SEMMELWEIS EGYETEM

DOKTORI ISKOLA

Ph.D. értekezések

3144.

PAPP SZILVIA

Pszichiátria

című program

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

Ph.D. thesis

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Budapest
2025

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List of Abbreviations

ACC anterior cingulate cortex
ADHD attention-deficit/hyperactivity disorder
ANCOVA analysis of covariance
ASD autism spectrum disorder
CAARS-SR:L Conners' Adult ADHD Rating Scale – Self-Report: Long version
CPT continuous performance test
DSM Diagnostic and Statistical Manual
ED emotional dysregulation
EEG electroencephalography
EF executive function
EMSE Electromagnetic Source Signal Imaging
EOG electrooculogram
ERP event-related potential
FDR false discovery rate
GFP global field power
GLIMMIX generalized linear mixed model
HLM hierarchical linear model
LSMean least-squares mean
NGA NoGo anteriorization
SAS Statistical Analysis System
SCL-90R Symptom Checklist 90R
swLORETA standardized weighted low resolution electromagnetic tomography

1 Introduction

1.1 Clinical characteristics of adult attention-deficit/hyperactivity disorder

Attention-deficit/hyperactivity disorder (ADHD) is a prevalent childhood neurodevelopmental disorder, which affects around 3-6% of children (1). Core symptoms of ADHD include developmentally inappropriate levels of inattention and/or hyperactivity and impulsivity (2). While ADHD symptoms and their consequences were thought to diminish with adulthood, research and clinical observations both report persistent symptoms and associated deficits (3). Epidemiological studies and meta-analyses reported a 2.5-4% prevalence of adult attention-deficit/hyperactivity disorder (4-6). Symptoms associated with ADHD hinder social and academic functioning and are leading to an impaired health-related quality of life (7,8), especially when the high rate of psychiatric comorbidity is considered (9,10).

When looking at the core symptoms of the disorder, attention deficit is often manifested in difficulty focusing: ADHD patients have trouble paying close attention to details or make seemingly careless mistakes at work or during other activities. They are easily distracted, and therefore often do not complete their tasks, since their attention shifts to new ones, abandoning the job they have been working on. Patients with ADHD often seem forgetful in their daily activities and tend to have trouble organizing tasks and managing time. Sustained mental practice is burdensome to some of them and therefore such tasks are frequently avoided or procrastinated (2). ADHD patients with inattentive symptoms are often unable to reach their potential in terms of academic functioning, their performance is poorer than their abilities (11).

Hyperactivity in adulthood usually fades compared to its childhood presence (12). It typically manifests itself in restlessness, difficulty sitting still for extended periods and in being unable to relax. Fidgeting and/or squirming is also a common experience among adult ADHD patients and fall under the category of hyperactive symptoms (2).

Impulsivity as a symptom manifests mainly in the patients' impatience: they answer questions before they are asked completely, have difficulty waiting their turn and during conversation they often interrupt others (2).

However, in addition to the above mentioned core symptoms, emotional dysregulation (ED) is a main characteristic of the disorder as well. From the earliest descriptions of ADHD, ED has been considered as its core feature and only with the implementation of

DSM-III did emotional symptoms become an associated feature only. Patients with ADHD often have a hard time bearing frustration and their reactions to it are exaggerated (13).

Another important aspect arising from the research of childhood ADHD is that besides the DSM core symptoms, ADHD also affects sensory processing and sensory modulation in the form of higher sensory dysfunction (14,15). Sensory processing problems are severe enough in every sixth child with ADHD to have a negative impact on their everyday life (16), and difficulties arising from altered sensory modulation are believed to adversely affect core ADHD symptomatology (17).

1.2 Diagnosis of adult ADHD

The definition of ADHD has undergone a significant change from its early descriptions to today's diagnostic systems. In 1952, when the first Diagnostic and Statistical Manual of Mental Disorders (DSM-I) was published, minimal brain damage and minimal brain dysfunction were used to describe ADHD (18). The disorder was long seen as a childhood phenomenon, up until the 1980's, when the view that ADHD symptoms significantly decrease or even disappear over time has started to be reconsidered. The revised version of DSM-III introduced the name attention-deficit/hyperactivity disorder, which is still used today (19).

DSM-IV, the next version of the manual, distinguished three subtypes of ADHD: mainly attention-deficit, mainly hyperactive-impulsive, and combined types (20). It was then the DSM-5 diagnostic system (2), which brought some changes into the diagnosis of adult ADHD compared to the DSM-IV-TR (21).

A novel difference is that although the diagnostic criteria themselves did not change between DSM-IV-TR and DSM-5, now only five symptoms of the attention-deficit and/or hyperactive/impulsive symptom groups must be met compared to the previous six to be able to diagnose adult ADHD. Furthermore, according to the DSM-5 ADHD diagnostic criteria, the symptoms must exist before the age of 12, while the age of onset used to be 7 years previously. DSM-5 classifies ADHD into predominantly attention-deficit, predominantly hyperactive/impulsive and combined subtypes, allowing for a change in symptom manifestation over time. Another novelty in the DSM-5 is that it also defines the severity of the current ADHD ranging from mild, moderate to severe. The

consideration of adult functionality has also changed: the DSM-5 is more permissive compared to the previous version, as it only mentions that clinical symptoms need to have a direct, negative impact on social and school/workplace activities (2).

1.3 Neuropsychological background

The aim to describe the relationship between the neurobiological, neuropsychological and symptomatic levels of ADHD has been present in the literature for decades; therefore, after the description of its core symptoms we intend to provide a quick overview of the neurophysiological deficits present in ADHD and relevant to the topic of the dissertation. The neuropsychological domain most widely suggested to be involved in ADHD is attention: over time essentially all conceptualizations of ADHD included attentional symptoms (22). Attention deficit appears primarily in the difficulty of maintaining attention, in increased distractibility, and is present in tasks examining focused attention, divided attention, and sustained attention (23,24). The appearance of attention deficit in neuropsychological tasks differs from child- to adulthood: while in children it mostly results in errors, in adults it is rather present in the variability of reaction time, reflecting periodic fluctuations of attentional vigilance (25). As attention dysfunction is thought to represent one of the core neuropsychological deficits in adults with ADHD, it seems essential to separate performance in the three subdomains of attention: simple, focused and sustained attention (22). In their meta-analysis, Bálint and colleagues (22) found the highest effect sizes for tests measuring focused and sustained attention, whereas for tests of simple attention a small to medium effect size was observed, meaning that performance on tasks of simple attention was found to be less impaired in adults with ADHD than performance on more complex attention tasks.

One of the most intensively researched cognitive problem - and in some views the cognitive hallmark of ADHD - is executive dysfunction. Executive functions (EFs) are higher order, top-down cognitive processes that control behaviour, emotion, and cognition and help achieving future goals (26, 27). Studies suggest that executive functions are best viewed as a set of interrelated, but distinguishable domains such as planning, impulse control, set shifting and working memory (27). According to literature, executive dysfunction is present in both childhood and adult ADHD (28–30), is stable over time and independent, at least in part, of symptom remission (31). In this regard, the

association between executive dysfunction and ADHD is one of the most consistent findings, which has led a number of researchers to describe ADHD as an executive function disorder (e.g., 27,30). Current research (33) emphasizes, that EF questionnaires and neuropsychological tests might catch two different constructs of EF, with tests capturing everyday life EF impairments better.

From the many subfunctions of executive function, inhibitory control deficit is the most consistently demonstrated in the ADHD group (33,34). It is usually examined in Go/NoGo tasks, which are based on the capability to overcome a prepared, but not initiated response (34). The important theoretical model of Barkley (35) connects inhibition with those EFs which seem to depend on it for their effective execution: working memory, self-regulation of affect–motivation–arousal, internalization of speech, and reconstitution (behavioural analysis and synthesis). Therefore, he argues that the general pattern of executive impairment associated with ADHD is grounded in more specific, early appearing deficits in inhibition (which therefore can be considered as the developmental precursor underpinning general executive dysfunctions) (27,35). Based on Barkley's model, the identification of the factors behind the inhibitory control deficit in ADHD has been a key research interest.

The executive dysfunction view has been challenged by models, which are rather based on motivation and see ADHD as a delay aversion. It is argued that ADHD children have elevated levels of delayed-reward discounting and therefore, delay aversion manifests in their attempts to escape or avoid delay resulting in difficulties in both waiting for desired outcomes and working effectively over longer time periods (27).

Towards a dual (or even multi-etiological) pathway: Sonuga-Barke (27) argues, that since the ADHD diagnosis is made on the basis of behavioural symptoms (and associated impairment) rather than the presence of underlying dysfunction, clinical and neuro-bio-psychological characteristics of ADHD are not necessarily matched one-to-one. Therefore, the single core deficit assumption may not provide an appropriate basis on which models of complex disorders such as ADHD can be built (27). Instead, the possibility that disorders (can) have multiple causal pathways each mediated by different psycho-pathophysiological processes needs to be taken seriously (27).

1.4. Neuropsychological tests in adult ADHD

Neuropsychological performance in subjects with adult ADHD differs from the performance of (non-ADHD) control subjects (22). Several tests are used in clinical practice to examine this difference, from which the description of those relevant to the dissertation is provided.

Continuous performance test (CPT) is a commonly applied neuropsychological test method, which measures a person's sustained and selective attention (36). Sustained attention is the ability to maintain a consistent focus on some continuous activity/stimuli (37). Selective attention is the ability to focus on relevant stimuli and ignore competing stimuli (38). During the continuous presentation of a series of stimuli, the subject must react when target stimuli appear, and cancellation of the prepared behavioural response is necessary when an infrequent (NoGo) signal is presented. There are a variety of CPTs of many modalities. In the adult ADHD literature, Go/NoGo paradigms (which are CPTs where both responding to and withholding a response is necessary to previously introduced target stimuli) are frequently applied in the visual modality. In these tasks, in addition to visual scanning, initiating and inhibiting rapid responses, the capacity of the reserved attention is also measured (39).

Based on the computerized CPT test we gain information on several behavioural indicators, among which average reaction time is key. Adult ADHD patients were found to be significantly slower compared to controls in some studies (e.g.: 40,41), while others reported that ADHD patients were not significantly different from healthy controls in terms of reaction time (e.g.: 42–45). The inconsistency regarding reaction time might arise from the fact that Go/NoGo studies differ in many aspects, including study size, applied tasks, task instructions and the clinical characteristics of study participants.

In addition to reaction time, error-related indicators derived from CPT (Go/NoGo) studies are mostly used in clinical studies of ADHD. One such important error indicator is the frequency of omission errors, which occur when the expected button press for the displayed stimuli is missed. The omission error indicates vigilance, and the differences found in this indicator support the disturbance of sustained attention in adult ADHD patients, since they are reported to have an increased rate of omission errors (46–48).

Another important error indicator obtained from Go/NoGo CPT tasks is the number of response inhibition errors, i.e., the commission errors. Commission errors occur when patients respond (e.g., press a button) instead of refraining from answering when an

infrequent and previously selected NoGo stimulus appears. If this inhibition fails, a commission error appears. A high commission error number indicates a deficit in behavioural response inhibition, which is typically seen in adult ADHD (e.g.: 49,50).

The performance of ADHD patients on the Go/NoGo CPT test is worse than that of healthy controls in terms of both error indicators: ADHD patients have a higher rate of omission errors and commission errors as well. Commission errors are considered to be indicators of higher impulsivity (49,50), while a higher rate of omission errors is considered to reflect attention deficit (46–48). However, it appears so, that although the Go/NoGo CPT is suitable for differentiating ADHD patients from healthy controls, it is not capable of differentiating them from other psychiatric patients (39). There are only a few studies that found differences between the performance of other patient groups and ADHD patients (46,51), but these were not significant (39).

1.5 Sensory processing deficits

While core symptoms (with emotional dysregulation) and executive functioning with their neuronal underpinnings have already been subjects of research, recently another aspect of adult ADHD came to the focus of studies: sensory processing. The electrophysiological background of sensory processing has been the focus of our first manuscript, in the dissertation therefore we provide an extended summary of the literature discussed and published previously by our research group (52).

Research of both childhood and adult ADHD suggests (53) that besides core symptoms, ADHD also affects sensory processing (the ability of the central nervous system to collect, process and organize responses to sensory information) and sensory modulation (the ability to regulate the degree, intensity and nature of responses to sensory input) (54, 55).

Children with ADHD differ in their sensory profile from children without any disability (56). Research shows that ADHD children have sensory processing deficits in the following modalities: visual, auditory, tactile, gustatory and multisensory. Also, in children with ADHD modulatory difficulties were described in terms of emotional and social responses (measured by both rating scales and by physiological reactions to stimuli) (14,15,56–58).

Dunn's Model of Sensory Processing proposes four basic patterns of sensory processing emerging from the interaction of the neurological sensitivity threshold and self-regulation (59): 1) sensation seeking (high threshold and active self-regulation strategy), 2) sensory avoiding (low threshold and active self-regulation strategy), 3) sensory sensitivity (low threshold and passive self-regulation strategy), and 4) low registration (high threshold and passive self-regulation strategy). Extreme responses to sensory events as a characteristic are likely to negatively affect daily life, and research provides evidence to this notion: sensory processing problems are severe enough in every sixth child with ADHD to have a negative impact on their everyday life (60). It is important to mention, that someone's ability to process sensory events is not categorical: one can be sensitive to certain events while being indifferent to others (58). With the help of the above-described Dunn's model (59) a sensory profile can be assessed which provides intervention strategies for therapists (58). In terms of ADHD symptomatology, it is assumed that a low threshold for sensory stimuli might be associated with distractibility, while a high threshold could rather be attributed to inattentive behaviour (55). Even though difficulties arising from altered sensory modulation seem to negatively affect core ADHD symptomatology, the distinct pattern of sensory processing deficits in ADHD patients is yet to be described (17).

1.6 Electrophysiological background of early information processing

It is important to study potential biomarkers, including ERPs in patients with ADHD, since their identification could be important in understanding the both clinically and etiologically heterogeneous nature of attention-deficit/hyperactivity disorder (33,61).

While as of now there is no biological marker which could be reliably used for the diagnosis of ADHD (61), during the search for promising candidates, electro-encephalography (EEG) and event-related potentials (ERPs) were commonly employed, since due to its high temporal, and good spatial resolution, EEG offers a detailed understanding of specific cognitive (dys)functions.

Since in task-related EEG cognitive ERPs are defined by the time they occur after stimulus presentation, they can be divided into early and later components reflecting the time course of task-related neural information-processing (33).

Current electrophysiological research of (adult) ADHD focuses rather on the later timeframe of information processing; however, there is growing evidence that ADHD affects not only the top-down attentional selection, but the early, bottom-up sensory processing as well (33,62,63).

Regarding ERP components, P1 and N1 represent the early stages of perceptual processing. While both components are generated in extrastriate visual cortex (64), the P1 (latency 80-150 ms) has traditionally been associated with basic visual processing and spatial attention. When attention is directed to the location of the stimulus, it is associated with increased amplitudes of the P1 and N1 components, which phenomenon sustains the "sensory gain control/amplification" hypothesis (65,66).

Although the studies published so far are difficult to compare because of their different methodology (66), for children with ADHD a reduced P1 component has been demonstrated with a wide range of paradigms including CPT tasks (e.g., 68,69) as well. In our first study (52) we provided a summary of findings regarding the P1 component in ADHD studies, and in the dissertation we further extend the literature overview both for childhood and adult ADHD.

1.6.1 Childhood studies

In the following part of the dissertation, we aim to provide an updated overview of visual CPT studies regarding the P1 component alterations in childhood ADHD based on the introduction of our first study (52).

While Perchet and colleagues failed to find a significant difference between control and ADHD groups regarding the P1 amplitudes, in their study the attenuation of early sensory responses revealed decreased attentional priming in ADHD subjects (67,68).

In their important visual cued CPT study, Nazari et al. (68) demonstrated a decreased P1 amplitude in children with ADHD in the NoGo condition as compared to their control peers. Their results suggest an early deficit in visual sensory integration. EEG data were collected from 64 surface electrodes, and peak amplitudes for P1 were measured at 3 occipital electrode sites. The source of the P1 component was localized to the occipital area by the swLORETA (standardized weighted low-resolution electromagnetic tomography) method.

In their study of children with ADHD and conduct disorder, Banaschewski and colleagues (69) found that during cue processing, differences between the ADHD and the control group was already observable regarding P1/N1 ERPs: reduced positive amplitudes were found at parietal and reduced negative amplitudes at right frontal sites.

By contrast, Brown et al. (70) did not find significant differences for the P1 component in their study investigating whether ERPs from an intermodal oddball task could differentiate ADHD children from controls.

Interestingly, when comparing the visual evoked potential between neurotypical, (only) autistic and autistic children with co-occurring ADHD presentation, Cremone-Craira and colleagues in their recent study (71) found a reduced P1 amplitude in autistic children with co-occurring ADHD presentation compared to both autistic and neurotypical children groups. This suggests a distinct pattern of brain activity in autistic children with co-occurring ADHD features, underlying the role of ADHD-related symptomatology in early sensory deficits (71). It is important to note, however, that their results are inconsistent with a previous study, in which no group differences were found regarding the P1 amplitude between children with autism spectrum disorder (ASD), ADHD, and ASD + ADHD (72). In summary, while there is growing evidence for the reduction in the P1 amplitude in case of children with ADHD compared to controls, as seen above, the results overall remain somewhat controversial.

1.6.2. Adult ADHD studies

In the following section we also provide an expanded outline (based on the introduction of our first study, 52) of adult ADHD literature regarding the P1 component elicited in a visual Go/NoGo paradigm.

An important study finding differences in the P1 amplitude is that of Barry and colleagues (73), where the authors found that the visual P1 component was “somewhat reduced” in ADHD subjects compared with controls, and this finding was significant at the midline electrodes. This suggests (together with their other findings) that adults with ADHD have atypical brain activity associated with sensory processing compared to controls, and this can be observed both in global and topographic differences as well (73).

Raz and Dan (74) used a visual-emotional oddball paradigm, in which subjects were confronted with neutral and emotional (happy and angry) faces. Using a 64-channel EEG

they found higher P1 amplitudes in the adult ADHD group at occipital and posterior-parietal scalp locations in response to emotional compared with neutral faces. In the neutral emotional valence setting (i.e., response to neutral faces), however, no such difference was found between patient and control groups. The difference between the two study groups regarding the P1 component to happy and angry faces, i.e., the augmentation of P1, is thought to reflect the recruitment of additional perceptual processing for emotion-inducing stimuli (74).

Woltering et al. (44), however, did not find group differences between adult ADHD and control groups regarding the P1 component in their dense array (129 channel) visual Go/NoGo study. They argue that this finding could be attributed to their sample of well-educated college students with ADHD and the relatively low perceptual processing demands of the paradigm, and may not generalize to other, more demanding tasks (44).

In their modified visual Go/NoGo CPT ERP study of 13 non-delinquent and 13 delinquent subjects with ADHD and 13 controls, Meier and colleagues (75) found that in the P1 time period, there was no significant main effect of group neither when comparing all three groups, nor when comparing groups pairwise.

Taking these results together, one could conclude that data of adult ADHD regarding the P1 early ERP component are methodologically diverse, rather limited and somewhat controversial.

1.7 Electrophysiological background of inhibitory control

In the following section we aim to provide a short summary on the electrophysiological background of inhibitory control, based on, and expanding the introduction of our second study (76).

During the Go/NoGo paradigm, when an infrequent NoGo signal is presented, it is necessary to cancel the already prepared behavioural response. At the electrophysiological level, the NoGo signal elicits a pronounced ERP component, the P3, which is a positive waveform typically measured between 300 and 600 ms post-stimulus with a fronto-central scalp distribution (e.g., 77,78).

The NoGo P3 has been proposed to reflect the activity of multiple cortical locations, including the frontal cortex and the anterior cingulate and is thought to index the evaluation of the inhibitory process and its behavioural outcome (79–81).

Up to date, a body of evidence has accumulated showing that inhibitory control deficits are present in children (82–84), adolescents and adults with ADHD (for review see: 33,34). This deficit in inhibition can be observed on the electrophysiological level as well: several studies 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 (e.g., 42,85).

As for the adult literature of the P3 event-related potential component, research is somewhat limited compared to the childhood data, although there is growing interest and evidence that this group of patients can also be characterized with significant alterations regarding the P3. An important meta-analysis (86) aimed to investigate target-related P3 (or P3b) characteristics in adult ADHD patients and found that adult patients with ADHD had a significantly reduced P3 amplitude across studies as compared with controls.

A more recent meta-analysis by Kaiser and colleagues (33) aimed to find the most robust neurophysiological deviations in terms of task-related ERPs in individuals with ADHD during the time course of cognitive processing. They reported (similarly to (86) and others) that individuals with ADHD show smaller NoGo P3 amplitudes (and longer NoGo P3 latencies) compared to controls without ADHD and argue that their findings support the idea that the P3 component is one of the most sensitive ADHD biomarkers.

However, growing evidence suggests, that not only the amplitude and latency, but also the topography of P3 contains critical information (87).

An important measure of scalp topography is the global field power (GFP), which has been shown to represent a robust measure of the spatiotemporal characteristics of brain activity, corresponding to the spatial standard deviation of the electrical potentials recorded at each time point across all electrodes (88). Therefore, GFP can be considered a reference-free, global descriptor of the potential field (89).

In addition to GFP, the NoGo anteriorization index (NGA) was proposed as a standard neurophysiological measure of scalp topography for cognitive response control by Fallgatter and colleagues (80). The NGA is derived from mathematical data reduction relying on the entire information gained from multichannel ERP-registrations (90). NGA is a comparison of EEG topographical maps between Go and NoGo ERPs, therefore it reflects the electrical differences in brain activity associated with the Go and the NoGo

trials (90, 91). There is consistent evidence for a more anterior located P3 topography in NoGo compared to Go trials (90–92). This forward-shift or "anteriorization" of the NoGo P3 is thought to be based on a strong electrical activity associated with the anterior cingulate cortex (ACC) during the NoGo condition. Increased frontal activation recruited to control or inhibit the prepotent motor response is thought to be reflected in higher NGA values (93).

In psychiatric disorders characterized by "disinhibition", such as childhood and adult ADHD, the above described P3 NGA has been shown to be reduced in related studies. In a prior study by Fallgatter and colleagues, a lower NGA was reported in children with ADHD compared to control subjects (85). Regarding adult ADHD, research by the same group (92) revealed reduced NGA values in adult patients with ADHD-related psychopathology during childhood, i.e., persisting ADHD. Another important study including a large number of adult ADHD patients found a tendency of lower NGA values in patients as compared to controls (94).

1.8 Rationale of the current research

High-density EEG, due to its excellent time-resolution and topographical information on the whole scalp area makes it possible to gain a more detailed insight into the early sensory ("bottom-up") processes. Previous research, which examined the topographical distribution of early ERP components in ADHD patients relied either on sparse spatial sampling or used a lower number of electrodes. High density EEG - such as our 128-electrode setting - increases topographical detail and augments the accuracy of EEG spatial frequency (95–97). In addition to the inferior EEG resolution, the results of previous adult ADHD research focusing on the P1 ERP component are somewhat controversial and methodologically diverse, which provided a rationale for conducting our first study (52).

As detailed above, while the P3 NGA has been proposed to be an indicator of inhibition and has been described to be reduced in adult patients with ADHD (92,94), the current literature is limited in terms of important details, such as clinically diagnosed adult ADHD patients, detailed information on clinical characteristics such as pharmacological treatment and behavioural measures, and of the knowledge regarding the association of these measures with NGA. Additionally, previous studies are also deficient in terms of

EEG recordings obtained with high spatial resolution, which is key when brain activity is aimed to be investigated with a high topographical accuracy. These considerations provided the rationale for our second study (76).

2. Objectives

Since the manifestation of attention-deficit/hyperactivity disorder is heterogenous with dimensionally present 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 (e.g.,33,62,63). 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 (52,76).

2.1 Objectives of the first study

In our first study (52) our main 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 predominantly examined in the literature. To reduce methodological issues, in the first study we applied a Go/NoGo paradigm successfully used in functional imaging studies (98,99). Our aim was to conduct a detailed investigation of the early sensory stages of information processing reflected in the P1 ERP component. Based on previous literature of childhood ADHD described in detail in the Introduction, we expected that P1 would be affected in adults with ADHD as well, with a lower P1 amplitude in ADHD patients. Our second goal was to investigate the relationship between P1 alterations in ADHD with psychopathological symptoms (52).

2.2 Objectives of the second study

In our second study (76) 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 literature indicating that patients with ADHD are characterized by a reduced P3 NGA,

we hypothesized that the P3 topographical distribution would be altered, with a diminished NoGo anteriorization in adult ADHD patients compared to controls. We also expected higher impulsivity to be associated with reduced anteriorization of the P3 brain potential in the applied Go/NoGo task (76).

3 Methods

Our first study investigated the behavioural and neurophysiological correlates of early visual processing reflected in the P1 ERP component in a visual Go/NoGo task in a cohort of adults with ADHD and their healthy controls (52).

In our second study we looked into the behavioural and electrophysiological correlates of inhibitory processing during a visual Go/NoGo study in subjects with adult ADHD and healthy controls (76). In the subsequent parts of this section, details of methodology are presented jointly for both studies, with differences (whenever present) highlighted with respect to each of the two investigations. The methodology of the studies has been published previously (52,76).

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

As described in the published manuscripts (52,76), 51 subjects participated in both studies, respectively, of which 26 were adult ADHD patients 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 (100). 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, which comprised of the following steps:

a) structured interview for assessing current and (retrospective) childhood DSM-IV-TR ADHD symptoms;
b) semi-structured and open interviews assessing background information, developmental data, functional impairment, psychiatric comorbidity;
c) medical history data obtained from medical documentation and close family members;

d) interpreting results of self-rated questionnaires, including the Conners' Adult ADHD Rating Scale – Self-Report: Long version (CAARS; 66-item, self-reported and long version (101).

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 (101).

To measure the severity on general domains of psychopathology and to exclude psychiatric comorbidity in the control group we used the total score on the SCL-90R (100). Based on the original criteria, a global severity index of >114 on the SCL-90R was considered high risk for a psychiatric disorder (100,102). None of the controls exceeded this score and had to be excluded (52,76).

3.1.3 Stimuli and procedure (as described in 52,76)

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 by Durston and colleagues (99). Similar to the prior study developed for children with ADHD, 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 whenever a Go picture appeared on the screen and to withhold response 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. Difficulty was manipulated by varying the number of Go trials preceding a NoGo. In accordance with the original study (99), foil trials (NoGo trials after 2 or 4 Go trials) were also administered to prevent learning;

however, those were not included in the analysis (for a visual overview of the applied paradigm, see *Figure 1*).

Figure 1. *Overview of the applied Go/NoGo paradigm based on the work of Durston and colleagues (99).*

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 as well as 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) (52,76).

Based on the above described threshold criteria less than 0.5% of the individual reaction time values were rejected in each of the two groups (0.39% and 0.42% in the control and patient group, respectively). The distribution of the reaction times was checked after excluding values that were outside the accepted range. As indicated by the Kolmogorov-Smirnov D-statistic, the distribution of reaction times deviated from the normal distribution ($p<0.01$ in both study groups). The distribution of error rates was also investigated, and we found that it - similarly to reaction times - deviated from the normal distribution in both study groups ($p<0.01$). The distribution of reaction times and error rates was right skewed with increasingly higher values occurring with increasingly lower

frequency, therefore, behavioural data were analysed by the Generalized Linear Mixed Model (GLIMMIX) analysis with a logarithmic link function. The GLIMMIX approach makes allowance for non-normally distributed data, such as the right skewed distribution of behavioural data in our study. Measure of central tendency for the reaction time and commission error rate in each group was characterized by the mean and 95% confidence limits, which we derived as back-transformed data from the GLIMMIX procedure from logarithmic to the original units (ms or error rate) (52,76).

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 (52,76).

3.1.6 EEG segmentation for stimulus-locked ERPs

3.1.6.1 EEG segmentation for stimulus-locked ERPs in the first study (52)

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 (76)

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, 52)

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 (103). 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 (42–44,49). Since early visual ERP components (such as P1) typically exhibit polarity reversal in the posterior-to-anterior direction (104), 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, 76)

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 following section we provide a detailed description of the two steps.

Step 1. Determination of global field power.

In accordance with the procedures of Fallgatter and colleagues (80), first we determined the GFP of the difference between the NoGo and the Go ERPs at each time point for the 500 ms period following stimulus onset. In the literature GFP has been described as a robust measure of the spatiotemporal characteristics of brain activity, corresponding to the spatial standard deviation of the electrical potentials recorded at each time point across all electrodes (88). As previously pointed out by Fallgatter et al. (80), the GFP curve of

the difference map includes both the differences in field strength and the topography of the ERP map series as well. Similar to the important study of Lehmann (88), we used the GFP curve for the component segmentation of the ERPs. Specifically, based on data from all participating subjects, we identified the GFP maximum in the P3 time-window of interest identified by Fallgatter et al. (80) for the Go/NoGo difference maps. Time points of the minima preceding and following the maximum were selected as the borders of the respective P3 segment.

Step 2. Computation of the amplitude centroid to measure the NoGo anteriorization

Centroids were computed based on the amplitude and topographical configuration of the respective map (88,105,106) within the time-window identified in Step 1. Centroids represent the "centre of gravity" of the brain activity, which means that centroids are the amplitude-weighted locations of the positive and the negative part of the topographical distribution of the brain's electrical activity (105,106). Locations of the centroids were calculated from average reference maps and were quantified by a coordinate system resulting from the planar projection of the BioSemi electrode array onto a circular angular grid, extending from 90 to -90 degrees, in both anterior-posterior and central to lateral directions. Higher positive value in anterior-posterior direction indicates a greater NGA (a more pronounced anteriorization of the scalp topographical distribution).

In our second study, we aimed to examine the robustness of the findings; therefore, we conducted analyses by computing the NGA (centroid) measure for the full time-window (i.e., 280 to 380 ms post-stimulus, see later); and for the peak GFP (in a 20 ms time interval around the GFP maximum of interest) as well. Our reasoning was that the peak GFP may delineate changes that are associated more closely and specifically with the event of interest (i.e., at the most pronounced manifestation of P3 in time). Moreover, we also determined the NGA (centroid) measure based both on the full set of 128 electrodes and also on the anterior midline electrodes, since these midline sensors are considered to represent the best established region of interest for the NoGo P3 ERP component. The effect size for the group difference in NGA was characterized by the Cohen D measure (107).

3.1.8. Statistical analyses

3.1.8.1 Statistical analyses of the first study (52)

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 (108) 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 Bonferroni 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 (76)

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 (52,76). The demographical (and clinical characteristics) of the study sample are summarized in *Table 1* (based on reference 52).

4.1.2 Clinical characteristics

Significant main effect of group was found for all Conners' Adult ADHD Rating Scale (CAARS) subscale measures (101). 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 (52,76).

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) (52,76).

The clinical (and demographical) characteristics of the study sample are summarized in *Table 1*.

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 (502.51ms vs. 508.5ms, 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 (52,76). Behavioural data are summarized in *Table 1*.

Table 1. Basic demographic and clinical characteristics. *Table 1 is based on Table 1 of reference (52)*

Characteristics	ADHD (N=26)	Control (N=25)		
			Chi²/F	*p*
Male, N (%)	18 (69.2)	19 (76.0)	0.29	0.76
Mean age, mean (SD)	28.9 (8.4)	27.3 (5.0)	0.71	0.40
Years of education, mean (SD)	14.0 (2.5)	16.3 (1.6)	13.94	0.0005
CAARS				
Inattention, mean (SD)	23.7 (7.0)	11.1 (7.9)	32.09	<0.0001
Hyperactivity, mean (SD)	20.1 (4.8)	10.1 (6.3)	36.74	<0.0001
Impulsivity, mean (SD)	17.6 (7.4)	9.1 (6.5)	16.98	0.0002
Problems with Self Concept (SD)	10.1 (5.5)	4.8 (4.4)	12.92	0.0008
SCL-90R, mean (SD)	86.3 (51.3)	33.1 (30.1)	16.48	0.0002
Medication				
Methylphenidate, N (%)	9 (34.6)	-	n/a	n/a
Antidepressant, N (%)	3 (11.5)	-	n/a	n/a
Anxiolytic, N (%)	1 (3.85)	-	n/a	n/a
Comorbidity				
Depressive disorder, N (%)	4 (15.4)	-	n/a	n/a
Anxiety disorder, N (%)	4 (15.4)	-	n/a	n/a
Both, N (%)	3 (11.5)	-	n/a	n/a
Behavioural measures				
Commission errors, %, mean (95% confidence limits)	8.85 (7.63-10.2)	3.04 (2.32-3.98)	46.33	<0.0001
Reaction time, msec, mean (95% confidence limits)	502.51 (475.27-531.31)	508.5 (480.12-538.55)	0.09	0.7670

4.3 Electrophysiological results

4.3.1 Electrophysiological results of the first study (52)

To demonstrate the scalp-distribution of ERPs the topographical map of the group differences in the 120-150 ms time-window were depicted. On *Figure 2* the false discovery rate (FDR)-corrected map of Type-I error-probabilities was provided as well.

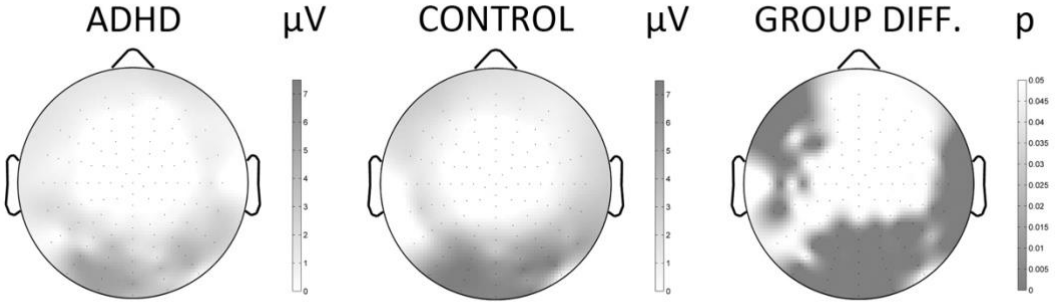

Figure 2. Topographical maps of the P1 component based on 128 channels for the NoGo condition in adult ADHD patients and in controls. *The scalp maps were generated on the basis of the average voltage values in the P1 time-window. Electrode clusters depicted here were defined as clusters of at least five adjacent scalp derivations with significant group difference in the same direction. For ADHD and control groups, black-and-white coding represents the amplitude value in microvolts, with darker colours corresponding to higher amplitudes. On the FDR-corrected map of Type-I error-probabilities for the group-difference (control-ADHD) of raw amplitude values (µV) darker shades represent larger group differences. Figure 2 is based on Figure 1 of reference (52).*

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. Detailed data are provided in *Table 2,* which also shows the covariance adjusted Least-Squares Mean (LSMean) estimates of the ERP amplitudes for both the ADHD and the control group.

Table 2. Group differences between ADHD and control subjects in the P1 ERP component (120-150 ms) on midline electrodes. *Table 2 is based on Table 2 of reference (52)*

CHANNEL	**GROUP (µv,)**		***F***	***p***
	ADHD*	**CONTROL***		
Fz	-0.87 (0.09)	-0.83 (0.09)	0.07	~1.0
FCz	-1.20 (0.09)	-1.63 (0.09)	11.82	0.1541
Cz	-0.85 (0.06)	-1.61 (0.06)	71.88	<.0001
Pz	0.94 (0.09)	1.49 (0.09)	18.57	0.0101
Oz	4.12 (0.15)	6.32 (0.15)	104.45	<.0001

**Least-Squares Mean estimates (Standard Error) of stimulus-locked event-related potential amplitudes for a given study group, adjusted for age, gender and years of education*

ADHD=attention-deficit/hyperactivity disorder

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.

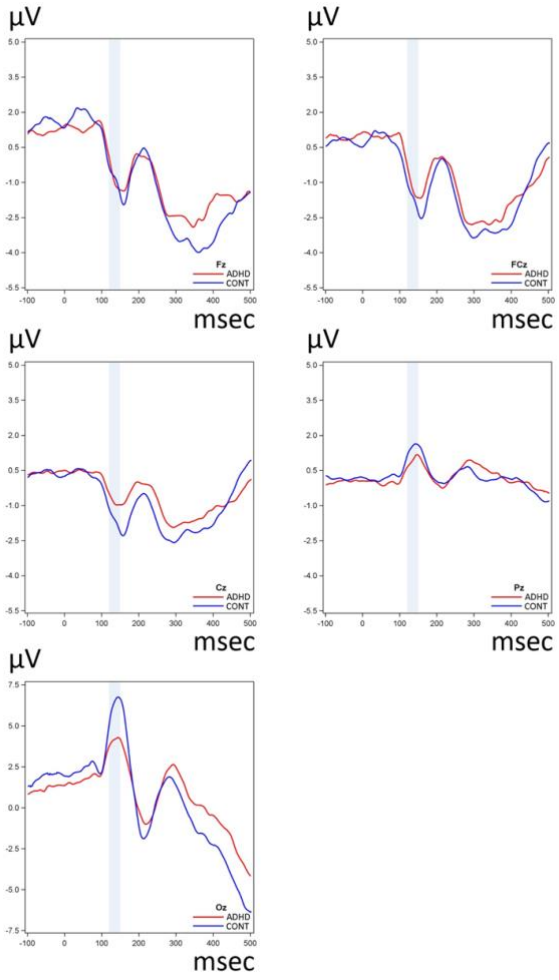

Figure 3. Waveforms for raw amplitude (μV) values for stimulus-locked ERPs in Fz, FCz, Cz, Pz, Oz scalp sites. *The waveforms are displayed for both groups for the NoGo condition. Shades areas highlight the time-window for the P1 ERP component. Figure 3 is based on Figure 2 of reference (52).*

The grand average ERPs of the midline electrodes for NoGo stimuli for the ADHD and the control groups was depicted on *Figure 3*. With respect to 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. 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. The relationship between altered early ERP activity and CAARS symptom dimensions is provided in *Table 3*.

Table 3. Relations between symptom severity (measured by CAARS) and P1 ERP amplitudes on midline electrode sites within the P1 time-frame (120-150 ms). *Table 3 is based on Table 3 of reference (52).*

CHANNEL	CAARS DOMAIN	SYMPTOM SEVERITY (μV, SE)		DIFFERENCE *	
		LOW	HIGH	*F*	*p*
Cz	HYPERACTIVITY	-0.37 (0.14)	0.05 (0.17)	4.54	0.04
	IMPULSIVITY	-0.41 (0.10)	-0.29 (0.18)	0.53	0.47
	INATTENTION	-0.91 (0.14)	-0.37 (0.14)	1.45	<.0001
Pz	HYPERACTIVITY	-0.35 (0.22)	0.75 (0.28)	11.71	0.0014
	IMPULSIVITY	0.52 (0.17)	0.01 (0.29)	4.23	0.05

	INATTENTION	1.57 (0.21)	0.19 (0.21)	58.56	<.0001
Oz	HYPERACTIVITY	2.78 (0.36)	2.56 (0.45)	0.19	0.6674
	IMPULSIVITY	2.36 (0.27)	1.58 (0.46)	3.77	0.0590
	INATTENTION	1.65 (0.35)	0.67 (0.35)	17.74	0.0001

*corrections for multiple comparisons were applied

CAARS=Conners' Adult ADHD Rating Scale

4.3.2 Electrophysiological results of the second study (76)

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 control group, which was considered as our basic benchmark based on empirical data *(Figure 3)*. 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. The validity of selecting this time-frame is supported by previous literature (80), which established a similar empirically determined time-window.

As for the grand average of Go-NoGo GFP amplitudes in the two groups (*Figure 4*), adult ADHD patients had significantly lower amplitudes compared to controls in the analysed 280-380 ms time-frame (F=66.62, p<.0001).

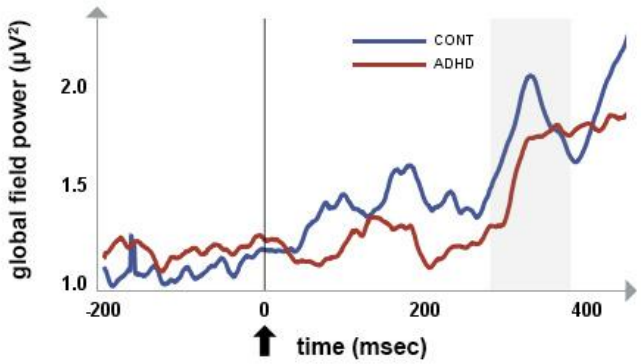

Figure 4. GFP difference waves in the adult ADHD and control groups. *The analyzed 280-380 ms time-window is shaded. Stimulus appearance is indicated by the arrow by 0 ms Figure 3 is based on Figure 2 of reference (76).*

We aimed to visualize the NoGo anteriorization in terms of the original ERP curves, therefore, on *Figure 5* 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 (*Figure 4)*

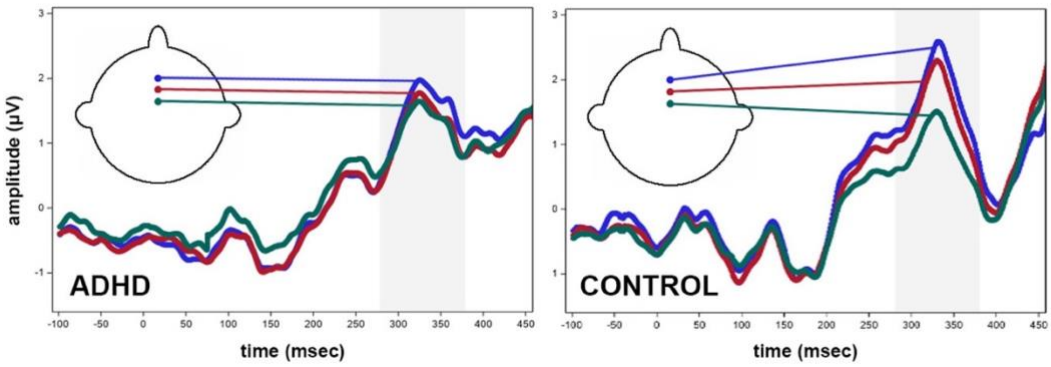

Figure 5. Waveforms for raw amplitude (μV) values for stimulus-locked ERPs on mid-anterior electrode sites (Fz, FCz in the International 10-20 System, and the midline electrode between them) for the NoGo condition in adult ADHD patients and controls*. The analyzed 280-380 ms time-window is shaded. The difference between the ADHD and control groups was significant (F=66.62, p<.0001 in the P3 time-window). Figure 5 is based on Figure 3 of reference (76).*

In our second investigation it was also studied 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 examined 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, see *Table 4* as well).

Table 4. Group differences in anteriorization (ADHD vs. control). *Table 4 is based on Table 2 of reference (76).*

	Group			
	ADHD	**Control**		
	estimated mean (SE)		***F***	***p***
NoGo anteriorization (NGA) in the P3 time-window				
NGA at GFP peak (defined as 20 ms around GFP maximum)	5.77 (1.60)	13.40 (1.63)	11.14	0.0016
NGA in full P3 window (280-380 ms)	32.68 (0.74)	40.18 (0.62)	60.76	<.0001

NGA=NoGo anteriorization, GFP=global field power, ADHD=attention-deficit/hyperactivity disorder

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 examined 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 CAARS 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 detailed relationship between NGA anteriorization and other CAARS symptom dimensions is shown in *Table 5*.

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.

Table 5. Relationship between symptom severity (CAARS subscales) and NGA amplitudes on mid-anterior electrode sites between 280-380 ms. *Table 5 is based on Table 3 of reference (76).*

CAARS domain	**NoGo anteriorization (estimated mean, SE) at low and high symptom severity on the four CAARS subscales**		**Difference (p)** *
	Low**	**High****	
Hyperactivity	1.40 (2.44)	6.64 (7.38)	0.94 (0.3437)
Impulsivity	-5.57 (2.39)	-16.21 (5.45)	9.39 (0.0059)
Inattention	-0.09 (1.71)	2.62 (4.32)	0.55 (0.4683)
Self-concept	2.95 (4.93)	6.25 (9.45)	0.50 (0.4879)

*corrections for multiple comparisons were applied

** 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

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 (*upper part of Table 6).*

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 *(lower part of Table 6).*

Table 6. Relationship between reaction time, number of correct responses, impulsivity and NoGo anteriorization. *Table 6 is based on Table 4 of reference (76).*

	Impulsivity	
	Low	**High**
Reaction time		
Fast *	-16.36 (3.43)	-65.74 (8.41)
Slow **	-3.61 (4.93)	-5.16 (10.70)
Number of correct responses		
Low ***	-5.65 (2.41)	-42.74 (5.28)
High ****	-12.02 (2.63)	-27.53 (6.12)

Notes: The values in the table represent NGA estimates and standard errors (SE) at low and high values of behavioural measure and impulsivity. Low and high values of the covariates were defined as a value representing the lower and upper quartile, respectively, of the empirical distribution of the covariates.

** NGA estimate (SE) for reaction time at the upper quartile (i.e., 75%) of the reaction time distribution*

***NGA estimate (SE) for reaction time at the lower quartile (i.e., 25%) of the reaction time distribution*

**** NGA estimate (SE) for number of correct responses at the upper quartile (i.e.,75%) of response accuracy distribution*

***** NGA estimate (SE) for number of correct responses at the lower quartile (i.e.,25%) of response accuracy distribution*

5 Discussion

5.1 Discussion of the first study (52)

5.1.1 Task performance and reaction times

ADHD patients in our study (52) made significantly more commission errors than controls, a finding which is in line with the literature (e.g.,29,40,44), despite the controversies previously discussed in this dissertation. Task performance regarding commission errors, however, was good in both study groups. The observed high performance could be explained by the applied long interstimulus interval. Regarding reaction times, in our first study (52) we found a rather modest, non-significant difference between ADHD and control subjects, where patients were faster than controls. This finding is in line with a significant number of previous observations of childhood ADHD (109,110), and is also congruent with some adult ADHD data (29,43,75,111). It is important to note, however, that prior results are equivocal both in terms of task performance and reaction time. This inconsistency might arise from the fact that available Go/NoGo studies of ADHD patients differ in many aspects including study size, task, instructions and clinical characteristics as well.

5.1.2 Reduction of the P1 early sensory ERP in adult ADHD patients

The main finding of our first study (52) is that adults with ADHD showed a reduced P1 amplitude. Since P1 is associated with basic visual processing and spatial attention and the amplitude of ERPs is believed to reflect the activation level of the activated neural population (68), a reduced P1 amplitude is thought to reflect an early sensory deficit in adults with ADHD.

While in the adult ADHD literature the study of later ERP components has been receiving the most attention, in schizophrenia research the P1 is considered an endophenotype measure (112), with consistently reduced amplitudes reflecting deficit in the early visual processing of the patients. In our first study, we also observed this P1 reduction with ADHD subjects, which can either be related to a limited capacity in focusing attention, or to a decreased gain control mechanism on early sensory responses (67,68). Some evidence, including Prox and colleagues (43) suggest that differences in later ERPs indicate that ADHD patients may overcome the described early sensory deficits by more effortful later processing. It is also stated that the P1 component is indeed “cognitively

penetrable", meaning that early information processing seems to be reciprocally modulated by higher processing areas (top-down effects). It could therefore be argued that in adult ADHD patients early sensory processing deficits contribute to susceptibility to distraction (inattention), and top-down control aims to adjust this impact on other ADHD core symptoms (such as inattention and impulsivity).

Evidence based on both parent-reported measures and psychological assessments suggests that the sensory profile of children with ADHD significantly differs from that of their typically developing peers, also in the visual domain (57).

We aimed to delineate these difficulties on the electrophysiological level, and in our first study we were able to observe early sensory processing in a detailed manner with a dense array EEG: altered P1 (with other early sensory ERP components) could provide further electrophysiological evidence to altered sensory processing in patients with ADHD.

With respect to the localization of the P1 amplitude alterations we found that those were not only observable on occipital regions, but differences between ADHD and control groups were found regarding the P1 component on left-inferior-frontal and infero-temporal EEG channels as well. Based on the this topographical distribution, it is conceivable that the findings may reflect, at least in part, the activity of he ventral pathway (going from V1 through V2 and V4 to areas of the inferior temporal lobe), but this would require further confirmation in future studies. Evidence suggests that the left inferior frontal gyrus (IFG) plays an important role in top-down control, and is reciprocally connected to more posterior regions, including lateral temporal cortices (113). For example, Bitan and colleagues (113) examined top-down control among various brain regions in a phonological test using functional magnetic resonance imaging (fMRI) and found that the left IFG elicits a selective enhancement of task-specific processing in posterior brain regions. In this region, we also found a decreased P1 amplitude in our first study, which is therefore congruent with the idea of a weakened top-down control in ADHD for the processing of task relevant versus task-irrelevant information (114), which may be due to neurodevelopmental changes that were described in ADHD, especially in the frontal areas (98,115).

5.1.3 Associations between P1 and clinical symptoms

In our first study (52) we also aimed to investigate whether alterations in the early sensory processing stages in ADHD are related to psychopathological symptoms. To measure clinical symptomatology, the Conners' Adult ADHD Rating Scale was used (101). Regarding P1 reduction, we found that it correlated with symptoms of inattention: namely, our subjects with higher inattention scores showed more pronounced electrophysiological changes at posterior scalp sites. However, regarding the connection between hyperactivity and P1 amplitude, we found that lower amplitudes were associated with lower symptom severity. These findings of our first study are consistent with the idea that symptom presentation in ADHD may be diverse and possibly reflect multiple aetiologies and are also in line with the ideas of Sokolova and colleagues (116). Their causal model considers inattention a driving factor for hyperactivity/impulsivity, while those factors leading to high hyperactivity/impulsivity do not necessarily conduct to higher inattention. From another perspective, we can view inattention in the context of a possible sensory deficit: in this context, poor inattention may be modulated by higher hyperactivity through a pathological compensatory gain control mechanism.

To our knowledge, our first study (52) was the first to examine whether alterations in the early sensory processing stages in ADHD are related to detailed psychopathological symptoms.

5.1.4 Limitations of the first study (52)

Our first study (52) has certain limitations, one of which is that a subset of patients received medication. However, it is important to note that we performed subsidiary analyses to examine the impact of medication status on our findings and found that results remained statistically significant even after the adjustment for medication status. Another limitation to note is that although the patient and control groups differed regarding task performance, the relatively good task performance in the ADHD group combined with the low probability of NoGo stimuli did not make it possible to perform separate analyses on correct and false NoGo trials.

5.2 Discussion of the second study (76)

In our second study (76) we aimed to investigate the behavioural and electrophysiological correlates of inhibitory processing during a visual Go/NoGo paradigm in adult ADHD patients and healthy controls.

5.2.1 Go-NoGo GFP in the P3 latency range

As for GFP, in our second study (76) we found that adult ADHD patients had a significant reduction in the Go-NoGo GFP in the P3 latency range compared to controls. This finding of an altered topographical distribution and less spatial variation of ADHD subjects suggests a complex neurophysiological dysfunction present in the disorder.

5.2.2 P3 NoGo anteriorization

We aimed to perform a thorough literature overview to interpret the main finding of our second study (i.e., that adult ADHD patients are characterized by a reduced P3 NGA) (76). The presence of a diminished NGA in ADHD is consistent with a prior study, which reported lower NGA in children with ADHD (85), and also with later findings of Fallgatter and colleagues (92), in which they reported that reduced NGA values were present in adult patients with ADHD-related psychopathology during childhood (i.e., persisting ADHD). Also congruent with our finding, past research including a large number of adult ADHD patients found a tendency of lower NGA values in patients as compared to controls (94). Contrary to previous research, which placed less emphasis on a thorough clinical diagnosis of adult ADHD and used low sensor density/sparse spatial sampling for EEG recordings, in our second study we included adult ADHD subjects with an established ADHD diagnosis and had an EEG spatial resolution superior to previous publications (85,92,94). Our results of a reduced P3 NoGo anteriorization are therefore in line with, and further extend previous findings in these relations.

Based on previous research supporting this EEG alteration, NGA is thought to reflect the mechanisms of prefrontal response control (90,91), however, some might argue that reduced NGA is instead a neural marker of a general executive dysfunction. Since in our second study we found that NGA was strongly associated with impulsivity, our findings also support the notion that NGA is more likely to reflect a more specific impairment of the inhibitory control subdomain rather than a general executive dysfunction. Other research, including the study of Nash at al. (91) is also consistent with the suggestion that

NGA reflects inhibitory control: in their study they demonstrated NGA to be a predictor of self-control in a social exchange game, more specifically they found that greater NGA was associated with better self-control.

Our finding of a lower NGA is in agreement with the presence of inhibitory control problems on the behavioural level and executive dysfunctions related to the prefrontal cortex supported by neuropsychological tests (e.g.,117) and also with neuroimaging studies describing lower brain activation in frontal regions of adult ADHD patients using various task paradigms focusing on inhibition and inattention (118,119).

In our second study we aimed to achieve a deeper understanding of the NGA alteration in ADHD, therefore we applied various analytical approaches to investigate the anteriorization and found that our results of a lower NGA in adult ADHD patients were observable regardless of the applied analysis. These data provide convergent evidence for the alteration of NoGo anteriorization and strengthen the validity of the findings.

The possibility that diminished NoGo anteriorization is a result of altered neurodevelopment in ADHD requires some consideration: since a growing number of neuroimaging studies demonstrate that the human brain has a high plasticity (120) throughout the lifespan (121–123), the lack/lessening/impairment of anteriorization could be the result of an altered neurodevelopmental pathway of prefrontal cortex maturation in attention-deficit/hyperactivity disorder.

5.2.3 The role of medication on NoGo anteriorization

As previously outlined, NoGo studies differ in clinical characteristics, making the comparison of results difficult. Medication is an often neglected, but important clinical aspect of electrophysiological studies on adult ADHD. Therefore, we believe it is necessary to investigate the role of medication on NGA. While EEG correlates of methylphenidate administration were reported earlier (e.g., 124–126), in those studies the NGA was not in the focus.

In our second study (76) we found that the use of methylphenidate was associated with a more pronounced NoGo anteriorization: the NGA values of patients taking methylphenidate were closer to the NGA values of controls. This electrophysiological finding is congruent with the behavioural effect of stimulants on impulsivity (e.g., 127).

While the primary goal in our second study was to investigate NoGo anteriorization deficits in our group of adult ADHD patients in a specific task condition, this above described finding of the "normalization" effect of methylphenidate on NGA further highlights the value of this measure. Since, as Fallgatter and colleagues (93) previously suggested, NGA is considered to be a neurophysiological correlate of response control, our findings, that clinically more severe impulsivity is linked with a lower NGA outline a connection between clinical characteristics, executive functions and electrophysiological measures.

5.2.4 Associations between NoGo anteriorization and clinical characteristics

As underlined earlier, in our second study (76) we wanted to put emphasis on the associations between NoGo anteriorization on clinical characteristics. To do so, we did not only analyse the role of medication on NGA as described in the previous section, but also the relations between NGA, symptom severity and behavioural measures (and a combination of these factors). Symptom severity was measured by the related CAARS subscales. To have a deeper understanding of these associations, we examined the relationship between a) reaction time, impulsivity and NGA, and b) number of correct responses, severity on the CAARS Impulsivity subscale and NoGo anteriorization. In our analyses, we found that the most the prominent alterations in NGA were linked to a covariation of certain behavioural and clinical measures, such as fast reaction times and high error rates combined with high impulsivity in ADHD subjects. The simultaneous presence of these factors which are associated with the most diminished NGA makes it possible to identify a group of patients where inhibitory control dysfunction is most prominent (on the electrophysiological level).

5.2.4 Limitations of the second study (76)

Our second study (76) has its limitations as well, the first one that needs to be addressed is the relatively small sample size, which - while similar to the sample sizes used in other ERP studies (41,45,92) - did not allow for detailed analyses regarding ADHD subtypes. Also, it is important to mention that while the ADHD and control groups significantly differed regarding task performance, the overall task performance was good, which did not enable adequate group separation in some aspects including correct and false NoGo

responses. A further study limitation is that the instruction we applied (to respond as quickly and accurately as possible) might have resulted in some participants focusing on speed and some on accuracy, leading to different behavioural outcomes. Additionally, it is important to mention that approximately half of the patients received medication, and about one-third had comorbidities. However, our main results were not influenced when we included medication and comorbidity status in the analyses. Finally, in terms of generalizability recruitment of controls from clinical staff and their relatives can also be considered as a limitation, although it is a common practice in the literature. Despite the above listed limitations, the decreased NGA observed in our second study underlines the importance of inhibitory control dysfunction in adult ADHD at the neurophysiological level and requires further research.

6 Conclusions

6.1 Conclusions of the first study (52)

Our first high density ERP study (52) 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 address these alterations more explicitly.

6.2 Conclusions of the second study (76)

The main finding of our second study (76) was 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 (85).

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 (85), 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. Also, the finding that the NGA values of patients taking methylphenidate were closer to the NGA values of controls indicates that NGA could serve as a predictor of pharmacotherapeutical response. When replicated, our findings suggest that clinical application of novel neuromodulation treatments such as neurofeedback or non-invasive brain stimulation could make use of NoGo anteriorization as a reliable index of prefrontal response control (deficit).

6.3 General conclusions

With the help of dense-array EEG recording, which makes allowance for a high topographical resolution, in two consecutive electrophysiological studies 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 at the neurophysiological level contribute to susceptibility to distraction (inattention) in the presence of a (deficient) top-down core control aiming to adjust this, consistent with growing evidence suggesting this phenomenon being reciprocal (33, 45, 62, 128). Therefore, in further studies it is key 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.

7 Summary

The aim of the two consecutive high-density EEG studies presented in this dissertation was to investigate the electrophysiological characteristics of early information processing and inhibitory control in adult ADHD, both of which have been shown to be deficient in the disorder on the symptomatic level.

In the first study (52) we applied a Go/NoGo task to investigate the P1 event-related potential and found that ADHD patients had a significantly reduced P1 component at occipital and inferotemporal scalp areas compared to controls. Regarding P1 reduction, we found that it correlated with symptoms of inattention and hyperactivity, however in an opposite direction, which is consistent with the idea that symptom presentation in ADHD may be diverse and possibly reflect multiple aetiologies. Our findings therefore indicate that deficits in early sensory processing are present in adult ADHD patients and are associated with symptom severity. These findings are suggestive of bottom-up cognitive deficits in ADHD driven by impairments in early visual processing, and provide evidence that sensory processing problems are present at the neurophysiological level in patients with adult ADHD.

In our second study (76) we investigated the anteriorization of the P3 brain response associated with the NoGo task condition in our adult ADHD patient population and found that patients with ADHD had a significantly diminished P3 NGA response compared to controls. The decrease in NGA was related to important clinical characteristics: patients with higher impulsivity scores had significantly lower NGA, while treatment with stimulant medication, as compared to the lack of such treatment, was associated with a correction of the lower NGA response in ADHD patients. The finding of a diminished NoGo anteriorization in adult ADHD patients is consistent with the inhibitory control and frontal lobe dysfunctions described in the disorder. The inverse relationship between NGA and impulsivity suggests that clinically more severe impulsivity is linked to a more pronounced frontal dysfunction in adult ADHD subjects.

Overall, the findings from the two consecutive studies (52, 76) highlight the importance of focusing 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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11 Acknowledgements

First of all, I would like to thank my supervisor, Dr. Pál Czobor for his time, support and patience. His deep knowledge and motivation have helped me through my PhD studies and further along in my professional carrier as well. I am very grateful for his continuous guidance. Without the insight he provided to research I could not have become the professional I am today.

I would also like to thank Professor István Bitter, former chair of the Department of Psychiatry and Psychotherapy, Semmelweis University for trusting me with the participation in this research and for his support along all these years.

I am grateful for Professor János Réthelyi, the current chair of our department for his support and encouragement.

It will always be a pleasure to remember the time I spent in Utrecht, under the supervison of Professor Sarah Durston, who became my inspiration in team leading and warm professional attitude. I would also like to thank her for her support.

I thank my fellow colleagues for the research work we did together. In particular, I am grateful for Dr. Brigitta Kakuszi and Dr. László Tombor for their help during the EEG recordings and processing and during the times when motivation and support was most needed.

I would also like to thank my colleagues at the Adult ADHD Outpatient Clinic for their clinical work, which enabled us to have our participants.

I am also grateful for all participants who took part in the research.

I also would like to thank my family for their support, not only during my studies, but through all my life. I will forever be grateful to my mother, who was my role model in patient care and hard work, and to my father, who has always believed I can reach any goal. As for supporting me during all these years, I am grateful for my close friends, my sister, my husband and our children and my wonderful colleagues.