ELECTROPHYSIOLOGICAL CORRELATES OF EARLY INFORMATION PROCESSING AND INHIBITORY CONTROL IN ADULT ATTENTION-DEFICIT/HYPERACTIVITY DISORDER

Ph.D. thesis

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1. Introduction

Attention-deficit/hyperactivity disorder (ADHD) is a prevalent childhood neurodevelopmental disorder, persisting into adulthood in a large number of cases. While core symptoms and executive functioning with their neurobiological underpinnings have already been subjects of research, recently another facet of adult ADHD came to the focus of studies: altered sensory processing. Although the severe impact that altered sensory processing has on everyday functioning has been demonstrated, the distinct pattern of sensory processing deficits in ADHD patients is yet to be described. Electro-encephalography (EEG) and event-related potentials (ERPs) offer a detailed understanding of the neurophysiological basis of specific cognitive (dys)functions due to EEG's high temporal and good spatial resolution. While current electrophysiological research of adult ADHD focuses primarily on the later timeframe of information processing, there is growing evidence that ADHD affects the early, bottom-up sensory processing as well. Regarding ERP components, P1 (and N1) are associated with the early stages of perceptual processing, with electrophysiological data demonstrating a reduced P1 component in (childhood) ADHD with a wide range of paradigms. However, current data of adult ADHD regarding the P1 early ERP component have been collected in a small set of methodologically diverse studies, and are somewhat controversial.

Up to date, a body of evidence has accumulated showing that inhibitory control deficits are present both in children, adolescents and adults with ADHD. This deficit in inhibition can be observed on the electrophysiological level as well: as mentioned earlier, several studies based on the Go/NoGo design (where one has to cancel the already prepared behavioural response in case of an infrequent NoGo signal) have documented differences between individuals with and without ADHD regarding the NoGo P3 component and found significantly lower NoGo P3 amplitudes in children and adolescents with ADHD compared to controls over central scalp regions during auditory and visual response-control tasks. Some even argue that the P3 component is one of the most sensitive ADHD biomarkers. However, not only the amplitude and latency, but also the topography of P3 contains critical information, which receives considerably less attention. Global field power can be considered as a standard neurophysiological measure of scalp topography, while another measure, the NoGo anteriorization index (NGA) has been proposed as an

indicator of cognitive response control. NGA is a comparison of EEG topographical maps between NoGo and Go ERPs, therefore it reflects the differences in brain's bioelectrical activity associated with the NoGo as compared to the Go trials. In psychiatric disorders characterized by disinhibition, such as childhood and adult ADHD, the P3 NGA has been shown to be reduced, however, the current literature is limited in terms of important details, such as clinically diagnosed adult ADHD patients, detailed information on clinical characteristics including pharmacological treatment and behavioural measures and of the knowledge regarding the association of these measures with NGA.

2. Objectives

Since the manifestation of attention-deficit/hyperactivity disorder is heterogenous with a dimensionally present set of symptoms, our aim was to perform a series of two electrophysiological studies in order to gain a more comprehensive insight into the neurophysiological basis of this multidimensional symptom presentation. A large body of evidence suggests that in ADHD both bottom-up and top-down processes are affected. We therefore considered of major interest to examine whether the manifestation of the known deficits, including early sensory processes and subsequent dysfunctions in inhibitory control, are underlied by potential alterations at the electrophysiological level.

2.1 Objectives of the first study

In the first study, our principal goal was to conduct a detailed topographical analysis of early processing of sensory information in adult ADHD patients and healthy controls based on high density (128-channel) EEG recordings. To make comparison with previous studies, we also performed analyses of "region of interest" electrodes which were predominantly examined in the literature. In the first study we adopted a Go/NoGo paradigm successfully used in functional imaging studies. Our specific aim was to conduct a detailed investigation of the early sensory stages of information processing as reflected in the P1 ERP component. Based on previous literature of childhood ADHD, we expected that P1, similar to the findings in the paediatric literature, would be altered in adults with ADHD as well, with a reduced P1 amplitude in ADHD patients as compared to healthy controls. Our second goal was to investigate the relationship between P1 alterations in ADHD with psychopathological symptoms.

2.2 Objectives of the second study

In our second study, we aimed to address the gaps of the current literature described above and to delineate the neurobiological basis of dysfunctional inhibitory processes by investigating the NoGo response in adult ADHD patients and healthy controls. We also wanted to assess whether neurobiological alterations are related to the behavioural measures and clinical symptoms of attention-deficit/hyperactivity disorder. Based on preliminary findings from literature raising the possibility that patients with ADHD are characterized by a reduced P3 NGA, we expected that the P3 topographical distribution would be altered, with a diminished NoGo anteriorization in adult ADHD patients compared to controls. We also posited higher impulsivity to be associated with reduced anteriorization of the P3 brain potential in the applied Go/NoGo task.

3. Methods

Our first study investigated the behavioural and neurophysiological correlates of early visual processing as reflected in the P1 ERP component in a visual Go/NoGo task in a group of adults with ADHD and their healthy controls.

In our second study, we examined the behavioural and electrophysiological correlates of inhibitory processing during a visual Go/NoGo study in subjects with adult ADHD and healthy controls. Further along details of methodology are described jointly for both studies, with differences (whenever present) highlighted with respect to each of the two investigations.

Both studies complied with the ethical standards of the Declaration of Helsinki and received approval from the Ethical Committee of Semmelweis University (approval number: 62-1/2013). All participants gave written Informed Consent for the studies.

3.1.1 Participants

Fifty-one subjects participated in each study, respectively, of which 26 were adult ADHD patients diagnosed according to the DSM-IV criteria and 25 healthy control subjects. Healthy control subjects were matched to the patients on age (±5 years), gender and level of education.

Exclusion criteria for control subjects included neurological or psychiatric history and severe head trauma. The absence of a current psychiatric condition was confirmed with the Symptom Checklist 90R (SCL-90R) in control subjects. No control subjects were excluded based on SCL-90 scores.

ADHD persisting into adulthood was diagnosed by an experienced psychiatrist based on a detailed clinical interview.

3.1.2 Psychopathological rating scales

In our study, we used the Conners' Adult ADHD Rating Scale-Self-Report: Long Version (66-item, self-reported version) to assess ADHD symptom severity across core psychopathological domains of ADHD including inattention, hyperactivity, impulsivity and problems with self-concept.

The total score on the SCL-90R was used to measure the severity on general domains of psychopathology and to exclude psychiatric comorbidity in the control group. Based on the original criteria, a global severity index of >114 on the SCL-90R was considered high risk for a psychiatric disorder. In our study, none of the controls exceeded this score and had to be excluded.

3.1.3 Stimuli and procedure

Participants were seated in a dimly lit, sound-attenuated room and performed the task between 10 a.m. and 2 p.m. The computer screen for stimuli was at a viewing distance of approximately 50 cm. The applied Go/NoGo paradigm was previously used and described in detail in prior functional magnetic resonance imaging studies developed for children with ADHD. Similar to those studies, characters from the Pokemon cartoon series were used as visual stimuli. The paradigm was programmed and presented with the Presentation 13.0 software (Neurobehavioral Systems, Inc.). Participants were instructed to respond with pressing a button when a Go picture appeared on the screen and to withhold responding in case of rare NoGo trials as quickly and accurately as possible. The task consisted of 5 runs, 57 pictures in each run, of which 75% were Go trials, and 25% were NoGo trials. All pictures were presented for 1 second with an interstimulus interval of 3 seconds. Different types of NoGo trials were presented in a pseudorandom order during the task: NoGos were preceded either by 1, 3, or 5 Go trials: the task

difficulty was manipulated by parametrically varying the number of Go trials preceding a NoGo trial.

3.1.4 Behavioural measures

To assess performance in terms of behavioural measures, mean reaction time and commission error rates were used. For reaction times, small values that were below the threshold of 250 ms and large values that exceeded the upper threshold of 1 sec (and were therefore unlikely to be stimulus-locked responses) were excluded from the analyses. The accepted reaction time range was therefore between 250 and 1000 ms (inclusive). Behavioural data were analysed by the Generalized Linear Mixed Model (GLIMMIX) analysis with a logarithmic link function.

3.1.5 EEG recording and preprocessing

EEGs were recorded using a 128-channel active electrode system (BioSemi Active Two) at a sampling rate of 1024 Hz. A band-pass filter of 0.5-70 Hz was applied. The signal was also filtered using the 48– 52 Hz Parks-McClellan stop-band Notch filter to remove any potential electric-interference from the 50-Hz line. Eye movements were monitored by two electrooculogram (EOG) electrodes placed below the left and above the right external canthi for artefact identification and rejection. Besides eye movements, epochs with a voltage exceeding ±90μV on any EEG or EOG channel were excluded based on the application of automatic artefact rejection criteria. Data were stored and analysed offline with the Electromagnetic Source Signal Imaging (EMSE) Suite and the Statistical Analysis System (SAS 9.4) software.

3.1.6 EEG segmentation for stimulus-locked ERPs

3.1.6.1 EEG segmentation for stimulus-locked ERPs in the first study

For our first study, epochs of 900 ms duration from 100 ms before stimulus to 800 ms after stimulus were extracted from the continuous EEG for stimulus-locked ERP. To establish pre-stimulus baseline the -100 ms timepoint (relative to stimulus onset) was chosen, while the 800 ms post-stimulus timepoint was selected to cover most of the stimulus presentation period, ending before its offset.

3.1.6.2 EEG segmentation for stimulus-locked ERPs in the second study

For our second study, the stimulus-locked data were segmented into epochs of 700 ms, including 200 ms before stimulus and 500 ms poststimulus. For the required minimum number of artefact-free segments for the ERP analyses a threshold cut-off of 50 was applied. In the analyses only correct trials were included. The stimulus-locked segments were baseline-corrected using a 200 ms pre-response window and averaged to obtain the ERP-waveforms for each subject and each condition (Go/NoGo).

3.1.7 EEG data processing

3.1.7.1 ERP analysis (first study)

ERPs during correct NoGo trials were recorded and averaged at all 128 electrode sites. We determined the time-windows for hypothesized components a priori. Particularly, P1 was defined as the mean amplitude deflection (i.e., area under curve) occurring in the window from 120 to 150 ms poststimulus. When investigating relationships between ERPs and clinical measures, midline electrodes (Fz, Cz, Pz and Oz) as sites of interests were defined based on a review of the literature of Go/NoGo tasks applied in adult ADHD studies. Since early visual ERP components (such as P1) typically exhibit polarity reversal in the posterior-to-anterior direction, P1 amplitude was expected to change along the sagittal axis from positive (occipitally) to negative sign (frontally) at the midline electrode sites of interest.

3.1.7.2 EEG data processing (second study)

In our EEG data analyses we followed a 2-step procedure, which included:

1) the determination of global field power as a function of time in relation to the stimulus onset to identify a data-driven time-window of interest and
2) the computation of the amplitude centroid to measure the NoGo anteriorization of the ERP NoGo responses relative to the Go responses in the specified time-window of interest.

In the dissertation we provide a detailed description of both two steps.

3.1.8. Statistical analyses

3.1.8.1 Statistical analyses of the first study

The primary statistical analysis for group difference between ADHD patients and control subjects was based on the random regression hierarchical linear model (HLM). In the HLM, amplitude (voltage) values within the time-window of interest (120-150 ms) served as dependent variable. Independent variables were group, time (sampling point) and their interaction, while age, gender and level of education served as covariates in all analyses. For each scalp site of interest (all 128 electrodes, including Fz, FCz, Cz, Pz and Oz) a separate analysis was performed. False Discovery Rate (FDR)-corrected p-values were computed for these topographical analyses using the full set of the 128 channels. For statistical significance the alpha-level of 0.05 (adjusted for multiple comparisons) was adopted. We investigated whether the EEG recording from multiple individual channels aggregated into electrode clusters with respect to group differences; we adopted this approach to delineate the topographical distribution of the differences. Electrode clusters were defined as a group of at least five adjacent scalp derivations with significant group difference in the same direction. For the scalp sites of interests which provided a significant group difference in the primary analysis (after correction for multiple testing), additional analyses were conducted to test whether psychopathological variables served as covariates in explaining the significant alterations in early sensory activity. These covariates included the total score on the following CAARS domains: Hyperactivity, Impulsivity, Inattention, and Problems with self-concept. In our subsidiary analyses, we also investigated whether comorbidity (present/absent) and medication status (stimulant treatment yes/no; any psychopharmacological treatment yes/no) impacted our results. In these analyses, the aforementioned variables were included as additional covariates in the HLM model.

3.1.8.2 Statistical analyses of the second study

In our second study, the primary statistical analyses for group difference between ADHD patients and control subjects were based on the random regression hierarchical linear model. In the HLM, in separate analyses, repeated measurements of the GFP amplitude (in microvolt-squares) in the P3 ERP time-window of interest were used as dependent variable. The principal independent variable of interest was study group (between-subjects factor). Time (sampling point in the component window, relative to stimulus onset) was included as a within-subject factor in the analysis. We also included gender

and age as independent variables in the analyses. In the HLM model a first-order autoregressive moving average correlation matrix among the sampling points was specified. In subsidiary analyses, the effect of several clinically important variables, including medication status, use of psychostimulants, measures of psychopathology as indexed by the subscales of the CAARS, and behavioural indices such as reaction time were examined. In separate analyses, these variables were introduced as additional covariates in the HLM, by that incorporating a regression estimation into the General Linear Mixed Model. This analysis let us estimate the NGA values for specific values of the covariates. To illustrate the sign and strength of the regression relationship within each group, for each covariate of interest a low and high value (representing, respectively, the lower and upper quartile of the distribution) was selected to estimate the NGA. To adjust for multiple testing the Hochberg procedure was used.

4. Results

4.1 Demographical and clinical characteristics

4.1.1 Demographics

No significant study group differences were found regarding age, gender, and years of education between the ADHD and control groups. Approximately three-fourths of the study sample consisted of males. The mean age was slightly below 30 years.

4.1.2 Clinical characteristics

Significant main effect of group was found for all Conners' Adult ADHD Rating Scale (CAARS) subscale measures. Compared to the controls, the ADHD patient group had significantly higher overall symptom severity (CAARS total score, F=38.84, p<.0001), inattention (CAARS Inattention/memory problems scale, F=32.09, p=<.0001), hyperactivity (CAARS Hyperactivity/restlessness scale, F=36.74, p<.0001), impulsivity (CAARS Impulsivity/emotional problems, F=16.98, p=0.0002) and affective symptoms (CAARS Problems with self-concept, F=12.92, p=0.0008). The ADHD group also had higher scores on the SCL-90R scale measuring general psychopathology. All of the adult ADHD patients belonged to the combined subtype.

As for comorbidity, 11 (42.3%) patients had another DSM-IV-TR psychiatric diagnosis. All comorbidities were affective disorders (unipolar depression and anxiety, or both, n=4,

n=4 and *n*=3, respectively). Psychopharmacological treatment was received in approximately half of ADHD cases (46.2%, *n*=12), methylphenidate was administered to nine patients (34.6%), antidepressants to 3 patients (11.5%), with 1 of them receiving anxiolytics as well. Specifically, non-stimulant medication was bupropion in 3 cases (combined with paroxetine in 1 patient and with clonazepam in another one).

4.2 Behavioural results

Behavioural data (including reaction times and accuracy) was collected by the Presentation software. Commission errors were represented by incorrect NoGo responses, omission errors were incorrect Go responses in our study. Reactions times and accuracy were compared between ADHD and control groups using the analysis of covariance (ANCOVA) procedure controlling for age, gender and education as implemented in SAS software version 9.4 (SAS Institute Inc., Cary, NC, USA). While mean reaction time was lower in ADHD patients than in controls, the difference did not reach the level of significance (502.51 ms vs. 508.5 ms, p=0.7670). ADHD patients made more commission errors (p<0.001) than omission errors. Commission error response rates were 8.85% in ADHD, and 3.04% in control groups.

4.3 Electrophysiological results

4.3.1 Electrophysiological results of the first study

To assess the scalp-distribution of ERPs the topographical map of the group differences in the 120-150 ms time-window were depicted. Differences regarding ERP amplitudes between ADHD and control groups were significant at several brain regions and remained so even after the correction for multiple testing: ADHD patients showed significantly reduced P1 amplitude at occipital and inferior-temporal areas compared to controls in the NoGo condition.

In the adult ADHD EEG literature midline electrodes traditionally have been used as electrode sites of interest. Therefore, besides our “whole brain” topographical approach, we also focused on ERP analyses at Fz, FCz, Cz, Pz and Oz 10-20 midline electrodes. Since our results showed that ADHD patients have significantly reduced NoGo P1 amplitude at occipital and inferior-temporal areas including Cz, Pz and Oz electrodes

sites, focusing on midline electrode sites made it possible to compare our results with previous literature.

As for the grand average ERPs of the midline electrodes for NoGo stimuli for the ADHD and the control groups for the 10-20 midline electrodes, a significant difference was found between the ADHD and the control group including and surrounding the Cz, Pz and Oz sites in the 120-150 ms timeframe: patients had lower ERP amplitudes. We also examined whether the above described group differences are present even after adjustment for comorbidity and medication status and found that all results which were statistically significant retained their significance.

Dimensional associations between the P1 ERP and symptom severity were examined using the data of all participants combined. Therefore, we did not perform a pair-wise comparison between groups, but rather applied a dimensional approach. ADHD symptom severity was assessed by the CAARS Hyperactivity, Impulsivity and Inattention subscales. The analysis was performed for those midline electrodes where a significant group-difference was present in the P1 time-window. To interpret the direction of the associations, we determined the LSMean for the P1 ERP amplitude for low and high severity of CAARS Hyperactivity, Impulsivity and Inattention subscales.

After correcting for multiple comparisons, the Inattention factor was found to be related to ERP changes at Cz, Pz and Oz electrode sites (F=1.45, p<.0001; F=58.56, p<.0001; F=17.74 p=0.0001, respectively). Investigation of the direction of the relationship revealed smaller P1 amplitudes among those subjects who had higher severity on Inattention, compared to subjects with lower subscale severity. Hyperactivity scores were also associated with ERP changes at Cz and Pz sites (F=4.54, p=0.04; F=11.71 p=0.0014, respectively), but with the opposite direction: ADHD patients with higher hyperactivity scores had significantly higher P1 amplitudes.

4.3.2 Electrophysiological results of the second study

The global field power curve of the difference map (derived by subtracting the GFP for NoGo trials from the GFP for Go trials in each group) showed a clear maximum at approximately 330 ms post-stimulus in the healthy control group, which we considered as our basic benchmark based on the empirical data. Since the respective data-driven

segment surrounding the GFP peak enclosed the post-stimulus time-window between 280 and 380 ms, this time frame was chosen as the P3 window of interest.

As for the grand average of Go-NoGo GFP amplitudes in the two groups, adult ADHD patients had significantly lower amplitudes compared to controls in the analysed 280-380 ms time-frame (F=66.62, p<.0001).

We aimed to visualize the NoGo anteriorization in terms of the original ERP curves, and, when we depicted the grand average ERPs for the ADHD and the control groups from three mid-anterior electrodes in the 280-380 ms time-frame larger P3 amplitudes were observable at more anterior electrodes in both groups, indicating the presence of an anteriorization effect. It is important to note, that the anteriorization of the NoGo P3 component was considerably more prominent in the control as compared to the adult ADHD group.

In our second investigation, we also investigated whether the statistical measure of the NGA (as described by the topographical centroid value) differed between the adult ADHD and control groups within the whole identified P3 time frame (full 280-380 ms window). We found that the NGA was significantly less pronounced in patients compared to healthy controls (32.68 vs. 40.18, F=60.76, p<.0001).

We also assessed whether this difference in NGA between adult ADHD and control groups is also observable at the peak GFP (defined as a P3 time-window of 20 ms around the GFP maximum) and found similar results as in the full time-window: ADHD patients had a significantly lower NGA than controls (5.77 vs. 13.40, F=11.14, p=0.0016).

In our subsequent analyses we focused on the GFP peak within the P3 time frame since this is considered to represent changes at the most pronounced manifestation of P3 in time. Results are provided below accordingly.

Examining the potential role of medication on NGA, we found that the difference in NGA between the ADHD and control group remained significant after correcting for medication status (2.50 of unmedicated vs. 9.57 of medicated patients F=4.52, p=0.0441).

We also performed a sensitivity analysis by comparing the NGA results between ADHD unmedicated and ADHD medicated groups to control subjects and had the following findings: NGA at GFP peak of the ADHD unmedicated group (n=14) was 2.50 (*SE* 2.18), while NGA of the ADHD medicated group (n=12) was 9.57 (*SE* 2.36). The direct comparison between the two ADHD groups and the control group revealed consistent

results with the approach we used previously (with medication as a covariate): patients with ADHD had lower NGA than controls. While the difference between the ADHD medicated and control groups did not reach significance (p=0.1877), the difference between the ADHD unmedicated and control groups was significant (p=0.0002), similar to the difference between the two ADHD groups (p=0.0325). Medication use by itself was associated with increased NGA, and the use of stimulant medication *per se* was also associated with a numerically more pronounced NGA: the difference between NGA of patients receiving stimulants compared to those not taking stimulant medication did not reach significance (F=2.55, p=0.1171). When we excluded ADHD patients who were taking stimulant medication (n=9) from the analyses, the NGA was still significantly diminished in ADHD patients compared to healthy controls (p<.0001). Comorbidity did not have a significant effect on our results.

We also studied the associations between NGA and ADHD symptom severity (measured by the CAARS Hyperactivity, Impulsivity, Inattention and Problems with Self-Concept subscales). For these analyses data of the ADHD group and for the mid-anterior electrodes (Fz, FCz and the electrode between them) was used. Low and high values of the CAARS subscales were defined as a value representing the lower and upper quartile, respectively, of the empirical distribution of the subscale scores.

As a result of these analyses, a significant inverse relationship between NGA values and CAARS Impulsivity scores (F=9.39, p=0.0059) was found: higher Impulsivity scores were associated with lower NGA values.

The relationship between symptom severity and NGA based on all 128 electrodes in the selected P3 time frame was also examined and the results were similar: there was a significant inverse relationship between NGA and CAARS Impulsivity score.

Additionally, we also examined the relationship between reaction time and NGA in connection with impulsivity (since this symptom dimension was significant in the analyses). These analyses were conducted again using the data from patients with ADHD only.

To investigate the joint impact of behavioural variables and impulsivity on NGA, analysis of covariance was performed. For each of the two behavioural measures, including reaction time and number of correct responses a separate analysis was conducted. Our

results revealed a statistically significant interaction between both examined behavioural measures and impulsivity.

We found that the interaction between reaction time and impulsivity was significant on NGA (F=22.78, p=0.0002). Specifically, lower reaction time (fast response) with high impulsivity (high score on the CAARS Impulsivity domain) was associated with the lowest NGA.

Our results also showed that the interaction between the rate of correct responses and impulsivity was significant on NGA (F=65.3, p<.0001). Low rate of correct NoGo responses (more commission errors) with high impulsivity (high score on the CAARS Impulsivity domain) was associated with the most diminished NGA in the ADHD group.

5. Conclusions

5.1 Conclusions of the first study

Our first high density ERP study revealed altered P1 amplitudes in adult ADHD patients, indicating that early sensory deficits are present in this patient population. These findings are suggestive of bottom-up cognitive deficits in adult ADHD driven by impairments in early visual processing and provide evidence that sensory processing problems are present at the neurophysiological level in this patient population. Dysfunctional early stages of information processing can result in deficits in later stages; therefore, further research efforts should delineate these alterations in more detail.

5.2 Conclusions of the second study

The main finding of our second study is that adult ADHD patients were characterized by a reduced P3 NGA. To our knowledge, our work was the first to describe the relationship between behavioural and clinical variables (including ADHD severity) and NoGo anteriorization, making it possible to connect specific ADHD symptoms and their severity to NoGo anteriorization, which is considered an electrophysiological correlate of prefrontal/cognitive response control.

Since it has been suggested that a core deficit in inhibition control might account for executive function deficits in ADHD, and executive dysfunction is believed to underlie most of the dysfunctional behaviours associated with attention-deficit/hyperactivity

disorder, further studying NGA with the use of high-density EEG may provide a better understanding of ADHD.

In the "biomarker era", it is important to highlight that the large effect size that we found for NGA, and the fact that it is a reliable and simple-to-use measure, make it a good candidate for a potential biomarker for adult ADHD. Additionally, the finding that the NGA values of patients taking methylphenidate were closer to the NGA values of controls indicates that NGA could be the predictor of good pharmacotherapeutic response. Our findings, if replicated in further studies, may open a new avenue to the clinical application of novel neuromodulation treatments such as neurofeedback or non-invasive brain stimulation, which could make use of NoGo anteriorization as a reliable index of prefrontal response control (deficit).

5.3. General conclusions

With the help of dense-array EEG recording, which makes allowance for a high topographical resolution, in two consecutive electrophysiological investigations we uncovered significant electrophysiological alterations behind the heterogenous symptom manifestation of ADHD. Overall, our findings further support the notion that in adult ADHD patients bottom-up deficits contribute to susceptibility to distraction (inattention) with (deficient) top-down core control aiming to adjust this, with evidence suggesting this phenomenon being reciprocal. Therefore, in further studies it is essential to focus on both the bottom-up and top-down deficits in ADHD, which is a multidimensional psychiatric condition with diverse clinical symptom clusters, in order to gain a more comprehensive insight into the potential underlying neurobiological causes of the disorder.

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