9, df=1.58, p=0.01).

Stimulus- and response-locked ERPs: Group Comparisons

N200

As shown in Table 2 (1st row), HLM analyses revealed significant group differences in all frontal areas including left, right and midline, whereas no statistically significant difference was found in the central areas. After Hochberg correction for multiple testing, the difference remained significant in the frontal areas. As indicated by the group averages in the Table, the N200 in all frontal areas was larger in the ADHD than in the control group. A visual display of the group differences in ERP waveforms is provided in Figure 1b.

Response-preceding activity

As shown by Table 2 (2nd row), significant group difference was detectable across all frontal areas, while there was no difference in the central areas. Group differences in the frontal areas remained significant after Hochberg adjustment. The group averages in Table 2 show that RPA was significantly larger in the frontal region in the ADHD than in the control group. To illustrate the group differences in response-preceding ERP waveforms, response-locked average ERPs are displayed in the frontal and central areas (Figure 1c). As the figure shows, a slow-going negative wave developed in the frontal areas starting from approximately 200ms prior to the motor response; it reached maximal amplitude after the execution of the response. RPA had a similar waveform in both groups; its amplitude, however, was substantially larger among subjects with ADHD (Figure 1c).

Post-response activity

Similar to the RPA, in the frontal region significant or marginally significant (left frontal region) group difference was detectable, with no difference in the central areas (Table 2, 3rd row). The differences remained significant for the right and the midline frontal areas after adjusting for multiple comparisons. The post-response ERP activity had significantly larger negative amplitude in the frontal areas in the ADHD group as compared to controls (3rd row, Table 2; and Figure 1c).

Moderators of altered stimulus and response-locked ERP components in the ADHD group

N200

We examined whether core psychopathological symptoms of ADHD (including hyperactivity, impulsivity and inattention), as well as errors on the Stroop CWI task, and Intra-individual RT variability were related to the ERP alterations found in the ADHD group. Table 3 displays statistical test results for each covariate. For each brain region, nominal levels of significance (p-value columns) which retained significance after Hochberg adjustment are marked with an asterisk. Results indicate that the number of errors on the Stroop CWI task was significantly related to the N200 amplitude in the left frontal region.

To examine the direction of the association, we computed the Least-Squares Means (LS-Means) of the N200 amplitude for high and low values of the covariate (Stroop CWI errors), defined as upper and lower interquartile limits (i.e., 75% and 25%), respectively. As shown by Table 3 (top, N200), poor performance on the Stroop task was associated with higher N200 amplitude as compared to good performance (i.e., no errors). Consistent with the results of inferential statistical analyses displayed in Table 3, empirical ERP averages in patients with high number of errors showed a substantially larger N200 than in patients with low number of errors (Figure 2a).

Significant associations were also found between the CAARS Inattention factor and the amplitude of N200 in all frontal areas. Investigation of the direction of the relationship showed that higher severity on this factor was associated with lower N200 amplitude.

With regard to the Intra-individual variability of RTs, a significant relationship was found for the left frontal region: higher variability was associated with greater N200.

Response-preceding activity

RPA was associated with the number of errors on the Stroop CWI task, and with the severity on the CAARS Hyperactivity and Inattention factors (Table 3 middle, RPA). After adjustment for multiple comparisons, the association with Hyperactivity was detectable in all frontal regions while the association with Impulsivity remained significant only in the left frontal area. Investigation of the direction of the relationship indicated larger RPA amplitude among those ADHD subjects who had worse performance on the Stroop task or higher severity on Hyperactivity as compared to subjects who had better Stroop performance or lower severity on Hyperactivity. To illustrate the latter association based on the observed data, ERP averages for patients with high and low severity on the Hyperactivity factor, respectively are displayed in Figure 2b. RPA also showed a highly significant association with Intra-individual variability in all frontal regions. Higher variability was associated with larger RPA amplitude as compared with smaller variability.

Post-response activity

Performance on the Stroop task and severity on the CAARS Hyperactivity and Impulsivity factors were associated with PRA across all frontal regions (Table 3 bottom, PRA). Specifically, higher number of errors and greater symptom severity were associated with larger PRA. Additionally, an association between the Inattention factor and the PRA in the midline frontal area was found, indicating that increasingly more severe Inattention scores were associated with an increasingly diminished PRA. Intra-individual RT variability showed no association with PRA in any of the frontal regions.

Subsidiary analyses

In subsidiary analyses, we investigated whether the patients' medication status impacted our principal findings. To this end, we included the dichotomous variable medication status as an additional covariate in the analyses described above. Specifically, in these analyses we included the set of patients who were either unmedicated (medication status=0, n=14, 42.4%) or received psychoactive medication (medication status=1, n=19, 57.6%). Medication status

did not obtain significance in the analyses, while those covariates that were significant in the main analyses retained their significance. We also investigated whether treatment with stimulant medication influenced the findings. For this purpose, we created a dichotomous variable to index whether a patient received any stimulant medication (stimulant absent/present = 0/1), and replaced medication status with the latter covariate for subsidiary analyses. Once again, results indicated that this covariate did not modify the principal findings.

DISCUSSION

The principal finding of this study is the marked enhancement of ERP amplitudes in ADHD patients compared to controls both in terms of the N200 and response-locked ERP components such as the RPA and the PRA. Besides the enhancement of the stimulus-locked N200 and response-locked RPA and PRA, we found that the ERP changes in the ADHD group were related to the performance on a standard measure of attentional allocation and executive functions, i.e., the errors on the Stroop CWI task. The extent of ERP amplitude enhancement increased with the number of errors on the Stroop task. Moreover, it showed positive correlation with the severity on two core psychopathological dimensions in ADHD, hyperactivity and impulsivity, and a negative correlation with inattention.

Moreover, our findings indicate that the ERP enhancement in the ADHD group was region-specific, restricted primarily to the frontal areas. In addition, we observed a greater pre-movement build-up of the negative wave prior to the onset of motor response in the ADHD than in the control group, albeit both groups displayed a pronounced RPA. It was manifested as a steady increase in amplitude up until the execution of motor response, and a gradual return to the baseline afterwards.

To the best of our knowledge such ERP changes during response preparation have not been reported in patients with ADHD. This may be due to the fact that previous studies of response preparation in ADHD focused predominantly on anticipatory preparation, using the contingent negative variation (CNV) paradigm, which entails preparation for "signaled movement and the simultaneous anticipatory attention" for an imperative stimulus (Brunia and van Boxtel, 2001). This approach yielded inconsistent results, with both enhancement (Spronk *et al.* 2008) and decrease in the CNV amplitude in subjects with ADHD (Albrecht *et al.* 2013; Banaschewski and Brandeis, 2007) . One of the most recent, methodologically sound studies (Tye *et al.* 2013), which controlled for comorbidity with autism spectrum disorders, reported a lack of significant abnormality in the CNV in "ADHD-only participants".

Our results of the enhancement of the response-locked RPA component, and its relationship with hyperactivity are consistent with the results of an fMRI study (Silk *et al.* 2005) of adolescent ADHD subjects with combined subtype, which reported increased activation under task conditions in the posterior cingulate and medium superior pre-frontal areas. Additionally, it is noteworthy that the area of increased activation in the medial superior frontal region corresponds to the area that has a larger structural extent in the ADHD combined subtype, correlating with levels of hyperactivity (Sowell *et al.* 2003).

With regard to psychiatric diagnoses other than ADHD, greater-than-normal activation of both prefrontal anterior cingulate cortex (pACC) and medial cingulate cortex (MCC) have

been reported in individuals with generalized anxiety disorders during tasks involving aversive stimuli (McClure *et al.* 2007; Nitschke *et al.* 2009). Furthermore, in patients with obsessive-compulsive disorder, the ACC has been found to be hyperactive at rest, during symptom provocation, and after commission of errors in cognitive tasks. The excessive activation was interpreted as a key mechanism that could underlie the hyperactive action-monitoring function in these diagnostic groups under tasks with conflict conditions involving errors (Maltby *et al.* 2005; Ursu *et al.* 2003).

Likewise, since the N200 is considered to reflect conflict monitoring and response preparation during a Go/Nogo paradigm, an enhanced N200 may be interpreted as a manifestation of heightened conflict monitoring in ADHD. With regard to RPA, it is noteworthy that electrophysiological studies revealed that movement-preceding periods are accompanied by a negative voltage deflection, the readiness potential (RP) (Kornhuber and Deecke, 1965). In scalp-recorded EEG, RP is typically detectable in frontal and central brain areas prior to the initiation of voluntary movements. EEG source localization and neuroimaging studies linking RP to specific brain regions showed that such movement-preceding periods engage both the pre-SMA and the posterior medial frontal cortex (Rushworth *et al.* 2004).

The readiness potential and the activation of the pre-SMA and the midline frontal areas in fMRI are thought to be a manifestation of a neural signal that co-occurs with movement preparation. They may also reflect the activity of other brain regions that are recruited to prepare and implement movements (Simmonds *et al.* 2007). With regard to the temporal sequence of neural activations, Ullsperger et al. (Ullsperger *et al.* 2014) suggested that the flow of information, accompanying response selection and preparation, would proceed from pre-SMA to ACC, and that partially overlapping regions in ACC may underlie the generation of N200 and the ERN. Our finding that the ERP changes in the ADHD group were region-specific, and manifested predominantly in frontal areas, are consistent with this suggestion.

Since RP has been observed not only before self-initiated movements but also prior to responses to external stimuli, or in cued-response tasks in ERP studies (Cunnington *et al.* 2002), it is conceivable that the negative-going voltage deflection preceding the onset of motor-response (i.e., RPA) that we found is a manifestation of RP. Indeed, similar to the ERP findings, in an event-related fMRI study, Cunnington et al. found (Cunnington *et al.* 2002) considerable overlap in activation patterns during movement preparation for self-initiated and externally-triggered movements. Preparation for both types of movements were associated with strong activation in medial motor areas including the pre-SMA, SMA proper, and rostral CC, as well as activation within the contralateral primary motor, superior parietal, and insular cortex (Cunnington *et al.* 2006). Based on recent ERP evidence, Hughes et al.(Hughes *et al.* 2013) also questioned the view that a clear-cut distinction exists between voluntary and stimulus-driven action systems. They concluded that the initial preparation for movements involves only one system, which serves as a common central preparatory mechanism in voluntary and stimulus-driven actions.

While the exact neural mechanism of response preparation remains unclear, it is noteworthy that single-cell electrophysiology studies indicate that a gradual build-up of neuronal activity starts before the initiation of movements, similar to the gradual build-up of the RP. In view of this, Schurger et al proposed that the "neural decision to execute a movement" is associated with "a threshold crossing of an accumulator of neural activity underlying the response decision" (Schurger *et al.* 2012). Given the faster build-up and the larger RPA in the ADHD group, under this model a threshold-crossing could occur earlier among patients with ADHD.

This, in turn, would lead to increased reactivity and faster responding including faster encoding and/or motor preparation/execution times which was reported in children with ADHD (Salum *et al.* 2014). Nonetheless, although these features are commonly viewed as part of the clinical symptom presentation in ADHD, further studies are needed to investigate their connection with the enhancement of the response-preceding ERP activity at the neural level.

In line with previous literature (Tamm *et al.* 2012; Tye *et al.* 2013), we found increased ISV in the response times in ADHD subjects. The increased ISV was related to RPA and N200: higher ISV was associated with greater negative deflection, i.e., with greater enhancement of the response-preceding ERP and N200 waveforms vs. controls. The finding that patients with ADHD evidence increased ISV has been viewed as an inefficiency of response preparation (Rubia *et al.* 2007). Enhancement of the ERP amplitude with higher ISV is consistent with fMRI findings, which indicated that higher ISV in typically developing children was associated with an enhanced activation of the prefrontal circuits, including the superior and middle frontal gyri.

Previous ERP studies focusing on cognitive control in ADHD examined retrospective adjustments after an erroneous response (van Meel *et al.* 2007). They highlighted deficits in utilizing feedback information to change behavior, as revealed by a lack of post-error slowing at the behavioral level (Balogh and Czobor, 2010), and reductions in post-error ERP components including ERN and POSe at the electrophysiological level (Rosch and Hawk, Jr., 2013).The current investigation complements prior studies as it concentrated on response preparation, using RPN and N200 as a probe for proactive control. Such a control is implemented before response, and subsumed in the process of selecting the action set (Hikosaka and Isoda, 2010; Ullsperger and King, 2010).Together, prior reports and our findings of N200 and movement-related ERP alterations, and the relationship of these alterations with impulsivity and hyperactivity, suggest that these alterations may underlie the non-reflective pattern of responding and the deficiency of self-regulation associated with ADHD.

LIMITATIONS

Limitations of this study include the fact that the probability of the NoGo stimuli was low. Given the small number of NoGo trials, we could not study NoGo responses and commission errors. However, in line with a previous fMRI investigation (Suskauer *et al.* 2008), the use of the simple Go/Nogo paradigm with a high probability of Go stimuli made it possible to investigate habitual responses and stimulus-response associations, and to focus on the Go condition. This has often been neglected in previous literature. Further limitation is that our sample included only ADHD patients with the combined subtype. It is worth noting, however, that this subtype represents the most common form of the disorder, which may increase the clinical relevance of the findings.

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CONFLICT OF INTEREST
"None"

ETHICAL STANDARDS

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

FIGURE LEGENDS

Figure 1. Group Differences in Stimulus-locked (Figure 1a, upper panel) and Response-locked ERPs Prior and Following Motor Response.

Figure 1a. Group difference of N200 in stimulus-locked ERPs.
Grand mean of stimulus-locked average ERPs for the ADHD (in red, dashed line) and control groups (in blue, solid line). Time window of interest for N200 (240-290ms post-stimulus) is shown as a shaded area. Scalp regions of interest: left, right, midline, both frontal and central. Random Regression Hierarchical Linear Model (HLM) analysis applying group, time and interaction as independent variables, with age and gender as covariates were conducted. Results indicated a significant enhancement of the N200 in frontal areas in the ADHD group as compared to controls after Hochberg correction for multiple testing.

Figure 1b. Group difference in response-locked ERPs .
Grand mean of response-locked average ERPs for the ADHD (in red, dashed line) and control groups (in blue, solid line). Time windows of interest, shown as subsequent shaded areas, were -100-0ms prior motor response for response-preceding activity (RPA) and 1-50ms after motor response for post-response activity (PRA). Scalp regions of interest: left, right, midline, both frontal and central. HLM analyses with Hochberg correction analogous to those described above revealed a significant enhancement of the response-preceding and post-response ERPs in frontal areas in the ADHD group as compared to controls.

Figure 2. Moderators of altered stimulus and response-locked ERP components in the ADHD group.
Figure 2a. Difference of N200 in patients who displayed high vs, low number of errors on the Stroop color-word incongruency task (CWI).

Grand mean of stimulus-locked average ERPs for patients with low (in blue, solid line) and high number of errors (in red, dashed line) are shown, respectively. Patients who committed more than 1 error were classified in the "high error" group (n=19); those who made only 1 or no mistake were classified in the "low error" group (n=12). (For 2 patients the CWI scores were missing).

Time window of interest for N200 (240-290ms post-stimulus) are shaded. HLM analyses with Hochberg correction revealed a significant enhancement of N200 in patients with high vs. low number of errors.

Figure 2b. Difference in response-locked ERPs in patients who displayed high vs. low severity on the CAARS Hyperactivity factor.

Grand mean of response-locked average ERPs for patients with low (in blue, solid line) and high severity on the CAARS Hyperactivity factor (in red, dashed line) are shown. Patients who scored below the mid-point (score=18) of the theoretical range of the Hyperactivity factor (range: 0-36) were classified in the "low hyperactivity" group (n=16); those whose score reached or exceeded the midpoint (≥18) were classified in the "high hyperactivity" group (n=17). Time windows of interest, displayed as subsequent shaded areas, were -100-0ms prior motor response for response-preceding activity (RPA) and 1-50ms after motor response for post-response activity (PRA). HLM analyses with Hochberg correction revealed significant enhancement of the response-preceding and post-response ERPs in patients with low as compared with high score of Hyperactivity.

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Figure(s)
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Figure 1a. Definition of Regions of Interest

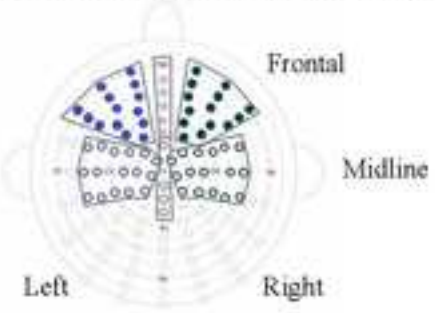

Figure 1b: Stimulus-locked ERPs in ADHD and Control Group

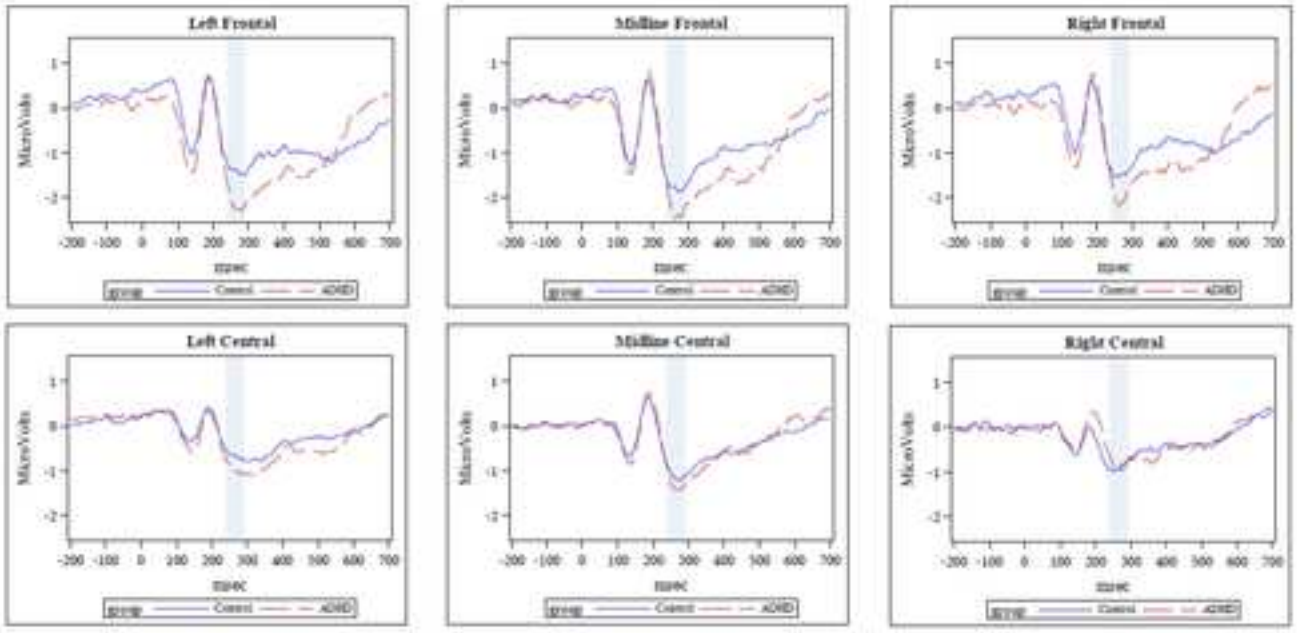

Figure 1c: Response-locked ERPs in ADHD and Control Group

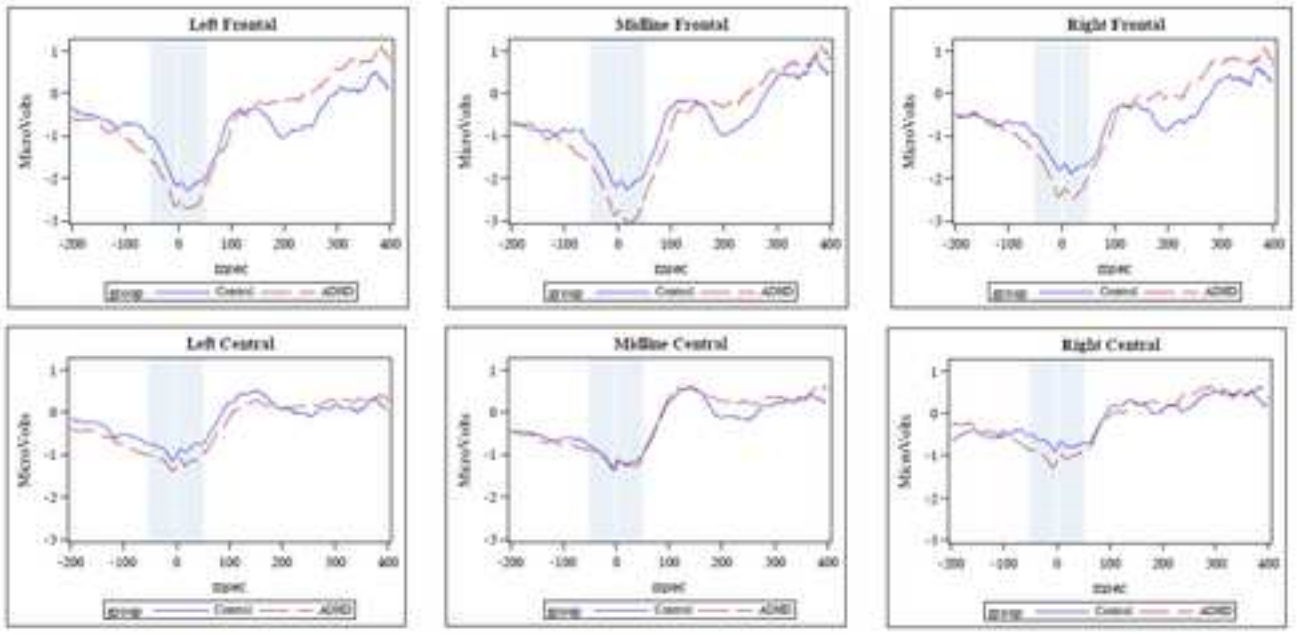

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Figure 2a: Stimulus-locked ERPs vs. Number of Errors in Stroop Color-Word Incongruency Task

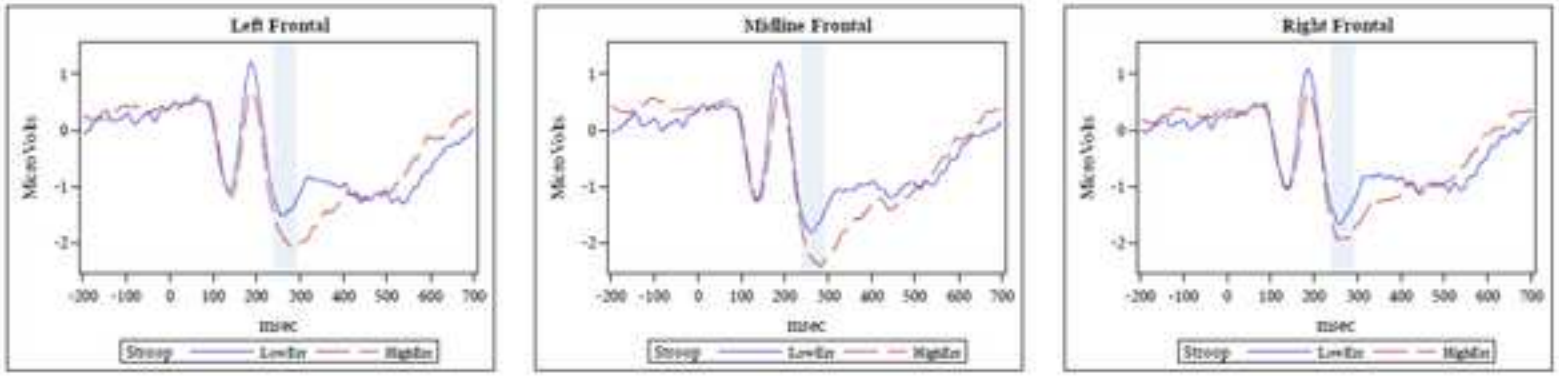
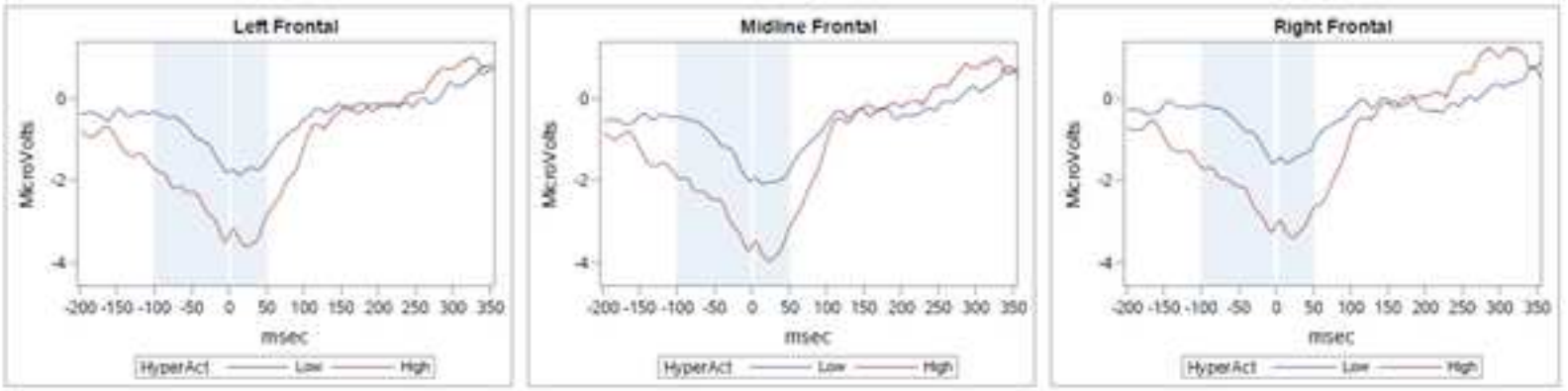


Figure 2b: Response-locked ERPs vs. Level of Hyperactivity as Measured by CAARS



Table(s)
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Table 1. Basic Demographic and Clinical Characteristics of the Study Sample[a]

Characteristics	**Control(N=29)**	**ADHD(N=33)**		
Categorical variables N (%)			Chi^2	p
Demographic				
Male, No. (%)	21 (72.4)	25 (75.8)		
Continuous variables: Mean (SD)			**F**	**p**
Mean age at randomization, y	32.9 (12.8)	31.64 (12.1)	0.14	.7074
Years of education	15.4 (2.1)	15.1 (2.7)		
CAARS[b]				
Hyperactive	10.9 (5.6)	19.9 (7.1)	27.75	.0001
Impulsivity	8.3 (4.7)	18.4 (7.0)	38.93	.0001
Inattention	8.0 (5.9)	24.3 (6.4)	99.41	.0001
Problems with Self Concept	4.08 (3.8)	10.6 (5.0)	29.82	.0001
Stroop Task				
Stroop_CWI[c]	0.8 (1.0)	1.7 (2.2)	4.27	.0434
SCL-90R[d]				
SCL- GSI	20.9 (22.5)	79.8 (64.8)	21.40	.0001
Mean reaction time	465.5 (52.1)	445.0 (96.2)	1.04	.3114
SD reaction time[e]	132.3 (34.2)	140.07 (61.7)	0.36	.5504

Notes:
[a]: Chi-square test for categorical, ANOVA for continuous variables
[b]: CAARS= Conners Adult ADHD Rating Scales (CAARS); four subscale scores of CAARS are shown below
[c]: Number of Errors on Stroop Color-Word Incongruency (Stroop_CWI) task
[d]: SCL-90R= The Symptom Checklist-90R; General Symptom Severity on SCL-90R (SCL-GSI)
[e]: Mean (SD) Intra-individual variability (SD) of reaction time

Table(s)
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Table 2. Group Differences in Stimulus-locked and Response-locked ERPs Prior and Following Motor Response[a]

Brain region[c]	F_L			F_R			F_s			C_L			C_R			C_S		
	cont[d]	adhd[d]	diff,Fp	cont[d]	adhd[d]	diff,Fp	cont[d]	adhd[d]	diff,Fp	cont[d]	adhd[d]	diff,Fp	cont[d]	adh[d]	diff,Fp	cont[d]	adhd[d]	diff,Fp
Stim. N200[b]	-1.4(0.2)	-2.1 (0.1)	11.88 .001*	-1.5(0.2)	-2.0(0.2)	4.99 .029*	-1.8(0.2)	-2.3(0.2)	5.27 .025*	-0.7(0.2)	-1.0(0.2)	1.2 .027	-0.9(0.2)	-0.9(0.2)	0.0 .874	-1.1(0.2)	-1.3(0.2)	0.4 .552
Resp. RPA[b]	-1.2 (0.1)	-1.6(0.1)	8.64 .0047*	-1.4(0.1)	-1.8(0.1)	8.90 .0042*	-1.11(0.1)	-1.45(0.1)	5.61 .021*	-0.78(0.2)	-1.0(0.2)	1.5 .220	-0.58(0.2)	-0.84(0.2)	1.5 .230	-0.86(0.2)	-0.94(0.2)	0.1 .740
Resp. PRA[b]	-2.2 (0.2)	-2.6(0.2)	2.93 .093	-1.8(0.2)	-2.3(0.2)	5.68 .020*	-2.1(0.2)	-2.8(0.2)	9.9 .003*	-0.8(0.2)	-1.4(0.2)	1.6 .212	-0.8(0.2)	-1.0(0.2)	0.7 .394	-1.2(0.2)	-1.2(0.2)	0.0 .087

Notes:

[a]: Random Regression Hierarchical Linear Model analysis with group, time and interaction as independent variables, with age and gender as covariates. Values marked with an asterisk remain significant after Hochberg correction for multiple testing.

[b]: Stimulus- (Stim.) and Response-locked (Resp.) Component time windows: N200= 240-290ms post-stimulus; response-preceding activity (RPA)=-100-0ms prior motor response; and PRA= 1-50ms after motor response.

[c]: Scalp regions: left (L), right (R), midline (S), both frontal (F) and central (S).

[d]: Least-squares mean estimates (SE) of ERP amplitudes for a given study group adjusted for age and gender.

Table(s)
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Table 3. Moderators of altered stimulus and response-locked ERP components in the ADHD group[a]

component	covar[b]	[c]F_L			[c]F_R			[c]F_S		
		Low[e]	High[e]	diff-F,p	Low	High	diff-F,p	Low	High	diff-F,p
Stim.-locked N200[d]	Stroop	-1.8(0.2)	-2.8(0.3)	8.03 .007*	-2.0(0.2)	-2.2(0.3)	0.40 .533	-2.1(0.2)	-2.8(0.3)	3.4 .075
	HYPE	-2.1(0.4)	-2.1(0.2)	0.02 .883	-1.6(0.4)	-1.9(0.2)	1.20 .282	-2.0(0.4)	-2.2(0.2)	0.7 .418
	IMP	-2.6(0.4)	-2.2(0.2)	1.25 .272	-2.8(0.4)	-2.1(0.2)	3.88 .058	-2.7(0.4)	-2.4(0.2)	0.9 .349
	INAT	-3.7(0.6)	-2.7(0.3)	8.25 .008*	-3.5(0.6)	-2.6(0.3)	6.94 .013*	-3.8(0.6)	-2.9(0.3)	7.4 .011*
	C.V.	-1.7(0.2)	-2.5(0.2)	9.00 .006*	-1.7(0.2)	-2.2(0.2)	4.4 .045	-2.0(0.2)	-2.0(0.2)	3.5 .070
Resp.-locked RPA[d]	Stroop	-1.2(0.2)	-2.5(0.3)	28.1 .0001*	-1.2(0.2)	-2.0 (0.2)	9.1 .0055*	-1.4(0.1)	-2.7(0.2)	50.6 .0001*
	HYPE	-0.3(0.3)	-1.3(0.1)	26.5 .0001*	0.0(0.3)	-1.2(0.1)	29.8 .0001*	-0.4(0.3)	-1.5(0.1)	26.7 .0001*
	IMP	-0.9(0.3)	-1.5(0.1)	8.03 .008*	-0.9(0.3)	-1.4(0.1)	4.64 .040*	-1.2(0.3)	-1.7(0.1)	4.42 .044*
	INAT	-1.5(0.4)	-1.6(0.2)	0.13 .72	-1.0(0.4)	-1.3(0.2)	1.44 .241	-1.8(0.4)	-1.8(0.2)	0.0 .99
	C.V.	-1.1(0.1)	-2.2(0.1)	28.4 .0001*	-1.1(0.1)	-1.8(0.1)	13.4 .001*	-1.3(0.1)	-2.3(0.1)	27.9 .0001*
Resp.-locked PRA[d]	Stroop	-2.1(0.2)	-3.7(0.3)	16.08 .0004*	-1.9(0.2)	-3.2(0.3)	9.45 .005*	-2.4(0.2)	-4.0(0.3)	17.5 .0003*
	HYPE	-1.5(0.5)	-2.3(0.2)	5.64 .024*	-1.0(0.2)	-2.0(0.2)	8.52 .007*	-1.6(0.5)	-2.5(0.2)	8.1 .008*
	IMP	-1.3(0.5)	-2.3(0.2)	7.24 .012*	-1.0(0.5)	-2.1(0.2)	7.66 .010*	-1.5(0.5)	-2.6(0.2)	8.9 .006*
	INAT	-3.6(0.7)	-2.9(0.3)	2.88 .100	-3.2(0.7)	-2.6(0.3)	1.82 .188	-4.2(0.7)	-3.4(0.3)	4.6 .040*
	C.V.	-2.2(0.2)	-2.8(0.2)	4.0 .056	-2.1(0.2)	-2.4(0.2)	1.1 .302	-2.5(0.2)	-3.2(0.2)	5.2 .030

Notes:

[a]:Random Regression Hierarchical Linear Model analysis including potential moderators of interest (covariates, listed below in[b]), and adjusted for age and gender used as additional covariates. Values marked with an asterisk remain significant after Hochberg correction for multiple testing.

[b]: Moderators (covariates) in the analyses included the following measures:

- Number of Errors on Stroop Color-Word Incongruency (Stroop CWI) task
- Scores on factors on the Conners Adult ADHD Rating Scales (CAARS), including Hyperactivity (HYPE), Impulsivity (IMP) and Inattention (INAT)
- Mean Intra-individual variability as measured by the Coefficient of Variation (C.V.) of reaction time

[c]: Scalp regions: left, right and midline frontal (F_L, F_R, F_S).

[d]: Component time windows: N200= 240-290ms post-stimulus; response-preceding activity (RPA)=-100-0ms prior motor response; and PRA= 1-50ms after motor response.

[e]: Least-squares mean estimates (SE) of ERP amplitudes for low and high values for a given covariate, defined as upper and lower interquartile limits of the distribution (75% and 25%, respectively)

Title:

Electrophysiological Indices of Aberrant Error-Processing in Adults with ADHD: A New Region of Interest.

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ABSTRACT

Background: Deficits in error-processing are implicated in core symptoms of ADHD, but the neurobiological basis of these deficits remains poorly understood.

Aims: To investigate the neurobiological basis of abnormal error-processing and adaptive adjustments in ADHD, and examine whether error-related alterations extend beyond traditional ROI-regions, particularly to those involved in adaptive adjustments, such as the salience network.

Method: We obtained event-related potentials(ERPs) during a Go/NoGo task from 22 adult-ADHD patients and 29 matched healthy controls using a high-density 256-electrode array. Error-related ERPs with the error-negativity(ERN) and error-positivity(Pe) served as probes of error-processing.

Results: In ADHD patients the error-related activity in the ERN and Pe time-windows was significantly reduced, and the reduction was associated with core psychopathological symptoms. The ERP-attenuation was prominent not only at traditional ROI-electrodes but across many other brain areas, with a distinctive subset of group-differences and symptom-correlations manifested at temporo-parietal sites, with a right-lateralization.

Conclusions: The neural patterns of impairments may be the result of altered interactions between a dorsal midline error-processing brain network involved in “error-processing proper” and a right lateralized temporo-parietal salience network, which is involved in the evaluation of significance of the error-signals, and has not been identified before.

Key words: ADHD, error-processing, ERN, Pe, response-locked ERP

Running title: Electrophysiology of Error-Processing in Adults with ADHD

INTRODUCTION

Deficits in error-processing and adaptive adjustments have been implicated in core symptoms of Attention Deficit Hyperactivity Disorder (ADHD), but the neurobiological basis of these deficits is poorly understood. Response-locked event-related potentials (ERPs) elicited by erroneous responses, and in particular the error-related negativity and positivity (ERN and Pe), are considered as principal biomarkers of error-processing. The ERN is a negative ERP-deflection with predominantly fronto-central scalp distribution[1], and reflects an initial automatic brain response after an error[1]. It typically emerges between 0 and 180 ms after an incorrect response – a commission error. ERN is followed by a positive wave, the Pe. There is evidence that Pe is related to the conscious recognition and motivational significance of the error [2-4]. Typically, the Pe is diminished for subjectively unaware errors[2], and may represent a context specific P3 - a component associated with attentional orienting to stimuli of motivational importance[5]. Dipole modeling has localized ERN sources to the caudal ACC, while Pe has been localized to more rostral ACC[1;6-8].

To date, error-processing in adult ADHD, as indexed by the ERN and Pe, has received limited attention. Most individual studies remained inconclusive, with only 2 of 7 studies yielding a significant finding[9]. Nonetheless, a recent meta-analysis[9] revealed a significant reduction of both ERN and Pe; and highlighted that each individual study showed the effect in terms of statistical effect-size. Evidence therefore supports the hypothesis that patients with ADHD receive malfunctioning error signals, leading them to repeat their erroneous behaviors. Nonetheless, two key limitations must be kept in mind regarding these data. *First*, former studies investigated a limited set of specific scalp regions of interest (ROIs) (typically the Fz, Cz and Pz channels). However, this research strategy ignores evidence indicating that the brain's error-processing network is highly functionally coupled with other widespread neural networks. Since erroneous outcomes represent salient events[10-12], a recently described network, the Salience Network (SN) system is of particular importance. It encompasses several major cortical areas including the dorsal anterior cingulate cortex(dACC), the left and anterior right insula, along with the adjacent inferior frontal gyri; and the temporo-parietal cortices, including the temporo-parietal junction (TPJ) in a right-lateralized fashion[12]. Emerging evidence indicates that errors are associated with robust SN activation [13;14], signaling the need for behavioral adaptation[15]. *Second*, previous studies did not recognize that deficits in error-processing may have a differential association with core clinical symptoms.

We aimed to investigate the neurobiological underpinnings of the deficits in error-processing and adaptive adjustments in ADHD with a twofold objective. First, we wanted to examine whether patients with ADHD differ from healthy controls in electrophysiological indices of error-processing, including the ERN and Pe. We exploited information from a high-density, 256-electrode sensor-array, investigating whether differences are observable beyond the traditional ROIs, particularly to those that are expected to be involved in adaptive adjustments, such as the SN system. Second, we also wanted to investigate whether alterations in post-error brain activity in ADHD are related to core psychopathology of ADHD. We expected that uncovering associations could provide important insights into why patients with ADHD are unable to detect or utilize error-related information.

METHODS

Study sample

Fifty one subjects participated in the study: 22 ADHD patients and 29 controls. Controls were individually matched to patients on age (±5years), gender and level of education. No history of psychiatric disease was required for controls. The 90-item Symptom CheckList (SCL-90R)[16] was used to select controls with no current psychiatric comorbidity. Patients were diagnosed using the DSM-IV criteria. Diagnosis was confirmed via semi-structured interview by the treating physician. No neurological illness in prior history was allowed for subjects for the study. All ADHD patients included in the study represented the combined subtype. Written consent was required from all participants according to a protocol approved by the institutional review board and compliant with the Declaration of Helsinki.

Measures

The Conners' Adult ADHD Rating Scale (66-item version) was used to delineate ADHD symptom severity across core psychopathological domains of ADHD: Inattention, Hyperactivity, Impulsivity and Problems with Self-Concept [17;18]. The Adult Self-Report Scale (ASRS) symptom Checklist [19] was administered to describe ADHD symptoms and to establish ADHD subtype. The total score on the SCL-90R was used to describe the severity on general domains of psychopathology.

Stimuli and procedure

Participants were seated in a dimly lit room, approximately 100cm from the monitor. A central fixation was required throughout the stimulus session. The International Affective Picture System (IAPS), a set of images with neutral, positive, and negative valences, were used as stimuli, and presented in random sequence with a probability of 0.45, 0.275, and 0.275, respectively. The stimuli were presented centrally every 1400ms for 800ms at an inter-stimulus-interval of 600ms. The emotional valence of the images was incidental to task performance. On the Go/NoGo Task, subjects had to respond quickly to Go stimuli, while withholding responses to the second presentation of any stimulus repeated twice in a row (NoGo stimuli). The probability of Go and NoGo trials was 0.85 and 0.15, respectively. A total of 478 stimuli were presented in two separate blocks.

EEG recording and pre-processing

EEG data were recorded using a high-density 256-channel BioSemi ActiveTwo amplifier. Two periocular electrodes were placed below the left and above the right external canthi for electrooculogram. Data were digitized at 24-bit resolution and a sampling rate of 512Hz. Built-in and self-developed functions and the freeware EEGLAB toolbox [20] in the Matlab (MathWorks, Natick, MA) development environment were used for off-line data analyses.

Continuous EEG data were visually inspected and the sections containing non-stereotype artifacts that would affect the quality of the ICA (Independent Component Analysis) decomposition were removed[21]. EEG was re-referenced to the common average potential and filtered off-line between 0.1 and 75 Hz using zero-phase shiftforward and reverse IIR Butterworth-filter. The signal was filtered using the 48-52Hz Parks-McClellan stop-band Notch filter in ERPLAB[22]. The average waveform — the ERP— was computed as follows. Data were segmented into 600ms epochs starting from 200ms preceding the response. Segments were baseline corrected over a 200ms pre-response window and averaged to obtain the ERP waveforms for each subject for each condition. To omit artifacts, we performed ICA decomposition (*CUDAICA;[23]*) individually on the epoched data. Artifact-related

components identified automatically by ADJUST[21] were removed. The ERPs for statistical analysis were reconstructed without these components. Epochs containing stimulus event(s) were automatically excluded from further analysis. Subject ERPs were averaged to compute the grand-average ERP for visualization purposes.

Statistical analyses

Because the neurobiological basis of abnormal error-processing in ADHD patients constituted the principal interest, we wanted to compare the study groups in terms of response-locked ERP changes during the NoGo error-responses relative to the correct Go-responses. Hence, the primary measure was the difference-waveform, which was computed as the difference between the response-locked average of the NoGo error-responses (commission errors) minus the response-locked average of the correct Go-responses. Due to the low number of error-responses in each of the emotion-categories, error-responses could not be broken down by emotional valence; they were pooled together in the investigation both in terms of behavioral and electrophysiological data.

Based on prior literature, the definition of component time-windows for the error-related ERP components were the following: ERN=20-180ms after the motor-response; Pe =200-400ms post-motor response [24;25]. Since the majority of prior studies selected minima and maxima within the component time-window of interest [9], we adopted this approach and used these values as statistical endpoints in the study. Specifically, based on the scalp distribution of difference-waveforms, for ERN we selected minima (largest negative value) for those channels where the average waveform within the time-window of interest had a negative value. Conversely, we selected the maxima (largest positive voltages) if the difference-waveform had positive value. An analogous procedure was used for the analyses of Pe.

Because the brain's error-processing network is highly functionally coupled with several other widespread neural circuits which underlie adaptive adjustments, we examined all five scalp regions including the frontal, central, temporal, parietal and occipital regions, broken down by laterality (left, right, midline) and by relative distance from the midline (lateral, medial).

Thus, a total of 20 regions were investigated: 6 frontal(left lateral/medial; right lateral/medial, midline frontopolar/frontal); 3 central(central left/midline/right), 2 temporal(left/right); 6 parietal (parietal left lateral/medial; right lateral/medial, midline centro-parietal/parieto-occipital), and 3 occipital regions(occipital left/midline/right). Figure 1 displays the definition of scalp regions used for the analyses.

The statistical analysis was based on the random-regression hierarchical linear modeling (HLM). Amplitude values for each of the pre-specified response-locked ERP components of interest were used as dependent variable in the HLM. Group, time and their interaction were used as independent variables; age and gender served as covariates. A separate analysis was performed for ERN and Pe, and for each of the above-described brain regions.

The Hochberg-procedure was applied for correction for multiple testing. In each scalp region, for each response-locked ERP component which reached significance after correction for multiple testing, we conducted additional analyses to examine whether psychopathological symptoms (total score on CAARS Hyperactivity, Impulsivity and Inattention factors) played a role in explaining the

significant ERP alterations among patients with ADHD. In ancillary analyses we examined the potential effects of medication on the principal findings. In exploratory analyses, we investigated the scalp distribution of the ERP waveforms in more detail. For these analyses, conducted for the full-set of the 256 channels, the False Discovery Rate(FDR)-corrected p-values[26] were computed. The alpha-level of 0.05 (adjusted for multiple comparisons) was adopted for statistical significance. The SAS9.4 version was used for inferential statistical analyses.

RESULTS

Demographics and basic descriptive characteristics

Basic demographic and descriptive characteristics of the study population are displayed in Table 1. Psychiatric symptoms are presented for the ADHD group. There were no significant between group differences on basic demographic variables including gender, age and years of education. The mean age of the sample was approximately 31years, with 15.7 and 14.5 years of education in the control and ADHD group, respectively; the sample showed a preponderance of males in both groups. The ADHD group evidenced significantly higher severity on specific symptom dimensions of the disorder, including the CAARS factors of Inattention, Hyperactivity, Impulsivity and Problems with Self-Concept. All ADHD subjects represented the combined subtype. Sixteen (72.7%) of the 22 patients were medicated in the ADHD sample. Fifteen (93.8%) of the 16 patients received methylphenidate; 1 patient (6.2%) was receiving an antidepressant alone. Four (26.7%) of the 15 patients who received methylphenidate also received another medication concomitantly.

Task Performance on behavioral parameters in the two groups: accuracy and reaction times.

Both groups demonstrated a low proportion of omission errors (<2%). Table 1 presents the results for the Go/NoGo behavioral parameters which include the percentage of hits (correctly responding to a Go stimulus) and false alarms (incorrectly responding to NoGo stimuli, i.e., commission errors), and the reaction times and the post-error slowing after the false alarms. Overall, patients made more errors whether of omission or commission than the healthy controls; and responded more quickly with less post-error slowing. Nonetheless, in this limited sample the group difference obtained statistical significance only in the percentage of commission errors; patients in the ADHD group made a substantially higher proportion of false alarms than healthy controls.

Error-related ERP activity in the two groups

Figure 2 (left side) presents response-locked ERPs in four scalp regions of interest typically investigated in studies of error-related ERP activity. Time-windows of interest for the two error-related ERP components, ERN and Pe are indicated as shaded areas. Panel A shows the response-locked ERPs separately for both groups for the NoGo condition (commission error-responses) and the Go condition (correct responses). The difference in the response-locked ERPs between the error and correct responses is also provided. As described in the Methods, this difference-waveform constituted the primary focus of the analyses. Panels B and C display for both groups the topographical-maps of the ERN and Pe responses derived based on the full-set of the 256 channels for the two conditions (NoGo, Go); and for their difference (NoGo-Go). Please note that the scalp maps were generated on the basis of the average amplitudes in the respective time-windows for the component of interest (ERN,Pe).

The maps of the respective error-related components show a distinct topographical distribution in the ERN time-window: a marked negative deflection in the fronto-central regions particularly at midline (i.e., error-negativity at typical ROI sites), and positive deflections in the difference waves in temporo-parietal and (to a lesser extent) central regions, especially on the right side. Thus, error-related ERP activity shows an enhancement of negativity in the fronto-central regions while an enhancement of positivity is present in the temporal and parietal regions, with a preponderance on the right side.

For the Pe time-window, the opposite is true: there is an enhancement of positivity in relation to commission errors in the midline fronto-central regions in a right lateralized fashion, and an enhancement of the *negativity* in the temporo-parietal and posterior frontal areas, restricted to the right-side. Although the topographical maps showed similar scalp distribution in both groups, both error-related components had a marked attenuation in the ADHD group compared to the control.

ERN

As shown in Table 2, there was a significant group difference at the midline frontal primary region of interest area, i.e., including and surrounding the Fz and FCz electrodes. The group differences were also significant in several other brain areas, and kept significance after Hochberg correction. Specifically, the differences were significant in the left anterior (frontal) areas. In more posterior areas, the difference reached significance for the right central, temporal as well as the parietal areas. The difference was marginally significant in the posterior parietal, occipital midline, and left parietal areas.

Apart from the probability of Type I error for each comparison, the table provides Least-Squares Mean (LSMean) estimates of ERP amplitudes for both groups along with the estimated LSMean group difference (ADHD–Control) adjusted for age and gender. As shown by the LSMean difference, in the ADHD group a significantly diminished negative voltage (i.e., ERN) is observable in scalp regions that are considered the most salient areas for ERN. In brain areas that exhibit a positive amplitude during ERN, a significantly diminished positivity is observable in the ADHD group.

Thus, albeit the error-related ERP components were enhanced in both groups, the enhancement in the ADHD group was significantly attenuated, in a topographically specific manner. To provide an overall view of the topographical distribution, Figure 3 (left panel) displays the scalp map of the group differences for the ERN time-window. The topographical map of raw amplitude values is juxtaposed with the FDR-corrected map of Type I error probabilities (right panel) for highlighting the most salient features of the distribution, including the aforementioned anterior-posterior and lateralized pattern.

Pe

Table 3 displays group differences for all scalp areas in the Pe time-window. The difference reached the nominal level of significance in several brain regions. However, after Hochberg adjustment it remained significant only at the following regions: right dorsolateral and midline frontal; central midline and right central; and the midline posterior parietal area. LSMean estimates indicate that the error-related ERP amplitude was greatly diminished in the ADHD group vs. controls. For a more detailed illustration of topographical specificity, Figure 4 (left panel) displays over the entire scalp distribution of the group differences in Pe amplitude, as well as the associated FDR-corrected values of Type I error probability (right panel).

Altered error-related ERP activity in the ADHD group:
Relationship with core psychopathological symptoms

ERN

We examined whether amplitude changes in the ERN time-window in the ADHD group were related to the severity of core psychopathological symptoms. HLM analyses indicated a differential association for the two groups in the right temporal (interaction $F=5.6;df=1,42;p=0.02$) and parietal (lateral) regions (interaction $F=5.0;df=1,42;p=0.03$). Specifically, while there was no significant association among controls ($p>0.1$ for both areas), the severity of hyperactivity was related to the amplitude changes in the right temporal ($F=6.5;df=1,15;p=0.02$) and lateral parietal areas in the ADHD group ($F=30.4;df=1,15;p<0.001$): the higher the severity, the greater the reduction of the error-related enhancement of the response-locked ERP amplitude. To illustrate the association, we computed LSMeans for the ERP amplitude for high and low values of hyperactivity. Low and high values were defined as 12 and 24 points, which respectively represent a value 1 point below or above the midpoint of the theoretical range of the item scores for each of 12 the constituting items of the subscale. Figure 5 displays the LSMean values for both groups in the right temporal region, together with the topographical map of the Pearson-correlations between the amplitude changes and symptom severity across the entire scalp.
Apart from the above associations, we found a relationship in the right parietal (lateral) region: higher severity of inattention was related to a greater reduction of the error-related ERP enhancement in the ADHD ($F=92.6;df=1,15;p<0.001$) but not in the control group ($F=2.7;df=1,25;p=0.11$).

Pe

The analyses described here were conducted for those scalp areas where a significant group difference was detectable for the Pe time-window. We found that the CAARS impulsivity factor was related to the ERP changes in the middle frontal region ($F=4.7;df=1,15;p=0.048$); higher severity was associated with a greater attenuation of the error-related enhancement of the ERP amplitude (i.e., with a lesser negativity in this region; Figure 2). For controls, the relationship did not obtain statistical significance ($F=1.3;df=1,25;p=0.18$). Furthermore, in the posterior parietal midline area an attenuation of the error-related ERP enhancement was associated with inattention in the ADHD group ($F=5.5;df=1,15;p=0.03$) while no such association was found in the control ($F=0.3;df=1,25;p=0.58$).

Subsidiary analyses

In subsidiary analyses, we investigated whether the patients' medication status impacted our principal findings. To this end, in the analyses described above we included as an additional covariate the dichotomous variable medication status (unmedicated n=[27.3%]; and medicated n=16 of 22 [72.7%]). Medication status did not obtain significance in the analyses, while covariates that were significant in the main analyses retained their significance. It is important to note, however, that the small sample size provided insufficient statistical power for these analyses. Nonetheless, our results indicated that unmedicated and medicated patients with ADHD were essentially identical in terms of the attenuation of the error-related activity that were shown by our findings.

DISCUSSION

Our first goal was to evaluate impairments in error-processing in individuals with ADHD. Error-processing plays an important role in the regulation of behavior; healthy individuals, even in the absence of explicit feedback, demonstrate characteristic reactions following an error and spontaneously adjust their response [4;27]. These behaviors suggest the activity of a performance monitoring system, which evaluates actions and allows adaptive adjustments in executive control mechanisms to lessen the likelihood of repeating an error [28].

Patients with ADHD differed from controls on most behavioral and ERP parameters. At the behavioral level, the patient group made significantly more commission errors than the controls, a finding which is consistent with the finding of poor response inhibition in ADHD [29;30]. ADHD patients also differed markedly from controls in the neural patterns elicited by the erroneous responses. In controls, the ERN and the Pe were both prominent at the traditional ROI electrode sites, and across many other brain areas. In the ADHD group, this error-related activity was greatly reduced both in the ERN and the Pe time-windows. The diminutions of error-related ERP amplitudes point to impairments in the neural circuit which underlies adaptive responding in ADHD patients.

These findings are consistent with those reported in a meta-analysis of previous electrophysiological studies of adult ADHD[9]. Besides, they are also in line with other complementary evidence of abnormal error monitoring in ADHD, in particular with reduced post-error slowing, a compensatory mechanism to improve performance on an error-following trial[31]. Since the evaluation of ongoing behavior and its consequences is necessary to determine whether current behavior adjustment strategies should be maintained, abnormal response monitoring and deficient adaptive correction may contribute to the high error-rates that are associated with ADHD on certain neuropsychological tasks.

A unique feature of the response-locked ERP approach is that it allows us to follow the different temporal stages of the error-processing with a high time resolution. The fact that we found a marked reduction in the error-related ERPs at two successive temporal stages (i.e., both in the ERN and Pe windows) in patients with ADHD suggests that there is an overall lack of reactive adaptation when they encounter errors. They show failures at the neurophysiological level both in the detection of errors and the integration of error signals properly. In other words, the impairment that patients with ADHD manifest at the early, more automatic levels of error-processing extends also to problems at a later “aware” state, as indexed by the reduction of both the ERN and Pe amplitudes, respectively.

While previous studies of error-processing in adult ADHD examined the traditional ROI electrode sites for ERN and Pe, we extended our inquiry to further scalp regions since emerging data indicate that the error-processing brain circuit is closely linked with other neural circuits underlying adaptive adjustments, especially with the SN network. The marked differences we found, particularly those at the temporo-parietal sites, with a right-lateralization, are consistent with the involvement of the SN network system; are in line with fMRI studies indicating a strong coactivation of the SN with the error-processing system. Overall, the SN system responds to behaviorally salient events, and is considered essential for the initiation of cognitive control[32], the maintenance and implementation of task sets[33;34], and the coordination of behavioral responses[35]. Output from the error-processing system may trigger a cascade of adaptive adjustments through the SN system.

Our second goal was to investigate whether alterations in post-error brain activity in ADHD are related to core psychopathological symptoms. We found that the reduction of the error-related activity was associated with the severity on these symptoms. The extent of ERP attenuation increased, in a topographically specific manner, with the severity of psychopathology as measured by the respective CAARS factors. Specifically, during the ERN time-window, an association with hyperactivity and inattention were present in the right temporo-parietal areas. The association in terms of Pe activity indicated that, within the ADHD group specifically, those who are more impulsive show more prominent electrophysiological changes in the mid-frontal region when they commit errors.

Limitations of this study include the fact that the probability of the NoGo stimuli was low. Given the small number of NoGo trials, we could not break down the NoGo error-responses according to the three basic types of emotions. Further studies should investigate whether the results vary as a function of emotional valence. An additional limitation is that more than two-thirds of the patients were medicated in the current study. Nonetheless, it is important to note that our results indicated that unmedicated and medicated patients with ADHD were essentially identical in terms of the attenuation of the error-related activity that were shown by our findings. Finally, our sample included only ADHD patients with the combined subtype. This subtype, however, represents the most common form of the disorder, which may increase the clinical relevance of the findings.

Together, these neurobiological alterations – which may underlie reduced detection, reduced awareness and deficient evaluation of salience of error signals - form a non-reflective, "error-blind" pattern of responding that results in a hyperactive and impulsive style, including premature responding rather than slowing down and reflecting. These deficits may underlie an inability to utilize feedback information, with a failure in self-regulation and disinhibited behavior associated with ADHD.

In sum, these findings allow us to see how basic deficiencies in error-processing are manifested at the neurophysiological level in ADHD, and provide a greater understanding of the neurobiological basis of the core symptoms of the disorder. The neural patterns may be the result of altered interactions between a dorsal midline error-processing brain network involved in "error-processing proper" and a right lateralized temporo-parietal salience network, which is involved in the evaluation of significance of the error-signals, and has not been identified before.

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CONFLICT OF INTEREST

None.

ETHICAL STANDARDS

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

FIGURE LEGENDS

Figure 1. Definition of the scalp regions used for the statistical analyses based on the 256-channel sensor system. The scalp regions included 6 frontal (left lateral/medial; right lateral/medial, midline frontopolar/frontal); 3 central (left/midline/right), 2 temporal (left/right); 6 parietal regions (left lateral/medial; right lateral/medial, midline centro-parietal/parieto-occipital), and 3 occipital regions (left/midline/right).

Figure 2. Response-locked ERP-s in four scalp regions of interest typically used in studies of error-related ERP activity. Time-windows for the two error-related ERP components, ERP and Pe are shaded. Panel A shows the response-locked ERPs separately for both groups for the NoGo condition (comission error-responses) and the Go condition (correct responses). The difference between the error (false alarms) and correct responses (actual signal detection) is also shown. Panels B and C display for both groups the topographical-maps of the ERN and Pe responses based on the full set of the 256 individual channels for the two conditions (NoGo, Go); and for their difference (NoGo - Go). The scalp maps were generated on the basis of the average voltage values in the respective time-windows for the component of interest (ERN and ERP).

Figure 3. Left panel: scalp map of the ADHD vs. Control group difference of raw amplitude (uV) values for the error-related negativity measure. Right panel: FDR-corrected map of Type I error probabilities.

Figure 4. Left panel: scalp map of the ADHD vs. Control group difference of raw amplitude (uV) values for the error-related positivity (Pe) measure. Right panel: FDR-corrected map of Type I error probabilities.

Figure 5. Left: LSMeans of Pe amplitude values in the right temporal region for high and low values of hyperactivity. Low and high values were defined as 12 and 24 points, which respectively represent a value 1 point below or above the middle of the theoretical range of the item scores for each of the constituting items (12) of the subscale. Right: topographical map of the Pearson-correlations

between the amplitude changes and symptom severity across the entire scalp. HLM analyses indicated a significant association between the severity of hyperactivity and the attenuation of Pe in the right temporal region in the ADHD but not in the Control group (interaction F=5.6, df=1,42, p=0.02).

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Table 1. Basic Demographic and Clinical Characteristics of the Study Sample[a]

Characteristics	**Control(N=29)**	**ADHD(N=22)**		
Categorical variables N (%)			Chi^2	p
Demographic				
Male, No. (%)	19 (65.5)	17 (77.3)	0.83	0.36
Continuous variables: Mean (SD)			**F**	**p**
Mean age, y	30.1 (9.0)	30.6 (9.7)	0.03	.8635
Years of education	15.7 (2.6)	14.5 (2.1)	2.79	.1012
CAARS[b]				
Inattention	9.2 (4.8)	25.4 (5.8)	110.8	.0001
Hyperactivity	10.8 (6.0)	20.3 (9.2)	18.45	.0001
Impulsivity	8.2 (4.2)	20.4 (5.6)	73.59	.0001
Problems with Self Concept	5.3 (3.6)	12.0 (5.4)	26.26	.0001
Behavioral measures				
omission errors (%)	0.3 % (0.4)	1.0 (2.3)	2.27	.1400
commission errors (%)	14.9%(7.0)	39.1%(22.5)	27.19	.0001
Reaction time (msec)	435.9 (63.5)	411.2 (95.6)	1.04	.3114
Post-error slowing (msec)	67.9 (14.9)	48.3 (14.8)	2.10	.1555

Notes:
[a]: Chi-square test for categorical, ANOVA for continuous variables
[b]: CAARS= Conners Adult ADHD Rating Scales (CAARS); four subscale scores of CAARS are shown above

Table 2. ADHD vs. Control: Group Differences[a] in Error-related Negativity (ERN)[b] in Each Brain Area.

Brain region[c]	Laterality	Position	ERN				
			Control[d]	ADHD[d]	Diff	F	p
Frontal	**Midline**	**Frontopolar**	4.2 (0.5)	3.1(0.6)	1.1(.0.7)	2.37	.1303
	Midline	**Frontal**	-5.4 (0.5)	-2.8(0.6)	-2.7(.0.7)	14.08	.0005*
	Left	**Lateral**	-2.1 (0.2)	-1.2(0.2)	-0.8(.0.2)	12.52	.0009*
	Left	**Medial**	-4.6 (0.4)	-3.0(0.4)	-1.7(.0.4)	14.69	.0004*
	Right	**Lateral**	3.0 (0.3)	3.2(0.4)	-0.2(.0.3)	0.77	.3848
	Right	**Medial**	-3.6 (0.4)	-3.2(0.4)	-3.2(.0.4)	1.09	.3015
Central	**Midline**	**Medial**	-3.2 (0.3)	-3.2(0.3)	-0.04(.0.3)	0.03	.8749
	Left	**Medial**	-3.4 (0.2)	-3.1(0.3)	-0.2(.0.2)	1.20	.2795
	Right	**Medial**	-1.1(0.2)	-1.7(0.2)	0.6(.0.1)	28.97	.0001*
Temporal	**Left**	**Lateral**	-1.3 (0.3)	-1.3(0.3)	-0.01(.0.4)	0.00	.9684
	Right	**Lateral**	4.6 (0.3)	2.6(0.3)	1.9(.0.4)	22.34	.0001*
Parietal	**Midline**	**Anterior**	- 2.2 (0.3)	-1.5(0.3)	0.6(.0.4)	2.59	.1100
	Midline	**Posterior**	3.5 (0.3)	2.3(0.4)	1.2(.0.5)	7.51	.0086
	Left	**Lateral**	4.3 (0.4)	3.6(0.4)	0.9(.0.5)	2.42	.1262
	Left	**Medial**	2.3 (0.2)	1.7(0.2)	0.6(.0.2)	8.05	.0067
	Right	**Lateral**	5.1 (0.4)	3.6(0.4)	1.6(.0.5)	10.78	.0019*
	Right	**Medial**	4.2 (0.3)	2.6(0.3)	1.5(.0.3)	26.36	.0001*
Occipital	**Midline**	**Medial**	5.0 (0.5)	3.0(0.5)	2.0(.0.7)	8.14	.0064
	Left	**Left**	5.3 (0.5)	3.6(0.6)	1.6(.0.7)	4.95	.0310
	Right	**Right**	5.1 (0.5)	3.8(0.5)	1.4(.0.6)	4.81	.0332

Notes:

[a]: Random Regression Hierarchical Linear Model analysis with group, time and interaction as independent variables, with age and gender as covariates. Values marked with an asterisk remain significant after Hochberg correction for multiple testing.

[b]: Component time window for ERN = 20-180 ms post-response.

[c]: See Figure 1 for a graphical illustration for the definition of scalp areas.

[d]: Least-squares mean estimates(SE) of response-locked ERP amplitudes (NoGo – Go) for a given study group with the ERN time-window, adjusted for age and gender.

Table 3. ADHD vs. Control: Group Differences[a] in Error-related Positivity (Pe)[b] in Each Brain Area.

Brain[c] region	Laterality	Position	Pe				
			Control[d]	ADHD[d]	Diff	F	p
Frontal	**Midline**	**Frontopolar**	-5.6(0.4)	-3.7(0.4)	-1.9(0.6)	11.12	.0017*
	Midline	**Frontal**	-1.8(0.3)	-2.3(0.4)	0.5(0.5)	1.09	.3018
	Left	**Lateral**	-4.9(0.3)	-3.9(0.3)	-0.7(0.3)	5.16	.0277
	Left	**Medial**	-1.7(0.3)	-2.1(0.3)	0.5(0.2)	4.07	.0494
	Right	**Lateral**	-5.5(0.3)	-2.9(0.3)	-2.6(0.4)	14.69	.0004*
	Right	**Medial**	-1.6(0.2)	-1.5(0.2)	-0.01(0.2)	0.00	.9641
Central	**Midline**	**Medial**	3.3(0.3)	2.3(0.3)	1.0(0.3)	9.03	.0043
	Left	**Medial**	0.5(0.1)	0.4(0.1)	0.1(.0.1)	0.23	.6353
	Right	**Medial**	2.2(0.2)	1.9(0.2)	0.4(.0.1)	16.15	.0002*
Temporal	**Left**	**Lateral**	-3.7(0.3)	-3.4(0.3)	-0.3(.0.4)	0.76	.3875
	Right	**Lateral**	-2.2(0.2)	-1.8(0.3)	-0.5(.0.3)	2.97	.0915
Parietal	**Midline**	**Anterior**	3.3(0.3)	2.3(0.3)	1.0(.0.4)	6.18	.0165
	Midline	**Posterior**	3.8(0.3)	2.6(0.3)	1.2(.0.4)	11.65	.0013*
	Left	**Lateral**	2.3(0.3)	2.3(0.3)	0.02(.0.3)	0.01	.9173
	Left	**Medial**	3.1(0.2)	2.6(0.2)	0.5(.0.2)	4.53	.0386
	Right	**Lateral**	3.8(0.3)	2.8(0.4)	1.0(.0.4)	5.79	.0201
	Right	**Medial**	3.7(0.3)	2.7(0.4)	1.0(0.5)	4.37	.0042
Occipital	**Midline**	**Medial**	3.6(0.3)	3.0(0.4)	0.6(0.4)	1.81	.1849
	Left	**Left**	1.6(0.3)	1.7(0.3)	-0.2(.0.4)	0.20	.6546
	Right	**Right**	3.7(0.3)	2.8(0.4)	0.9(0.5)	3.30	.0076

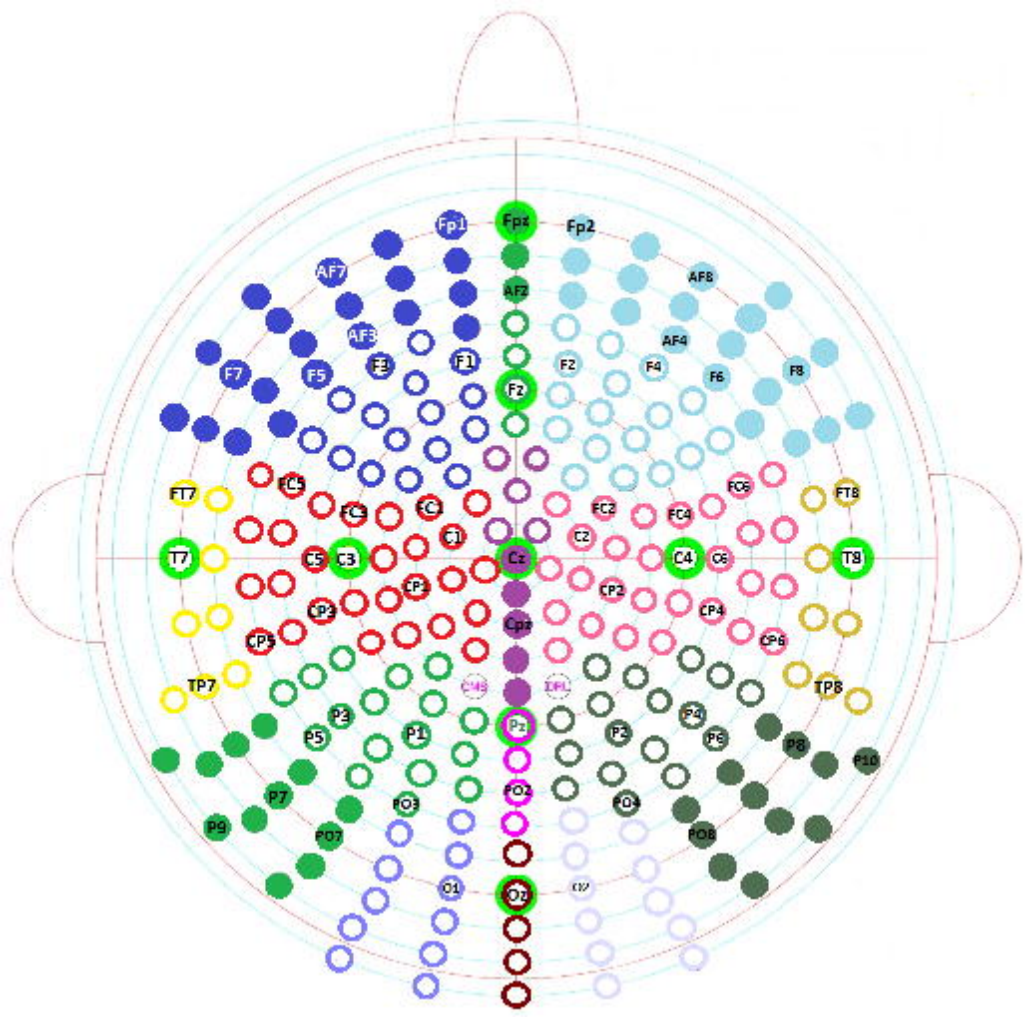
Notes:

[a]: Random Regression Hierarchical Linear Model analysis with group, time and interaction as independent variables, with age and gender as covariates. Values marked with an asterisk remain significant after Hochberg correction for multiple testing.

[b]: Component time window for Pe = 200-400 ms post-response.

[c]: See Figure 1 for a graphical illustration for the definition of scalp areas.

[d]: Least-squares mean estimates(SE) of response-locked ERP amplitudes (NoGo – Go) for a given study group with the Pe time-window, adjusted for age and gender.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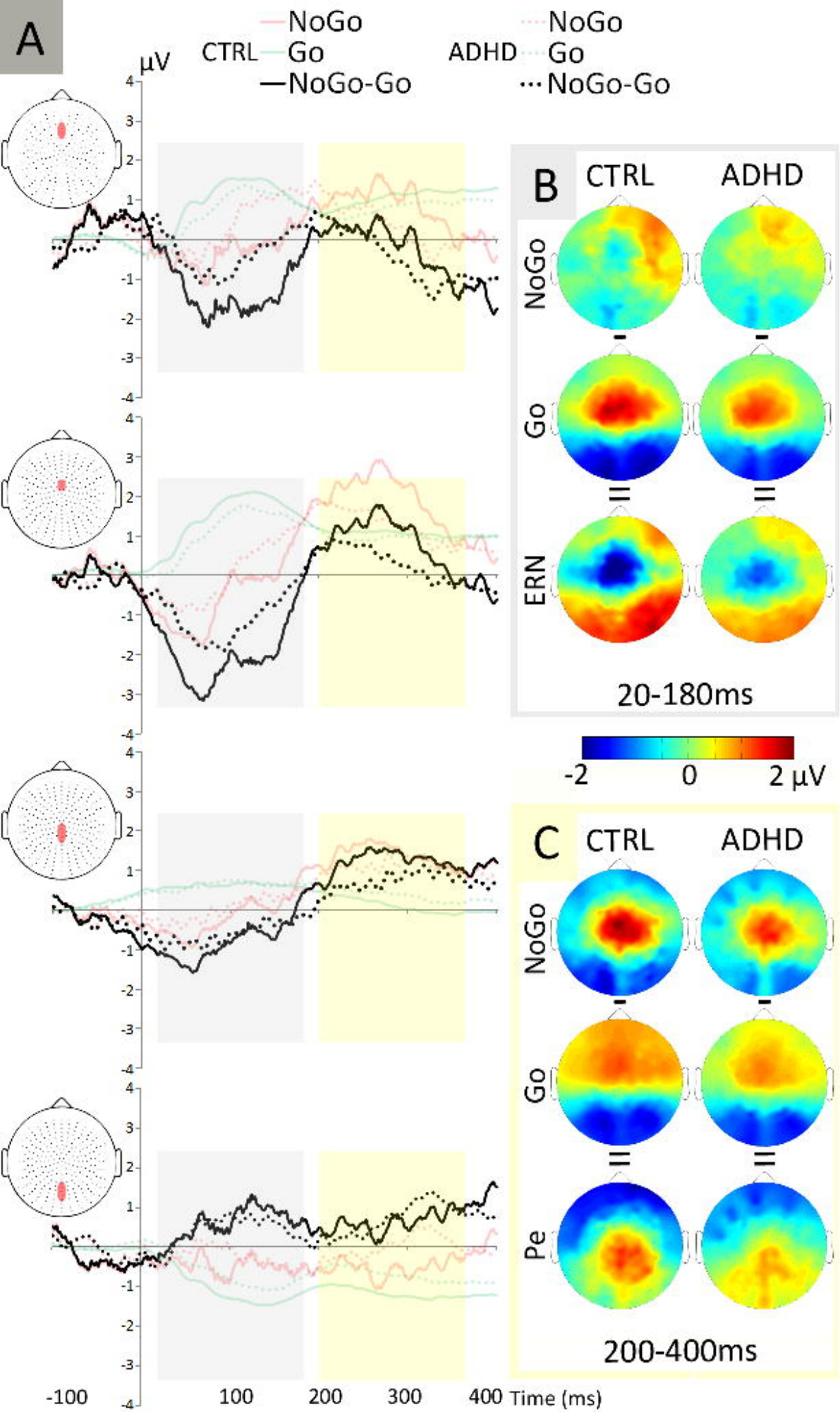
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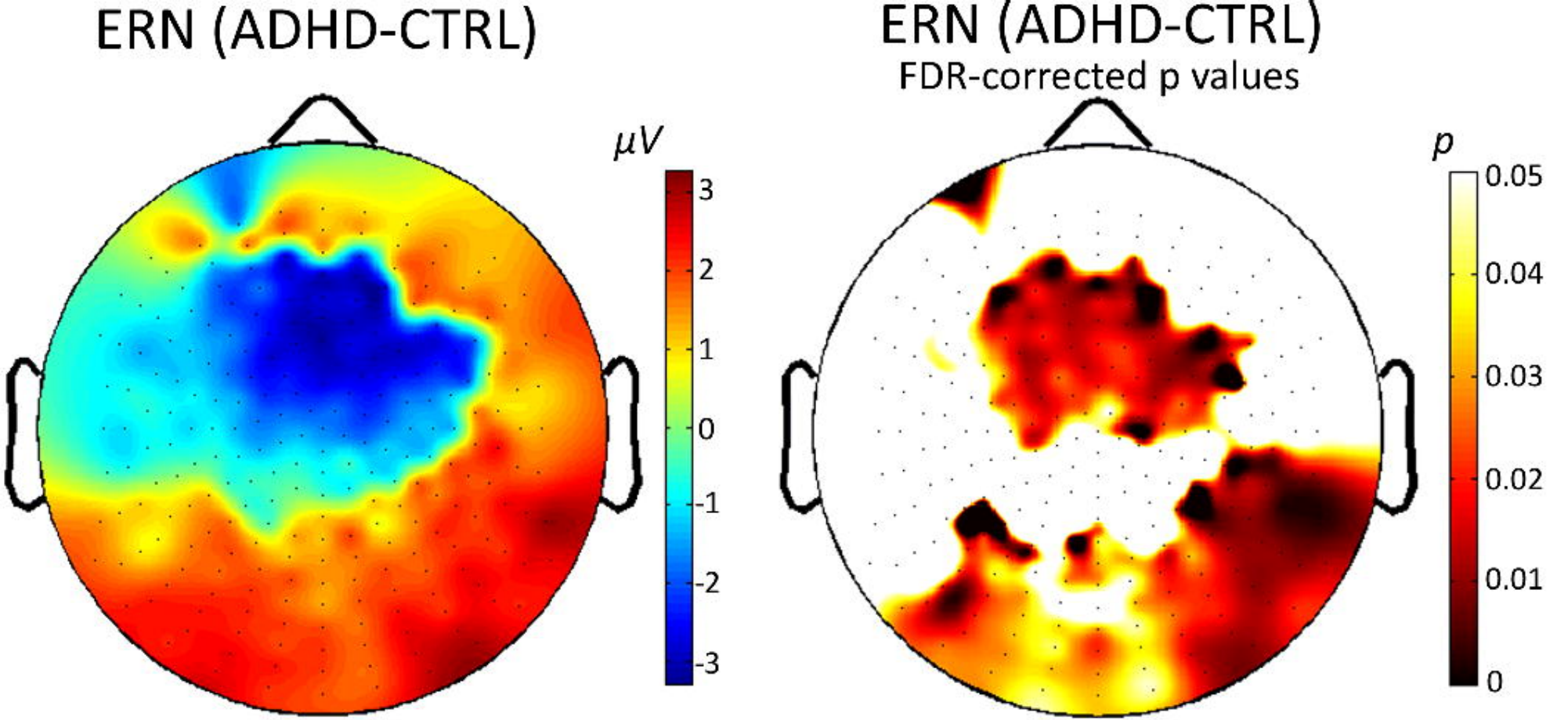
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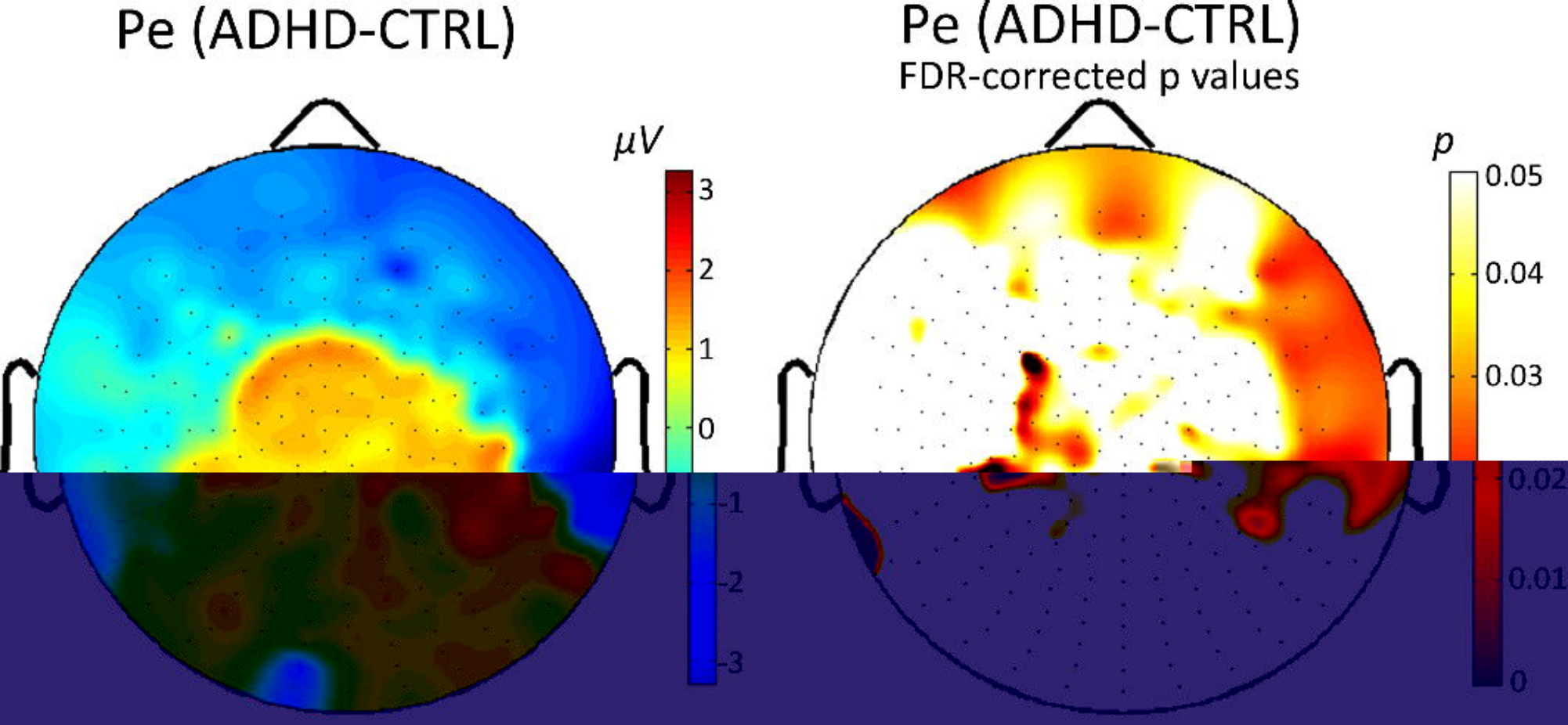
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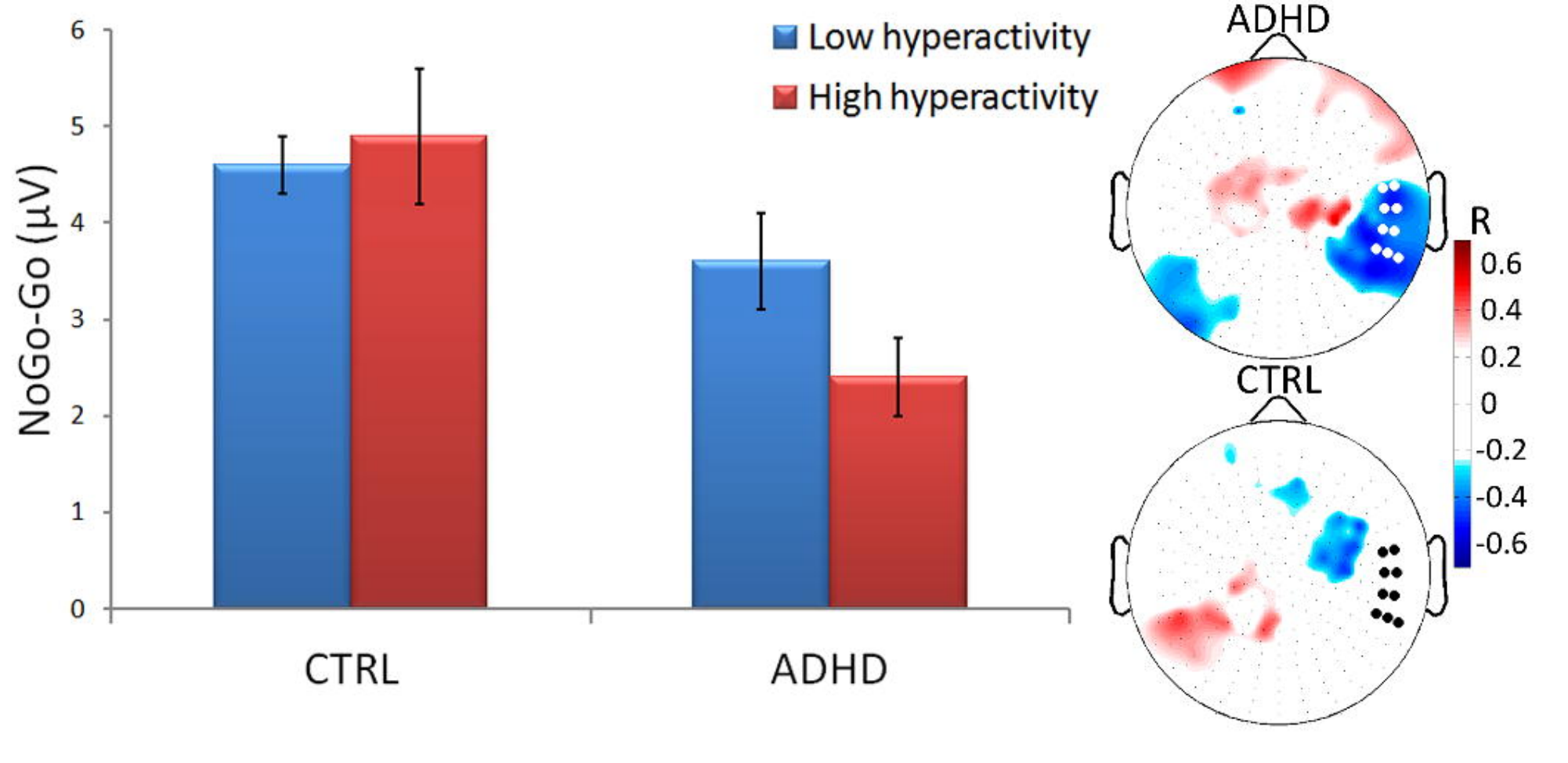
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Biológiai mozgás érzékelésének neurofiziológiai vizsgálata felnőttkori ADHD-ban

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HÁTTÉR

A felnőttkori figyelemhiányos hiperaktivitásos zavar (Attention-Deficit Hyperactivity Disorder, ADHD) a figyelmi, végrehajtási, és viselkedés-gátlási funkció-károsodások mellett jelentős szociális interakciós problémákkal is társul, melyek neurobiológiai alapja tisztázatlan. A biológiai mozgás (BM) - azaz más személyek/élőlények mozgása - a szociális információfeldolgozás egyik fontos forrása; értékelése segít mások szándékainak és érzelmeinek megértésében, így a társas interakciók alapvető tényezője.

CÉLKITŰZÉS

Tekintettel a BM-percepció szociális interakciókban betöltött központi szerepére, valamint az ADHD-ban tapasztalt szociális interakciós problémákra, célunk a biológiai mozgással összefüggő neurobiológiai folyamatok elemzése volt felnőttkori ADHD-ban szenvedő betegek esetén, illesztett egészséges kontroll személyekkel összehasonlítva.

MÓDSZER

Biológiai mozgással (BM) összefüggő agyi esemény-kapcsolt potenciálok (ERP), nagy denzitású, 256-csatornás BioSemi érzékelő rendszerrel történő regisztrálása és elemzése. A BM ingerek megjelenítése az irodalomban használatos pont-ingerek (Point Light Display) alkalmazásával történt, amelyek standard emberi mozgásokat (pl. ugrás, séta) egy kis-számú pontból álló digitalizált ponthalmaz segítségével jelenítenek meg. Kontroll helyzetként a BM mozgásban használt pont-konfigurációk (véletlenszerű, biológiai mozgásként értelmezhetetlen) mozgásait jelenítettük meg ('scrambled motion', SM). Érdeklődésre számottartó régióként (ROI) biológiai képalkotó eljárásokkal azonosított, BM feldolgozására specializálódott agyi hálózatok elemeit használtuk (látókéreg, extrastriatalis és parietális látóterületek, poszterior temporális sulcus (PTS), temporo-parietális kapcsolódás (temporo-parietal junction, TPJ) feletti bioelektromos jelek).

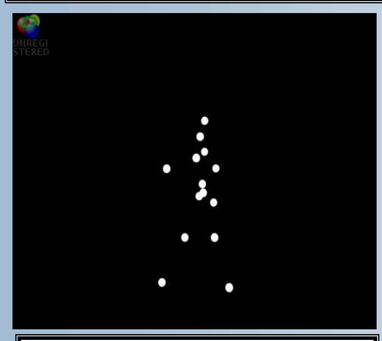


Figure 1. Biológiai mozgás (BM) ingerekhez használt ún. Point Light Display (PLD). Az ábrán egy képkeret (frame) látható, amelynek bemutatása dinamikus mozgásban 200 msec expoziciós idővel történt.

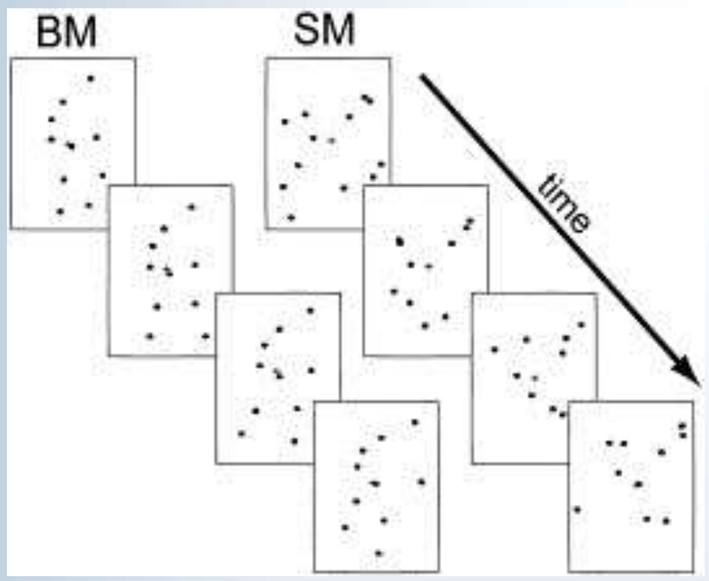


Figure 2. A biológiai mozgást valamint a véletlenszerű (biológiailag értelmezhetetlen) mozgást (scrambled motion, SM) bemutató ingerek megjelenítése átlagosan 1500 msec-oidőközökkel történt, random sorrendben (pl. BM, SM, BM, BM, SM..).

ERP & KLINIKAI VÁLTOZÓK

Table 1. ERP változók és agyi régiók

amplitudó értékek, előzetes irodalom alapján meghatározott ERP komponensekre:
P1, N1, P2 (lásd Figure 3)
agyi régiók (ROI), elsődleges elemzéshez:
jobb temporo-parietalis kapcsolódás (TPJ) (TP8 elektróda és környezete)
jobb extrastriatalis és parietális látóterületek (P4 elektróda és környezete)

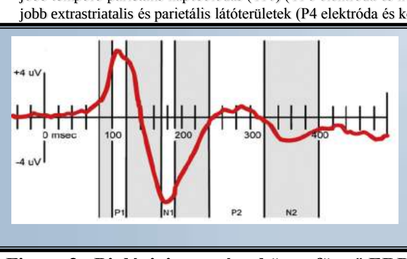


Figure 3. Biológiai mozgással összefüggő ERP komponensek Krakowski és mtsai alapján (Krakowski et al. Neuroimage 56, 2011, 373-383.)

Table 2. Pszichopathológiai tünet-dimenziók a Connners-skála alapján (Conners Adult ADHD Rating Scale, CAARS)

- Inattention/Memory Problems
- Hyperactivity/Restlessness
- Impulsivity/Emotional Lability
- Problem with Self-Concept.

Table 3. Demográfiai és klinikai változók

kor, nem, iskolázottság

DSM-IV változók (felnőttkori ADHD ra

anamnézis (betegségkezdet, komorbiditás)

gyógyszerelés

STATISZTIKAI ELEMZÉS

A ERP komponensek amplitúdó-értékeit kétféle megközelítéssel elemeztük: (1) egyrészt a „nyers" adatokat (ERP-k microvoltban mért amplitúdója, másrészt (2) a BM és SM ingerekre keletkező ERP-k különbségeit. Ez utóbbi ún. „különbség görbék" a biológiai mozgással specifikusan összefüggő idegi aktivitás mutatói. Az elemzésekhez random-regressziós, hierarchikus lineáris modell-elemzést használtunk. Az életkor és nem minden elemzésben kovariánsként szerepelt.

A kutatás az OTKA támogatással valósult meg (Grant#:NN103325)

EREDMÉNYEK

leíró statisztikák

	Kontroll mean (n=21)	SD	ADHD mean (n=16)	SD
életkor (év)	28.6	7.1	28.3	6.7
iskolai évek	15.6	2.7	14.4	2.1
Férfi (%)	61.9%	-	75.0%	-
Conners Adult ADHD Rating Scale				
Inattention/Memory Problem	9.2	4.8	26.2	4.4
Hyperactivity/Restlesness	11.5	5.8	20.6	9.0
Impulsivity/Emot. Lability	7.8	3.5	21.0	5.0
Problems with Self-Concept	6.0	3.9	12.0	5.0

Table 4. A vizsgálati minták leíró statisztikai adatai. A betegmintába bevont személyek az ADHD-ra vonatkozó DSM-IV kritériumok alapján kerültek kiválasztásra. A kontroll csoportba választott személyek a betegekhez életkor (±5év), nem és iskolázottság szintje alapján egyénileg kerültek illesztésre. A vizsgált betegek az ADHD kombinált altípusába tartoznak. Jelen prezentációban az előzetes feldolgozás eredményeit mutatjuk be, további adatfeldolgozás folyamatban.

Különbség-görbék: biológiai vs. véletlen mozgás

Bal- és jobb agyfélteke, ADHD vs. kontroll

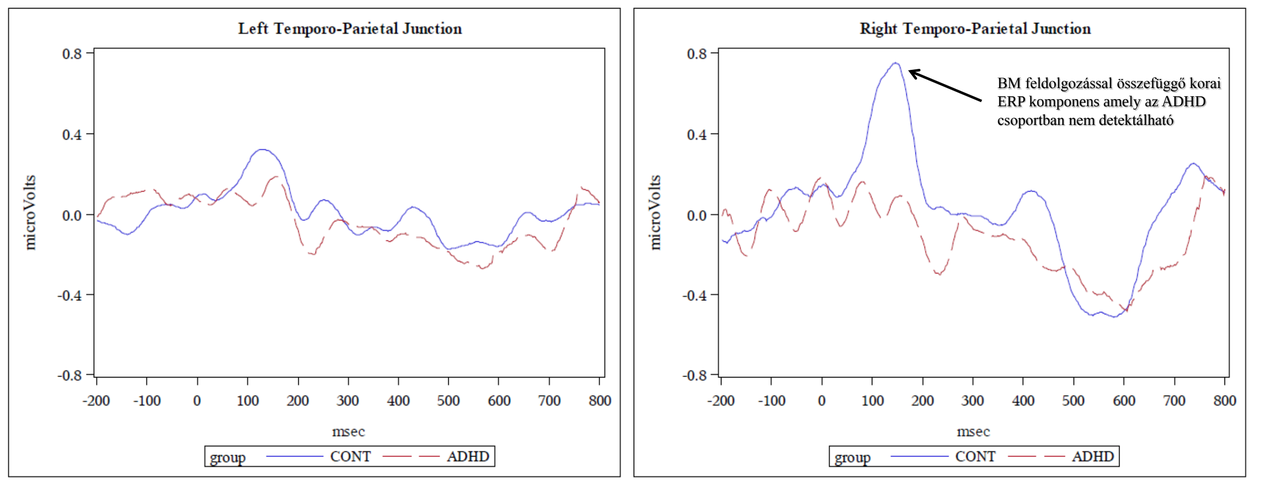
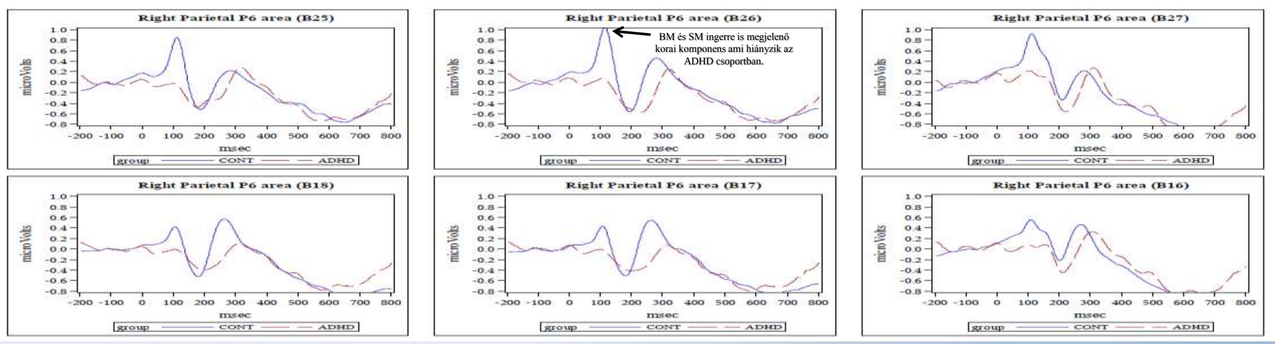


Figure 4. Az ábra a BM – SM különbség-görbéket ábrázolja a jobb és a bal temporo-parietális kapcsolódás (temporo-parietal junction,TPJ) feletti régióban. A különbség-görbe 0 microvolt-értéktől való eltérése a BM-re jellemző specifikus aktivitás mutatója. Irodalmi adatok alapján a BM feldolgozásának egyik központi területe a jobb agyféltekében található TPJ. Eredményeink alapján ebben az agyi régióban (jobb TPJ) a kontroll és ADHD-s csoportok statisztikailag szignifikáns különbséget mutatnak ($p<0.005$) az N2 és egy későbbi ERP komponens (latencia: ~500-600 msec) vonatkozásában. Nevezetesen, a kontroll csoport vonatkozásában a biológiai mozgással specifikusan összefüggő ERP aktivitás figyelhető meg, míg az ADHD csoportban ilyen aktivás nem detektálható. A kontralaterális (baloldali) TPJ területen a biológiai mozgással összefüggő ERP aktivitás egyik csoportban sem figyelhető meg (0 microvolt-értéktől nincs jelentős eltérés).

Biológiai mozgással kiváltott ERP-k



Véletlen mozgással kiváltott ERP-k

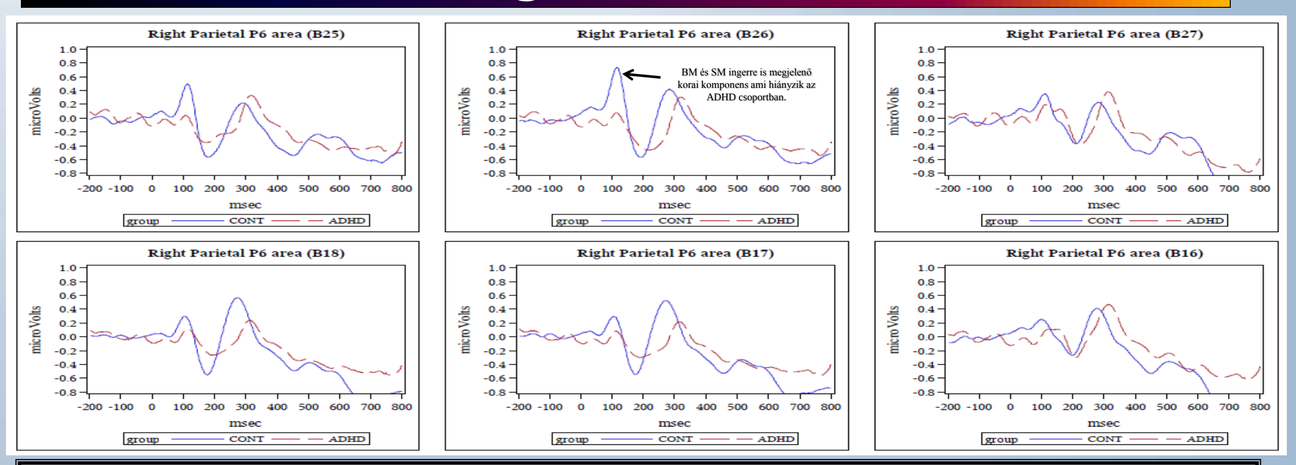


Figure 4. A korai ERP komponensek (~100 msec) amplitúdójában szignifikáns ($p<0.05$) különbség mutatható ki a vizsgált régiók felett az ADHD-ban szenvedő személyekben a kontrollokhoz képest. Az amplitúdó csökkenése ADHDs betegekben mindkét mozgási inger (BM,SM) esetén megjelenik, és különösen jelentős az extrastriatalis és parietális látóterületeken, melyeket a fenti ábrán illusztrálunk.

ÖSSZEFOGLALÁS & KÖVETKEZTETÉS

Eredményeink mind a mozgás mind a biológiai mozgás feldolgozásának károsodására utalnak felnőttkori ADHD-ban. A BM-percepció deficitje az ADHD-ban megfigyelhető szociális interakciós problémák egyik tényezője lehet. A mozgás feldolgozásának elemi szintű károsodása pedig összefüggésben állhat az ADHD-ban tapasztalható mozgás-koordinációs és szenzorimotor szinkronizációs problémákkal; konzisztens továbbá a mozgásfejlődési rendellenesség diagnózisok ADHD-ban leírt magas arányával (pl. developmental coordination disorder).