Behavioural and cognitive relevance of evoked gamma-band responses in ADHD patients and healthy children

Dissertation

zur Erlangung des akademischen Grades

doctor rerum naturalium
(Dr. rer. nat.)

genehmigt durch die Fakultät für Naturwissenschaften
der Otto-von-Guericke-Universität Magdeburg

von Dipl.-Psych. Daniel Lenz
geb. am 8. Dezember 1979 in Magdeburg

Gutachter: Prof. Dr. Christoph S. Herrmann
Prof. Dr. Canan Başar-Eroglu

eingereicht am: 28. Juli 2009
verteidigt am: 29. Oktober 2009

I am among those who think that science has great beauty. A scientist in his laboratory is not only a technician: he is also a child placed before natural phenomena which impress him like a fairy tale.

Marie Curie

Contents

List of Figures

List of Tables

CHAPTER 1

Introduction

Justin is a ten year old boy. His school teachers often complain that he is easily distracted and not able to persistently work in class, disturbing the learning environment for the other schoolmates. In a similar vein, his parents also stress that he often jumps between different activities such as playing various games or doing his homework, bringing none of them to an end. During the meals, he shows difficulties to remain seated, stands up, and runs around in the dining room. He is constantly on the move, even during playing or watching TV. His parents report that Justin already showed this behaviour since early childhood in kindergarten, but they are bothered more and more because of the growing number of problems at school and at home.

Justin shows typical symptoms associated with attention-deficit/hyperactivity disorder (ADHD), which is one of the most frequently diagnosed and most stable psychiatric disorders in childhood and adolescence (Biederman and Faraone, 2005). Starting as early as in preschool ADHD often persists up to adulthood (see Faraone et al., 2000, for review). According to the Diagnostic and Statistical Manual (DSM-IV), patients are characterised by developmentally inappropriate degrees of inattention, impulsivity, and hyperactivity, affecting their life in a variety of contexts such as school, family, and peer relationships (American Psychiatric Association, 1994). Although ADHD is extensively studied employing various research approaches, there is still no clear picture on the exact etiology of this disorder.

The current thesis closes a gap in neuropsychiatric research on the etiology of this disorder: During the past 30 years there has been a growing number of electrophysiological studies aiming to identify neural correlates of ADHD in the elec-

troencephalogram (EEG) by means of analysis of spontaneous as well as event-related brain activity. In different tasks and conditions, the spontaneous EEG of ADHD patients was characterised by cortical slowing reflected in significantly enhanced activity in lower frequencies of the human EEG and, at the same time, decreases of amplitudes at higher frequency ranges (e.g. Mann et al., 1992; Monastra et al., 1999).

Furthermore, event-related potentials (ERPs; see Chapter 4.2) were also used to assess the nature of the cognitive impairments in ADHD. Amplitude differences in various components associated with attending to and processing of incoming information have been observed (e.g. Satterfield et al., 1988; Brandeis et al., 2002; Barry et al., 2003a), especially indicating deficient preferential processing of attended stimuli (Satterfield et al., 1994). However, these studies typically focused on brain activity up to 30 Hz of human EEG, neglecting EEG activity in the gamma frequency range (30 Hz - 80 Hz). This is surprising since gamma oscillations in human EEG correlate with attention and memory processes being impaired in ADHD (Herrmann et al., 2004c). In addition, high-frequency EEG activity in the gamma range was also found to be associated with coding information associated with motor activity (Schnitzler and Gross, 2005; Gonzalez et al., 2006). Thus, it seems plausible to assume that ADHD problems such as inattention or hyperactive behaviour might be directly related to altered excitation levels reflected in the gamma-band (Herrmann and Demiralp, 2005). As evoked gamma-band responses (GBRs; see Chapter 4.3.1 for an introduction on the classification of brain oscillations) belong to the first cortical responses measureable in the EEG, impairments at this early stage could have large impact on further information processing. The etiology of ADHD rises further support for associating possible gamma-band abnormalities with ADHD: Although multiple factors are thought to account for the disorder (Spencer et al., 2002; Swanson et al., 2007), there is broad evidence for a genetic component (Thapar et al., 2005). Interestingly, genetic variations within the dopamine neurotransmitter system that are linked to ADHD (DAT1 and DRD4 polymorphisms) have been also related to high-frequency activity in the gamma-band (Demiralp et al., 2007). Thus, it seems plausible to assume that impairments of ADHD patients in cognition and behaviour might be directly related to altered gamma oscillations. Therefore, the studies presented in this thesis aimed to elucidate the role of altered gamma oscillations in ADHD patients during sensory encoding, evaluation, and classification of incoming visual information.

In the following chapter, I give a brief overview on the primary symptoms of ADHD (Chapter 2.1.1) and its neurobiological (Chapter 2.1.2) and neurophysiological background (Chapter 2.1.3) as well as the role of gamma oscillations in healthy states of cognition and behaviour (Chapter 2.2). Subsequently, I outline my research questions (Chapter 3) and the general methodological approach be-

ing the basis for the studies presented in this thesis (Chapter 4). Afterwards, I describe three experiments that were designed to specifically investigate early visual processing of ADHD patients in comparison to healthy participants by means of evoked GBR analysis.

In Experiment I (Chapter 5) I assessed gamma-band activity of ADHD patients during memory encoding in a short-term memory paradigm and compared the results with those revealed in healthy participants. In a subsequent recognition test, participants had to judge pictures as being old or new. Besides the comparison of evoked GBRs of ADHD children and healthy controls, a possible link between evoked GBRs during stimulus encoding and performance in the recognition test was investigated to associate behavioural performance with evoked GBR amplitudes in both groups.

In Experiments II & III (Chapter 6) the role of evoked GBRs in healthy participants and ADHD patients during early classification of visual information was more precisely examined as evoked GBRs have also been assigned a pivotal role during early stimulus evaluation and memory based classification (Herrmann et al., 2004c). Therefore, disturbed early memory based classification processes reflected by evoked GBRs could be a possible neuronal correlate of an early dysfunction in information processing that might be directly related to the ADHD pathophysiology. The experimental procedure was based on a paradigm that emphasised the crucial role of evoked GBRs during early visual processing in healthy adults (Herrmann et al., 2004b), showing clear enhancements of evoked GBRs following stimuli already represented in memory. Experiment II served as a pilot study to elucidate whether healthy children already demonstrate enhanced evoked GBRs for known stimuli as reported for healthy adults employing the identical experimental procedure and stimulus material as in the investigation of healthy adults (Herrmann et al., 2004b, Chapter 6.2). A modified stimulus set was utilised in Experiment III, enabling the direct comparison of evoked GBRs of ADHD patients during early memory processes with an age matched sample of healthy participants. I investigated whether these evoked GBR patterns at an early processing stage could be indicative of an early visual processing deficit in ADHD patients (Chapter 6.3).

CHAPTER 2

Theoretical background

2.1 Attention-Deficit/Hyperactivity Disorder

2.1.1 Prevalence and primary symptoms

ADHD children are characterised by developmentally inappropriate degrees of inattention and distractability, impulsivity, and hyperactivity (Barkley, 2006), affecting a wide range of their life and yielding a variety of impairments including academic and social dysfunction, fine and gross motor skill deficits, and poor self-esteem (Spencer et al., 2002). They often show permanent activity shifts, daydreaming behaviour, a low frustration tolerance, or seem to be always 'on the run'. As summarised by Spencer et al. (2002), a worldwide prevalence between 3% and 9% can be assumed for children to get diagnosed with ADHD. On average, the number of males has been found to be six times higher than of females (Barkley, 2006). In contrast to earlier reports suggesting a full symptom remission in adulthood, 15% of the patients still meet the full criteria of ADHD at the age of 25 and 65% show only partial remission (Faraone et al., 2006).

The Diagnostic and Statistical Manual in its 4th revision classifies three different ADHD subtypes according to the presence and severity of the specific symptom clusters *inattention* and *hyperactivity-impulsivity* (redrawn from DSM-IV, American Psychiatric Association, 1994):

Inattention

The criterion of *inattention* is met, if six or more of the following symptoms have persisted throughout the last six month.

The child

- often fails to give close attention to details or makes careless mistakes in schoolwork, work, or other activities.
- often has difficulty sustaining attention in tasks or play activities.
- often does not seem to listen when spoken to directly.
- often does not follow through on instructions and fails to finish school work, chores, or duties in the workplace (not due to oppositional behaviour or failure to understand instructions).
- often has difficulty organising tasks and activities.
- often avoids, dislikes, or is reluctant to engage in tasks that require sustained mental effort (such as schoolwork or homework).
- often loses things necessary for tasks or activities (e.g. toys, school assignments, pencils, books, or tools).
- is often easily distracted by extraneous stimuli.
- is often forgetful in daily activities.

The criterion of *hyperactivity-impulsivity* is met, if six (or more) of the following symptoms of hyperactivity or impulsivity have persisted for at least 6 months to a degree that is maladaptive and inconsistent with developmental level.

Hyperactivity

The child

- often fidgets with hands or feet or squirms in seat.
- often leaves seat in classroom or in other situations in which remaining seated is expected.
- often runs about or climbs excessively in situations in which it is inappropriate.
- often has difficulty playing or engaging in leisure activities quietly.
- is often 'on the run' or often acts as if 'driven by a motor'.
- often talks excessively.

Impulsivity

The child

- often blurts out answers before questions have been completed.
- often has difficulty awaiting turn.

- often interrupts or intrudes on others (e.g. butts into conversations or games)

According to these symptom clusters, the predominantly inattentive type (fulfilling the criterion *inattention* but not *hyperactivity-impulsivity*), predominantly hyperactive-impulsive type (fulfilling the criterion *hyperactivity-impulsivity* but not *inattention*), and combined type (fulfilling both criteria for the last six month) can be distinguished. As summarised by Spencer et al. (2007), the combined subtype is the most commonly diagnosed subgroup (50%-75%), followed by the predominantly inattentive subgroup (20%-30%), and the predominantly hyperactive-impulsive subtype (less than 15%). However, it has to be noted that there is an ongoing discussion whether these DSM-IV defined subtypes exist at all or whether especially the inattentive and combined subtype might represent qualitatively different syndromes with diverging physiological and neuronal background (Clarke et al., 2002; Barkley, 2003). Barkley (1997) emphasised that the inattentive subtype, typically showing daydreaming behaviour and being easily confused, has a general deficit in information processing speed and specific problems in focused or selective attention, whereas the combined subtype can be characterised by impaired sustained attention and enhanced distractability.

To meet the diagnosis of ADHD, the described symptoms have to

- be present before the age of 7 years.
- be present in at least two or more settings (e.g. at school as well as at home).
- be clinically significant in social, academic, or occupational functioning.
- not occur exclusively during the course of a pervasive developmental disorder, schizophrenia, or other psychotic disorder and are not better accounted for by another mental disorder (e.g. mood disorder, anxiety disorder).

However, although these criteria sound relatively clear and straightforward, diagnosis of ADHD is often difficult as the child's behaviour has to be estimated within a continuum between normal, non-pathological and pathological states, not being separated by a clear boundary between both extremes. Thus, ADHD is a disorder that cannot be assessed by objective testing, resulting in a score that indicates its presence or absence. Rating scales may help during the assessment of individual ADHD symptoms and document therapy progress, but should not be used as a substitution for an elaborated diagnostic evaluation by experienced clinicians incorporating information from different sources such as parents, teachers, and the child himself (Collett et al., 2003).

Besides the described ADHD symptoms, patients often present other comorbid

disorders: Epidemiological as well as clinical studies reported especially the co-occurrence of oppositional defiant disorder (ODD) and conduct disorder (CD) in 30% to 50% of the ADHD patients (Biederman et al., 1991; Spencer et al., 2002). Furthermore, also learning disabilities (Mayes et al., 2000; McGillivray and Baker, 2009), tic disorders (Spencer et al., 1999; Banaschewski et al., 2007), and anxiety disorders (Schatz and Rostain, 2006) have been found to coexist with ADHD.

2.1.2 Neurobiological and cognitive models

ADHD has been identified as a biopsychosocial disorder (Tannock, 1998) whose etiology incorporates multiple interacting developmental and environmental factors (Spencer et al., 2002; Swanson et al., 2007) such as low birth weight and complications during pregnancy and birth (Mick et al., 2002) as well as maternal cigarette or alcohol abuse during pregnancy (Huizink and Mulder, 2006). However, there is also broad evidence for an interaction of these factors with neurobiological influences, involving e.g. a genetic component (Thapar et al., 2005): Studies reporting an increased ADHD probability for parents and siblings of ADHD children support the notion of a familial heritability and high involvement of genetic factors in ADHD (Thapar et al., 1995; Faraone and Biederman, 1998; Durston, 2008). In molecular genetic approaches, candidate genes especially involved in dopaminergic neurotransmission have been most widely confirmed (Durston et al., 2009), e.g. the 7-repeat isoform of the 48-base pair variable number of tandem repeats (VNTR) polymorphism in exon 3 of the dopamine D4 receptor gene DRD4 (LaHoste et al., 1996; Faraone et al., 1999, 2001; Langley et al., 2004) and a 10-repeat allel polymorphism at the dopamine transporter gene DAT1 (Cook et al., 1995; Gill et al., 1997). Studies using knock-out mice provide an animal model for the association between specific candidate genes and ADHD (Giros et al., 1996). Furthermore, it has been demonstrated that these variations might result in an increased density and activity of striatal dopamine transporters in ADHD patients (Dougherty et al., 1999; Krause et al., 2000), leading to lowered dopamine concentrations within the synaptic cleft (Solanto, 2002; Vles et al., 2003). Hyperactive behaviour has been associated with hypo- as well as hyperfunctioning of dopaminergic signal transmission, indicating that both extremes could produce behavioural and cognitive dysregulations (Castellanos and Tannock, 2002). Grace (2001) proposed a model of this dopamine dysfunction that distinguishes between tonic and phasic dopaminergic activity. Here, ADHD patients are characterised by lowered tonic dopaminergic activity resulting in a decline of tonic stimulation of presynaptic inhibitory autoreceptors. These autoreceptors modulate stimulus driven, phasic dopamine discharges. Thus, decreased activation of autoreceptors yields enhanced phasic activity that might cause dysregulated motor and impulse control (Grace, 2001). Notably, medical treatment employing methylphenidate blocks dopamine transporters (Kuczenski

and Segal, 1997; Solanto, 2002; Krause, 2008) and increases the level of extracellularly available dopamine (Krause et al., 2000; Volkow and Swanson, 2003). As a result, tonic dopamine levels elevate the stimulation of presynaptic autoreceptors and, therefore, attenuate phasic dopamine release and postsynaptic activation to normal levels (Grace, 2001; Seeman and Madras, 2002; Levy, 2004).

These results suggest that specific genetic polymorphisms especially within neurotransmission might increase the risk for ADHD involving especially a catecholamine dysregulation. Moreover, these genetic factors also interact with environmental conditions, possibly causing the heterogeneous picture of ADHD (Castellanos and Tannock, 2002). Additionally, there is evidence that the reported genetic variations might not only affect brain biochemistry, but also brain structure: Structural imaging studies reported associations between DAT1 genotype and caudate volume as well as DRD4 genotype and prefrontal gray matter volume, respectively (Durston et al., 2005). These results were not caused by a general reduction in volume, but have been specifically observed in those regions where the genes are predominantly expressed. Preliminary data by Durston et al. (2008) suggested differential effects of DAT1 genotype also on functional brain activiation of ADHD patients, e.g. striatal activity during Go/No-Go tasks. However, it has to be noted that similar gene variations can also be observed in healthy humans (Demiralp et al., 2007) and, that not all ADHD patients exhibit the reported polymorphisms (LaHoste et al., 1996). Therefore, an interaction of several genes with modest effects might account, at least in parts, for ADHD origin (Faraone and Biederman, 1998).

The imbalances in dopaminergic and noradrenergic neurotransmission reported above can also be linked to specific cognitive dysfunctions observed in ADHD patients within the fronto-striatal executive network (Cropley et al., 2006; Durston, 2008): The ability to inhibit prepotent courses of action is one of the internally driven acts of self-regulation within the higher-order executive functions system (Tannock, 1998). ADHD has been linked to dysfunctions in response inhibition, working memory, and other aspects of executive functions (Doyle, 2006; Biederman et al., 2007). ADHD patients demonstrate a response inhibition deficit (Oosterlaan et al., 1998; Nigg, 2001; Johnstone and Clarke, 2009), as evident in poor inhibitory reactions to stop-signals. Barkley (1997) argued that this deficit might also account for further executive dysfunctions that depend upon behavioural inhibition. The assumption of impaired inhibition underlying the cognitive deficits is challenged by the delay aversion theory involving altered reward mechanisms as represented in a shortened delay gradient (Sonuga-Barke, 2002). Delay aversion has been investigated in ADHD patients and is expressed as intolerance or aversion for waiting, e.g. choosing immediate rewards instead of larger, but delayed rewards (Tripp and Alsop, 2001; Castellanos and Tannock, 2002; Sonuga-Barke, 2005; Bitsakou et al., 2009). Within this theory, hyperac-

tive behaviour might indicate stimulation seeking behaviour as a compensation for unavoidable and aversive delays (Antrop et al., 2000; Thorell, 2007). Interestingly, a shortened delay gradient has also been associated with a higher striatal dopamine transporter density that reduces the availability of dopamine in the synaptic cleft (Madras et al., 2002; Castellanos and Tannock, 2002). Thus, the delay aversion hypothesis conceptualises ADHD symptoms not as an impaired ability of response inhibition, but rather as a rational choice to avoid an aversive delay suggesting that the overall delay rather than prerewarded delay or reward size is a key motivational factor involved in the reported impulsive behaviour (Solanto et al., 2001).

With respect to one of the core symptoms of this disorder, inattention, an impaired ability in sustained and selective attention has been reported (Konrad et al., 2006) causing dysfunctions in the ability to direct and reallocate attentional resources and ignoring irrelevant information (Tamm et al., 2006). This is also evident in a poor performance in continuous performance tasks: Here, ADHD patients demonstrate a slower and less efficient performance during visual serial search tasks originating from a disproportionately interference by distracting stimuli also affecting fluent shifts of the attentional focus (Carter et al., 1995; Weiler et al., 2002; Shalev and Tsal, 2003). Similar support for difficulties in restricting the attentional spotlight has been demonstrated using flanker tasks that require the ability to direct attention selectively to a limited part of available information (Shalev and Tsal, 2003).

Thus, Castellanos and Tannock (2002) summarised these findings in a psychological construct of ADHD that includes three major dysfunctions: a shortened delay gradient (aversion of delays), impaired response inhibition (executive motor inhibition deficit), and a deficit in arousal regulation.

Within the last years, neurophysiological research on ADHD pointed out several structural and functional brain abnormalities that are involved in the aforementioned processes. For a direct assessment of brain structure and functioning imaging studies allow the localisation of brain dysfunctions, whereas electrophysiological studies assess the time course of deficits during information processing. As stated above, the underlying neuronal correlates of the mentioned executive deficits are presumed in prefrontal regions associated with planning, attention, and behavioural inhibition supporting the concept of a dysfunction of frontosubcortical pathways in ADHD (Spencer et al., 2002). Although often not consistent (Tannock, 1998), structural and functional brain abnormalities in the frontal cortex, but also parietal regions, the anterior cingulate cortex, cerebellum, the basal ganglia, or even a total decline of cerebral volume could be observed (e.g. Rubia et al., 1999; Castellanos et al., 2002; Bush et al., 2005; Konrad et al., 2006; Sheridan et al., 2007).

However, while structural or functional imaging studies allow the localisation of brain dysfunctions in ADHD patients, they are imprecise on the temporal course underlying those deficits. Here, electrophysiological approaches utilising the EEG are advantageous. Even more, EEG studies revealed that ADHD patients present deficits at very early stages of information processing that could lead to the above mentioned dysfunctions. Therefore, the current state of research on EEG differences between ADHD patients and healthy participants is summarised in the next chapter.

2.1.3 Neurophysiology

Characteristics of spontaneous EEG

Quantitative EEG involves the analysis of the spectral characteristics of the raw EEG signal in circumscribed frequency bands of oscillatory brain activity (see Chapter 4.3 for an introduction) and reveals the power of electrophysiological activity in dependence of the studied frequency range.

Studies based on quantitative analysis of raw EEG consistently show differences between ADHD patients and healthy participants during rest as well as different cognitive states such as reading or drawing (Barry et al., 2003a). Among the most prominent findings, increased slow wave activity in the theta-range has been observed especially over frontal areas, whereas beta power is decreased which is also evident in an enhanced theta/beta ratio (e.g. Mann et al., 1992; Chabot and Serfontein, 1996). Monastra et al. (1999) provided interesting support for utilising these EEG measures for neurometric testing within ADHD diagnostic and revealed a sensitivity of 86% and a specifity of 98% for ADHD classification based on theta/beta power ratio. In contrast, there is evidence that a specific EEG subtype of ADHD patients presents elevated alpha levels (Swartwood et al., 2003) as well as enhanced beta power (Chabot and Serfontein, 1996; Clarke et al., 2001c) representing increased cerebral activity. Studies aiming to differentiate ADHD subtypes based on the analysis of the EEG frequency spectrum yielded no clear solutions how these subtypes differ in their spectral power. In a study by Clarke et al. (1998), ADHD children of the predominantly inattentive subtype were found to be significantly different from those of the combined subtype, being more closer to the EEG profiles of healthy children. They concluded that this might represent a difference in the severity of ADHD symptoms rather than a different neurological dysfunction. However, there also seem to exist distinct EEG subtypes that are independent from the current subtype classification defined in the DSM-IV (Clarke et al., 2001b,a). According to Clarke et al. (2002), three different EEG subtypes can be distinguished, comprising a cortical hypoarousal subtype, a maturational-lag subtype, and a subtype with an excess of beta ac-

tivity. Although these results were based on diverging clinical samples, EEG assessments, and mental states of the participants, they point to a distinction of ADHD patients in different EEG subtypes. These subtypes either demonstrate underarousal or neuronal hyperfunctioning in the EEG, respectively, and do not necessarily correspond to the ADHD subtype classification of the DSM-IV (Clarke et al., 2002).

Interestingly, these distinctive differences in the EEG power spectrum of ADHD patients have been targeted by new treatment approaches such as neurofeedback therapy (Monastra et al., 2005; Heinrich et al., 2007). As early as in 1976, Lubar and Shouse (1976) were the first to observe behavioural improvements in a hyperactive child after neurofeedback training aiming to reduce theta power and, at the same time, reinforcing power of the sensory motor rhythm (SMR; 12–14 Hz) that is associated with motor inhibition abilities. Subsequently, similar results have been reported in other studies applying also protocols to decrease theta activity and increase beta or SMR power (e.g. Lubar et al., 1995; Linden et al., 1996; Thompson and Thompson, 1998; Gevensleben et al., 2009). Furthermore, Fuchs et al. (2003) demonstrated comparable improvements of ADHD symptoms after neurofeedback treatment as in a control group that was treated with methylphenidate. When neurofeedback is used supportive to a medical treatment employing methylphenidate, these improvements even seem to persist after discontinueing the medication (Monastra et al., 2002).

Event-related potentials

Analysis of ERPs allows the investigation of the exact time-course of neuronal processing of incoming information. Being time-locked to the onset of some event, the signals can be evaluated with respect to the amplitude or latency of specific ERP components involved in event processing (see Chapter 4.2 for an introduction).

Several ERP differences have been reported for ADHD patients compared to healthy participants (Barry et al., 2003b). One of the most common findings is an altered P3 response, a component associated with attended processing and discrimination of sensory information (Polich, 2007). ADHD patients exhibit smaller amplitude differences between attended (relevant) and unattended (irrelevant) stimuli when compared to healthy children, indicating insufficient preferential processing of task-relevant stimuli (Satterfield et al., 1994). However, while differential P3 differences and overall diminished P3 amplitudes have been consistently reported (e.g. Johnstone and Barry, 1996; Kemner et al., 1996; Jonkman et al., 1997; Brandeis et al., 2002), it is less clear whether these deficits are preceded by impaired earlier processing stages that might indicate inefficient early filter stages (Tannock, 1998; Jonkman et al., 2004). For the auditory domain,

impaired early processing stages have been concluded from amplitude differences at various components: Smaller N1 amplitudes following target stimuli were related to selective attention problems found in ADHD patients (Satterfield et al., 1994; Johnstone and Barry, 1996; Kemner et al., 1996). Furthermore, enhanced P2 amplitudes (Oades et al., 1996; Satterfield et al., 1994) were associated with an atypical inhibition of sensory input from further processing (Johnstone et al., 2001). Diminished N2 amplitudes to attended target as well as standard stimuli were linked to an impaired discrimination of task-relevant stimuli (Satterfield et al., 1990, 1994; Johnstone and Barry, 1996). However, contrary findings are reported for early visual processing (Tannock, 1998): Impaired filtering or orienting during early stages of visual stimulus evaluation have been demonstrated in reduced P1 (Kemner et al., 1996) and enhanced P2 amplitudes (Robaey et al., 1992) as well as delayed peak latency of the N1 (Karayanidis et al., 2000). These results are in contrast to findings of intact early visual processing at these early stages (Satterfield et al., 1994; Novak et al., 1995; Strandburg et al., 1996). Therefore, it is still unclear whether early visual processing deficits contribute to the ADHD pathology or not.

Event-related oscillations

Another approach to study event processing in ADHD patients in comparison to healthy participants is the analysis of frequency dynamics reflected by event-related changes in the amplitude of specific oscillatory EEG responses (event-related oscillations, EROs).

In the past, there have been only two studies investigating EROs of ADHD patients in comparison to healthy participants, highlighting differences in the theta as well as gamma frequency range of the EEG. Yordanova et al. (2006) analysed event-related theta oscillations in an auditory selective attention task in an early (0-200 ms) and late (200-450 ms) time interval. They observed enhanced early event-related theta oscillations only in ADHD children with coexisting tic disorder, whereas ADHD patients without tics and children with tic disorder without coexisting ADHD did not differ significantly from healthy participants (Yordanova et al., 2006). Additionally, they reported enhanced late event-related theta oscillations in both groups, ADHD-only and ADHD+tics. However, this effect was mediated by a generally enhanced spontaneous theta level in ADHD patients. In a second study, Yordanova et al. (2001) assessed event-related gamma oscillations in an auditory target detection paradigm. They reported enhanced oscillatory activity in the gamma range over motor areas in ADHD patients for stimuli presented to the right ear, irrespective whether these were attended or unattended. They interpreted this finding to be a result of impaired motor inhibition during early stages of auditory stimulus processing.

As can be derived from this introduction on ADHD neurophysiology, most electrophysiological studies investigating spontaneous or event-related EEG differences of ADHD patients and healthy children focus on EEG activity between 4 and 30 Hz neglecting higher frequency ranges. Hence, there is a lack of studies investigating spontaneous or event-related oscillatory activity in the EEG gamma-band of ADHD patients. This notion is surprising since gamma-band activity has been reported to be a correlate of numerous cognitive processes and shows a high relevance for perception and behaviour (Başar et al., 1999; Herrmann et al., in revision). Allowing a precise temporal coordination of and communication between spatially distributed cortical networks during information processing (Fries, 2005), GBRs are involved in integrating sensory information and enable a rapid analysis, encoding, and categorisation of incoming information in a variety of cognitive processes, e.g. feature binding (Engel and Singer, 2001), object processing (Tallon-Baudry and Bertrand, 1999), attention (Tiitinen et al., 1993; Debener et al., 2003), and memory (Herrmann et al., 2004c; Kaiser and Lutzenberger, 2005; Gruber and Müller, 2006). Therefore, a relationship between GBRs and pathological brain states involving impairments in these processes is obvious (Herrmann and Demiralp, 2005; Uhlhaas and Singer, 2006; Başar and Güntekin, 2008). Altered GBRs have been reported in neuropsychiatric disorders such as schizophrenia (Haig et al., 2000; Spencer et al., 2003; Başar-Eroglu et al., 2007), Parkinson's disease (Bosboom et al., 2006; Moazami-Goudarzi et al., 2008), or Alzheimer's disease (Koenig et al., 2005; van Deursen et al., 2008). Considering the role of oscillatory activity in child psychiatric disorders (Rothenberger, 2009), enhanced GBRs have been related to autism (Orekhova et al., 2007, 2008) and ADHD (Yordanova et al., 2001).

Thus, gamma oscillations might be involved in the ADHD pathophysiology. Therefore, the next chapter describes their role in healthy cognition and behaviour.

2.2 Oscillatory activity in the gamma-band of human EEG

2.2.1 Gamma-band activity during cognitive processing

In recent years, high-frequency oscillatory activity in the gamma-band has received particular interest within the field of research on EEG frequency dynamics (see Chapter 4.3 for an introduction on EEG oscillations). Especially, their functional correlates have been outlined suggesting multifold functions in sensory and cognitive processing (Başar-Eroglu et al., 1996). Gamma oscillations have been initially proposed as a correlate of feature binding and integrated object representations, when Gray et al. (1989) demonstrated neural synchronisation in the gamma-band in the visual cortex of cats in response to visual stimulation with two bars moving into the same direction and, therefore, being perceived as parts of one coherent object. This finding could be replicated in humans later on (Müller et al., 1996).

Subsequently, human GBRs were thoroughly investigated in the visual (Tallon-Baudry et al., 1996; Keil et al., 1999; Gruber et al., 2008) as well as the auditory system (Pantev et al., 1991; Knief et al., 2000; Crone et al., 2001; Kaiser et al., 2008c). Dealing with GBRs requires the differentiation between an early phase-locked and a late non-phase-locked component (Galambos, 1992). The first is referred to as evoked activity appearing within the first 100 ms after stimulus onset, whereas the second component, the so-called induced activity, occurs later at about 200 ms (see Chapter 4.3.1 for a detailed description).

While many authors consider gamma oscillations as correlates of cognitive functions (Engel and Singer, 2001), others failed to find this type of activity in humans at all (Juergens et al., 1999). This is most likely due to the fact that gamma oscillations strongly depend on the physical characteristics of the stimuli used in the experiments, which is especially the case for evoked GBRs. There is strong evidence that evoked GBRs are correlates of sensory processing (Karakaş and Başar, 1998). Busch et al. (2004) revealed a large bottom-up influence on evoked GBRs, driven by stimulus parameters such as size, duration, and eccentricity. Furthermore, modulations of evoked GBRs were also observed after systematic variations of stimulus features such as spatial frequency (Bodis-Wollner et al., 2001; Fründ et al., 2007a) and contrast (Schadow et al., 2007b) of visual stimulation, or loudness (Schadow et al., 2007a) and pitch (Lenz et al., 2008a) of auditory stimuli. From these bottom-up driven modulations of early GBRs it can be concluded that evoked GBRs are generated at a very early stage of sensory information processing which is still modulated by physical stimulus characteristics. This implies an origin at primary sensory brain areas (Pantev et al., 1991; Schadow et al., 2009b). Notably, there is evidence that even these very early stages are associated with top-down processes, too, and that evoked GBRs represent an early

interface of interacting bottom-up factors and top-down processes as it has been shown e.g. for the interaction of stimulus size and attention processes (Busch et al., 2006).

Thus, in the last years a number of studies raised evidence that GBRs are involved in cognitive processes. In a series of experiments, Tallon-Baudry and Bertrand (1999) reported enhanced gamma activity in human EEG for stimuli which could be bound to and perceived as coherent objects. In a subsequent study, Herrmann et al. (1999) adapted an experiment from Tallon-Baudry et al. (1996) and revealed that target stimuli evoke a stronger GBR than all other stimuli, irrespective of their object features. They concluded that object selective attention has a larger impact on the evoked GBR than binding processes (Herrmann and Mecklinger, 2001). Furthermore, it turned out that the similarity of a stimulus with the target was associated with the strength of the evoked GBR: The more features of a stimulus matched to the target template the more enhanced evoked GBRs could be observed.

Within the auditory domain, Debener et al. (2003) compared target sine tones to novel environmental sounds which were irrelevant for the task. Even though these novel sounds attracted the subject's attention as reflected in an enhanced P3 component in their ERPs, only the target sound evoked significantly augmented evoked GBRs compared to the standard stimuli, suggesting that the target role of a tone is more important than its novelty. These findings support results from Tiitinen et al. (1993) who also demonstrated enhanced evoked GBRs in response to attended target sine tones. It is noteworthy to mention that a close connection between selective attention to a target stimulus and memory can be assumed: If a subject is asked to identify a target stimulus, a template of this target has to be retained in short-term memory (STM) at the beginning of the experiment. Subsequently, the participant is required to compare any presented stimulus with this memory stored template. This template could be determined by either simple object features like colour, form, size, or even the spatial position of the object. Furthermore, as the number of features a stimulus shares with the target is related to the amplitude of the evoked GBRs, this suggests that these successful matches of sensory input with memory representations are a crucial process underlying the reported modulations of GBRs during information processing. Moreover, these matches with memory guide the attentional focus to the corresponding object and lead to faster behavioural responses. Along the same line, several studies investigated the role of GBRs in different aspects of visual memory. Tallon-Baudry et al. (1998) found that the recall of object representations as well as their maintenance in STM induces higher GBRs. In addition, both perceptual learning tasks (Gruber et al., 2002) and the recall of previously learned stimuli (Gruber et al., 2001) were accompanied by enhanced gamma oscillations. Jung-Beeman et al. (2004) also showed that tasks involving verbal problem solving with aspects of recall

of relevant information from long-term memory (LTM) induce gamma activity around 300 ms prior to the actual reaction. Furthermore, it has been demonstrated that matches of perceived images with LTM representations evoke early GBRs (Herrmann et al., 2004b). In that study, the stimulus material consisted of two different types of black and white images, either depicting line-drawings of objects for which subjects already had a representation in LTM because they were well-known, real-world objects, or unknown, new items being composed of the same, but rearranged components of the known items. The participants were instructed to judge whether the perceived figure appeared to be either edgy or curvy. Therefore, they were naive about the purpose of the experiment and the differentiation between known and unknown items. As a result, line-drawings of known items for which subjects possessed LTM representations evoked stronger activity over occipital areas than physically similar stimuli without such representations, even though stimulus familiarity was not task-relevant (see Figure 2.1). This finding has been replicated in other studies, too (Morup et al., 2006; Freunberger et al., 2007; Roye et al., 2009). Moreover, Schadow et al. (2009b) recently demonstrated that evoked GBRs reflect even anticipatory top-down modulation in the auditory cortex as these are significantly increased when a perceived sound within a tone sequence matches the mental representation of its anticipation.

Thus, this early matching process can be considered as a general stage during information processing enabling an early automatic classification of sensory input. Based on the conclusions from this study and integrating existing results on the GBR involvement in attention, object and language perception, Herrmann et al. (2004c) designed a framework incorporating these results: the 'Match-and-utilisation model' (MUM). The authors assume that memory contents are stored as strengthened synaptic connections. If thalamic input reaches primary cortices, matching with existing memory representations could lead to enhanced activity due to stronger feedback from higher visual areas. As demonstrated in our study (Herrmann et al., 2004b), such matching processes take place at a very early stage of visual processing. Thus, according to the MUM, successful matching processes could facilitate further processing starting at a very early time-point.

This section clearly emphasises that evoked GBRs are generated in very early sensory areas and that they are modulated by bottom-up factors as well as cognitive processes in different experimental conditions, tasks, and modalities. However, there is much less evidence for the actual behavioural and perceptual relevance of these oscillations. More precisely, as suggested by Sejnowski and Paulsen (2006), if oscillations are essential for and related to perception and behavioural responses, these processes should be impaired by disturbing the oscillations which should lead to behavioural changes. This issue linking behavioural performance measures with GBRs is discussed in the next chapter.

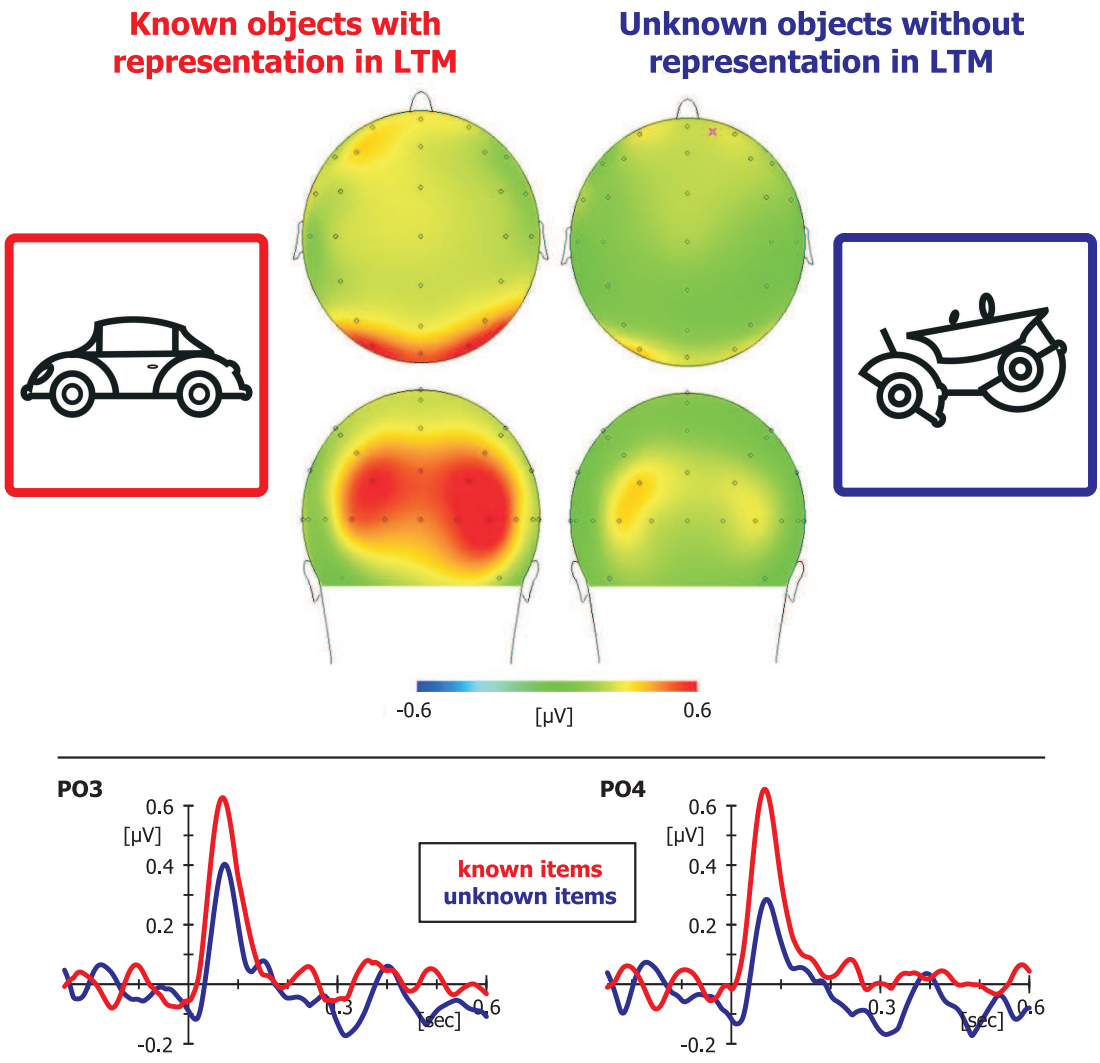

Figure 2.1: As early as 90 ms after stimulus onset, the grand-average of the individually adapted time-course of evoked GBRs shows a significant enhancement in response to known line-drawings already represented in LTM (red) compared to line-drawings without such representation (blue). This difference is also visible in the topographical maps, revealing augmented evoked GBRs over parieto-occipital areas for known objects (adapted from Herrmann et al., 2004b).

2.2.2 Direct links of GBRs to perception and behaviour

This chapter is part of the following review-article, currently in revision:

Herrmann CS, Fründ I, Lenz D (in revision)
Human gamma-band activity: A review on cognitive and behavioural correlates and network models
Neuroscience and Biobehavioral Reviews

There are several ways how direct relationships can be assessed even without experimental interference. First of all, in a between-subject approach, one can compare subjects exhibiting low GBRs with subjects showing higher GBRs and associate these differences with behavioural responses. Even though this classification is done in the opposite direction (e.g. comparison of GBRs between good and bad performers) in the majority of studies, this is also indirect evidence for GBR involvement in behavioural performance. Secondly, a more rigorous solution is the direct correlation of GBR with a behavioural measure. Finally, on the within-subject level, single-trial analyses enable us to directly compare intra-subject performance differences and their relation to GBRs.

In this section, I will focus on the question, whether and how gamma oscillations are related to behavioural responses and whether they are associated with perceptual decisions or behavioural events. Thereby, I will concentrate on performance measures such as reaction times or response accuracy. The relevance of GBRs for memory encoding, recognition performance, and perceptual processes will also be addressed throughout this section.

Reaction times

There are several studies that presented evidence for a strong association of GBRs with behavioural response speed. The first evidence has been raised by Jokeit and Makeig (1994). In their study, slow and fast responders in an auditory reaction-time task using click sounds were compared with respect to high-frequency activity. Slow responders were characterised by enhanced prestimulus GBRs, whereas fast responders showed shortened peak-latencies of poststimulus GBRs and enhanced amplitudes of the later induced GBR. Along the same line, single-trial analysis done by Haig et al. (1999) revealed a robust correlation between gamma peak-latency and reaction time in an auditory oddball paradigm, with slower reaction times corresponding to delayed peak latencies. Fründ et al. (2007b) were the first to show an association between the amplitude of evoked GBRs and performance speed in a simple reaction task where subjects were asked to press a button as fast as possible immediately after the appearance of a large visual stimulus. After classifying trials with fast and slow responses, they found that fast

trials were accompanied by stronger phase-locked gamma oscillations around 100 ms after stimulus onset, whereas slow trials showed significantly reduced evoked GBRs that were delayed in comparison to fast response trials. The robustness of these results is supported by other studies that also associated response speed and GBRs (Gonzalez Andino et al., 2005; Schadow et al., 2009a). Neuronal oscillations in the gamma-range before and after a behaviourally relevant stimulus seem to be predictive for response speed. Thus, higher GBR synchrony or amplitude might be advantageous for faster processing and fast classification processes. Interestingly, reaction times not only reflect the overall time that is required for a cognitive task. If all other parameters are held constant, while the features of an object are manipulated from trial to trial, reaction times can reflect more specific cognitive processes such as the time needed to recognise an object (Martinovic et al., 2008). In an object recognition task, Martinovic et al. (2007) demonstrated that the latency of induced gamma responses correlates with the time needed to identify objects of different rotation angles. Taken together, it is plausible to assume that both the strength (amplitude or phase-locking) and the latency of GBRs mirror the time course of cognitive processes.

Response accuracy

Besides the analysis of reaction times, the response accuracy as represented by the number of correct responses or hitrate is another behavioural measure which seems to be linked to oscillatory activity in the gamma-range.

In an auditory spatial delayed matching-to-sample paradigm, Kaiser et al. (2008b) investigated the association of performance in maintaining the lateralisation angle of a sample sound and subsequent comparison with a test stimulus with GBR characteristics. Interestingly, the difference between the GBRs of the two possible sample sounds, specifying the degree to which oscillatory signals differentiated between sample sounds, positively correlated with the rate of correct responses. Participants who maintained a distinctive differentiation of oscillatory activity emerging after presentation of the sample sounds until presentation of the probe stimulus showed better performance. Additionally, good performers showed this consistent differentiation for a longer duration than average or poor performers. Focussing on the test stimulus, Kaiser et al. (2008a) also reported an association between GBR and response accuracy. GBRs were more pronounced in good performers than in bad performers. This difference was particularly manifested around the onset of the test stimulus. These results suggest the relevance of GBRs for optimal differentiation between stimulus characteristics. Furthermore, correct responses are related to GBR components elicited by the processing of differences between sample and test stimuli (Kaiser et al., 2008a,b,c).

The role of GBR in detection of illusory or real acoustic changes has been in-

vestigated in a study by Kaiser et al. (2006). Illusory acoustic changes were induced by incongruent audiovisual stimuli (incongruent visual stimulus leading to a different auditory percept). The detection rate for these illusory deviants was closely associated with gamma-band activity, yielding a positive correlation with induced oscillatory activity over occipital areas. Interestingly, the detection of real acoustic changes (actual variation of the auditory stimulus) was positively associated with GBRs, too. Contrary to illusory induced changes, this effect for real changes was found over auditory areas.

These results substantiate the involvement of early sensory areas in the detailed analysis of auditory and visual stimulus features. Hence, GBRs seem to contribute largely to correct responses in different tasks and modalities as the magnitude of GBR components appears to have predictive value for task performance.

Memory encoding and recognition performance

There are several studies suggesting a prominent role of gamma oscillations in successful memory encoding and subsequent memory performance. Sederberg et al. (2003) recorded electrophysiological activity during a memory paradigm in epileptic patients with electrode grids subdurally on the cortical surface where subjects had to study wordlists. Subsequent free recall was predicted by increases in GBR power during the encoding phase, found in widespread cortical sites. Similar results were reported by Gruber et al. (2004) who found significantly higher induced GBRs during the encoding of words that were subsequently remembered as compared to forgotten ones. Comparable enhancements of GBRs during successful encoding were described by Summerfield and Mangels (2006). Osipova et al. (2006) investigated the encoding of pictorial stimuli and compared brain activity during encoding of subsequently remembered items with electrophysiological activity during encoding of subsequently forgotten items ('subsequent memory effect'). Subsequently remembered stimuli were characterised by enhanced induced GBR during encoding in occipital areas. As a between-subject-approach, Busch et al. (2008a) compared good performers with bad performers. After an initial study phase, during which participants were asked to perform a visual discrimination task of abstract line drawings, subjects had to judge items being old or new in a subsequent test phase. Presentation of old items evoked stronger GBRs than new items. This old/new effect differed between both groups and was only visible in good performers. Thus, differentiation of electrophysiological data of both groups reflected behavioural performance data and supports the relevance of GBRs for recognition memory.

In conclusion, associations of GBRs and behavioural performance suggest a direct relationship between electrophysiology and memory processes, where GBRs seem to facilitate memory encoding predicting subsequent recall.

Perceptual relevance

Besides this behavioural significance, there are also reports showing a strong association of GBR with subjects' perceptual abilities. When subjects are grouped according to the number of reversals of multistable figures into high-rate and low-rate switchers, GBRs seem to differentiate between the two groups (Strüber et al., 2000). High-rate switchers are characterised by augmented phase-locked and non-phase-locked GBRs compared to low-rate switchers. In a similar manner, Ohla et al. (2007) divided naive subjects in those that were aware of a task-irrelevant global structure in a set of random dots (Glass patterns), and participants who were not. Enhanced evoked GBRs were observable after the presentation of circular patterns compared to random patterns only for those participants that were subjectively aware of this global pattern structure. Additionally, compared to unaware subjects, participants that were aware of the structure also showed a general enhancement of evoked GBR as well as stronger phase-locking and a more pronounced early total activity. Thus, early evoked GBRs are engaged in conscious perception as they indicate whether or not a participant has a specific perceptual experience.

Along these lines, Hanslmayr et al. (2007) demonstrated differences in prestimulus EEG and effects on subsequent perceptual abilities in a recent study. In a masked perception and discrimination task, subjects were instructed to distinguish four shortly presented letters. A within-subject analysis revealed higher prestimulus phase-coupling in trials, where subjects were able to correctly perceive the presented letter, suggesting a link between enhanced GBR phase-coupling and correct performance. Single-trial analysis also yielded a strong linear relationship between perception performance and prestimulus deviation from the mean phase of GBR, whereas the detection performance was nearly perfect in trials with low deviation and decreased to lower levels with higher deviations from mean phase. Thus, prestimulus synchrony in the gamma-range predicts performance on single-trial basis with higher synchrony being advantageous for visual perception abilities.

Therefore, GBRs seem to have substantial relevance in perceptual processing. Human perceptual abilities appear to be strongly associated with activity in the gamma-range not only after stimulus presentation, but even in prestimulus time-ranges.

CHAPTER 3

Research questions

Previous electrophysiological as well as imaging research has contributed to the understanding of impairments in attention, executive functions, and memory in patients with ADHD. However, although gamma activity is strongly associated with cognitive processes impaired in ADHD patients such as attention and is also modulated by dopaminergic polymorphisms that are linked to ADHD, there is a lack of studies investigating ADHD related differences in the gamma band of human EEG. Furthermore, there are indicators that ADHD patients demonstrate deficits at very early stages of visual processing, although converging evidence can be found, too. Visual evoked GBRs, appearing as early as 90 ms after stimulus onset, can therefore be considered a suitable measure to assess those deficits at very early processing stages.

Three experiments aim to comprehensively characterise early cognitive processes in the visual system by means of analysis of evoked GBRs to answer the question in which way visual evoked GBRs differ between ADHD children and age matched healthy participants. Moreover, the employed paradigms were designed to allow the investigation of possible group differences in EEG activity, but enable also the direct estimation of the relevance of evoked GBRs in cognition and behaviour in both groups.

1. Do ADHD patients demonstrate altered evoked GBRs during sensory evaluation and encoding of visual stimuli? Are evoked GBRs of ADHD patients similarly related to recognition performance as in healthy participants?

The first study (presented in Chapter 5) assesses associations between evoked

GBRs during encoding of visual stimuli in a short-term memory paradigm and subsequent behavioural performance in a recognition test where the participants had to judge pictures as being old or new. Given the reported involvement of GBRs in memory processes, this approach allows the comparison of evoked GBRs of ADHD patients with those of healthy participants and emphasises whether both groups show a similar association of evoked GBRs during stimulus encoding and later performance in a recognition test or not.

2. Are evoked GBRs of healthy children also related to early memory matching processes as it has been demonstrated for healthy adults? If so, evoked GBRs should be enhanced following known stimuli that are already represented in memory.

Experiments II and III (see Chapter 6) focus on a pivotal cognitive function of evoked GBRs, reflected in early memory matching processes. As a prerequisite, a pilot study (Experiment II) elucidates whether evoked GBR patterns during these very early stages of information processing can be similarly observed in healthy children and adolescents as it has been reported for healthy adults. This should be the case, if memory matching represents a fundamental process during visual stimulus encoding and is indeed reflected in enhanced evoked GBRs. The experimental procedure and stimulus material was identical to that formerly employed in the investigation of healthy adults. The participants were asked to decide as fast as possible, whether they perceived visual line-drawings as either edgy or curvy. Irrespective of this task, the stimuli either depicted known real-world items which were supposed to activate a representation in LTM or unknown items.

3. Do ADHD patients present the same early, memory based classification processes as healthy participants represented by the differentiation of evoked GBRs between known and unknown visual stimuli?

In Experiment III, I investigated early memory based classification processes reflected by evoked GBRs in ADHD patients as well as in age matched healthy participants. Evoked GBRs could be a possible neuronal correlate of an early dysfunction in visual information processing that might be, according to the MUM, directly related to the ADHD pathophysiology. Additionally, evoked GBRs can be considered as a suitable measure for elucidating the question whether early visual processing in ADHD patients is impaired or not.

CHAPTER 4

General methods

In this chapter I will focus on the general methodology underlying the reported experiments. The specific experimental procedures of each study are outlined in the corresponding sections.
The EEG served as the preferred method to assess the time-course of electrical brain activity. Therefore, I will describe the basic principles of EEG recording and analysis in the next paragraphes.

4.1 Electroencephalogram

Even in the era of functional neuroimaging the EEG, first described in 1929 by the German neurologist Hans Berger (Berger, 1929), is an important method for studying cognitive processes in healthy as well as pathological states. Offering an excellent temporal resolution within the range of milliseconds, the EEG enables a more precise assessment of the time-course of cortical processes, compared to functional brain imaging that demonstrates a lower temporal but therefore higher spatial resolution. The EEG reflects fluctuations of the electrical activity of a sizeable population of synchronised neurons, being non-invasively registered with Ag/AgCl-electrodes placed at the scalp surface and connected to a hardware amplifier.

In order to account for interindividual differences in head size and form, a specific approach has to be followed during the placement of these electrodes: For facilitating the comparisons between laboratories and to allow between-subject comparisons, Jasper (1958) suggested an internationally standardised positioning guide termed the '10-20-system' (meanwhile extended to the '10-10-system').

According to this guideline, electrodes should be placed in a certain order with specific relative distances between each other (in steps of 10% or 20%, respectively), starting at defined landmarks on the skull such as the nasion or inion. Additionally, he introduced a consistent nomenclature for labelling the electrode positions, starting with a letter for the underlying area (Fp - frontal pole, F - frontal, C - central, P - parietal, O - occipital) and followed by odd numbers for electrodes above the left hemisphere, whereas even numbers index electrodes above the right hemisphere. Starting with 'z' for midline electrodes (zero), the numbering is higher the more lateral the electrode is positioned. This approach allows an adequate coverage of all parts of the head and, at the same time, enables interindividual comparisons. In modern systems, electrodes are already placed in an elastic cap according to this standard.

The scalp measured EEG signals, typically showing amplitudes between 1-200 μV, reflect summed synchronised post-synaptic potentials generated by cortical pyramidal cells (Zschocke, 2002, Chapter 1): If an excitatory (or inhibitory) input reaches the apical dendrites of a cortical pyramidal cell, this causes a current flow between extracellular space and the cell at this region. Additionally, there is also current flow between the cell body and its basal dendrites and the extracellular space. This results in a cortical field potential exhibiting a dipolar structure, represented by charge differences between the region around the apical dendrites and the region around the cell body (Luck, 2005). If many pyramidal cells receive identical input at the same time and the resulting neuronal dipoles have a similar spatial orientation, their individual electrical fields summate and create an electrical dipole with current flows between positive and negative charges (Coles and Rugg, 1995). These summed voltages are measureable at the scalp surface and therefore constitute the EEG.

However, EEG recording from outside the head distant from the original cortical source of the measured signals makes it vulnerable for contaminations with electrical potential fluctuations not originating from the human brain. These can be distinguished into physiological and technical artifacts. Physiological artifacts can be attributed to the measured participant and are caused by extracerebral sources within the human body, including e.g. eye-movement artifacts, cardiobalistic artifacts, and artifacts resulting from swallowing, pulsation, and respiratory or body movements. On the other hand, technical artifacts derive from failures during the measurement itself, comprising e.g. poor or even fluctuating electrode-impedances, broken electrodes or wire contacts, cable movements, and electromagnetic or electrostatic inductions (Zschocke, 2002, Chapter 20).

Within this thesis, all raw data of the described experiments were first examined for non-stereotyped artifacts like swallowing and excessive electromyographic activity. Sections containing these types of artifacts were removed from further EEG

analysis. Subsequently, stereotyped artifacts resulting from eye-movement activity were corrected using Independent-Component-Analysis (ICA) based on the extended infomax algorithm implemented in the open source toolbox EEGLAB (Delorme and Makeig, 2004, http://www.sccn.ucsd.edu/eeglab). The ICA decomposes data into spatially fixed and maximally temporally independent components by applying spatial filters to multi-channel EEG data. The sources of stereotyped artifacts like eye-blinks show a distinct spatial distribution and time-course, and are independent from EEG signals. Therefore, the ICA results in independent and separable components for eye-movement activity, which can be extracted from the original EEG data, determined by inspection of the topographical component maps, and removed afterwards. An additional automatic artifact rejection excluded epochs from further analysis, if the standard deviation in a moving 200 ms time-window exceeded 50 μV. Furthermore, all trials were visually inspected for possible remaining artifacts and rejected if necessary.

Although EEG is superior in assessing the exact time-course of cognitive processes, the method also presents some constraints: While it fosters conclusions about the temporal dynamics of cortical processes, it is less informative concerning the localisation of the cortical source of the measured activity. As stated above, the EEG registers superficial sources while being less susceptible for signals with subcortical origin as the detectable signal strength caused by the source decreases with increasing scalp distance (Zschocke, 2002, Chapter 1). Furthermore, the scalp measured EEG signals are mostly not generated by just one cortical source, but are the result of a summation and superposition of multiple sources. This makes it difficult to infer the neuronal sources from the scalp signal (the so called 'inverse problem', see e.g. Niedermeyer, 1996). However, new recording techniques using up to 256 electrodes enabling a more exact source reconstruction and improved analysis methods are considered to overcome this issue (see Grech et al., 2008, for review).

Within the field of EEG research, different methodological techniques were established for investigation of electrical brain activity associated with cognitive processes. In case of the studies presented within this thesis, data were assessed based on the examination of event-related potentials as well as time-frequency analysis of oscillatory brain activity. These approaches are introduced in the following sections.

4.2 Event-related potentials

If visual, auditory, somatosensory, or even mental events are associated with measurable EEG voltage fluctuations, these are termed 'event-related potentials' (ERPs, Makeig et al., 2004). Typically, the processing of such events is not visible

in the raw EEG as it demonstrates much lower amplitudes in the range of 1 to 20 μV being superimposed by the much higher amplitudes of the spontaneous background EEG. However, it is assumed that the electrical activity reflecting the time-course of event processing is constant during each event repetition. Therefore, averaging of a sufficient number of trials should yield activity related to event processing to sum up while the random background EEG signals cancel out. This is the basic principle for studies comparing different experimental conditions: Each condition is repeated a number of times and each time-point within a specified time-window of trials belonging to the same condition is averaged. As this improves the ratio between 'signal' and 'noise', this yields only signal fractions that are directly associated with the event while background EEG noise is diminished with the increasing number of trial repetitions. The resulting EEG voltage fluctuation demonstrates a modality specific, characteristic sequence of minima and maxima that are considered as the ERP components. These components can be analysed regarding their amplitude, latency, and duration and constitute the real-time characteristics of neuronal processes directly associated with the event (Picton et al., 2000).

4.3 Oscillatory brain activity

Since the beginning of the research on EEG activity, oscillatory rhythms of electrical brain activity have been observed and analysed. Moreover, a number of studies demonstrated that brain oscillations are more than irrelevant background activity, but are instead related to mental states as well as cognitive processes (Başar et al., 1999, 2001). Thus, it seems plausible to also expect altered oscillatory EEG activity in psychiatric patients demonstrating cognitive deficits. In fact, this has been repeatedly demonstrated (see e.g. Başar and Güntekin, 2008, for a review) and, therefore, EEG and its oscillatory rhythms have gained more attention in providing additional indications for the diagnose of psychiatric disorders (e.g. Hughes and John, 1999; Boutros and Struve, 2002; O'Sullivan et al., 2006; Rothenberger, 2009).

The next chapter will outline the classification of oscillatory EEG activity according to specific parameters characterising the EEG signal.

4.3.1 Classification of brain oscillations

Oscillatory EEG signals in the human brain can be described as overlapping sine waves, characterised by different frequencies (the number of cycles per second in Hz), amplitudes (typically measured in μV), and phase-angles within the current period (ranging from 0 to 2π). The first rhythm already described by Hans Berger is the alpha–rhythm (α), containing activity within the frequency range of 8–12 Hz and showing amplitudes up to 50 mV (Berger, 1929). This

alpha–rhythm was considered by Berger as the 'basic rhythm'. Starting at 13 Hz, the chronologically next identified frequency range up to 30 Hz was named consequently the beta–rhythm (β). Later, even faster oscillations in the EEG between 30 and 80 Hz could be detected in hedgehogs and were termed gamma–oscillations (γ; Adrian, 1942). The brain rhythms covering frequencies below the alpha range were divided into the delta (δ, 0–4 Hz) and theta (ϑ, 4–8 Hz) rhythm.

In addition to the number of cycles per second, EEG oscillations are also determined by their phase-angle. With respect to the degree of phase-locking, two types of oscillations can be distinguished (besides spontaneous activity) (Galambos, 1992):

1. *Evoked activity*
   Triggered by an external or internal event (e.g. onset of stimulation), these oscillations show a high phase-locking to event onset with a high phase-stability across trials. Therefore, they can be extracted by averaging the single-trial signals with respect to the event onset which yields the ERP (see Chapter 4.2). However, high-frequency oscillations typically show much lower amplitudes than lower frequency components and are therefore not visible in the ERP. According to that, specific methods have to be applied. One way to assess event-related oscillations is subsequent band-pass filtering of the ERP resulting the amplitudes of activity at a selected frequency range while rejecting signal portions containing higher and lower frequencies. This is illustrated in Figure 4.1B. However, the more exact time-frequency analysis based on Morlet wavelets allows a more accurate analysis of the time-course of frequency dynamics (see Chapter 4.3.2).
   Evoked oscillations in the gamma-frequency range that are subject of the current thesis typically appear around 50-60 ms after auditory stimulation and about 100 ms after visual stimulation, showing a modality specific, local topography.

2. *Induced activity*
   Although elicited by stimulation, too, induced oscillations exhibit decreased phase-locking across trials and are therefore not visible in the ERP.
   Induced oscillations in the gamma-frequency range mostly occur around 200 ms after stimulus onset. Even though there is a number of studies pointing out their crucial role in cognitive processes, recent evidence suggested that scalp measured induced GBRs are contaminated with signals originating from micro-saccadic eye-movements (Yuval-Greenberg et al., 2008; Fries et al., 2008; Yuval-Greenberg and Deouell, 2009). Therefore, I abstain from reporting results of induced GBRs and focus the results presented in this thesis on evoked GBRs.

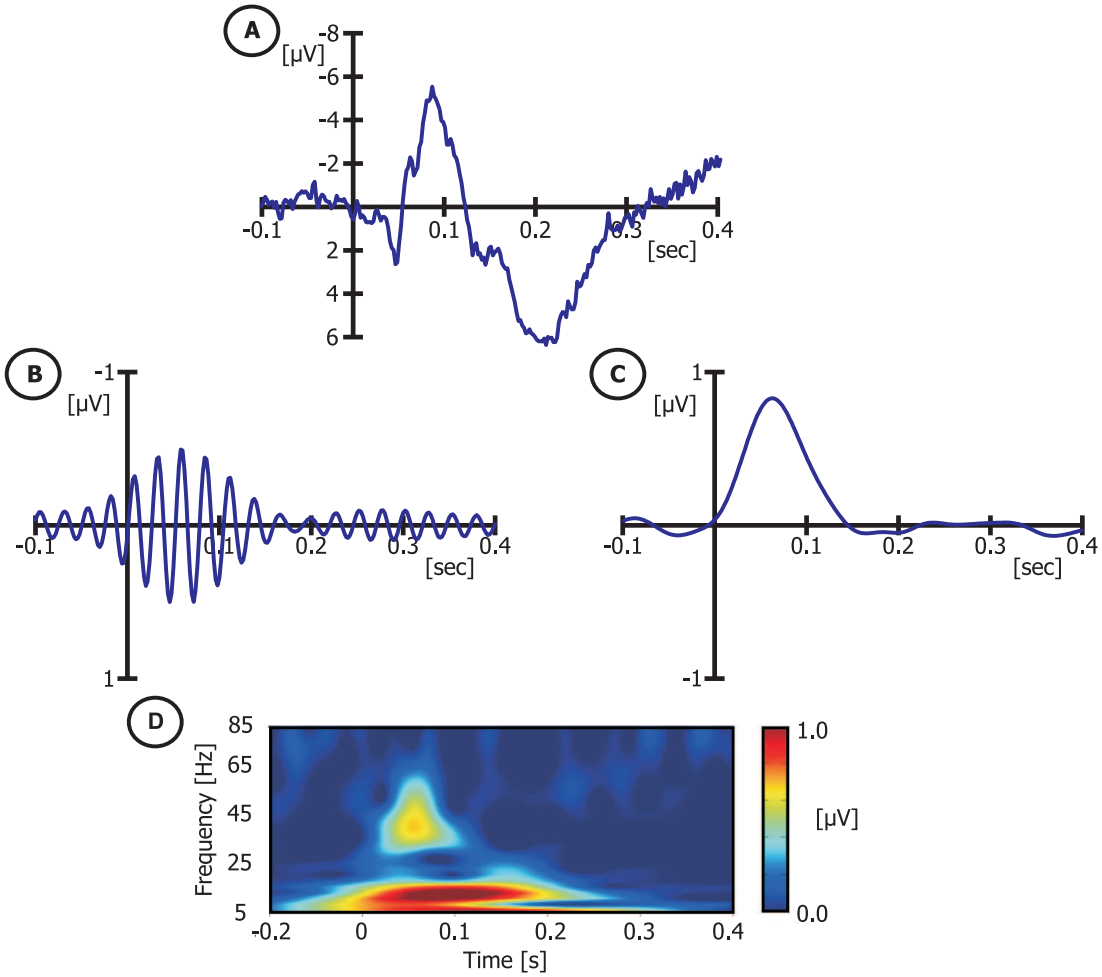

Figure 4.1: (A) The unfiltered ERP is obtained by averaging the single-trial signals with respect to stimulus onset. (B) Bandpass filtering at 35-43 Hz yields a clear increase of activity around 60 ms after stimulus onset, not visible in the unfiltered ERP. (C) Wavelet transformation at a frequency of 39 Hz reveals the exact time-course of the activity at this frequency, being detected as peak-frequency in the gamma-band in the time-frequency decomposition of the signal (D).

The methodological approach for the analysis of oscillatory dynamics in the gamma-band is outlined in the following section.

4.3.2 Time-frequency analysis based on Morlet wavelets

Until the early nineties of the last century, the conventional analysis of EEG frequency dynamics was based on a Fast Fourier Transformation (FFT) of the data. Using this approach, the complex source data is decomposed into simpler components consisting of sine-waves of different frequencies, each contributing with a different magnitude to the original signal. Afterwards, the amplitude of each of

these frequency components can be revealed from the 'frequency spectrum' of the signal. However, although an FFT can be performed on short subsequent data segments yielding a rough estimation of spectral changes, it disregards the exact time-course of underlying frequency dynamics within the range of milliseconds that can be observed for higher frequencies.

This insufficiency has been overcome by employing wavelet transformation within the data analysis. Wavelet transformations enable the evaluation of the time-course of frequency dynamics: The use of complex wavelets directly yields the amplitude and phase of non-stationary oscillatory components at a specified time-point. Within this thesis, complex Morlet wavelets, invented by the French geophysicist Jean Morlet, have been applied to investigate evoked GBRs. Thereby, the original time-domain data is convolved with a mother-wavelet, showing a Gaussian envelope in time and frequency (c.f. Herrmann et al., 2004a). At 40 Hz, the applied wavelets had a time resolution of $2\sigma_t = 50$ ms and a frequency resolution of $2\sigma_f = 13$ Hz. Being advantageous to other approaches, the exact time-frequency resolution of the wavelet depends on the analysed frequency by adapting the length of the time window according to the analysed frequency. The window length decreases with higher frequencies, yielding a finer temporal resolution for higher frequencies. Unfortunately, this also results in a poorer frequency resolution with increasing frequency.

An exact decomposition of the EEG signal can be achieved by performing wavelet transformations for multiple frequencies to cover the whole EEG frequency spectrum. Wavelet transformations of all frequencies between 1 and 100 Hz in frequency steps of 1 Hz therefore reveal the detailed distribution of specific frequency components at a given time-point in a so-called 'time-frequency-diagram', where the amplitude of the signal fraction is represented by different colours with 'red' being related to the highest activity (see Figure 4.1D for an example). Besides the benefit of accurate analysis of event-related spectral EEG dynamics, only the detailed data inspection based on a time-frequency-decomposition of the EEG signal allows a further, more exact analysis according to the individual frequency peak that has been reported to show an interindividual variability especially in the gamma-band (see Figure 5.2 for an example).

Two different approaches for time-frequency analysis have to be distinguished in order to separate evoked and induced signal fractions: Evoked activity can be assessed by employing the wavelet transformation on the averaged and unfiltered signal (the ERP), yielding only signal portions phase-locked to stimulus onset while omitting non-phase-locked, induced signals that are cancelled out during averaging. For analysis of induced oscillations, the wavelet transformation has to be applied separately on the signals of each single-trial. Afterwards, the results of the frequency transformation of each single-trial are averaged. This method

obtains evoked as well as induced signal fractions. Therefore, it is also referred to as 'total' activity.

The methodological differences between the analysis of evoked and induced oscillations are depicted in Figure 4.2.

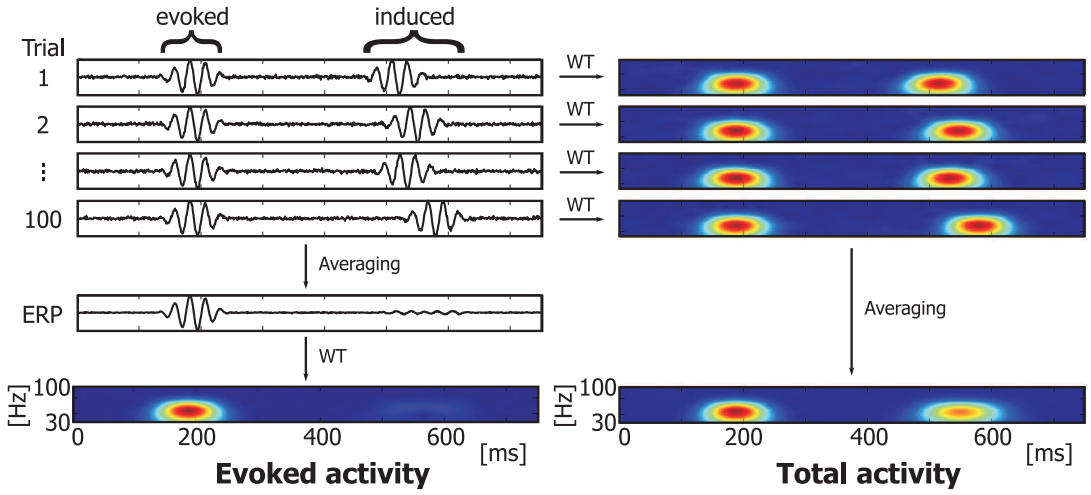

Figure 4.2: In order to separate evoked and induced signal fractions, averaging and wavelet transform (WT) have to be applied in a certain order. The figure illustrates 100 simulated single-trials, containing both early evoked and late induced gamma bursts (upper left). The ERP is revealed by averaging all trials. Subsequent wavelet transform yields only evoked activity that shows high phase-locking to stimulus onset (bottom left). Transforming the single-trials into the frequency domain (upper right) and subsequent averaging of the absolute values of each single-trial's WT (bottom right) results in total activity, comprising evoked as well as induced activity (modified from Herrmann et al., 2004c; Lenz et al., 2008b).

CHAPTER 5

Experiment I: Behavioural relevance of evoked GBRs in ADHD children and healthy participants

The data from the following chapter have been published in:
Lenz D, Krauel K, Schadow J, Baving L, Duzel E, Herrmann CS (2008).
Enhanced gamma-band activity in ADHD patients lacks correlation with memory performance found in healthy children.
Brain Research 1235:117-32

and:

Krauel K, Duzel E, Hinrichs H, Lenz D, Herrmann CS, Santel S, Rellum T, Baving L. (2009)
Electrophysiological correlates of semantic processing during encoding of neutral and emotional pictures in patients with ADHD.
Neuropsychologia 47(8-9):1873-1882

5.1 Introduction

ADHD is one of the most frequently diagnosed and most stable psychiatric disorders in childhood and adolescence (Biederman and Faraone, 2005). There are also indications that it can persist in adulthood (see Faraone et al., 2000, for review). According to the DSM-IV, patients are characterised by developmentally inappropriate degrees of inattention, impulsivity, and hyperactivity, which appear in more than one environment (American Psychiatric Association, 1994).

Because of its high prevalence and social impact, there is a wide range of re-

search on ADHD, pointing out impairments in different aspects of cognition, e.g. attention (Konrad et al., 2006), executive functions (Doyle, 2006), or memory (Martinussen et al., 2005; Sheridan et al., 2007; Krauel et al., 2007). Electrophysiological studies support these findings since they consistently show neurophysiological differences between ADHD patients and healthy children of the same age (Barry et al., 2003a; Banaschewski and Brandeis, 2007). In different tasks and conditions, ADHD patients are characterised by cortical slowing reflected by significant excess of activity in lower frequencies of human EEG, primarily the theta range, and decreases of amplitudes in the beta range (Mann et al., 1992; Chabot and Serfontein, 1996; Monastra et al., 1999; El-Sayed et al., 2002). In comparison to healthy controls, ADHD patients exhibit amplitude differences in various ERP components associated with attending to and processing of incoming information (e.g. Satterfield et al., 1988, 1990; Jonkman et al., 1997; Brandeis et al., 2002), especially indicating deficient preferential processing of attended stimuli (Satterfield et al., 1994). Analysis of event-related oscillatory activity also strengthens the evidence for abnormal processing of task relevant stimuli, demonstrated by Yordanova et al. (2001). They reported enhanced oscillatory activity in the gamma range over motor areas in ADHD patients in an auditory target detection paradigm. They interpreted this finding to be a result of impaired motor inhibition. To my knowledge this is the only study associating gamma-band responses (GBR) with the pathology of ADHD, even though there are multiple indications to assume a crucial role of high-frequency oscillations in the neurophysiology of ADHD.

As pointed out in Chapter 2.2, gamma oscillations in human EEG correlate with processes of attention (Tiitinen et al., 1993; Debener et al., 2003) and memory (Herrmann et al., 2004c; Lenz et al., 2007). In addition, gamma activity was also found to be associated with motor activity (Schnitzler and Gross, 2005). Thus, it seems plausible to assume that the hyperactive behaviour of ADHD patients results from a neuronal hyper-excitation reflected by enhanced gamma activity (Herrmann and Demiralp, 2005). Along the same lines, the attention and memory deficits could also stem from altered gamma oscillations.

The etiology of ADHD further supports the notion of a correlation between gamma-band abnormalities and ADHD: Although multiple factors are thought to account for the disorder (Spencer et al., 2002; Swanson et al., 2007), there is broad evidence for a large genetic component (Thapar et al., 2005). Most widely confirmed are candidate genes involved in dopaminergic pathways, especially the 7-repeat isoform of the 48-base pair variable number of tandem repeats (VNTR) polymorphism in exon 3 of the dopamine D4 receptor gene (DRD4) (Faraone et al., 1999, 2001; Langley et al., 2004) and a polymorphism at the dopamine transporter gene DAT1 (Cook et al., 1995; Gill et al., 1997). The latter results in an increased density and activity of dopamine transporters in ADHD patients

(Dougherty et al., 1999) and therefore leads to lowered dopamine concentrations in the synaptic cleft (Vles et al., 2003). Interestingly, Demiralp et al. (2007) were able to show that these very polymorphisms yield significantly augmented gamma-band activity in healthy subjects in a target detection task. However, it may at first seem counterintuitive to assume higher GBRs in ADHD as Herrmann and Demiralp (2005) suggested a positive correlation between dopamine availability and gamma activity based on findings of Ahveninen et al. (2000). Therefore, it is necessary to distinguish between phasic, stimulus driven dopamine responses and the tonic, extracellular dopamine level as some authors suppose an increased phasic dopamine response in ADHD patients due to the lower tonic dopamine resulting in reduced inhibition via presynaptic autoreceptors (Seeman and Madras, 1998; Grace, 2001; Sagvolden et al., 2005). The low tonic dopamine level is targeted by stimulant treatments such as methylphenidate, which blocks dopamine transporters resulting in augmented extracellular dopamine availability (Dresel et al., 2000; Krause et al., 2000; Spencer et al., 2000; Volkow and Swanson, 2003). Seeman and Madras (2002) hypothesize that this in turn yields a lower phasic dopamine release. Thus, increased phasic dopamine activity in unmedicated patients would be in line with the assumption of augmented GBRs.

Based on these findings, I investigated whether gamma-band oscillations are disturbed in ADHD children and compared them to healthy subjects. As suggested by Barceló and Gale (1997), I did not investigate gamma activity in spontaneous EEG but event-related gamma-band oscillations in a cognitive experiment. In line with the recommendation of Başar and Güntekin (2007), I have chosen an experimental design which tests an impaired cognitive function of ADHD patients that has been associated with a physiological parameter, i.e. gamma activity in case of memory processes. Therefore, I analysed data from a study, which investigated ERP differences in a visual memory paradigm (Krauel et al., 2009), now focussing on the analysis of activity in the gamma-band. This experiment started with an encoding phase, where 240 pictures were presented in the context of two different encoding tasks. In a later recognition test, the pictures were presented again along with 120 new stimuli and subjects had to distinguish between old and new pictures. I hypothesized, that patients should exhibit stronger stimulus related visual GBRs than healthy children. I further investigated the interaction between evoked GBRs during stimulus encoding and subsequent memory performance.

5.2 Experimental procedure

5.2.1 Participants

Thirteen male ADHD patients and thirteen male healthy control subjects participated in this study. The patients were referred to us by the Department of Child

and Adolescent Psychiatry at the University of Magdeburg as well as local paediatricians. Initially, all subjects and their parents were interviewed separately by clinical child psychologists or psychiatrists with a German translation of the Revised Schedule for Affective Disorders and Schizophrenia for School-Age Children: Present and Lifetime Version (Kaufman et al., 1997; Delmo et al., 2000). The patients met diagnostic criteria for ADHD according to the DSM-IV (10 combined type, 3 inattentive; see Chapter 2.1.1) and six patients also fullfilled criteria of ODD or CD. Patients who met present or lifetime criteria for any other psychiatric disorder were excluded from the study. Eight patients received medical treatment, but had to discontinue their medication at least 24 hours prior to the EEG session.

Healthy control subjects were recruited by local press announcements and had no evidence of any previous or current psychiatric disorder according to the structured clinical interview. Furthermore, none of the subjects had a history of any neurological disorder and past or present substance abuse. As I aimed to avoid possible confounds resulting from age differences (Böttger et al., 2002; Yordanova et al., 2002), I focussed on a more narrow age range (11 - 15 years) than the companion ERP study (Krauel et al., 2009) and both groups were pairwise age matched, yielding to slightly different sample sizes between this report and that of Krauel et al. (2009). Demographic and clinical characteristics of both groups are presented in Table 5.1. As additional measures, the Child Behaviour Checklist (CBCL; Achenbach, 1991a) as well as the Youth Self-Report (YSR; Achenbach, 1991b) were employed and all subjects had to score higher than 80 on the Culture Fair Intelligence Test (Weiss, 1997). To exclude severe memory impairments, all participants performed a standardised figural memory screening (Lamberti and Weidlich, 1999). There were no significant differences in intelligence or figural memory between the two groups. Handedness was determined with the Edinburgh Handedness Inventory (Oldfield, 1971) and the participants had normal or corrected to normal vision.

The study was approved by the ethics committee of the Otto-von-Guericke-University Magdeburg and was conducted in accordance with the Declaration of Helsinki concerning human experimentation. All participants as well as their parents gave a written informed consent/assent. The subjects were reimbursed with vouchers for their attendance.

5.2.2 Stimuli and task

Subjects performed a well established levels-of-processing paradigm (Krauel et al., 2007). The present chapter reports a reanalysis of a study which illustrates de-

Table 5.1: Demographic and clinical characteristics of the current sample

	ADHD (N=13) mean ± SD	**Controls (N=13)** mean ± SD	**p-value**
Age	12.8 (1.0)	12.6 (1.1)	n.s.
IQ	107.4 (11.3)	111.0 (9.9)	n.s.
Figural Memory	46.9 (25.8)	64.5 (23.7)	.08
CBCL			
Attention problems	70.6 (4.4)	51.3 (3.9)	<.001
Delinquent rule-breaking behaviour	65.3 (7.6)	52.6 (5.9)	<.001
Aggressive behaviour	69.8 (9.5)	51.7 (3.3)	<.001
Internalising	62.5 (8.7)	48.0 (6.2)	<.001
Externalising	68.3 (8.4)	47.4 (7.7)	<.001
YSR			
Attention problems	62.3 (6.6)	52.1 (3.1)	<.001
Delinquent rule-breaking behaviour	61.8 (4.5)	52.6 (4.2)	<.001
Aggressive behaviour	61.5 (8.5)	52.1 (3.7)	.002
Internalising	54.4 (18.7)	46.5 (5.3)	n.s.
Externalising	62.3 (8.6)	49.1 (6.2)	<.001

tailed results of behavioural and ERP analyses (Krauel et al., 2009). The experiment started with an encoding phase, in which 240 pictures of either neutral (50%) or emotional (50%) content were presented, each picture superimposed by a rectangular or an oval contour. Most of the pictures were chosen from the International Affective Picture System (IAPS; Lang et al., 2001). Additional pictures (40%), which were similar in content to the IAPS stimuli, were included. Emotional pictures could be either of positive or negative content (50:50), but were matched in arousal. Participants had to decide either whether there was a rectangle or an oval in the picture (shallow task) or whether there was a human being in the picture or not (deep task). Since I focussed the analysis on visual processing per se, both tasks were collapsed in all analyses. Tasks alternated across six runs (three runs of each kind, 40 pictures per run), which were counterbalanced across subjects. To avoid confounding effects of task switching, subjects worked on only one task per run, but were reminded about the current task before each stimulus with an instruction screen starting 1000 ms before stimulus onset. Afterwards, the pictures were displayed for 600 ms and were followed by a fixation cross at the centre of the screen (see Figure 5.1 for details). The participants responded via button press and were allowed to correct their response. Before the

EEG session, subjects were made familiar with both encoding tasks, but were not instructed about the later recognition test which started with a 5 minute delay after the encoding phase. Here, all 240 pictures from the encoding phase were presented again along with 120 randomly displayed new stimuli. These were carefully matched in salience and content with pictures from the encoding phase. All pictures were shown for 1000 ms without the superimposed contour and the delay between each picture was set to 3000 ms. The task of the subjects was to judge the pictures via button press being old or new.

All pictures were shown on a 17 inch computer screen against a black background and spanned a visual angle of 11°. The experiment was performed using Presentation® software (Version 0.53, http://www.neurobs.com).

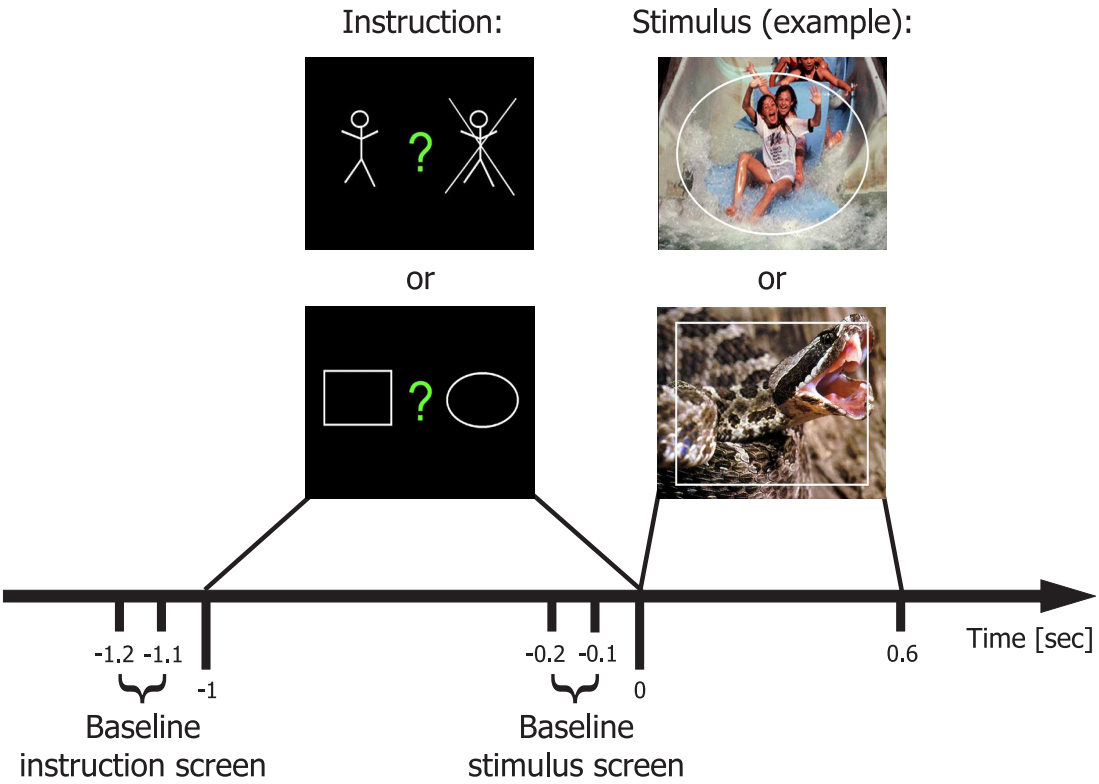

Figure 5.1: Trials in the encoding phase started with an instruction screen, reminding the subjects either to perform the deep task (human being or no human being) or the shallow task (rectangle or oval). The tasks did not vary within one run. Afterwards, the stimulus was displayed for 600 ms and the trial ended with a fixation cross at the centre of the screen.

5.2.3 Data acquisition

The electroencephalogram was recorded using 32 sintered Ag/AgCl-electrodes mounted in an elastic cap (Easycap GmbH, Herrsching-Breitbrunn). These were

placed according to the 10-10 system and connected to a SynAmps amplifier (Compumedics Neuroscan, Charlotte). Signals were referenced to Pz, the ground electrode was placed at AFz. Eye-movement activity was recorded using electrodes at the outer canthi of both eyes and the left sub- and supraorbital positions. All signals were sampled at 500 Hz and analog filtered between 0.01 Hz and 70 Hz. Additionally, a 50 Hz notch filter was applied to remove interferences by line frequency. Electrode impedances were kept below 10 kΩ. Data were digitally saved for later offline analysis.

5.2.4 Data analysis

Behavioural data

Reaction times and responses were recorded and analysed in the encoding phase as well as the recognition test. Reaction times of incorrect responses were removed from further behavioural analysis.

The performance in the recognition test was additionally measured by subtracting false alarms (new pictures misjudged as old) from correctly recognised old items. This so-called 'corrected hit-rate' is a well-established measure to correct for response biases and therefore provides an assessment of memory accuracy (Spaniol and Bayen, 2004).

Electrophysiological data

The EEG analysis was conducted using EEProbe (ANT Software, Enschede). Raw data were first examined for non-stereotyped artifacts like swallowing and excessive electromyographic activity. Sections containing these types of artifacts were removed from further analysis. As described in Chapter 4.1, stereotyped artifacts resulting from eye-movement activity were corrected using Independent-Component-Analysis (ICA) implemented in the open source toolbox EEGLAB (Delorme and Makeig, 2004, http://www.sccn.ucsd.edu/eeglab). Subsequently, the data were digitally high-pass filtered at 0.1 Hz and re-referenced to mean values of all electrodes except ocular electrodes and electrodes T7 and T8, as they were often contaminated by activity of the masseter muscles. Further analysis was conducted on two different epochs: The first epoch ranged from 200 ms before to 600 ms after onset of the instruction screen (instruction epoch, IE), the second epoch lasted from 200 ms before until 600 ms after stimulus onset to investigate stimulus related activity (stimulus epoch, SE). An automatic artifact rejection excluded epochs from further analysis, if the standard deviation in a moving 200 ms time-window exceeded 50 μV. Additionally, all trials were visually inspected for possible remaining artifacts and rejected if necessary. Both groups did not differ in percentage of remaining epochs after artifact rejection (ADHD patients: 86.9% ± 6%, healthy controls: 89.7% ± 7.1%; $t_{24} = 1.104$, $p = 0.281$). To avoid

a decline in signal-to-noise ratio, I did not differentiate between trials correctly recognised or forgotten in the later recognition test and kept all trials in the analysis. Baseline activity was calculated and subtracted from each epoch using the time-window between 200 ms and 100 ms before onset of the instruction screen and stimulus onset, respectively.

Time-frequency analyses were performed on a parieto-occipital region of interest (ROI), which exhibited strongest activation in the gamma-band after visual stimulation and comprised the electrodes P3, P4, P7, P8, O1, and O2. GBR can be distinguished in evoked and induced activity. Evoked activity has been analysed by transforming the averaged single-trials into the frequency domain (see Chapter 4.3.2 for an detailed description). I focussed the analysis on evoked GBRs and abstained from the investigation of the total GBRs since there was no such activity visible in the current study.

Because of considerable interindividual variability in subjects' peak-frequencies in the evoked GBR (exemplary shown in Figure 5.2), I used each subject's individual peak-frequency in the gamma-band (30-80 Hz) for the wavelet transform, defined as the highest GBR in the time-frequency plots averaged across all ROI electrodes, separately for IE and SE, in the time interval between 50 ms and 150 ms (see e.g. Senkowski and Herrmann, 2002; Herrmann et al., 2004b; Lenz et al., 2007, for a similar approach). The wavelet transform was computed by convolving the raw EEG signal with a complex modulated Gaussian, allowing a continuous measure of amplitudes for a given frequency component (Herrmann et al., 2004a). At 40 Hz, the wavelet had a time resolution of $2\sigma_t = 50$ ms and a frequency resolution of $2\sigma_f = 13$ Hz. The exact time-frequency resolution of the wavelet depended on the analysed frequency.

Statistical analysis

Demographic and clinical characteristics between groups were investigated using t-tests for independent samples.

For the encoding phase, averages and standard deviations were computed for reaction times as well as correct responses and effects of GROUP (ADHD patients vs. healthy controls) were analysed using a t-test for independent samples.

Effects of GROUP on the corrected hit-rate were investigated using a t-test for independent samples. As the evoked GBR showed a latency of around 80 ms in IE and SE, statistical analyses of evoked GBRs in both epochs were performed on mean amplitudes in the time window between 60 ms and 100 ms. To detect GROUP differences in the evoked GBRs, t-tests for independent samples were run separately for IE and SE. In order to assess relations between behavioural perfor-

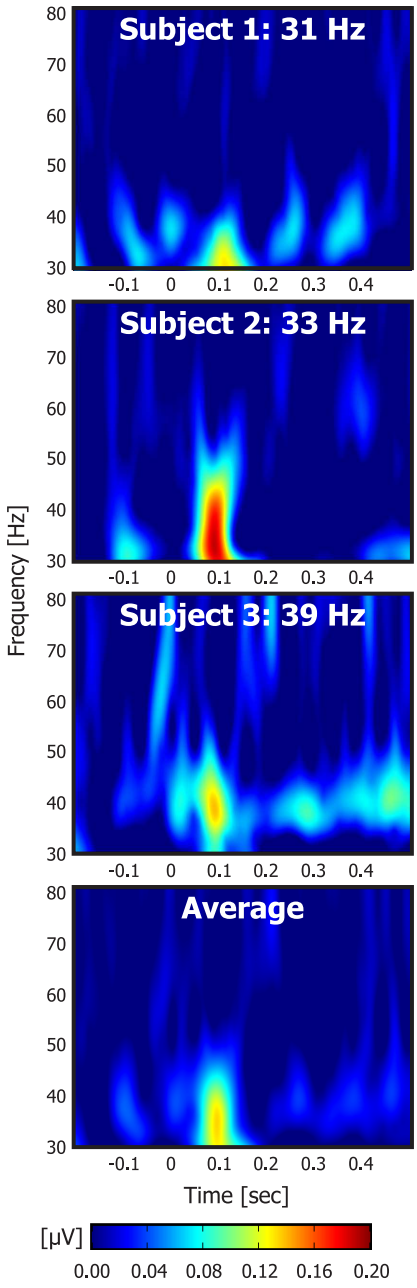

Figure 5.2: Depicted are the time-frequency plots for 3 single subjects (healthy controls), averaged across the analysed ROI and both task conditions. Each subject shows a distinct and well-defined maximum in the gamma range at a specific frequency. However, averaging the plots of all subjects results in a more widespread activity covering a broader frequency range and therefore leading to an activity pattern that looks less distinct.

mance in the recognition test and evoked GBR in the encoding phase, post-hoc Pearson correlations between the overall corrected hit-rate and GBR amplitudes during IE and SE were calculated.

The alpha level for t-tests was a priori determined as 0.05. For all statistical analyses the Statistical Package for the Social Sciences (SPSS), version 15 was used (SPSS Inc., http://www.spss.com).

5.3 Results

5.3.1 Behavioural performance

Participants performed the tasks in the encoding phase with high accuracy (see Table 5.2). ADHD patients and healthy control subjects neither differed in reaction time (t_{24} = -0.319; p = 0.752) nor in percentage of correct responses (t_{24} = 0.550; p = 0.587).

In the recognition test, ADHD patients showed a slightly diminished recognition performance. However, this difference did not reach statistical significance (t_{24} = 1.332; p = 0.195). Analysis of reaction times also yielded no significant GROUP effects (t_{24} = -0.544; p = 0.591).

Table 5.2: Behavioural performance for ADHD patients and healthy control subjects. Although ADHD patients showed longer reaction times and a slightly reduced performance in the recognition test, these differences did not reach significance.

	ADHD (N=13) mean ± SD	**Controls (N=13)** mean ± SD
Encoding phase		
Reaction times in ms	670.8 (145.2)	649.9 (185.9)
Correct responses in %	96.8 (3.1)	97.6 (3.8)
Recognition test		
Reaction times in ms	1034.0 (199.4)	989.4 (217.8)
Corrected hit-rate in %	41.7 (12.5)	47.6 (10.1)

5.3.2 Evoked gamma-activity

An analysis in the parieto-occipital ROI yielded no significant GROUP differences in gamma-band activity evoked by the instruction screen, which reminded the subjects about the current task (t_{24} = -0.444, p = 0.661; see Figure 5.3A). However, comparison of stimulus related GBR resulted in a significant GROUP difference (t_{24} = -2.170; p = 0.04). ADHD patients exhibited enhanced amplitudes as compared to healthy subjects (Figure 5.3A and B) in the parieto-occipital ROI (Figure 5.3C).

5.3.3 Associations between behavioural performance and evoked GBR

Healthy control subjects showed a significant positive correlation between evoked GBRs during the encoding phase and subsequent recognition performance as

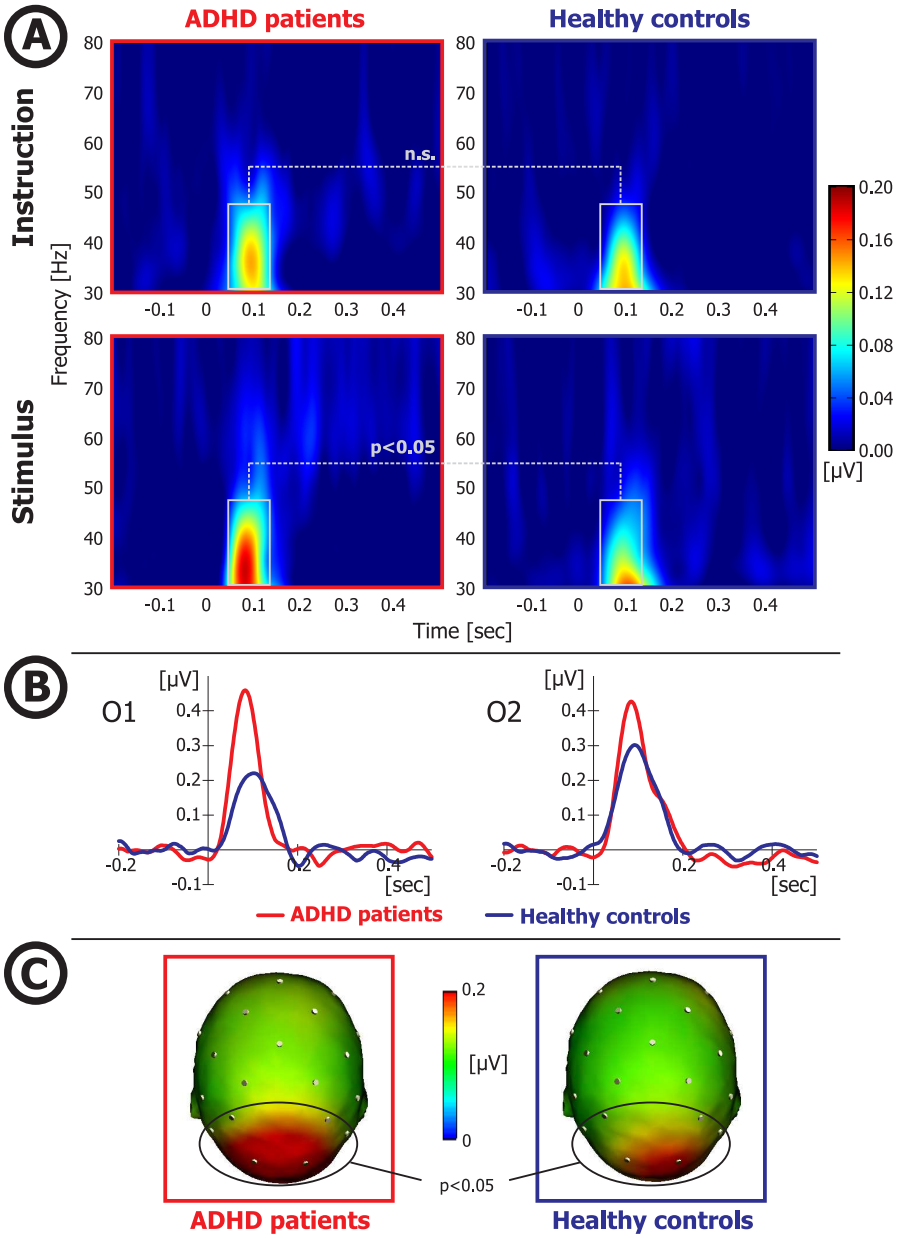

Figure 5.3: A: Time-frequency plots averaged across electrodes of the parieto-occipital ROI and both task conditions reveal clear differences between healthy subjects and ADHD patients in the GBR evoked by the stimulus (second row), while the instruction screen evoked comparable activation in both groups (top row). B: Averaging the individual time courses of the wavelet transform according to the peak frequency of each subject also demonstrates higher GBR amplitudes for ADHD patients (red) compared to healthy subjects (blue). Data are exemplary displayed for electrodes O1 and O2 and all stimuli were averaged, irrespective of the task condition. C: The topographical maps, here depicted as mean of stimulus evoked GBR in the analysed time-window, indicate strong GBR enhancements for ADHD patients in the parieto-occipital ROI, which is emphasised by the oval.

represented by corrected hit-rate (r = 0.636; p = 0.019). This indicated a better performance for subjects who exhibited higher amplitudes in evoked GBRs during encoding. Interestingly, this association was absent in the ADHD group (r = 0.063, p = 0.839). This is depicted in Figure 5.4.

Recognition performance and GBRs evoked by the instruction screen were not significantly correlated, neither in ADHD patients (r = -0.299; p = 0.320) nor in healthy control subjects (r = 0.425; p = 0.148).

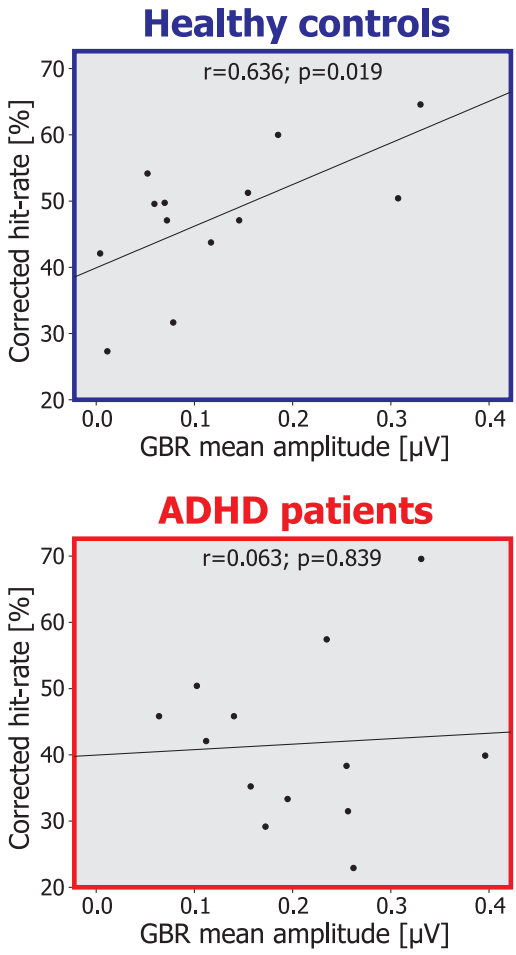

Figure 5.4: Correlations between average corrected hit-rate (ordinate) and stimulus evoked GBR in the parieto-occipital ROI (abscissa). While the relationship between GBR during the encoding phase and later recognition performance is clearly visible for healthy subjects (top), this association is absent in the ADHD group (bottom).

5.4 Discussion

This is the first study revealing differences between ADHD patients and healthy control subjects in electrophysiological activity above 30 Hz during visual processing. The intention was to shed further light on the role of evoked GBR

accompanying pathological states such as ADHD and its relevance for memory performance.

5.4.1 Group differences in evoked GBRs

Brain activity in the gamma-range has been repeatedly correlated with a multitude of perceptual (Busch et al., 2004; Karakaş and Başar, 1998; Tallon-Baudry et al., 1996) and cognitive functions (Başar-Eroglu et al., 1996; Başar et al., 1999, 2001; Engel et al., 2001). For the latter, modulations by tasks involving attention or memory processes could be elucidated, both for evoked (Tiitinen et al., 1993; Herrmann and Mecklinger, 2001; Debener et al., 2003; Herrmann et al., 2004b; Freunberger et al., 2007) and induced gamma oscillations (Tallon-Baudry et al., 1998; Gruber et al., 2004; Lenz et al., 2007). As these processes are often impaired in psychiatric disorders, there is a growing body of research associating GBR variations with different pathological states (Herrmann and Demiralp, 2005; Uhlhaas and Singer, 2006). Altered high-frequency oscillatory activity has been described in disorders like schizophrenia (Clementz et al., 1997; Lee et al., 2003; Gallinat et al., 2004; Başar-Eroglu et al., 2007), autism (Grice et al., 2001; Brown et al., 2005; Orekhova et al., 2007), or affective disorders (Strelets et al., 2007), where increased as well as decreased GBRs have been found to be associated with impairments in different cognitive functions. However, to date there was only one study investigating GBRs in ADHD patients. In an auditory target detection paradigm, Yordanova et al. (2001) encountered enhanced evoked GBRs for stimuli presented to the right ear for both attended and ignored stimuli. They interpreted their finding as a marker of impaired motor inhibition in ADHD. I also observed comparable enhancements in these data. While there were no significant differences between healthy subjects and ADHD patients in the behavioural performance, the electrophysiological results highlight a clear augmentation of visual evoked GBRs in a parieto-occipital region, which is involved in the processing of visual stimuli. Interestingly, this augmentation could only be found for stimuli, that were directly relevant for solving the required task and demanded a behavioural response. The difference was not visible in the evoked GBR following the instruction screen, which reminded the subjects about the current task. This absence of an effect probably results from the fact that the instruction screen remained constant across a whole run and the repeated extraction of stimulus features was not necessary.

According to Yordanova et al. (2001), one could assume impaired motor inhibition to be the crucial factor for the observed GBR increases regarding task-relevant stimuli since all stimuli required motor responses. However, the enhancement affected a parieto-occipital area and for this reason a pure relation to impaired motor preparation seems improbable. In my opinion, the stronger evoked GBRs could be indicative of additional neural activation in ADHD patients to compen-

sate for less efficient processing during extraction of stimulus features and integration of the perceived sensory input. Imaging studies support this assumption demonstrating task-related compensatory activation as response to developmental deviations from normal maturational processes (Durston et al., 2003; Krauel et al., 2007; Sheridan et al., 2007). Interestingly, GBRs also show a direct relation to task demands (Yordanova et al., 1997; Senkowski and Herrmann, 2002) and vigilance (May et al., 1994) as well as voluntary allocation of attentional resources (Landau et al., 2007). Hence, it seems convincing to assume a higher activation of processing resources in ADHD patients for task-relevant stimuli, reflected by enhanced activity in the gamma-range.

It has been argued that electromyographic activity (EMG), possibly generated by neck muscles, could account for the described GBR difference (Whitham et al., 2007), potentially originating from the distinct hyperactive behaviour of ADHD patients. There are several points that suggest a brain origin of the measured activity: First of all, I removed even minimal myogenic activity after exact visual inspection of the raw data. Thus, I avoided artifact contamination as far as possible. Secondly, if the signal would merely reflect EMG activity stemming from pronounced motor hyperactivity in ADHD patients, this GBR enhancement should also appear during the instruction epoch, which was not the case. Finally, the investigated signals are strongly phase-locked to the stimulus-onset. Thus, it is very unlikely that they represent the mostly randomly occurring EMG activity. Instead, these oscillations can be interpreted as a marker of active stimulus processing, which is essential for successful task performance.

5.4.2 Association between evoked GBRs and subsequent memory performance

A relation between evoked GBRs and cognitive processes is also supported by the observed correlation between the amplitude of evoked GBR during stimulus encoding (but not during the instruction epoch) and the performance in the recognition test as measured by the corrected hit-rate, which was only present in healthy subjects. The link between brain activity during encoding and later item recognition has been previously demonstrated for oscillatory activity in the alpha and theta range (Klimesch et al., 1996; Klimesch, 1999; Doppelmayr et al., 2000) as well as induced GBR (Sederberg et al., 2003; Osipova et al., 2006; Busch et al., 2008b). Gruber et al. (2004) also reported this association for induced GBR. However, the induced activity in their study peaked around 200 - 300 ms after stimulus onset. For the first time, the current study reveals a significant correlation between evoked GBR during the first 100 ms of stimulus encoding and subsequent recognition performance. Thus, these data suggest a direct link between electrophysiology and behaviour in healthy subjects, reflected by a better recognition performance of those subjects which exhibited enhanced evoked

GBRs during stimulus encoding. Hence, one could argue that ADHD patients, who are characterised by augmented GBR during stimulus encoding, should benefit and show a better recognition performance. However, the corrected hit-rates of ADHD patients did not significantly differ from healthy subjects in the current study and the described correlation was not visible for the patient group. If anything, the patients demonstrated a tendency for a slightly reduced recognition performance. This is another evidence for an unspecific neuronal excitation reflected by enhanced gamma activity. The unspecific and uncorrelated enhancement of excitation probably resulted in a downgraded signal-to-noise ratio and might be the reason for different aspects of ADHD pathology like an impairment to maintain attentional focus or hyper-active behaviour.

5.4.3 Possible interactions of ADHD neurobiology and evoked GBRs

Interestingly, neuronal fine-tuning of the enhanced excitation in ADHD patients can be achieved by medical treatment with methylphenidate, which blocks dopamine transporters (Kuczenski and Segal, 1997; Seeman and Madras, 1998; Solanto, 2002), resulting in an increased concentration of extracellular dopamine (Krause et al., 2000; Spencer et al., 2000; Volkow and Swanson, 2003). This raises the signal-to-noise ratio with enhanced task-related cell firing (Volkow et al., 2001) by changing the relation between excitatory and inhibitory actions in tonic and phasic dopaminergic neural activity (Devilbiss and Berridge, 2006). According to the model of dopamine dysfunction by Grace (2001), ADHD patients are characterised by lowered tonic dopaminergic activity leading to decreased tonic stimulation of inhibitory autoreceptors. This results in enhanced phasic activity causing dysregulated motor and impulse control (Grace, 2001). Treatment with methylphenidate augments tonic dopamine levels elevating stimulation of presynaptic autoreceptors, attenuating phasic dopamine release to normal levels and yielding less postsynaptic activation (Grace, 2001; Seeman and Madras, 2002; Levy, 2004). Thus, dopamine tone is increased and phasic release is diminished facilitating inhibition and increasing the signal-to-noise ratio (Silk et al., 2005). This enhanced phasic dopaminergic cell firing in unmedicated patients is in line with the postulated positive correlation between dopaminergic activity and GBRs (Herrmann and Demiralp, 2005) and the results of enhanced GBRs in ADHD patients.

Further insights for stronger GBRs can be recovered from genetic research on ADHD unveiling polymorphisms, which seem to contribute to the pathology (Swanson et al., 2000), in candidate genes in the dopaminergic pathway such as the DRD4 (Faraone et al., 2001; Roman et al., 2001; Gornick et al., 2007) and DAT1 polymorphism (Cook et al., 1995; Gill et al., 1997). Several studies demonstrated an increased transporter density and activity in ADHD patients (Dougherty et al., 1999; Dresel et al., 2000; Madras et al., 2002). This results

in a lower availability of dopamine in the synaptic cleft (Vles et al., 2003) causing ineffective dopaminergic neurotransmission and impaired ability to suppress background neural noise, especially in brain regions involved in attention and behaviour (Swanson et al., 2000). It is noteworthy, that the above-mentioned polymorphisms are also associated with high-frequency EEG activity. Demiralp et al. (2007) studied GBRs in healthy subjects with and without these DRD4 and DAT1 variants in an auditory target detection experiment. They observed augmentations of evoked and induced gamma-band activity in response to all stimuli in subjects exhibiting the DRD4 polymorphism and enhanced evoked GBRs only for target stimuli in the DAT1 group, in the absence of any effect on any other investigated frequency band (delta, theta, alpha, beta) or wideband ERP waveforms. Hence, ADHD patients, bearing a higher probability to show these polymorphisms, are also likely to exhibit stronger GBRs related to impaired dopaminergic neurotransmission. This notion is supported by the current results. The differential effect of a GBR enhancement for attentively processed stimuli but not for the instruction screen is in line with selectively enhanced gamma activity for targets in the DAT1 group of Demiralp et al. (2007). Additional evidence is illustrated by studies describing clinical differences between ADHD patients in dependency on the polymorphisms, for instance a more likely diagnosis as ADHD combined type (Waldman et al., 1998) or rather more distinctive hyperactive behaviour (Bellgrove et al., 2005) for patients with the DAT1 polymorphism. Thus, although there is no information about the genetic background of the participating subjects, more patients in the current sample show ADHD combined type. This could be an indicator for a higher number of subjects having the DAT1 polymorphism which predisposes for ADHD and resulted enhanced gamma activity in the study by Demiralp et al. (2007), resulting in enhanced GBR to task relevant stimuli in this experiment. Unfortunately, the sample size did not suffice to test for differences between ADHD subtypes. This could be subject of future work, particularly since this could contribute to the discussion about the existence of these DSM-IV defined subtypes (Clarke et al., 2002; Barkley, 2003). However, the direct linkage between ADHD, genetic polymorphisms and GBR remains to be established in future studies, as well as expected differences during GBR measurement under methylphenidate treatment, which could be assumed to yield normalised activity in the gamma-band.

5.5 Conclusions

The current study revealed stimulus-related augmentations of evoked GBRs during early visual processing of task relevant stimuli in ADHD patients and assume them to be a result of enhanced excitation levels and unspecific activation of processing resources. This compensation for inferior performance by enhanced activity could potentially result in an increase of performance to the level of healthy

subjects. However, it may also lead to a downgraded neuronal signal-to-noise ratio, partially caused by impaired dopaminergic neurotransmission, contributing to different aspects of the pathology of ADHD.

CHAPTER 6

Experiments II & III: Cognitive relevance of evoked GBRs in ADHD children and healthy participants

The study described in this chapter is currently under review:
Lenz D, Krauel K, Flechtner HH, Schadow J, Hinrichs H, Herrmann CS (under review)
Altered evoked gamma-band responses reveal impaired early visual processing in ADHD children
Biological Psychiatry

6.1 Introduction

Epidemiological studies indicate that an estimated number of 4% to 7% of children worldwide is affected by developmentally inappropriate degrees of inattention, impulsivity, and hyperactivity (Spencer et al., 2007). Thus, attention-deficit/hyperactivity disorder (ADHD) is one of the most frequently diagnosed psychiatric disorders in childhood and adolescence (Biederman and Faraone, 2005). In order to investigate one of the core symptoms, inattention, experimental paradigms require participants to selectively shift their attentional focus to a specific stimulus while ignoring other stimuli appearing within a stream of visual or auditory events. In those tasks, ADHD patients typically show a higher number of omission errors or false alarms than healthy children (e.g. Jonkman et al., 1997). The EEG allows the analysis of the exact time-course underlying these impairments (Loo and Barkley, 2005; Banaschewski and Brandeis, 2007; Rothenberger, 2009), indicating smaller amplitude differences between attended (relevant) and unattended (irrelevant) stimuli in ADHD patients in comparison to healthy children in those components of the event-related potential (ERP) associ-

ated with task-relevant processing (e.g. the P3; Satterfield et al., 1994; Jonkman et al., 1997; Brandeis et al., 2002). Thus, insufficient preferential processing of task-relevant stimuli could arise from deficits in discriminating relevant and irrelevant information (Satterfield et al., 1994). In auditory information processing, there is agreement that these deficits around 300 ms are preceded by impairments at earlier stages, representing inefficient filtering of relevant information (Johnstone et al., 2001; Jonkman et al., 2004). However, contrary findings are reported for visual processing (Tannock, 1998). Impaired filtering or orienting during early stages of stimulus evaluation in the visual modality have been reported (Robaey et al., 1992; Jonkman et al., 1997; Karayanidis et al., 2000), but are in contrast to findings of intact early visual processing (Satterfield et al., 1994; Novak et al., 1995; Strandburg et al., 1996).

Therefore, it is still unclear whether early visual processing deficits contribute to the ADHD pathology. In order to investigate this discrepancy, evoked gamma-band responses (GBRs) can be considered as a suitable measure for elucidating early visual processing in ADHD patients: Occurring as early as 100 ms after visual stimulation, high-frequent oscillatory activity in the gamma-band (30-80 Hz of human EEG) is one of the earliest cortical responses associated with important aspects of visual processing (Başar et al., 2001). Due to the fact that evoked GBRs are stable within an individuum but vary across individuals (Fründ et al., 2007), they have been considered a trait variable (Zaehle et al., 2009). Allowing a precise temporal coordination of and communication between spatially distributed cortical networks during information processing (Fries, 2005), GBRs are involved in integrating sensory information and enable a rapid analysis, encoding, and categorisation of incoming information in a variety of cognitive processes (Başar-Eroglu et al., 1996; Herrmann et al., in revision), e.g. feature binding (Engel and Singer, 2001), object processing (Tallon-Baudry and Bertrand, 1999), attention (Tiitinen et al., 1993; Debener et al., 2003), and memory (Herrmann et al., 2004c; Kaiser and Lutzenberger, 2005; Gruber and Müller, 2006). This, in turn, facilitates a fast allocation of attentional resources that is necessary for the estimation of the importance of e.g. external events, but also requires a fast extraction and analysis of stimulus features and an internally driven comparison with representations stored in memory. Evoked GBRs have been demonstrated to be involved in such memory processes as they are enhanced when known stimuli match their representation stored in memory (Herrmann et al., 2004b). Thus, as attentional capacity is limited, this fast mechanism allows a rough classification of incoming information with respect to their relevance at a very early processing stage, indicating an early processing advantage for stimuli that already have a representation in memory and, afterwards, enabling an efficient allocation of attentional resources. This link between attentional and memory processes has been summarised in the 'Match-and-Utilisation-Model' (MUM) (Herrmann et al., 2004c). In this model, attention gains the role of a modulating factor that en-

ables the matching process, but is, in turn, also modulated by the result of this match. Therefore, as evoked GBRs gain a pivotal role in early visual processing and index disordered perceptual abilities (Spencer et al., 2004), they can be considered a suitable measure for assessing early visual processing in ADHD patients.

As demonstrated in Experiment I, altered very early stages (<100 ms) of visual processing can be observed in ADHD children (see Chapter 5): During the encoding phase of a visual short-term memory paradigm, ADHD patients showed enhanced evoked GBRs compared to an age-matched sample of healthy children. Interestingly, evoked GBR amplitudes of healthy participants were associated with their task performance in the subsequent recognition test, where participants yielded a better recognition rate when they exhibited higher evoked GBRs during stimulus encoding. In contrast, the augmented evoked GBRs of ADHD patients were not related to recognition performance. Thus, the ADHD patients showed unspecifically increased evoked GBRs, but did not benefit from these. Additional support for altered early stages of information processing in ADHD was raised by the result of enhanced evoked GBRs in ADHD patients during auditory stimulus processing (Yordanova et al., 2001). To my knowledge, these are the only reports associating early GBRs with the pathology of ADHD, even though a dysfunction at this early automatic processing stage could influence subsequent processing, yielding impairments in the ability to discriminate relevant from irrelevant information and inappropriate reallocation of attentional resources as it is reported for ADHD patients.

The aim of the current experiments was to shed additional light on early visual processes in ADHD patients. In particular, I investigated early memory based classification processes reflected by evoked GBRs as a possible neuronal correlate of an early dysfunction in information processing that could, according to the MUM, be directly related to the ADHD pathophysiology. The experimental procedure was based on a paradigm that elucidated the crucial role of evoked GBRs during early visual processing in healthy adults (Herrmann et al., 2004b), showing clear enhancements of evoked GBRs following stimuli already represented in long-term memory. However, before examining ADHD patients I aimed to investigate whether employing the identical paradigm in healthy children yields comparable results as demonstrated in healthy adults.

6.2 Experiment II: Pilot study on evoked GBRs in healthy children

Prior studying early visual memory matching processes reflected in the evoked GBR of ADHD patients, it is essential to elucidate whether healthy children show similar enhanced evoked GBRs for known stimuli as reported for healthy adults.

This is an important issue since human development during childhood is characterised by major structural and functional brain changes (Sowell et al., 2003; Toga et al., 2006). Electrophysiological correlates of these major developmental changes have been detected in the ERP (Dustman et al., 1993; de Haan, 2008) as well as evoked GBRs (Böttger et al., 2002; Yordanova et al., 2002; Yordanova and Kolev, 2008). Moreover, there is recent evidence that the extent of neural synchrony in the gamma-band is directly mirrored by different stages of brain maturation during human development, demonstrating peaks and troughs at different age groups (Uhlhaas et al., 2009). Thus, it is plausible to assume that children and adolescents might show a different pattern of evoked GBRs during the sensory encoding, evaluation, and classification of visual input.

Within a pilot study, I addressed this question by recording EEG from fifteen male, healty children and adolescents (mean age: 14.4 ± 1.5 years). The experimental procedure and stimulus material was identical to that employed in the investigation of healthy adults (see Herrmann et al., 2004b, for a detailed description). In short, the participants were asked to decide as fast as possible, whether they perceived visual stimuli as either edgy or curvy. Irrespective of this task, the stimulus set consisted of 96 stimulus pairs, either depicting known real-world items which were supposed to activate a representation in LTM, or physically similar, unknown items. Each figure subtended a visual angle of 5° to 10° and was presented at center of the screen for 1000 ms, followed by an interstimulus interval randomised between 1300 and 1700 ms, during which a black fixation cross was shown. Assessment and analysis of evoked GBRs were identical to Experiment III of this thesis and are illustrated in detail in Chapter 6.3.1.

The analysis within a posterior ROI yielded no effect of stimulus type (known vs. unknown). Thus, in contrast to healthy adults there was no enhanced evoked GBR for known items that were already represented in LTM ($F_{1,24} = 1.48$; n.s.). However, as visible in Figure 6.1B, the grand-average of the individually adapted time-courses of evoked GBRs demonstrated no peak at all within the time-range typically characterised by GBR enhancements after visual stimulation (50 ms to 150 ms). In order to test, whether this post-stimulus activity was actually enhanced compared to pre-stimulus activity, I contrasted the amplitude maxima during a pre-stimulus time-interval (-100 ms to 0 ms) and this post-stimulus interval, revealing no significant amplitude differences between both ($F_{1,14} = 0.95$; n.s.).

Thus, these results support the fact of age dependent variations of scalp measured evoked GBRs (Böttger et al., 2002; Yordanova and Kolev, 2008). More importantly in the context of the aim of this pilot study, the stimuli used in this paradigm did not evoke a distinct GBR in healthy children. This clearly indicates that the stimulus material in its current form cannot be identically transferred from adult participants to children and is not suitable for comparing early top-

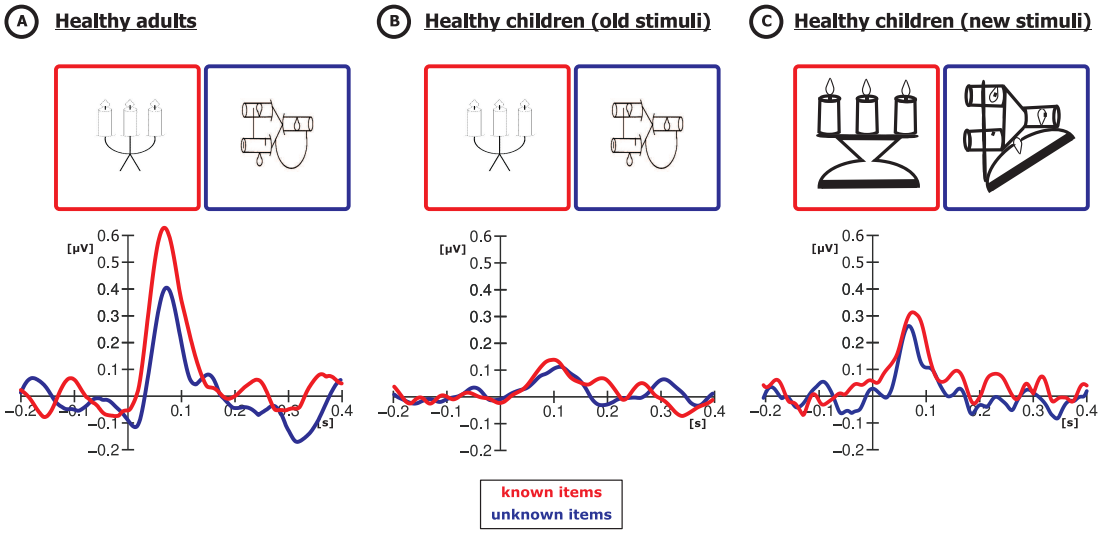

Figure 6.1: A) The time-courses of evoked GBRs of healthy adults at a posterior electrode site demonstrate a clear peak around 90 ms after stimulus onset that is significantly enhanced when stimuli match a representation stored in memory. B) Employing the same stimulus material in healthy children, no clear peak deviating from background noise is detectable and evoked GBRs do not differentiate with respect to memory contents. C) After modification of the stimulus-set by increasing the stimulus size, line thickness, and trial number (improving the signal-to-noise ratio), healthy children presented a clear peak in evoked GBR, too. Furthermore, evoked GBRs at 90 ms were also significantly enhanced for known items already stored in memory (see the full description of this experiment in the following Chapter 6.3).

down processes in healthy children and ADHD patients. A possible explanation for this finding can be drawn from a recent report by Busch et al. (2006): The authors demonstrated that modulations of early evoked GBRs reflect not only bottom-up (Busch et al., 2004; Schadow et al., 2007b) and top-down (Herrmann et al., 2004b; Schadow et al., 2009b) processes, but an early interaction between both (Busch et al., 2006). According to that, the detection of top-down effects on evoked GBRs in scalp measured EEG depends on a sufficient bottom-up input, e.g. an adequate size and intensity of the stimulation. Interestingly, there is evidence that bottom-up driven modulations also interact with the age of investigated subjects: Children and adolescents necessitate larger stimuli to exhibit evoked GBR amplitudes that are similar to GBR amplitudes evoked by smaller stimuli in adult participants (Werkle-Bergner et al., 2009). These results suggest that the converging findings concerning the evoked GBR patterns of children in the current study and healthy adults might be caused by inadequate bottom-up stimulus features being more pivotal in the investigation of children and adolescents. Therefore, a modification of the bottom-up input with respect to the stimulus size and salience could enhance stimulus evoked GBRs and facilitate the detection of top-down effects in children.

To account for this, I adjusted the stimulus-set to be used in Experiment III by increasing the size and line thickness of the presented stimuli. Additionally, new stimulus pairs were added to improve the signal-to-noise ratio.

6.3 Experiment III: Altered evoked GBRs reveal impaired early visual processing in ADHD children

6.3.1 Experimental procedure

Participants

Twentysix boys were included in the current study (13 ADHD patients and 13 healthy participants). Patients were referred to the study by the Clinic of Child and Adolescent Psychiatry in Magdeburg, healthy children were recruited through local press announcements. All children as well as their parents were interviewed separately by clinical child psychologists with the German translation of the Revised Schedule for Affective Disorders and Schizophrenia for School-Age Children: Present and Lifetime Version (Kaufman et al., 1997; Delmo et al., 2000). All patients met diagnostic criteria for ADHD according to the DSM-IV (8 combined type, 5 inattentive) (American Psychiatric Association, 1994) and showed no present or lifetime criteria for any other psychiatric disorder except five patients who also met criteria for ODD or CD. Six patients received medical treatment, but discontinued their medication at least 24 hours prior to the EEG session. According to the structured clinical interview, there was no evidence for any previous or current psychiatric disorder in the group of healthy participants. Additionally, for none of the children in both groups present or past neurological disorders or substance abuse were reported. As human GBR varies with age (Böttger et al., 2002; Yordanova et al., 2002), both groups were pairwise age matched in a range between 11 and 17 years to avoid confounds resulting from age differences. All participants scored higher than 90 on the Culture Fair Intelligence Test (Weiss, 1997), IQ scores did not differ significantly between both groups.

The Child Behaviour Checklist (CBCL; Achenbach, 1991a) and the Youth Self-Report (YSR; Achenbach, 1991b) served as additional measures to characterise the current sample. One participant in each group was left handed, determined with the Edinburgh Handedness Inventory (Oldfield, 1971). All children had normal or corrected to normal vision. The demographic and clinical characteristics of the sample are presented in Table 6.1.

This study was approved by the local ethics committee of the Otto-von-Guericke-University Magdeburg. All participants as well as their parents gave written informed consent/assent. The children were reimbursed with vouchers for their attendance.

Table 6.1: Demographic and clinical characteristics of the current sample

	ADHD (N=13) mean (± SD)	**Controls (N=13)** mean (± SD)	**p-value**
Age	13.9 (2.0)	13.8 (2.0)	n.s.
IQ	103.3 (8.0)	109.9 (11.3)	n.s.
CBCL			
Attention problems	66.7 (4.9)	54.58 (5.7)	<.001
Delinquent rule breaking behaviour	55.8 (5.1)	52.6 (5.6)	n.s.
Aggressive behaviour	59.3 (6.4)	53.3 (3.3)	<.05
Internalising	54.1 (5.6)	50.0 (7.8)	n.s.
Externalising	58.2 (5.3)	48.2 (10.1)	<.001
YSR			
Attention problems	60.5 (8.2)	53.2 (6.6)	<.05
Delinquent rule-breaking behaviour	55.3 (7.1)	54.0 (4.3)	n.s.
Aggressive behaviour	58.4 (8.2)	51.3 (2.2)	<.05
Internalising	52.7 (11.7)	49.5 (8.3)	n.s.
Externalising	54.0 (11.0)	48.7 (5.9)	n.s.

Stimuli and task

The participants performed a simple forced choice reaction task adapted from a previous study (Herrmann et al., 2004b). They were asked to decide as fast as possible, whether they perceived visual stimuli as either edgy or curvy. The decision was indicated by pressing one of two buttons with the left or right index finger, respectively. The mapping of left or right key to the two response conditions was counterbalanced across all participants. The picture set consisted of 130 pairs of black and white line drawings, either depicting real-world items (e.g. elephant, guitar, pencil) or unknown, new items. The current paradigm was modified considering the results of Experiment II: 34 new picture pairs were added to increase the trial number. Additionally, all stimuli were revised and modified increasing line-width and stimulus size (8° to 12° visual angle) to evoke clearly visible responses deviating from background noise. To avoid confounds resulting from differences in physical stimulus characteristics such as the number of black and white pixels, edges, and the overall form of the stimuli, these features were kept roughly unchanged between both stimulus conditions by constructing unknown items through a rearrangement of parts of the real-world items. Thus, 130 pictures had an existing representation in memory (known items), whereas 130 physical similar pictures had none (unknown items). The children were not

informed about this differentiation.

Prior to the experiment, all children received a written task instruction displayed on the computer screen and performed a short practice block containing ten stimulus pairs with known and unknown items, being not used in the actual experiment. They were also informed that their judgement was subjective and no correct or wrong answer could be given. The experiment consisted of five blocks of equal length (52 stimuli in each block), separated by brief pauses. The stimulus sequence was pseudorandomised and identical for each participant. The figures were shown at the centre of the screen against a white background for 1000 ms, followed by an interstimulus interval randomised betweeen 1300 and 1700 ms where a black fixation cross was shown. The experiment was performed using Presentation® (http://www.neurobs.com). The temporal sequence of the paradigm as well as stimulus examples are depicted in Figure 6.2.

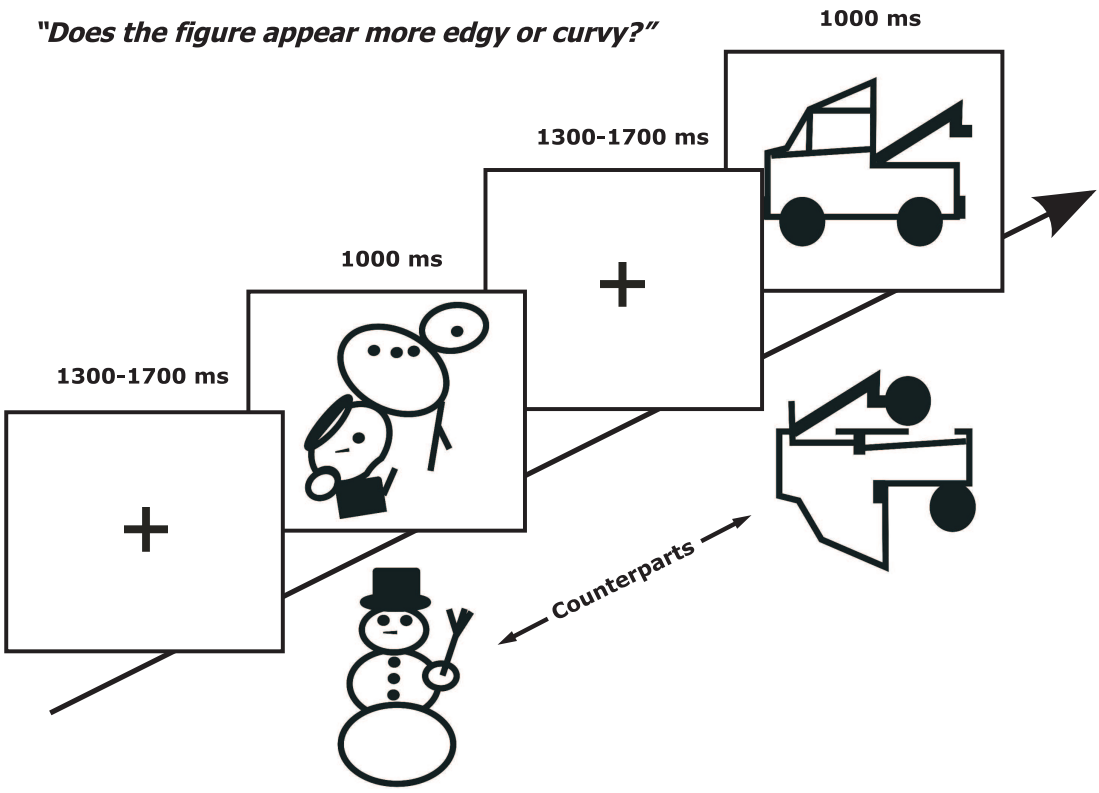

Figure 6.2: Children were instructed to decide as fast as possible, whether the picture appeared more curvy or edgy. They were not informed about the differentiation between known and unknown items. Each item occurred in its original form (e.g. the lorry truck) and also as rearranged unknown item (e.g. the not identifiable snowman). Please note the counterparts of these examples below the drawings that were also presented during the experiment and displayed similar physical characteristics.

Data acquisition

In order to avoid electrical interferences from line frequency, the experiment was performed in an electrically and acoustically shielded cabin, where no devices requiring AC power supply were operated (IAC GmbH, Niederkrüchten, Germany). Visual stimulation was provided by a Dell 24" TFT display (model 2405 FPW), placed at a distance of 100 cm outside the cabin behind an electrically shielded glass window.

The EEG was recorded using 31 sintered Ag/AgCl-electrodes mounted in an elastic cap (Easycap GmbH, Herrsching-Breitbrunn, Germany). These were placed according to the 10-10 system and connected to a BrainAmp amplifier (Brain Products, Munich, Germany). Signals were referenced to a nose-tip electrode, and the ground electrode was placed at AFz. Eye-movement activity was monitored using an additional electrode placed suborbitally to the right eye. All signals were digitised at 500 Hz and analog filtered between 0.016 Hz and 250 Hz. Electrode impedances were kept below 10 kΩ and the digitised signal was transferred to a computer outside the cabin using a fiber optic cable for later offline analysis.

Data analysis

Reaction times (RT) were recorded and analysed. Trials in which the RT exceeded two standard deviations from the mean were removed from the behavioural analysis. Mean RTs and standard deviations were statistically assessed by repeated measures ANOVAs with the within-subject factor CONDITION (known vs. unknown) and the between-subject factor GROUP (ADHD patients vs. healthy participants).

The analysis of electrophysiological data was conducted using EEProbe (ANT Software, Enschede, The Netherlands). Raw data were examined for non-stereotyped artifacts like swallowing and excessive electromyographic activity which were removed when necessary. Afterwards, eye-movement artifacts were corrected as described in Chapter 4.1 using Independent-Component-Analysis (ICA), based on the extended infomax algorithm implemented in the open source toolbox EEGLAB (Delorme and Makeig, 2004, http://www.sccn.ucsd.edu/eeglab). Subsequently, a digital high-pass filter of 0.1 Hz was applied and data were epoched starting 300 ms before until 600 ms after stimulus onset. An additional automatic artifact rejection excluded epochs from analysis, if the standard deviation in a moving 200 ms time-window exceeded 40 μV. Afterwards, all trials were visually inspected for remaining artifacts and rejected if necessary. Baseline activity was calculated and subtracted from each epoch using the time window between 200 ms and 100 ms before stimulus onset for time-frequency as well as ERP analysis.

To avoid loss of statistical power, electrodes which exhibited strongest activations in the gamma-band were pooled in a posterior region of interest (ROI), comprising the electrodes P3, P4, P7, P8, Pz, O1, and O2. GBRs can be distinguished in evoked and induced activity. Evoked activity as analysed in the current study is strictly phase-locked to the stimulation and appears within the first 150 ms after stimulus onset. Analysis is conducted by transforming the averaged single-trials (the ERP) into the frequency domain (see Chapter 4.3.2). There is broad evidence for a notable interindividual variability in the frequency of oscillatory activity (see Figure 6.3 for an illustration). Therefore, I used each participants' individual peak-frequency in the gamma-band for the wavelet transform. To determine this individual frequency, the wavelet transformation was performed for each frequency bin in the gamma-frequency range (30-80 Hz) in steps of 1 Hz. A peak was defined as the highest response in the time interval between 50 ms and 150 ms in the time-frequency plots of the ROI average, separately for each of the two conditions. Both groups did not differ significantly in the mean peak frequencies (ADHD patients: 50 Hz ± 11; Healthy participants: 55 Hz ± 12). Additionally, peak amplitudes of the ERP components were analysed for P1 (90

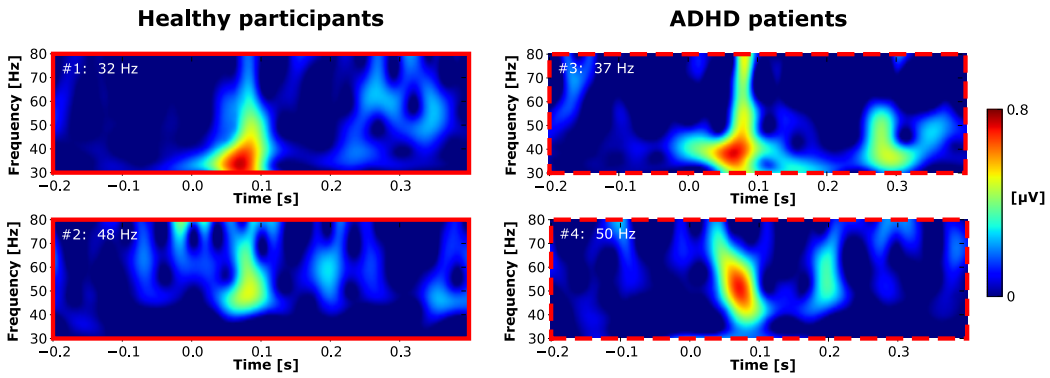

Figure 6.3: Depicted are the ROI-averaged time-frequency plots of four representative participants for the 'known'-condition (left: two healthy participants; right: two ADHD patients). For each participant, a well-defined peak activity at a specific frequency in the gamma range is visible. However, individual differences in the peak frequency are also observable (top: maximum at lower frequency, bottom: maximum at higher frequency). Thus, averaging the plots of all participants results in spreading of activity over a broader frequency range. Therefore, the activity patterns of averaged time-frequency plots as depicted in Figure 6.4 look less distinct.

ms - 160 ms), N1 (150 ms - 200 ms), P2 (210 ms - 250 ms), and frontal negativity (260 ms - 400 ms). Mean amplitudes were computed to assess the posterior P3 component (280 ms - 400 ms). ERP analyses were also run on two ROIs that showed the highest activity according to the analysed component: a frontal ROI for analysis of the frontal negativity (electrodes Fp1, Fp2, F3, F4, F7, F8, and Fz) and a posterior ROI for analysis of the remaining components comprising the same electrodes as in the time-frequency analysis.

Statistical analysis on evoked GBRs as well as ERP components were run using separate repeated measures ANOVAs with the within-subject factor CONDITION and the between-subject factor GROUP. Significant interactions were assessed by repeated measures ANOVAs (factor: CONDITION) separately for each group. The alpha-level for all statistical tests was a priori determined as 0.05.

6.3.2 Results

Behavioural data

The analysis of behavioural data revealed no main effects of GROUP or CONDITION on reaction times (ADHD patients: 729 ± 76 ms; healthy participants: 731 ms ± 203 ms). Although not statistically significant, there was a trend for a slightly higher within-subject response variability in the patient group (mean standard deviation of healthy participants: 113 ms; ADHD patients: 135 ms; $F_{1,24} = 3.05$; $p = .093$).

Electrophysiological data

As depicted in Figure 6.4, the time-frequency analysis within the posterior ROI yielded clearly visible evoked GBRs in both conditions and groups peaking around 90 ms after stimulus onset. Figure 6.1 also contrasts the results of evoked GBRs of healthy subjects in Experiment II and III, repsectively, depicting a strong augmentation of evoked GBRs after employing the modified stimulus material in the current study. Although there was no significant main effect of CONDITION or GROUP, there was a significant CONDITION × GROUP interaction ($F_{1,24} = 5.58$; $p = .027$): Only healthy participants showed significantly enhanced evoked GBRs following known items compared to responses evoked by unknown, new pictures ($F_{1,12} = 5.32$; $p = .04$). In contrast, ADHD patients failed to show such early differentiation between known and unknown items as they evoked similar GBRs in both conditions ($F_{1,12} = 1.47$; n.s.). The ERP analysis revealed no statistically significant main effects of CONDITION or GROUP on the amplitudes of early components such as P1 and N1. Within the time range of P2 and P3, there was a stronger positivity for unknown items compared to known items (CONDITION: P2: $F_{1,24} = 36.20$; $p < .001$; P3: $F_{1,24} = 132.33$; $p < .001$). Overall, the amplitudes were significantly decreased in the patient group (GROUP; P2: $F_{1,24} = 10.97$; $p = .003$; P3: $F_{1,24} = 6.48$; $p = .018$). Analysis of the frontal negativity revealed a larger amplitude following known items ($F_{1,24} = 14.05$; $p < .001$). However, there was a significant interaction of GROUP × CONDITION ($F_{1,24} = 5.46$; $p = .028$). Separate ANOVAs in each group resulted in a significant main effect of CONDITION only in the patient group, revealing a

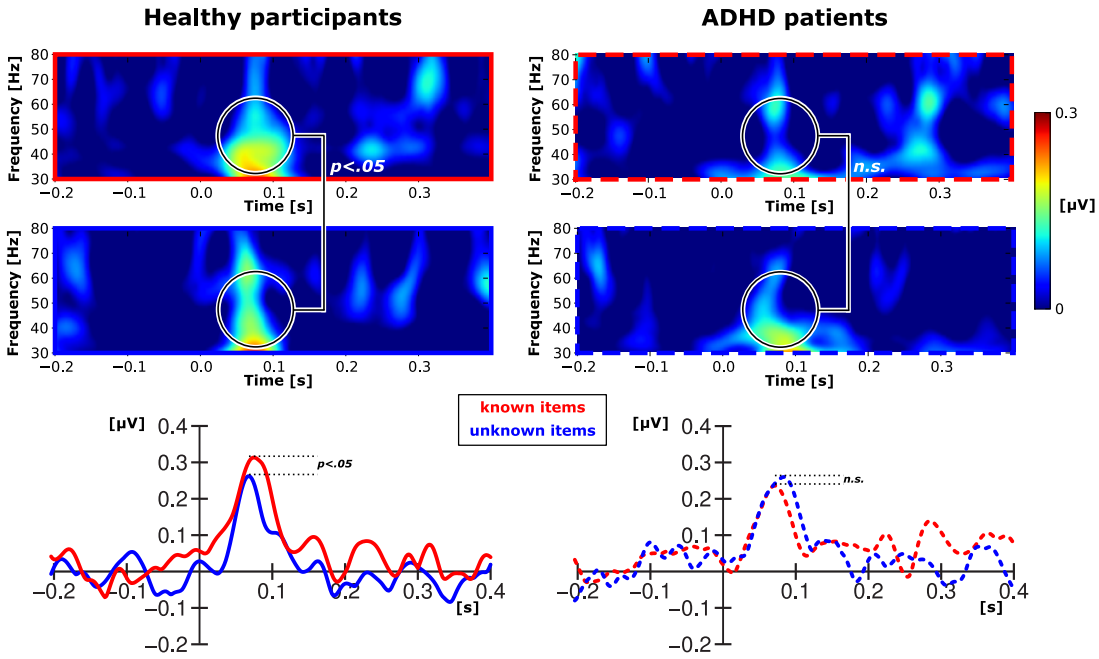

Figure 6.4: Top: The time-frequency plots averaged across all seven ROI electrodes depict strong differences in the memory based activation pattern of healthy participants (left) and ADHD patients (right): Healthy participants showed significantly augmented GBRs following stimuli that matched with a representation already stored in memory (red line) compared to new items without such memory representation (blue line) as early as 90 ms after stimulus onset, whereas evoked GBRs of ADHD patients did not differentiate between these conditions yielding similar amplitudes. Bottom: Averaging the individual time-courses of the wavelet transform according to the peak frequency of each participant across all ROI electrodes also demonstrates larger evoked GBR amplitudes for known items in the group of healthy participants only.

higher negativity for known stimuli in this group (ADHD patients: $F_{1,12} = 22.75$; $p < .001$; healthy participants: $F_{1,12} = 0.84$; $p = .377$). The ERP time-courses at representative electrodes are depicted in Figure 6.5.

6.4 Discussion of Experiments II & III

The current studies examined early visual processing of ADHD patients as well as healthy participants with the aid of measuring evoked GBRs during a simple forced choice reaction task.

Contrary to the results of Experiment II, healthy children demonstrated a clear peak of evoked GBRs during processing of the modified stimulus material employed in Experiment III. This raises support for evoked GBRs being an early interface of interacting bottom-up and top-down processes (Busch et al., 2006) as well as a link between bottom-up processing and brain development (Werkle-Bergner et al., 2009). These results suggest, that the stimulus material employed to study top-down driven processes has to be carefully selected and cannot be

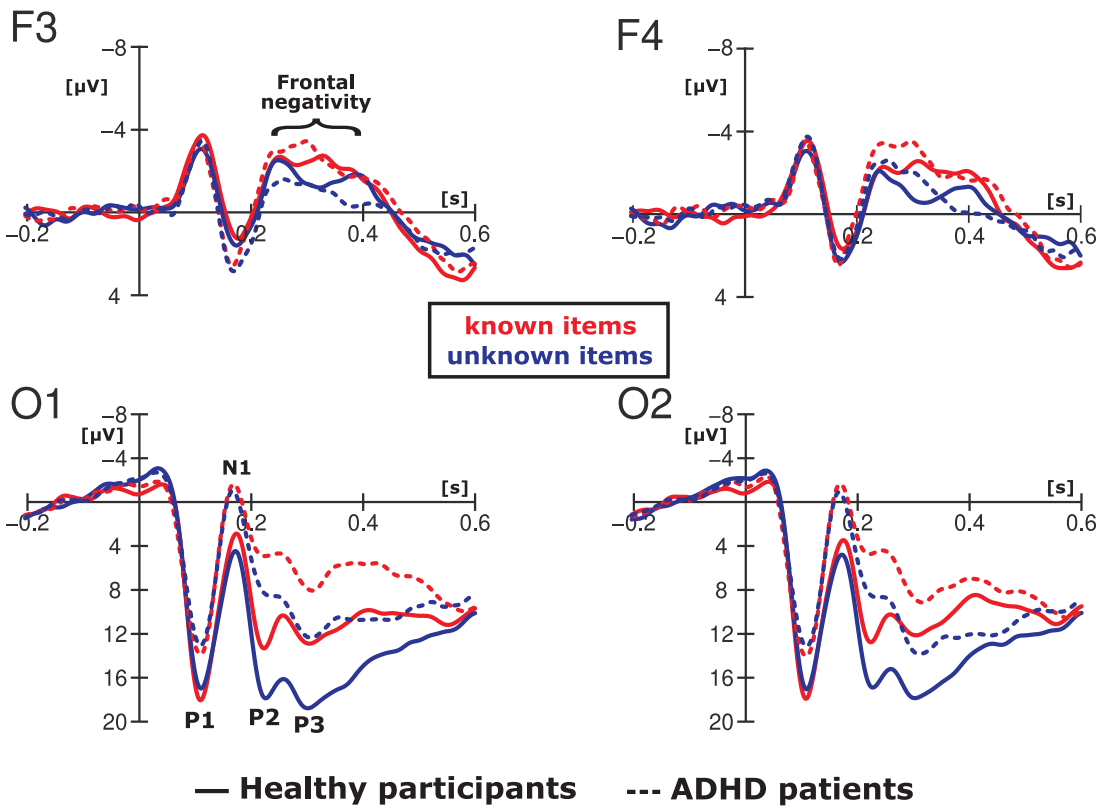

Figure 6.5: Grand-average of event-related potentials at electrodes selected from the frontal (F3/F4) as well as posterior ROI (O1/O2). While P1 and N1 amplitudes differed neither between both groups (ADHD patients: dashed lines; healthy participants: solid lines) nor between both conditions (red lines: known items already stored in memory; blue lines: new items without memory representation), amplitudes of P2 and P3 were more positive for unknown, new items and in the group of healthy participants. Over frontal areas and starting at about 200 ms, only ADHD patients showed a significantly higher negativity following pictures with memory representation. Please note the different amplitude scalings at frontal and posterior electrodes.

easily transferred from one investigated age group to another.

Furthermore, Experiment III revealed enhanced evoked GBRs in healthy children following visual stimuli that matched with a representation stored in memory. This confirms that evoked GBRs play a fundamental role in early visual memory matching processes as demonstrated for healthy adults (Herrmann et al., 2004b). Similar results were reported for the auditory domain: A very recent study revealed that ones own cell phone ringtones that have a high personal significance and are individually represented in each participant's memory, elicit an enhanced evoked GBR during the first 60 ms after stimulus onset compared to new, unknown ringtones (Roye et al., 2009). Moreover, I could demonstrate that early evoked GBRs reflect anticipatory top-down modulation in the auditory cortex as

these are significantly increased when a perceived sound within a tone sequence matches the mental representation of its anticipation (Schadow et al., 2009b). These results highlight the importance of evoked GBRs during early automatic classification processes, enabling a fast and efficient memory based categorisation of incoming information as outlined in the MUM (Herrmann et al., 2004c). In this model, attention as a central factor during information processing, facilitates the matching process between incoming information and stored memory contents. In turn, the successful completion of this match also improves attentional processes such as resource reallocation.

This study demonstrates for the first time that ADHD patients, in contrast to healthy participants, do not exhibit an implicit differentiation between known and unknown items in the evoked GBRs, implying that already the very early categorisation of incoming information is impaired. This result extends the contradictory reports concerning the impairment of early visual processing stages in ADHD patients (Jonkman et al., 2004): Early ERPs (P1 and N1) in the current study also did not differentiate between healthy children and ADHD patients as it has been reported elsewhere (Strandburg et al., 1996). However, at an even earlier processing stage around 90 ms, ADHD patients demonstrated a deviating activity pattern of evoked GBRs. As the current study focused on automatic visual processing per se, not requiring participants to actively shift the attention to a specific relevant stimulus, this is a strong evidence for dysfunctional early stages of visual information processing. Furthermore, these findings support results reporting evoked GBRs to be more sensitive than early ERPs (Schadow et al., 2007a).

According to the MUM, two conclusion can be derived: First, as attended processing of incoming information facilitates stimulus evaluation and, therefore, the comparison with memory contents, impaired matching at this early stage could originate from a diminished stimulus evaluation caused by higher attentional fluctuations in ADHD patients (Castellanos and Tannock, 2002). This is also evident in the trend of an increased intrapersonal response variability observed in the ADHD group. In line with similar reports (Leth-Steensen et al., 2000; Martino et al., 2008; Rubia et al., 2007), this higher variability in response speed is considered to be caused by fluctuations and lapses of attention, resulting in higher performance inconsistency (Castellanos et al., 2005). Furthermore, attentional lapses lead to reduced stimulus-evoked activity in sensory cortices, indicating a failure of attention to facilitate the formation of behaviourally relevant representations of the perceived input (Weissman et al., 2006). Thus, brief attentional lapses in ADHD patients might cause an interruption of top-down signals that foster processing in primary sensory cortices (Woldorff et al., 1993; Kastner et al., 1999), resulting in a reduced quality of stimulus evaluation and differentiation, and, at the same time, enhancing the influence of distracting in-

formation (Weissman et al., 2006).

Second, lacking fast classifications of incoming information with respect to their relevance could further affect the ability to rapidly shift the attentional focus from irrelevant to important information. As a result, filtering of irrelevant information could be dysfunctional, represented in selective attention deficits, also yielding an enhanced distractability to novel information as observed in ADHD patients (Satterfield et al., 1994; van Mourik et al., 2007). This corresponds to fMRI data, highlighting decreased brain activation in several brain regions associated with sustaining or shifting attention to relevant stimuli in ADHD patients (Rubia et al., 2007; Stevens et al., 2007). Furthermore, it is conceivable that the reported GBR differences in ADHD patients could also impact later processing (Barry et al., 2003a): In target detection tasks that are applied to investigate attentional processes, a diminished differentiation between relevant and irrelevant stimuli is usually observed in ADHD patients, yielding more omissions and false alarms (e.g. Satterfield et al., 1994; Jonkman et al., 1997). Interestingly, these tasks also require a fast stimulus evaluation, comparison with a target representation held in memory, and subsequent categorisation for driving a correct response. These data as well as recent findings consider evoked GBRs, being one of the earliest scalp measured signals, to have a fundamental role in such classification of incoming information (Tiitinen et al., 1993; Herrmann and Mecklinger, 2001; Busch et al., 2006). Hence, unsuccessful early matching processes might impact later stages (e.g. at the P3 latency range). This is also consistent with the current data, revealing a higher P3 amplitude for unknown stimuli in both groups, but an overall diminished P3 amplitude in the ADHD group. The P3 has been associated with attention (Polich, 1986) and memory processes (Schendan and Maher, 2009) and is larger following unidentifiable pictures, reflecting higher cortical activity for feature encoding (Holcomb and McPherson, 1994; McPherson and Holcomb, 1999). Compared to healthy participants, ADHD patients consistently show smaller P3 amplitudes during auditory (Holcomb et al., 1986; Johnstone and Barry, 1996) as well as visual stimulus processing (Frank et al., 1996; Satterfield et al., 1990). As this has been interpreted as a marker of decreased cognitive processing and attentional allocation, it is directly related to ADHD pathology (Barry et al., 2003a).

Additionally, the disadvantage of ADHD patients during early classification might also necessitate more detailed stimulus integration during later processing stages. This is evident in the enhanced frontal negativity following known items compared to unknown items observed in the ADHD group, starting at around 200 ms after stimulus onset. This N4-like fronto-central component is also related to familiarity categorisation processes, indicating the depth of semantic processing associated with meaningful stimuli (Kutas and Iragui, 1998). This negative deflection represents the degree of effort that is required to integrate the meaning

of a concept into a higher level representation (Holcomb and McPherson, 1994). An enhanced negativity at this time range for familiar stimuli (Lenz et al., 2007; Kirmse et al., 2009) has been interpreted as marker of perceptual expertise activating semantic knowledge (Tanaka et al., 2006). Thus, as a successful early memory comparison is compromised in ADHD patients, they seem to activate more processing resources for stimulus evaluation and classification at later processing stages.

So far and to the best of my knowledge, only two studies assessed evoked GBRs in ADHD patients. In an auditory target detection paradigm, Yordanova et al. encountered enhanced evoked GBRs for stimuli presented to the right ear, while there was no enhancement for stimuli presented to the left ear (Yordanova et al., 2001). The authors interpreted their finding as a marker of impaired motor inhibition in ADHD. I also observed enhanced evoked GBRs in Experiment I during the encoding of visual stimuli in a short-term memory paradigm, highlighting clear augmentations of visual evoked GBRs in a parieto-occipital region, which is involved in the processing of visual stimuli. Interestingly, this augmentation only followed task stimuli, while it did not occur in response to the instruction screens appearing before each stimulus. Similarly to the GBRs evoked by the instructions screens in that study, I also did not reveal enhanced evoked GBRs in ADHD patients in the current study. This suggests that different results in evoked GBRs of ADHD patients may be related to task demands or stimulus complexity: The instruction screen in the former study also depicted line drawings comparable to the line drawings used in the current study, while the stimuli in the last study were complex photographs of natural scenes. Furthermore, all three studies slightly differ regarding the age of the investigated samples. Thus, differences in evoked GBRs of ADHD patients may show a similar age-dependency as reported for early ERPs (Johnstone et al., 2001), particularly, as age dependent variations of evoked GBRs have been demonstrated (Böttger et al., 2002; Yordanova et al., 2002). Additionally, neural synchrony in the gamma-band has also been suggested to index brain maturation, showing synchrony peaks at different developmental stages (Uhlhaas et al., 2009). This is of special interest as ADHD patients demonstrate a delay in brain maturation, reaching the peak of cortical thickness later than their peers (El-Sayed et al., 2003; Shaw et al., 2007). Given that neural synchrony also indexes modulation through higher cortical areas in a top-down fashion (Uhlhaas et al., 2009), this could indeed be related to the present findings. However, additional longitudinal research is needed to clarify this issue.

6.5 Conclusions

In summary, the data emphasise the relevance of evoked GBRs in early classification processes as they facilitate rapid stimulus processing, yielding advantages for important, meaningful stimuli. Furthermore, while early visual processing of healthy participants is more efficient as it is already shaped by long-term representations stored in memory, ADHD patients demonstrate disadvantages during early phases of visual processing. This could result in an impaired ability to rapidly reallocate processing resources and could also affect filtering of irrelevant information, suggesting that ADHD patients are not only characterised by problems of selective or sustained attention, but that these problems could also be directly related to a more general visual processing deficit during early automatic classification of incoming information.

CHAPTER 7

General discussion

Although electrophysiological as well as imaging research significantly enhanced our knowledge on the pathophysiology of ADHD, the details on the exact etiological factors causing ADHD as well as their interactions and neural correlates are still not enlightened to the full extent and are a matter of ongoing research.

Within this thesis, I aimed to close a gap in research on the electrophysiological manifestations of the cognitive and behavioural impairments of ADHD patients. During the last two to three decades, numerous studies reported several differences in the spontaneous as well as event-related EEG of ADHD patients. However, with one exception by Yordanova et al. (2001) all of those studies disregarded faster oscillatory activity in the gamma-band of human EEG, starting at 30 Hz. This fact astonishes since a lot of reports attribute GBRs to important cognitive functions such as attention or memory (Herrmann et al., 2004c). Furthermore, cognitive deficits in other pathological states such as schizophrenia or autism are also accompanied by altered gamma activity (Herrmann and Demiralp, 2005; Uhlhaas and Singer, 2006; Başar and Güntekin, 2008). Therefore, the present experiments were intended to shed further light on the role of evoked gamma-band activity in ADHD patients. Moreover, I also assessed the direct relevance for behaviour as well as cognition and compared these with healthy children. With respect to the research questions stated at the beginning, three main findings can be derived from my investigations:

1. ADHD patients exhibit enhanced evoked GBRs during encoding of visual stimuli. These enhancements are rather unspecific and are not related to behavioural performance.

Analysis of evoked GBRs during stimulus encoding revealed a strong task-related enhancement for ADHD patients in parieto-occipital areas, being involved in the processing of visual stimuli. These stronger evoked GBRs were only found in response to stimuli that were directly relevant for solving the task and could therefore be indicative of the activation of additional neural resources in ADHD patients as a compensation for inefficient processing during extraction and integration of stimulus features. This notion gains support by recent imaging studies where task-related compensatory activation has been observed (Durston et al., 2003; Krauel et al., 2007; Sheridan et al., 2007). Thus, it seems convincing to assume a higher allocation of processing resources in ADHD patients for task-relevant stimuli as reflected by enhanced evoked GBRs, especially since these were related to task-demands in the past, too (Yordanova et al., 1997; Senkowski and Herrmann, 2002).

Within the context of the behavioural relevance of evoked GBRs, the study yielded another interesting finding: Healthy children exhibited a strong positive correlation between evoked GBRs during stimulus encoding and subsequent performance in a recognition test represented in the corrected hit-rate. Thus, participants who demonstrated higher amplitudes of evoked GBRs were more successful in the subsequent recognition test. Similar associations have been reported for alpha and theta oscillations (Klimesch, 1999; Doppelmayr et al., 2000) and induced GBRs (Sederberg et al., 2003; Osipova et al., 2006; Busch et al., 2008b). However, for the first time the present data corroborate that also early evoked GBRs, appearing as early as 90 ms after stimulus onset, are strongly linked to stimulus encoding and facilitate the later recognition of visual stimuli. In contrast, this finding could not be observed in ADHD patients. This lack of an association to memory retrieval performance indicates that the observed GBR augmentation in ADHD children was rather unspecific and did not foster a better behavioural performance. The unspecific and uncorrelated enhancement of brain excitation probably yields a downgraded signal-to-noise ratio and could be involved in different aspects of ADHD pathology like an impairment to maintain the attentional focus or in motor inhibition.

Neuronal fine-tuning of the enhanced excitation in ADHD patients is achieved by medical treatment with methylphenidate that blocks dopamine transporters (Solanto, 2002). This raises the signal-to-noise ratio during task-related processing by increasing the concentration of extracellular dopamine (Krause et al., 2000; Spencer et al., 2000; Volkow and Swanson, 2003) changing the relation between excitatory and inhibitory actions in tonic and phasic dopaminergic neural activity (Devilbiss and Berridge, 2006). As explained in the Introduction, ADHD patients demonstrate lowered tonic dopaminergic activity and enhanced phasic activity that causes dysregulated motor and impulse control (Grace, 2001) and which is targeted by treatment with methylphenidate (Seeman and Madras, 2002;

Levy, 2004). This increases dopamine tone and diminishes phasic dopamine release. Therefore, a facilitation of inhibition is achieved and the signal-to-noise ratio is enhanced (Silk et al., 2005). The enhanced phasic dopaminergic cell firing in unmedicated ADHD patients can be linked to the postulated association between dopaminergic activity and evoked GBRs (Herrmann and Demiralp, 2005). An additional link can be derived from genetic research on ADHD and the observed higher probability for specific polymorphisms which seem to contribute to the pathology (Swanson et al., 2000), such as the DRD4 (Faraone et al., 2001) and DAT1 polymorphism (Cook et al., 1995). Similar polymorphisms were associated with high-frequency EEG activity, too, whereas no link to any other investigated electrophysiological parameter was visible (Demiralp et al., 2007). This is further support for the observed involvement of evoked GBRs in ADHD that could be related to impaired dopaminergic neurotransmission. Additionally, there is a strong relationship between GBR and performance in recognition tasks that seems to be impaired in neuropsychiatric disorders.

2. Healthy children demonstrate enhanced evoked GBRs following stimuli that are already represented in memory. This result is similar to healthy adults, but necessitates an adequate bottom-up input to be detectable in the EEG.

Before investigating the involvement of evoked GBRs in early visual memory matching processes in ADHD patients, I aimed to clarify whether healthy children show enhanced evoked GBRs for stimuli already represented in memory. In the pilot study, no evoked GBRs deviating from background noise were visible. This could be attributed to an interaction of bottom-up (Busch et al., 2004; Schadow et al., 2007a) as well as age-dependent (Böttger et al., 2002; Yordanova and Kolev, 2008) influences on the evoked GBR. Werkle-Bergner et al. (2009) revealed that children and adolescents require larger stimuli to exhibit evoked GBR amplitudes comparable to those evoked by smaller stimuli in adult participants. This indicates that the stimulus material employed in the pilot study (Experiment II) was not suitable to investigate cognitive processes in child samples. Therefore, I modified all stimuli with respect to their line-width and encompassed visual angle and added further stimuli to improve the signal-to-noise ratio. Applying those updated line-drawings in Experiment III resulted in clearly visible evoked GBR peaks around 90 ms that were augmented for stimuli with LTM representation. This is in line with the results of healthy adults (Herrmann et al., 2004b) and highlights that memory matching reflected by evoked GBRs is a crucial process within early visual processing and is already observeable at earlier stages of brain development. Similar reports can be found for the auditory domain (Roye et al., 2009; Schadow et al., 2009b). This stresses that evoked GBRs are important for an early automatic classification that enables fast and efficient memory based categorisation of incoming information. As outlined in the MUM,

attention is a cardinal factor and facilitates these matching processes between incoming information and stored memory contents (Herrmann et al., 2004c). In turn, a successful completion of this match improves attentional processes such as resource reallocation and, therefore, fosters processing of relevant information.

3. ADHD patients lack an early, memory based classification of incoming information as reflected in evoked GBRs. This implies that already very early stages of visual processing are impaired.

Evoked GBRs of ADHD patients indicate disadvantages at early visual processing stages: In contrast to healthy participants, ADHD patients lack an early memory based classification, possibly resulting in an impaired ability to rapidly reallocate attentional resources to relevant information. This finding suggests that impaired early automatic stimulus classification in ADHD patients could be involved in deficits of selective and sustained attention as these matches with memory guide the attentional focus and lead to faster behavioural responses.

These results raise further support for studies reporting impaired early stages of visual stimulus processing in the visual ERP of ADHD patients (Jonkman et al., 2004) as evoked GBRs are among the first cortical responses that can be observed in scalp measured EEG (Başar et al., 2001). This suggests an early processing deficit in the evaluation of incoming information. Therefore, automatic stimulus classification might be affected as the participants accomplished the task independently from memory and no active discrimination with respect to memory was required. As a consequence, lacking this early categorisation might prevent a facilitated information processing and could boost the influence and processing of distracting information at the same time. Especially with respect to the limited attentional capacity, this filter deficit could have major impact on the ability to turn and keep the attentional spotlight at necessary information and could therefore be associated to the attentional problems reported for ADHD patients (Weiler et al., 2002; Shalev and Tsal, 2003). Figure 7.1 illustrates this link between an early processing deficit and impaired later processing stages. The early deficit seems to be compensated at a later processing stage as evident in a higher differentiation between known and unknown items in the frontal negativity, a component also associated with memory access and classification processes (Kutas and Iragui, 1998; Lenz et al., 2007). Imaging studies suggest that such enhanced activity might indeed represent task-related compensatory activation (Durston et al., 2003; Krauel et al., 2007; Sheridan et al., 2007).

However, with respect to the results of Experiment II and III and bearing in mind the maturational delay hypothesis of ADHD (El-Sayed et al., 2003), one could ask whether ADHD patients would show a differentiation between known and unknown items, if the bottom-up input would be even larger evoking higher

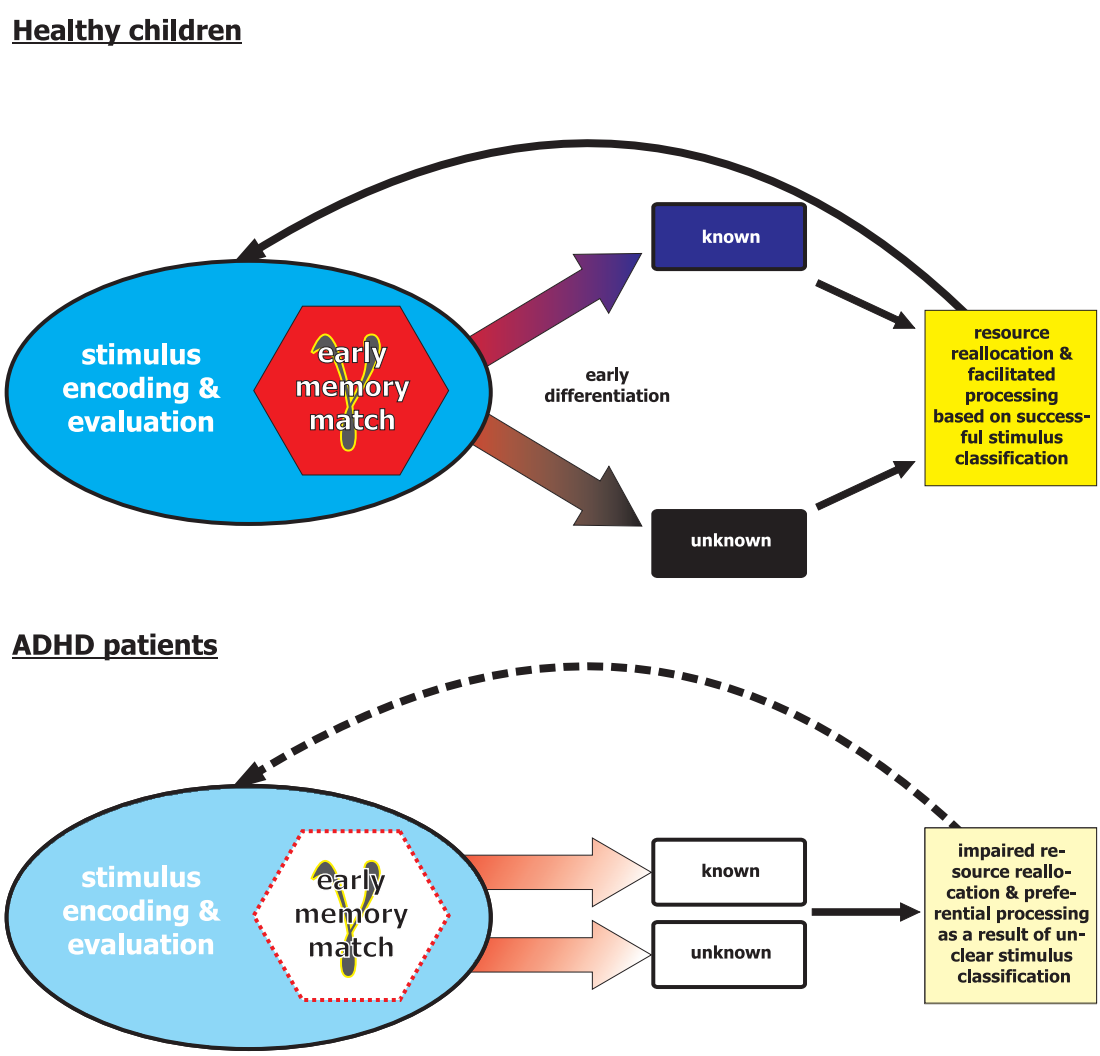

Figure 7.1: TOP: In healthy children, memory matches during stimulus encoding are represented in evoked GBRs. A successful match, occuring as early as 90 ms after stimulus onset, enables to shift the attentional focus to relevant information for facilitated processing and inhibition of further processing of irrelevant information. BOTTOM: Evoked GBRs of ADHD patients, however, do not reflect successful memory matching. This lack of a first rough classification of incoming information at this early stage impairs the ability to rapidly shift the attentional focus to relevant information causing a higher possibility for interference through distracting information.

GBRs (Busch et al., 2004). Hence, it has to be noted that there was no overall group difference in the evoked gamma-band amplitude as well as early ERPs. This suggests similar sensory processing levels of bottom-up input in both groups. Nevertheless, ADHD patients miss an early differentiation of evoked GBRs that originates from top-down modulations through higher cortical areas in healthy participants.

Given the results of the two visual experiments presented here, two different conclusions can be drawn for the evoked GBR of ADHD patients: In Experiment I, as similarly shown in an auditory study by Yordanova et al. (2001), evoked GBRs of ADHD patients were enhanced compared to healthy children. In contrast, the results of Experiment III revealed no overall main effect of group on the evoked GBR amplitudes, but ADHD patients showed an altered activity pattern compared to healthy children as represented in a missing differentiation between known and unknown stimuli. This discrepancy could be explained by several reasons. ADHD is a very heterogeneous disorder with different emphases regarding the presence and severity of specific symptom clusters in its subtypes (Tannock, 1998). Thus, evoked GBRs might be associated with specific ADHD symptoms: Yordanova et al. (2001) investigated only ADHD patients diagnosed as combined type and the ADHD sample investigated in Experiment I also comprised more combined type children than the sample in Experiment III. Hence, while the presence of hyperactivity symptoms might be related to inhibitory deficits and could be represented in augmented evoked GBRs, dominance of inattention could be rather linked to more specific deficits in evoked GBRs not mirrored by pure amplitude differences, but instead an altered activity pattern during cognitive processes. However, the sample size of the presented studies does not suffice to differentiate between ADHD subtypes to shed light on this question. This is a very important point that should be addressed in future studies to account for the heterogeneity observed in the ADHD group.

Furthermore, the different results in evoked GBRs of ADHD patients may also be related to different task demands and varied stimulus complexity. In Experiment I, the instruction screen before each stimulus also depicted simple black and white line-drawings comparable to the line-drawings used in the current study. In contrast, the stimuli following the instruction screens encompassed complex photographs of natural scenes. While there was no amplitude difference in evoked GBRs following the instruction screen, a GBR enhancement in the ADHD group was observed for the more complex task stimuli. As Experiment III also employed more simple line-drawings yielding no GBR augmentation in the patient group, this could be an indicator that the reported effects might be linked to an interaction of ADHD electrophysiology and bottom-up parameters.

Moreover, all three studies slightly differ in regard to the age of the investi-

gated samples. Therefore, differences in evoked GBRs of ADHD patients may also demonstrate an age-dependency as reported for the ERPs of ADHD patients (Johnstone et al., 2001), particularly, as age dependent variations of evoked GBRs have also been reported (Böttger et al., 2002; Yordanova et al., 2002). Notably, neural synchrony in the gamma-band has also been suggested to index brain maturation, showing synchrony peaks and troughs at different developmental stages, also representing an enhanced or reduced modulation through higher cortical areas in a top-down fashion (Uhlhaas et al., 2009; Werkle-Bergner et al., 2009). This is of special interest within the context of the maturational delay hypothesis of ADHD: Child development is characterised by major structural and functional brain changes (Sowell et al., 2003; Toga et al., 2006) and there is an ongoing discussion whether ADHD results from a maturational delay within brain development (El-Sayed et al., 2003). This hypothesis is supported by recent neuroanatomic findings indicating that ADHD patients reach the peak of cortical thickness later than their peers (Shaw et al., 2007). According to Yordanova and Kolev (2008), the differential task-specific functional reactivity of evoked GBRs might change during development, possibly reflecting different task processing strategies at different developmental stages. Thus, the differences in evoked GBR patterns of ADHD patients in this three studies might be related to the stage of brain development at which the measurement was conducted and an assessment at a younger or older sample could yield different patterns of evoked GBRs in both groups, ADHD patients as well as healthy participants.

CHAPTER 8

Conclusions and implications for future studies

The experiments presented in this thesis clearly demonstrate for the first time that visual evoked GBRs are indeed involved in the pathophysiology of ADHD. ADHD patients show altered gamma-band amplitudes during visual stimulus encoding lacking a behavioural relevance for short-term memory performance. Furthermore, whereas the results in healthy children confirm the notion that evoked GBRs are functional relevant for early memory based classification processes during visual stimulus evaluation, ADHD patients exhibit a different pattern of evoked GBRs not reflecting such cognitive processes. These reported evoked GBR variations, potentially associated with genetic variations within the dopaminergic pathway, could be a possible marker of impaired neurotransmission in ADHD. Moreover, they indicate an early disadvantage within processing of visual information that might also impact later processing stages.

These results on evoked GBRs in ADHD patients implicate new research questions that should be focused on in future studies. Until now, the association of evoked GBRs in ADHD patients and genetic polymorphisms is rather indirect and speculative. Therefore, it would be fruitful to investigate evoked GBRs in ADHD patients in dependence whether they show a specific genetic polymorphism (e.g. DAT1) or not. This is especially interesting within the context of medical treatment employing methylphenidate that targets the dopamine transporter. Studying the question whether such medical treatment yields a normalisation of evoked GBRs as it has been observed for other frequency components and the ERP (Klorman et al., 1990; Wienbruch et al., 2005) could offer new insights why some ADHD patients show a lower responsiveness to treatment with methylphenidate. Additionally, besides medical treatment, new approaches based on neurofeedback showed promising results in ADHD therapy as they enable the

children to normalise electrophysiological activity within frequencies up to the beta range (Monastra et al., 2005; Heinrich et al., 2007). Hence, bearing in mind the involvement of GBRs in fundamental cognitive processes as well as the altered patterns in ADHD patients raises the question whether neurofeedback incorporating the gamma frequency range might further enhance the effectiveness of a treatment using neurofeedback. Knowledge of the activity pattern in the whole frequency spectrum also allows a more individualised neurofeedback treatment targeting the actual neurophysiological impairments.

Furthermore, extending the research on GBRs in ADHD patients could also facilitate the utilisation of EEG and GBRs as an electrophysiological biomarker with possible diagnostic value in ADHD. Considering irregularities on a broader frequency spectrum than between the theta and beta range as well as the potential interaction between the frequency bands could yield a more precise electrophysiological endophenotype of ADHD. Here, investigation of spontaneous gamma-band activity could also lead new insights. Along the same line, GBR patterns might also resemble the presence or absence of specific symptom clusters of ADHD patients. A differentiation according to the ADHD subtype could stimulate the discussion whether these subtypes belong to the same disorder or constitute rather different diseases. However, taking into account a possible age dependency of the reported altered GBR patterns, longitudinal approaches should clarify at which developmental stage evoked GBR patterns start or end differing from healthy children.

Bibliography

Achenbach, T. M., 1991a. Manual for the Child Behavior Checklist/4-18 and 1991 Profile. Burlington, VT: Department of Psychiatry, University of Vermont.

Achenbach, T. M., 1991b. Manual for the Youth Self-Report and 1991 Profile. Burlington, VT: Department of Psychiatry, University of Vermont.

Adrian, E. D., 1942. Olfactory reactions in the brain of the hedgehog. J Physiol 100 (4), 459–473.

Ahveninen, J., S. Kähkönen, S., Tiitinen, H., Pekkonen, E., Huttunen, J., Kaakkola, S., Ilmoniemi, R. J., Jääskeläinen, I. P., 2000. Suppression of transient 40-Hz auditory response by haloperidol suggests modulation of human selective attention by dopamine D2 receptors. Neurosci Lett 292 (1), 29–32.

American Psychiatric Association, 1994. Attention-deficit and disruptive behavior disorders. In: Diagnostic and Statistical Manual of mental disorders. Vol. 4. Washington, D.C.: American Psychiatric Association, pp. 78–85.

Antrop, I., Roeyers, H., Oost, P. V., Buysse, A., 2000. Stimulation seeking and hyperactivity in children with ADHD. Attention Deficit Hyperactivity Disorder. J Child Psychol Psychiatry 41 (2), 225–231.

Başar, E., Başar-Eroglu, C., Karakaş, S., Schürmann, M., 1999. Are cognitive processes manifested in event-related gamma, alpha, theta and delta oscillations in the EEG? Neurosci Lett 259 (3), 165–168.

Başar, E., Başar-Eroglu, C., Karakaş, S., Schürmann, M., 2001. Gamma, alpha, delta, and theta oscillations govern cognitive processes. Int J Psychophysiol 39 (2-3), 241–248.

Başar, E., Güntekin, B., 2007. A breakthrough in neuroscience needs a "Nebulous Cartesian System" Oscillations, quantum dynamics and chaos in the brain and vegetative system. Int J Psychophysiol 64 (1), 108–122.

Başar, E., Güntekin, B., 2008. A review of brain oscillations in cognitive disorders and the role of neurotransmitters. Brain Res 1235, 172–193.

Başar-Eroglu, C., Brand, A., Hildebrandt, H., Kedzior, K. K., Mathes, B., Schmiedt, C., 2007. Working memory related gamma oscillations in schizophrenia patients. Int J Psychophysiol 64 (1), 39–45.

Başar-Eroglu, C., Strüber, D., Schürmann, M., Stadler, M., Başar, E., 1996. Gamma-band responses in the brain: a short review of psychophysiological correlates and functional significance. Int J Psychophysiol 24 (1-2), 101–112.

Banaschewski, T., Brandeis, D., 2007. Annotation: what electrical brain activity tells us about brain function that other techniques cannot tell us - a child psychiatric perspective. J Child Psychol Psychiatry 48 (5), 415–435.

Banaschewski, T., Neale, B. M., Rothenberger, A., Roessner, V., 2007. Comorbidity of tic disorders & ADHD: conceptual and methodological considerations. Eur Child Adolesc Psychiatry 16 Suppl 1, 5–14.

Barceló, F., Gale, A., 1997. Electrophysiological measures of cognition in biological psychiatry: some cautionary notes. Int J Neurosci 92 (3-4), 219–239.

Barkley, R., 2006. Attention-Deficit Hyperactivity Disorder - A Handbook for Diagnosis and Treatment, 3rd Edition. The Guilford Press, New York.

Barkley, R. A., 1997. Attention-deficit/hyperactivity disorder, self-regulation, and time: toward a more comprehensive theory. J Dev Behav Pediatr 18 (4), 271–279.

Barkley, R. A., 2003. Issues in the diagnosis of attention-deficit/hyperactivity disorder in children. Brain Dev 25 (2), 77–83.

Barry, R. J., Clarke, A. R., Johnstone, S. J., 2003a. A review of electrophysiology in attention-deficit/hyperactivity disorder: I. Qualitative and quantitative electroencephalography. Clin Neurophysiol 114 (2), 171–183.

Barry, R. J., Johnstone, S. J., Clarke, A. R., 2003b. A review of electrophysiology in attention-deficit/hyperactivity disorder: II. Event-related potentials. Clin Neurophysiol 114 (2), 184–198.

Bellgrove, M. A., Hawi, Z., Kirley, A., Gill, M., Robertson, I. H., 2005. Dissecting the attention deficit hyperactivity disorder (ADHD) phenotype: sustained attention, response variability and spatial attentional asymmetries in relation to dopamine transporter (DAT1) genotype. Neuropsychologia 43 (13), 1847–1857.

Berger, H., 1929. Über das Elektrenkephalogramm des Menschen. Arch. Psychiat. Nerverkr. 87, 527–570.

Biederman, J., Faraone, S. V., 2005. Attention-deficit hyperactivity disorder. Lancet 366 (9481), 237–248.

Biederman, J., Newcorn, J., Sprich, S., 1991. Comorbidity of attention deficit hyperactivity disorder with conduct, depressive, anxiety, and other disorders. Am J Psychiatry 148 (5), 564–577.

Biederman, J., Petty, C. R., Fried, R., Doyle, A. E., Spencer, T., Seidman, L. J., Gross, L., Poetzl, K., Faraone, S. V., 2007. Stability of executive function deficits into young adult years: a prospective longitudinal follow-up study of grown up males with ADHD. Acta Psychiatr Scand 116 (2), 129–136.

Bitsakou, P., Psychogiou, L., Thompson, M., Sonuga-Barke, E. J. S., 2009. Delay Aversion in Attention Deficit/Hyperactivity Disorder: an empirical investigation of the broader phenotype. Neuropsychologia 47 (2), 446–456.

Bodis-Wollner, I., Davis, J., Tzelepi, A., Bezerianos, T., 2001. Wavelet transform of the EEG reveals differences in low and high gamma responses to elementary visual stimuli. Clin Electroencephalogr 32 (3), 139–144.

Bosboom, J. L. W., Stoffers, D., Stam, C. J., van Dijk, B. W., Verbunt, J., Berendse, H. W., Wolters, E. C., 2006. Resting state oscillatory brain dynamics in Parkinson's disease: an MEG study. Clin Neurophysiol 117 (11), 2521–2531.

Böttger, D., Herrmann, C. S., von Cramon, D. Y., 2002. Amplitude differences of evoked alpha and gamma oscillations in two different age groups. Int J Psychophysiol 45 (3), 245–251.

Boutros, N. N., Struve, F., 2002. Electrophysiological assessment of neuropsychiatric disorders. Semin Clin Neuropsychiatry 7 (1), 30–41.

Brandeis, D., Banaschewski, T., Baving, L., Georgiewa, P., Blanz, B., Warnke, A., Steinhausen, H.-C., Rothenberger, A., Scheuerpflug, P., 2002. Multicenter P300 brain mapping of impaired attention to cues in hyperkinetic children. J Am Acad Child Adolesc Psychiatry 41 (8), 990–998.

Brown, C., Gruber, T., Boucher, J., Rippon, G., Brock, J., 2005. Gamma abnormalities during perception of illusory figures in autism. Cortex 41 (3), 364–376.

Busch, N. A., Debener, S., Kranczioch, C., Engel, A. K., Herrmann, C. S., 2004. Size matters: effects of stimulus size, duration and eccentricity on the visual gamma-band response. Clin Neurophysiol 115 (8), 1810–1820.

Busch, N. A., Groh-Bordin, C., Zimmer, H. D., Herrmann, C. S., 2008a. Modes of memory: early electrophysiological markers of repetition suppression and recognition enhancement predict behavioral performance. Psychophysiology 45 (1), 25–35.

Busch, N. A., Groh-Bordin, C., Zimmer, H. D., Herrmann, C. S., 2008b. Modes of memory: Early electrophysiological markers of repetition suppression and recognition enhancement predict behavioral performance. Psychophysiology 45 (1), 25–35.

Busch, N. A., Schadow, J., Fründ, I., Herrmann, C. S., 2006. Time-frequency analysis of target detection reveals an early interface between bottom-up and top-down processes in the gamma-band. Neuroimage 29 (4), 1106–1116.

Bush, G., Valera, E. M., Seidman, L. J., 2005. Functional neuroimaging of attention-deficit/hyperactivity disorder: a review and suggested future directions. Biol Psychiatry 57 (11), 1273–1284.

Carter, C. S., Krener, P., Chaderjian, M., Northcutt, C., Wolfe, V., 1995. Abnormal processing of irrelevant information in attention deficit hyperactivity disorder. Psychiatry Res 56 (1), 59–70.

Castellanos, F. X., Lee, P. P., Sharp, W., Jeffries, N. O., Greenstein, D. K., Clasen, L. S., Blumenthal, J. D., James, R. S., Ebens, C. L., Walter, J. M., Zijdenbos, A., Evans, A. C., Giedd, J. N., Rapoport, J. L., 2002. Developmental trajectories of brain volume abnormalities in children and adolescents with attention-deficit/hyperactivity disorder. JAMA 288 (14), 1740–1748.

Castellanos, F. X., Sonuga-Barke, E. J. S., Scheres, A., Martino, A. D., Hyde, C., Walters, J. R., 2005. Varieties of attention-deficit/hyperactivity disorder-related intra-individual variability. Biol Psychiatry 57 (11), 1416–1423.

Castellanos, F. X., Tannock, R., 2002. Neuroscience of attention-deficit/hyperactivity disorder: the search for endophenotypes. Nat Rev Neurosci 3 (8), 617–628.

Chabot, R. J., Serfontein, G., 1996. Quantitative electroencephalographic profiles of children with attention deficit disorder. Biol Psychiatry 40 (10), 951–963.

Clarke, A. R., Barry, R. J., McCarthy, R., Selikowitz, M., 1998. EEG analysis in Attention-Deficit/Hyperactivity Disorder: a comparative study of two subtypes. Psychiatry Res 81 (1), 19–29.

Clarke, A. R., Barry, R. J., McCarthy, R., Selikowitz, M., 2001a. EEG-defined subtypes of children with attention-deficit/hyperactivity disorder. Clin Neurophysiol 112 (11), 2098–2105.

Clarke, A. R., Barry, R. J., McCarthy, R., Selikowitz, M., 2001b. Electroencephalogram differences in two subtypes of attention-deficit/hyperactivity disorder. Psychophysiology 38 (2), 212–221.

Clarke, A. R., Barry, R. J., McCarthy, R., Selikowitz, M., 2001c. Excess beta activity in children with attention-deficit/hyperactivity disorder: an atypical electrophysiological group. Psychiatry Res 103 (2-3), 205–218.

Clarke, A. R., Barry, R. J., McCarthy, R., Selikowitz, M., Brown, C. R., 2002. EEG evidence for a new conceptualisation of attention deficit hyperactivity disorder. Clin Neurophysiol 113 (7), 1036–1044.

Clementz, B. A., Blumenfeld, L. D., Cobb, S., 1997. The gamma band response may account for poor P50 suppression in schizophrenia. Neuroreport 8 (18), 3889–3893.

Coles, M., Rugg, M., 1995. Event-Related Brain Potentials: An Introduction. In: Rugg, M., Coles, M. (Eds.), Electrophysiology of Mind – Event-Related Brain Potentials and Cognition. Oxford University Press, New York, pp. 1–26.

Collett, B. R., Ohan, J. L., Myers, K. M., 2003. Ten-year review of rating scales. V: scales assessing attention-deficit/hyperactivity disorder. J Am Acad Child Adolesc Psychiatry 42 (9), 1015–1037.

Cook, E. H., Stein, M. A., Krasowski, M. D., Cox, N. J., Olkon, D. M., Kieffer, J. E., Leventhal, B. L., 1995. Association of attention-deficit disorder and the dopamine transporter gene. Am J Hum Genet 56 (4), 993–998.

Crone, N. E., Boatman, D., Gordon, B., Hao, L., 2001. Induced electrocorticographic gamma activity during auditory perception. Clin Neurophysiol 112 (4), 565–582.

Cropley, V. L., Fujita, M., Innis, R. B., Nathan, P. J., 2006. Molecular imaging of the dopaminergic system and its association with human cognitive function. Biol Psychiatry 59 (10), 898–907.

de Haan, M., 2008. Event-Related Potential (ERP) Measures in Visual Development Research. In: Schmidt, L., Segalowitz, S. (Eds.), Developmental Psychophysiology - Theory, Systems, and Methods. Cambridge University Press, New York, USA, pp. 103–126.

Debener, S., Herrmann, C. S., Kranczioch, C., Gembris, D., Engel, A. K., 2003. Top-down attentional processing enhances auditory evoked gamma band activity. Neuroreport 14 (5), 683–686.

Delmo, C., Weiffenbach, O., Gabriel, M., Bölte, S., Marchio, E., Poustka, F., 2000. Fragebogen für affektive Störungen und Schizophrenie für Kinder im Schulalter (6-18 Jahre). Frankfurt: Klinik für Psychiatrie und Psychotherapie des Kindes- und Jugendalters.

Delorme, A., Makeig, S., 2004. EEGLAB: an open source toolbox for analysis of single-trial EEG dynamics including independent component analysis. J Neurosci Methods 134 (1), 9–21.

Demiralp, T., Herrmann, C. S., Erdal, M. E., Ergenoglu, T., Keskin, Y. H., Ergen, M., Beydagi, H., 2007. DRD4 and DAT1 polymorphisms modulate human gamma band responses. Cereb Cortex 17 (5), 1007–1019.

Devilbiss, D. M., Berridge, C. W., 2006. Low-dose methylphenidate actions on tonic and phasic locus coeruleus discharge. J Pharmacol Exp Ther 319 (3), 1327–1335.

Doppelmayr, M., Klimesch, W., Schwaiger, J., Stadler, W., Röhm, D., 2000. The time locked theta response reflects interindividual differences in human memory performance. Neurosci Lett 278 (3), 141–144.

Dougherty, D. D., Bonab, A. A., Spencer, T. J., Rauch, S. L., Madras, B. K., Fischman, A. J., 1999. Dopamine transporter density in patients with attention deficit hyperactivity disorder. Lancet 354 (9196), 2132–2133.

Doyle, A. E., 2006. Executive functions in attention-deficit/hyperactivity disorder. J Clin Psychiatry 67 Suppl 8, 21–26.

Dresel, S., Krause, J., Krause, K. H., LaFougere, C., Brinkbäumer, K., Kung, H. F., Hahn, K., Tatsch, K., 2000. Attention deficit hyperactivity disorder: binding of [99mTc]TRODAT-1 to the dopamine transporter before and after methylphenidate treatment. Eur J Nucl Med 27 (10), 1518–1524.

Durston, S., 2008. Converging methods in studying attention-deficit/hyperactivity disorder: what can we learn from neuroimaging and genetics? Dev Psychopathol 20 (4), 1133–1143.

Durston, S., de Zeeuw, P., Staal, W. G., 2009. Imaging genetics in ADHD: a focus on cognitive control. Neurosci Biobehav Rev 33 (5), 674–689.

Durston, S., Fossella, J. A., Casey, B. J., Pol, H. E. H., Galvan, A., Schnack, H. G., Steenhuis, M. P., Minderaa, R. B., Buitelaar, J. K., Kahn, R. S., van Engeland, H., 2005. Differential effects of DRD4 and DAT1 genotype on fronto-striatal gray matter volumes in a sample of subjects with attention deficit hyperactivity disorder, their unaffected siblings, and controls. Mol Psychiatry 10 (7), 678–685.

Durston, S., Fossella, J. A., Mulder, M. J., Casey, B. J., Ziermans, T. B., Vessaz, M. N., Engeland, H. V., 2008. Dopamine transporter genotype conveys familial risk of attention-deficit/hyperactivity disorder through striatal activation. J Am Acad Child Adolesc Psychiatry 47 (1), 61–67.

Durston, S., Tottenham, N. T., Thomas, K. M., Davidson, M. C., Eigsti, I.-M., Yang, Y., Ulug, A. M., Casey, B. J., 2003. Differential patterns of striatal activation in young children with and without ADHD. Biol Psychiatry 53 (10), 871–878.

Dustman, R. E., Shearer, D. E., Emmerson, R. Y., 1993. EEG and event-related potentials in normal aging. Prog Neurobiol 41 (3), 369–401.

El-Sayed, E., Larsson, J.-O., Persson, H. E., Rydelius, P.-A., 2002. Altered cortical activity in children with attention-deficit/hyperactivity disorder during attentional load task. J Am Acad Child Adolesc Psychiatry 41 (7), 811–819.

El-Sayed, E., Larsson, J. O., Persson, H. E., Santosh, P. J., Rydelius, P. A., 2003. "Maturational lag" hypothesis of attention deficit hyperactivity disorder: an update. Acta Paediatr 92 (7), 776–784.

Engel, A., Singer, W., 2001. Temporal binding and the neural correlates of sensory awareness. Trends Cogn Sci 5 (1), 16–25.

Engel, A. K., Fries, P., Singer, W., 2001. Dynamic predictions: oscillations and synchrony in top-down processing. Nat Rev Neurosci 2 (10), 704–716.

Faraone, S. V., Biederman, J., 1998. Neurobiology of attention-deficit hyperactivity disorder. Biol Psychiatry 44 (10), 951–958.

Faraone, S. V., Biederman, J., Mick, E., 2006. The age-dependent decline of attention deficit hyperactivity disorder: a meta-analysis of follow-up studies. Psychol Med 36 (2), 159–165.

Faraone, S. V., Biederman, J., Spencer, T., Wilens, T., Seidman, L. J., Mick, E., Doyle, A. E., 2000. Attention-deficit/hyperactivity disorder in adults: an overview. Biol Psychiatry 48 (1), 9–20.

Faraone, S. V., Biederman, J., Weiffenbach, B., Keith, T., Chu, M. P., Weaver, A., Spencer, T. J., Wilens, T. E., Frazier, J., Cleves, M., Sakai, J., 1999. Dopamine D4 gene 7-repeat allele and attention deficit hyperactivity disorder. Am J Psychiatry 156 (5), 768–770.

Faraone, S. V., Doyle, A. E., Mick, E., Biederman, J., 2001. Meta-analysis of the association between the 7-repeat allele of the dopamine D(4) receptor gene and attention deficit hyperactivity disorder. Am J Psychiatry 158 (7), 1052–1057.

Frank, Y., Seiden, J., Napolitano, B., 1996. Visual event related potentials and reaction time in normal adults, normal children, and children with attention deficit hyperactivity disorder: differences in short-term memory processing. Int J Neurosci 88 (1-2), 109–124.

Freunberger, R., Klimesch, W., Sauseng, P., Griesmayr, B., Hüller, Y., Pecherstorfer, T., Hanslmayr, S., 2007. Gamma oscillatory activity in a visual discrimination task. Brain Res Bull 71 (6), 593–600.

Fries, P., 2005. A mechanism for cognitive dynamics: neuronal communication through neuronal coherence. Trends Cogn Sci 9 (10), 474–480.

Fries, P., Scheeringa, R., Oostenveld, R., 2008. Finding gamma. Neuron 58 (3), 303–305.

Fründ, I., Busch, N. A., Körner, U., Schadow, J., Herrmann, C. S., 2007a. EEG oscillations in the gamma and alpha range respond differently to spatial frequency. Vision Res 47 (15), 2086–2098.

Fründ, I., Busch, N. A., Schadow, J., Körner, U., Herrmann, C. S., 2007b. From perception to action: phase-locked gamma oscillations correlate with reaction times in a speeded response task. BMC Neurosci 8, 27.

Fründ, I., Schadow, J., Busch, N. A., Körner, U., Herrmann, C. S., 2007. Evoked gamma oscillations in human scalp EEG are test-retest reliable. Clin Neurophysiol 118 (1), 221–227.

Fuchs, T., Birbaumer, N., Lutzenberger, W., Gruzelier, J. H., Kaiser, J., 2003. Neurofeedback treatment for attention-deficit/hyperactivity disorder in children: a comparison with methylphenidate. Appl Psychophysiol Biofeedback 28 (1), 1–12.

Galambos, R., 1992. A comparison of certain gamma band (40 Hz) brain rhythms in cat and man. In: Başar, E., Bullock, T. (Eds.), Induced rhythms in the brain. Birkhäuser, Boston, pp. 201–216.

Gallinat, J., Winterer, G., Herrmann, C. S., Senkowski, D., 2004. Reduced oscillatory gamma-band responses in unmedicated schizophrenic patients indicate impaired frontal network processing. Clin Neurophysiol 115 (8), 1863–1874.

Gevensleben, H., Holl, B., Albrecht, B., Vogel, C., Schlamp, D., Kratz, O., Studer, P., Rothenberger, A., Moll, G. H., Heinrich, H., 2009. Is neurofeedback an efficacious treatment for ADHD? A randomised controlled clinical trial. J Child Psychol Psychiatry 50 (7), 780–789.

Gill, M., Daly, G., Heron, S., Hawi, Z., Fitzgerald, M., 1997. Confirmation of association between attention deficit hyperactivity disorder and a dopamine transporter polymorphism. Mol Psychiatry 2 (4), 311–313.

Giros, B., Jaber, M., Jones, S. R., Wightman, R. M., Caron, M. G., 1996. Hyperlocomotion and indifference to cocaine and amphetamine in mice lacking the dopamine transporter. Nature 379 (6566), 606–612.

Gonzalez, S. L., de Peralta, R. G., Thut, G., del R Millán, J., Morier, P., Landis, T., 2006. Very high frequency oscillations (VHFO) as a predictor of movement intentions. Neuroimage 32 (1), 170–179.

Gonzalez Andino, S. L., Michel, C. M., Thut, G., Landis, T., de Peralta, R. G., 2005. Prediction of response speed by anticipatory high-frequency (gamma band) oscillations in the human brain. Hum Brain Mapp 24 (1), 50–58.

Gornick, M. C., Addington, A., Shaw, P., Bobb, A. J., Sharp, W., Greenstein, D., Arepalli, S., Castellanos, F. X., Rapoport, J. L., 2007. Association of the dopamine receptor D4 (DRD4) gene 7-repeat allele with children with attention-deficit/hyperactivity disorder (ADHD): an update. Am J Med Genet B Neuropsychiatr Genet 144 (3), 379–382.

Grace, A. A., 2001. Psychostimulant Actions on Dopamine and Limbic System Function: Relevance to the Pathophysiology and Treatment of ADHD. In: Solanto, M. V., Arnsten, A. F. T., Castellanos, F. X. (Eds.), Stimulant Drugs and ADHD. Basic and Clinical Neuroscience. Oxford University Press: New York, pp. 134–157.

Gray, C. M., König, P., Engel, A. K., Singer, W., 1989. Oscillatory responses in cat visual cortex exhibit inter-columnar synchronization which reflects global stimulus properties. Nature 338 (6213), 334–337.

Grech, R., Cassar, T., Muscat, J., Camilleri, K. P., Fabri, S. G., Zervakis, M., Xanthopoulos, P., Sakkalis, V., Vanrumste, B., 2008. Review on solving the inverse problem in EEG source analysis. J Neuroeng Rehabil 5, 25.

Grice, S. J., Spratling, M. W., Karmiloff-Smith, A., Halit, H., Csibra, G., de Haan, M., Johnson, M. H., 2001. Disordered visual processing and oscillatory brain activity in autism and Williams syndrome. Neuroreport 12 (12), 2697–2700.

Gruber, T., Keil, A., Müller, M. M., 2001. Modulation of induced gamma band responses and phase synchrony in a paired associate learning task in the human EEG. Neurosci Lett 316 (1), 29–32.

Gruber, T., Maess, B., Trujillo-Barreto, N. J., Müller, M. M., 2008. Sources of synchronized induced Gamma-Band responses during a simple object recognition task: a replication study in human MEG. Brain Res 1196, 74–84.

Gruber, T., Müller, M. M., 2006. Oscillatory brain activity in the human EEG during indirect and direct memory tasks. Brain Res 1097 (1), 194–204.

Gruber, T., Müller, M. M., Keil, A., 2002. Modulation of induced gamma band responses in a perceptual learning task in the human EEG. J Cogn Neurosci 14 (5), 732–744.

Gruber, T., Tsivilis, D., Montaldi, D., Müller, M. M., 2004. Induced gamma band responses: an early marker of memory encoding and retrieval. Neuroreport 15 (11), 1837–1841.

Haig, A. R., Gordon, E., Pascalis, V. D., Meares, R. A., Bahramali, H., Harris, A., 2000. Gamma activity in schizophrenia: evidence of impaired network binding? Clin Neurophysiol 111 (8), 1461–1468.

Haig, A. R., Pascalis, V. D., Gordon, E., 1999. Peak gamma latency correlated with reaction time in a conventional oddball paradigm. Clin Neurophysiol 110 (1), 158–165.

Hanslmayr, S., Aslan, A., Staudigl, T., Klimesch, W., Herrmann, C. S., Bäuml, K.-H., 2007. Prestimulus oscillations predict visual perception performance between and within subjects. Neuroimage 37 (4), 1465–1473.

Heinrich, H., Gevensleben, H., Strehl, U., 2007. Annotation: neurofeedback - train your brain to train behaviour. J Child Psychol Psychiatry 48 (1), 3–16.

Herrmann, C. S., Demiralp, T., 2005. Human EEG gamma oscillations in neuropsychiatric disorders. Clin Neurophysiol 116 (12), 2719–2733.

Herrmann, C. S., Fründ, I., Lenz, D., in revision. Human gamma-band activity: A review on cognitive and behavioral correlates and network models. Neurosci Biobehav Rev (in revision).

Herrmann, C. S., Grigutsch, M., Busch, N. A., 2004a. EEG Oscillations and Wavelet Analysis. In: Handy, T. C. (Ed.), Event-Related Potentials: A Methods Handbook. Cambridge, MA: Bradford Book, pp. 229–259.

Herrmann, C. S., Lenz, D., Junge, S., Busch, N. A., Maess, B., 2004b. Memory-matches evoke human gamma-responses. BMC Neurosci 5, 13.

Herrmann, C. S., Mecklinger, A., 2001. Gamma activity in human EEG is related to high-speed memory comparisons during object selective attention. Vis Cogn 8 (3-5), 593–608.

Herrmann, C. S., Mecklinger, A., Pfeifer, E., 1999. Gamma responses and ERPs in a visual classification task. Clin Neurophysiol 110 (4), 636–642.

Herrmann, C. S., Munk, M. H. J., Engel, A. K., 2004c. Cognitive functions of gamma-band activity: memory match and utilization. Trends Cogn Sci 8 (8), 347–355.

Holcomb, P. J., Ackerman, P. T., Dykman, R. A., 1986. Auditory event-related potentials in attention and reading disabled boys. Int J Psychophysiol 3 (4), 263–273.

Holcomb, P. J., McPherson, W. B., 1994. Event-related brain potentials reflect semantic priming in an object decision task. Brain Cogn 24 (2), 259–276.

Hughes, J. R., John, E. R., 1999. Conventional and quantitative electroencephalography in psychiatry. J Neuropsychiatry Clin Neurosci 11 (2), 190–208.

Huizink, A. C., Mulder, E. J. H., 2006. Maternal smoking, drinking or cannabis use during pregnancy and neurobehavioral and cognitive functioning in human offspring. Neurosci Biobehav Rev 30 (1), 24–41.

Jasper, H., 1958. The ten twenty electrode system of the international federation. Electroencephalogr Clin Neurophysiol 10 (2), 371–375.

Johnstone, S. J., Barry, R. J., 1996. Auditory event-related potentials to a two-tone discrimination paradigm in attention deficit hyperactivity disorder. Psychiatry Res 64 (3), 179–192.

Johnstone, S. J., Barry, R. J., Anderson, J. W., 2001. Topographic distribution and developmental timecourse of auditory event-related potentials in two subtypes of attention-deficit hyperactivity disorder. Int J Psychophysiol 42 (1), 73–94.

Johnstone, S. J., Clarke, A. R., 2009. Dysfunctional response preparation and inhibition during a visual Go/No-go task in children with two subtypes of attention-deficit hyperactivity disorder. Psychiatry Res 166 (2-3), 223–237.

Jokeit, H., Makeig, S., 1994. Different event-related patterns of gamma-band power in brain waves of fast- and slow-reacting subjects. Proc Natl Acad Sci U S A 91 (14), 6339–6343.

Jonkman, L. M., Kemner, C., Verbaten, M. N., Koelega, H. S., Camfferman, G., vd Gaag, R. J., Buitelaar, J. K., van Engeland, H., 1997. Event-related potentials and performance of attention-deficit hyperactivity disorder: children and normal controls in auditory and visual selective attention tasks. Biol Psychiatry 41 (5), 595–611.

Jonkman, L. M., Kenemans, J. L., Kemner, C., Verbaten, M. N., van Engeland, H., 2004. Dipole source localization of event-related brain activity indicative of an early visual selective attention deficit in ADHD children. Clin Neurophysiol 115 (7), 1537–1549.

Juergens, E., Guettler, A., Eckhorn, R., 1999. Visual stimulation elicits locked and induced gamma oscillations in monkey intracortical- and EEG-potentials, but not in human EEG. Exp Brain Res 129 (2), 247–59.

Jung-Beeman, M., Bowden, E. M., Haberman, J., Frymiare, J. L., Arambel-Liu, S., Greenblatt, R., Reber, P. J., Kounios, J., 2004. Neural activity when people solve verbal problems with insight. PLoS Biol 2 (4), E97.

Kaiser, J., Heidegger, T., Lutzenberger, W., 2008a. Behavioral relevance of gamma-band activity for short-term memory-based auditory decision-making. Eur J Neurosci 27 (12), 3322–3328.

Kaiser, J., Heidegger, T., Wibral, M., Altmann, C. F., Lutzenberger, W., 2008b. Distinct gamma-band components reflect the short-term memory maintenance of different sound lateralization angles. Cereb Cortex 18 (10), 2286–2295.

Kaiser, J., Hertrich, I., Ackermann, H., Lutzenberger, W., 2006. Gamma-band activity over early sensory areas predicts detection of changes in audiovisual speech stimuli. Neuroimage 30 (4), 1376–1382.

Kaiser, J., Lutzenberger, W., 2005. Cortical oscillatory activity and the dynamics of auditory memory processing. Rev Neurosci 16 (3), 239–254.

Kaiser, J., Rahm, B., Lutzenberger, W., 2008c. Temporal dynamics of stimulus-specific gamma-band activity components during auditory short-term memory. Neuroimage.

Karakaş, S., Başar, E., 1998. Early gamma response is sensory in origin: a conclusion based on cross-comparison of results from multiple experimental paradigms. Int J Psychophysiol 31 (1), 13–31.

Karayanidis, F., Robaey, P., Bourassa, M., Koning, D. D., Geoffroy, G., Pelletier, G., 2000. ERP differences in visual attention processing between attention-deficit hyperactivity disorder and control boys in the absence of performance differences. Psychophysiology 37 (3), 319–333.

Kastner, S., Pinsk, M. A., Weerd, P. D., Desimone, R., Ungerleider, L. G., 1999. Increased activity in human visual cortex during directed attention in the absence of visual stimulation. Neuron 22 (4), 751–761.

Kaufman, J., Birmaher, B., Brent, D., Rao, U., Flynn, C., Moreci, P., Williamson, D., Ryan, N., 1997. Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version (K-SADS-PL): initial reliability and validity data. J Am Acad Child Adolesc Psychiatry 36 (7), 980–988.

Keil, A., Müller, M. M., Ray, W. J., Gruber, T., Elbert, T., 1999. Human gamma band activity and perception of a gestalt. J Neurosci 19 (16), 7152–7161.

Kemner, C., Verbaten, M. N., Koelega, H. S., Buitelaar, J. K., van der Gaag, R. J., Camfferman, G., van Engeland, H., 1996. Event-related brain potentials in children with attention-deficit and hyperactivity disorder: effects of stimulus deviancy and task relevance in the visual and auditory modality. Biol Psychiatry 40 (6), 522–534.

Kirmse, U., Jacobsen, T., Schröger, E., 2009. Familiarity affects environmental sound processing outside the focus of attention: an event-related potential study. Clin Neurophysiol 120 (5), 887–896.

Klimesch, W., 1999. EEG alpha and theta oscillations reflect cognitive and memory performance: a review and analysis. Brain Res Brain Res Rev 29 (2-3), 169–195.

Klimesch, W., Doppelmayr, M., Russegger, H., Pachinger, T., 1996. Theta band power in the human scalp EEG and the encoding of new information. Neuroreport 7 (7), 1235–1240.

Klorman, R., Brumaghim, J. T., Salzman, L. F., Strauss, J., Borgstedt, A. D., McBride, M. C., Loeb, S., 1990. Effects of methylphenidate on processing negativities in patients with attention-deficit hyperactivity disorder. Psychophysiology 27 (3), 328–337.

Knief, A., Schulte, M., Bertrand, O., Pantev, C., 2000. The perception of coherent and non-coherent auditory objects: a signature in gamma frequency band. Hear Res 145 (1-2), 161–168.

Koenig, T., Prichep, L., Dierks, T., Hubl, D., Wahlund, L. O., John, E. R., Jelic, V., 2005. Decreased EEG synchronization in Alzheimer's disease and mild cognitive impairment. Neurobiol Aging 26 (2), 165–171.

Konrad, K., Neufang, S., Hanisch, C., Fink, G. R., Herpertz-Dahlmann, B., 2006. Dysfunctional attentional networks in children with attention deficit/hyperactivity disorder: evidence from an event-related functional magnetic resonance imaging study. Biol Psychiatry 59 (7), 643–651.

Krauel, K., Duzel, E., Hinrichs, H., Lenz, D., Herrmann, C. S., Santel, S., Rellum, T., Baving, L., 2009. Electrophysiological correlates of semantic processing

during encoding of neutral and emotional pictures in patients with ADHD. Neuropsychologia 47 (8-9), 1873–1882.

Krauel, K., Duzel, E., Hinrichs, H., Santel, S., Rellum, T., Baving, L., 2007. Impact of emotional salience on episodic memory in attention-deficit/hyperactivity disorder: a functional magnetic resonance imaging study. Biol Psychiatry 61 (12), 1370–1379.

Krause, J., 2008. SPECT and PET of the dopamine transporter in attention-deficit/hyperactivity disorder. Expert Rev Neurother 8 (4), 611–625.

Krause, K. H., Dresel, S. H., Krause, J., Kung, H. F., Tatsch, K., 2000. Increased striatal dopamine transporter in adult patients with attention deficit hyperactivity disorder: effects of methylphenidate as measured by single photon emission computed tomography. Neurosci Lett 285 (2), 107–110.

Kuczenski, R., Segal, D. S., 1997. Effects of methylphenidate on extracellular dopamine, serotonin, and norepinephrine: comparison with amphetamine. J Neurochem 68 (5), 2032–2037.

Kutas, M., Iragui, V., 1998. The N400 in a semantic categorization task across 6 decades. Electroencephalogr Clin Neurophysiol 108 (5), 456–471.

LaHoste, G. J., Swanson, J. M., Wigal, S. B., Glabe, C., Wigal, T., King, N., Kennedy, J. L., 1996. Dopamine D4 receptor gene polymorphism is associated with attention deficit hyperactivity disorder. Mol Psychiatry 1 (2), 121–124.

Lamberti, G., Weidlich, S., 1999. DCS - A Visual Learning and Memory Test for Neuropsychological Assessment. Göttingen: Hogrefe.

Landau, A. N., Esterman, M., Robertson, L. C., Bentin, S., Prinzmetal, W., 2007. Different effects of voluntary and involuntary attention on EEG activity in the gamma band. J Neurosci 27 (44), 11986–11990.

Lang, P. J., Bradley, M. M., Cuthbert, B. N., 2001. International Affective Picture System (IAPS): Instruction Manual and Affective Ratings. University of Florida: The Center for Research in Psychophysiology.

Langley, K., Marshall, L., van den Bree, M., Thomas, H., Owen, M., O'Donovan, M., Thapar, A., 2004. Association of the dopamine D4 receptor gene 7-repeat allele with neuropsychological test performance of children with ADHD. Am J Psychiatry 161 (1), 133–138.

Lee, K.-H., Williams, L. M., Haig, A., Gordon, E., 2003. "Gamma (40 Hz) phase synchronicity" and symptom dimensions in schizophrenia. Cognit Neuropsychiatry 8 (1), 57–71.

Lenz, D., Jeschke, M., Schadow, J., Naue, N., Ohl, F. W., Herrmann, C. S., 2008a. Human EEG very high frequency oscillations reflect the number of matches with a template in auditory short-term memory. Brain Res 1220, 81–92.

Lenz, D., Krauel, K., Schadow, J., Baving, L., Duzel, E., Herrmann, C. S., 2008b. Enhanced gamma-band activity in ADHD patients lacks correlation with memory performance found in healthy children. Brain Res 1235, 117–132.

Lenz, D., Schadow, J., Thaerig, S., Busch, N. A., Herrmann, C. S., 2007. What's that sound? Matches with auditory long-term memory induce gamma activity in human EEG. Int J Psychophysiol 64 (1), 31–38.

Leth-Steensen, C., Elbaz, Z. K., Douglas, V. I., 2000. Mean response times, variability, and skew in the responding of ADHD children: a response time distributional approach. Acta Psychol (Amst) 104 (2), 167–190.

Levy, F., 2004. Synaptic gating and ADHD: a biological theory of comorbidity of ADHD and anxiety. Neuropsychopharmacology 29 (9), 1589–1596.

Linden, M., Habib, T., Radojevic, V., 1996. A controlled study of the effects of EEG biofeedback on cognition and behavior of children with attention deficit disorder and learning disabilities. Biofeedback Self Regul 21 (1), 35–49.

Loo, S. K., Barkley, R. A., 2005. Clinical utility of EEG in attention deficit hyperactivity disorder. Appl Neuropsychol 12 (2), 64–76.

Lubar, J. F., Shouse, M. N., 1976. EEG and behavioral changes in a hyperkinetic child concurrent with training of the sensorimotor rhythm (SMR): a preliminary report. Biofeedback Self Regul 1 (3), 293–306.

Lubar, J. F., Swartwood, M. O., Swartwood, J. N., O'Donnell, P. H., 1995. Evaluation of the effectiveness of EEG neurofeedback training for ADHD in a clinical setting as measured by changes in T.O.V.A. scores, behavioral ratings, and WISC-R performance. Biofeedback Self Regul 20 (1), 83–99.

Luck, S., 2005. An Introduction to Event-Related Potentials and their Neural Origins. In: An Introduction to the Event-Related Potential Technique. The MIT Press, Cambridge, Massachusetts, pp. 1–20.

Madras, B. K., Miller, G. M., Fischman, A. J., 2002. The dopamine transporter: relevance to attention deficit hyperactivity disorder (ADHD). Behav Brain Res 130 (1-2), 57–63.

Makeig, S., Debener, S., Onton, J., Delorme, A., 2004. Mining event-related brain dynamics. Trends Cogn Sci 8 (5), 204–210.

Mann, C. A., Lubar, J. F., Zimmerman, A. W., Miller, C. A., Muenchen, R. A., 1992. Quantitative analysis of EEG in boys with attention-deficit-hyperactivity disorder: controlled study with clinical implications. Pediatr Neurol 8 (1), 30–36.

Martino, A. D., Ghaffari, M., Curchack, J., Reiss, P., Hyde, C., Vannucci, M., Petkova, E., Klein, D. F., Castellanos, F. X., 2008. Decomposing intra-subject variability in children with attention-deficit/hyperactivity disorder. Biol Psychiatry 64 (7), 607–614.

Martinovic, J., Gruber, T., Hantsch, A., Müller, M. M., 2008. Induced gamma-band activity is related to the time point of object identification. Brain Res 1198, 93–106.

Martinovic, J., Gruber, T., Müller, M. M., 2007. Induced gamma band responses predict recognition delays during object identification. J Cogn Neurosci 19 (6), 921–934.

Martinussen, R., Hayden, J., Hogg-Johnson, S., Tannock, R., 2005. A meta-analysis of working memory impairments in children with attention-deficit/hyperactivity disorder. J Am Acad Child Adolesc Psychiatry 44 (4), 377–384.

May, P., Tiitinen, H., Sinkkonen, J., Näätänen, R., 1994. Long-term stimulation attenuates the transient 40-Hz response. Neuroreport 5 (15), 1918–1920.

Mayes, S. D., Calhoun, S. L., Crowell, E. W., 2000. Learning disabilities and ADHD: overlapping spectrumn disorders. J Learn Disabil 33 (5), 417–424.

McGillivray, J. A., Baker, K. L., 2009. Effects of comorbid ADHD with learning disabilities on anxiety, depression, and aggression in adults. J Atten Disord 12 (6), 525–531.

McPherson, W. B., Holcomb, P. J., 1999. An electrophysiological investigation of semantic priming with pictures of real objects. Psychophysiology 36 (1), 53–65.

Mick, E., Biederman, J., Prince, J., Fischer, M. J., Faraone, S. V., 2002. Impact of low birth weight on attention-deficit hyperactivity disorder. J Dev Behav Pediatr 23 (1), 16–22.

Moazami-Goudarzi, M., Sarnthein, J., Michels, L., Moukhtieva, R., Jeanmonod, D., 2008. Enhanced frontal low and high frequency power and synchronization in the resting EEG of parkinsonian patients. Neuroimage 41 (3), 985–997.

Monastra, V. J., Lubar, J. F., Linden, M., VanDeusen, P., Green, G., Wing, W., Phillips, A., Fenger, T. N., 1999. Assessing attention deficit hyperactivity

disorder via quantitative electroencephalography: an initial validation study. Neuropsychology 13 (3), 424–433.

Monastra, V. J., Lynn, S., Linden, M., Lubar, J. F., Gruzelier, J., LaVaque, T. J., 2005. Electroencephalographic biofeedback in the treatment of attention-deficit/hyperactivity disorder. Appl Psychophysiol Biofeedback 30 (2), 95–114.

Monastra, V. J., Monastra, D. M., George, S., 2002. The effects of stimulant therapy, EEG biofeedback, and parenting style on the primary symptoms of attention-deficit/hyperactivity disorder. Appl Psychophysiol Biofeedback 27 (4), 231–249.

Morup, M., Hansen, L. K., Herrmann, C. S., Parnas, J., Arnfred, S. M., 2006. Parallel Factor Analysis as an exploratory tool for wavelet transformed event-related EEG. Neuroimage 29 (3), 938–947.

Müller, M. M., Bosch, J., Elbert, T., Kreiter, A., Sosa, M. V., Sosa, P. V., Rockstroh, B., 1996. Visually induced gamma-band responses in human electroencephalographic activity–a link to animal studies. Exp Brain Res 112 (1), 96–102.

Niedermeyer, E., 1996. Dipole theory and electroencephalography. Clin Electroencephalogr 27 (3), 121–131.

Nigg, J. T., 2001. Is ADHD a disinhibitory disorder? Psychol Bull 127 (5), 571–598.

Novak, G. P., Solanto, M., Abikoff, H., 1995. Spatial orienting and focused attention in attention deficit hyperactivity disorder. Psychophysiology 32 (6), 546–559.

Oades, R. D., Dittmann-Balcar, A., Schepker, R., Eggers, C., Zerbin, D., 1996. Auditory event-related potentials (ERPs) and mismatch negativity (MMN) in healthy children and those with attention-deficit or tourette/tic symptoms. Biol Psychol 43 (2), 163–185.

Ohla, K., Busch, N. A., Herrmann, C. S., 2007. Early electrophysiological markers of visual awareness in the human brain. Neuroimage 37 (4), 1329–1337.

Oldfield, R. C., 1971. The assessment and analysis of handedness: the Edinburgh inventory. Neuropsychologia 9 (1), 97–113.

Oosterlaan, J., Logan, G. D., Sergeant, J. A., 1998. Response inhibition in AD/HD, CD, comorbid AD/HD + CD, anxious, and control children: a meta-analysis of studies with the stop task. J Child Psychol Psychiatry 39 (3), 411–425.

Orekhova, E. V., Stroganova, T. A., Nygren, G., Tsetlin, M. M., Posikera, I. N., Gillberg, C., Elam, M., 2007. Excess of high frequency electroencephalogram oscillations in boys with autism. Biol Psychiatry 62 (9), 1022–1029.

Orekhova, E. V., Stroganova, T. A., Prokofyev, A. O., Nygren, G., Gillberg, C., Elam, M., 2008. Sensory gating in young children with autism: relation to age, IQ, and EEG gamma oscillations. Neurosci Lett 434 (2), 218–223.

Osipova, D., Takashima, A., Oostenveld, R., FernÃ¡ndez, G., Maris, E., Jensen, O., 2006. Theta and gamma oscillations predict encoding and retrieval of declarative memory. J Neurosci 26 (28), 7523–7531.

O'Sullivan, S. S., Mullins, G. M., Cassidy, E. M., McNamara, B., 2006. The role of the standard EEG in clinical psychiatry. Hum Psychopharmacol 21 (4), 265–271.

Pantev, C., Makeig, S., Hoke, M., Galambos, R., Hampson, S., Gallen, C., 1991. Human auditory evoked gamma-band magnetic fields. Proc Natl Acad Sci U S A 88 (20), 8996–9000.

Picton, T. W., Bentin, S., Berg, P., Donchin, E., Hillyard, S. A., Johnson, R., Miller, G. A., Ritter, W., Ruchkin, D. S., Rugg, M. D., Taylor, M. J., 2000. Guidelines for using human event-related potentials to study cognition: recording standards and publication criteria. Psychophysiology 37 (2), 127–152.

Polich, J., 1986. Attention, probability, and task demands as determinants of P300 latency from auditory stimuli. Electroencephalogr Clin Neurophysiol 63 (3), 251–259.

Polich, J., 2007. Updating P300: an integrative theory of P3a and P3b. Clin Neurophysiol 118 (10), 2128–2148.

Robaey, P., Breton, F., Dugas, M., Renault, B., 1992. An event-related potential study of controlled and automatic processes in 6-8-year-old boys with attention deficit hyperactivity disorder. Electroencephalogr Clin Neurophysiol 82 (5), 330–340.

Roman, T., Schmitz, M., Polanczyk, G., Eizirik, M., Rohde, L. A., Hutz, M. H., 2001. Attention-deficit hyperactivity disorder: a study of association with both the dopamine transporter gene and the dopamine D4 receptor gene. Am J Med Genet 105 (5), 471–478.

Rothenberger, A., 2009. Brain oscillations forever–neurophysiology in future research of child psychiatric problems. J Child Psychol Psychiatry 50 (1-2), 79–86.

Roye, A., Jacobsen, T., Gruber, T., Schröger, E., 2009. Zur willkürlichen und unwillkürlichen auditiven Verarbeitung persönlich bedeutsamer Reize - Elektrophysiologische und Verhaltensindikatoren. In: 35. Arbeitstagung Psychophysiologie und Methodik. Leipzig.

Rubia, K., Overmeyer, S., Taylor, E., Brammer, M., Williams, S. C., Simmons, A., Bullmore, E. T., 1999. Hypofrontality in attention deficit hyperactivity disorder during higher-order motor control: a study with functional MRI. Am J Psychiatry 156 (6), 891–896.

Rubia, K., Smith, A. B., Brammer, M. J., Taylor, E., 2007. Temporal lobe dysfunction in medication-naive boys with attention-deficit/hyperactivity disorder during attention allocation and its relation to response variability. Biol Psychiatry 62 (9), 999–1006.

Sagvolden, T., Johansen, E. B., Aase, H., Russell, V. A., 2005. A dynamic developmental theory of attention-deficit/hyperactivity disorder (ADHD) predominantly hyperactive/impulsive and combined subtypes. Behav Brain Sci 28 (3), 397–419; discussion 419–68.

Satterfield, J. H., Schell, A. M., Nicholas, T., 1994. Preferential neural processing of attended stimuli in attention-deficit hyperactivity disorder and normal boys. Psychophysiology 31 (1), 1–10.

Satterfield, J. H., Schell, A. M., Nicholas, T., Backs, R. W., 1988. Topographic study of auditory event-related potentials in normal boys and boys with attention deficit disorder with hyperactivity. Psychophysiology 25 (5), 591–606.

Satterfield, J. H., Schell, A. M., Nicholas, T. W., Satterfield, B. T., Freese, T. E., 1990. Ontogeny of selective attention effects on event-related potentials in attention-deficit hyperactivity disorder and normal boys. Biol Psychiatry 28 (10), 879–903.

Schadow, J., Dettler, N., Paramei, G. V., Lenz, D., Fründ, I., Sabel, B. A., Herrmann, C. S., 2009a. Impairments of Gestalt perception in the intact hemifield of hemianopic patients are reflected in gamma-band EEG activity. Neuropsychologia 47 (2), 556–568.

Schadow, J., Lenz, D., Dettler, N., Fründ, I., Herrmann, C. S., 2009b. Early gamma-band responses reflect anticipatory top-down modulation in the auditory cortex. Neuroimage 47 (2), 651–658.

Schadow, J., Lenz, D., Thaerig, S., Busch, N. A., Fründ, I., Herrmann, C. S., 2007a. Stimulus intensity affects early sensory processing: sound intensity modulates auditory evoked gamma-band activity in human EEG. Int J Psychophysiol 65 (2), 152–161.

Schadow, J., Lenz, D., Thaerig, S., Busch, N. A., Fründ, I., Rieger, J. W., Herrmann, C. S., 2007b. Stimulus intensity affects early sensory processing: visual contrast modulates evoked gamma-band activity in human EEG. Int J Psychophysiol 66 (1), 28–36.

Schatz, D. B., Rostain, A. L., 2006. ADHD with comorbid anxiety: a review of the current literature. J Atten Disord 10 (2), 141–149.

Schendan, H. E., Maher, S. M., 2009. Object knowledge during entry-level categorization is activated and modified by implicit memory after 200 ms. Neuroimage 44 (4), 1423–1438.

Schnitzler, A., Gross, J., 2005. Normal and pathological oscillatory communication in the brain. Nat Rev Neurosci 6 (4), 285–296.

Sederberg, P. B., Kahana, M. J., Howard, M. W., Donner, E. J., Madsen, J. R., 2003. Theta and gamma oscillations during encoding predict subsequent recall. J Neurosci 23 (34), 10809–10814.

Seeman, P., Madras, B., 2002. Methylphenidate elevates resting dopamine which lowers the impulse-triggered release of dopamine: a hypothesis. Behav Brain Res 130 (1-2), 79–83.

Seeman, P., Madras, B. K., 1998. Anti-hyperactivity medication: methylphenidate and amphetamine. Mol Psychiatry 3 (5), 386–396.

Sejnowski, T. J., Paulsen, O., 2006. Network oscillations: emerging computational principles. J Neurosci 26 (6), 1673–1676.

Senkowski, D., Herrmann, C. S., 2002. Effects of task difficulty on evoked gamma activity and ERPs in a visual discrimination task. Clin Neurophysiol 113 (11), 1742–1753.

Shalev, L., Tsal, Y., 2003. The wide attentional window: a major deficit of children with attention difficulties. J Learn Disabil 36 (6), 517–527.

Shaw, P., Eckstrand, K., Sharp, W., Blumenthal, J., Lerch, J. P., Greenstein, D., Clasen, L., Evans, A., Giedd, J., Rapoport, J. L., 2007. Attention-deficit/hyperactivity disorder is characterized by a delay in cortical maturation. Proc Natl Acad Sci U S A 104 (49), 19649–19654.

Sheridan, M. A., Hinshaw, S., D'Esposito, M., 2007. Efficiency of the prefrontal cortex during working memory in attention-deficit/hyperactivity disorder. J Am Acad Child Adolesc Psychiatry 46 (10), 1357–1366.

Silk, T., Vance, A., Rinehart, N., Egan, G., O'Boyle, M., Bradshaw, J. L., Cunnington, R., 2005. Fronto-parietal activation in attention-deficit hyperactivity disorder, combined type: functional magnetic resonance imaging study. Br J Psychiatry 187, 282–283.

Solanto, M. V., 2002. Dopamine dysfunction in AD/HD: integrating clinical and basic neuroscience research. Behav Brain Res 130 (1-2), 65–71.

Solanto, M. V., Abikoff, H., Sonuga-Barke, E., Schachar, R., Logan, G. D., Wigal, T., Hechtman, L., Hinshaw, S., Turkel, E., 2001. The ecological validity of delay aversion and response inhibition as measures of impulsivity in AD/HD: a supplement to the NIMH multimodal treatment study of AD/HD. J Abnorm Child Psychol 29 (3), 215–228.

Sonuga-Barke, E. J. S., 2002. Psychological heterogeneity in AD/HD–a dual pathway model of behaviour and cognition. Behav Brain Res 130 (1-2), 29–36.

Sonuga-Barke, E. J. S., 2005. Causal models of attention-deficit/hyperactivity disorder: from common simple deficits to multiple developmental pathways. Biol Psychiatry 57 (11), 1231–1238.

Sowell, E. R., Peterson, B. S., Thompson, P. M., Welcome, S. E., Henkenius, A. L., Toga, A. W., 2003. Mapping cortical change across the human life span. Nat Neurosci 6 (3), 309–315.

Spaniol, J., Bayen, U. J., 2004. Formal modeling in research on episodic memory and aging. Psychology Science 46, 477–513.

Spencer, K. M., Nestor, P. G., Niznikiewicz, M. A., Salisbury, D. F., Shenton, M. E., McCarley, R. W., 2003. Abnormal neural synchrony in schizophrenia. J Neurosci 23 (19), 7407–7411.

Spencer, K. M., Nestor, P. G., Perlmutter, R., Niznikiewicz, M. A., Klump, M. C., Frumin, M., Shenton, M. E., McCarley, R. W., 2004. Neural synchrony indexes disordered perception and cognition in schizophrenia. Proc Natl Acad Sci U S A 101 (49), 17288–17293.

Spencer, T., Biederman, J., Wilens, T., 2000. Pharmacotherapy of attention deficit hyperactivity disorder. Child Adolesc Psychiatr Clin N Am 9 (1), 77–97.

Spencer, T., Biederman, M., Coffey, B., Geller, D., Wilens, T., Faraone, S., 1999. The 4-year course of tic disorders in boys with attention-deficit/hyperactivity disorder. Arch Gen Psychiatry 56 (9), 842–847.

Spencer, T. J., Biederman, J., Mick, E., 2007. Attention-deficit/hyperactivity disorder: diagnosis, lifespan, comorbidities, and neurobiology. J Pediatr Psychol 32 (6), 631–642.

Spencer, T. J., Biederman, J., Wilens, T. E., Faraone, S. V., 2002. Overview and neurobiology of attention-deficit/hyperactivity disorder. J Clin Psychiatry 63 Suppl 12, 3–9.

Stevens, M. C., Pearlson, G. D., Kiehl, K. A., 2007. An FMRI auditory oddball study of combined-subtype attention deficit hyperactivity disorder. Am J Psychiatry 164 (11), 1737–1749.

Strandburg, R. J., Marsh, J. T., Brown, W. S., Asarnow, R. F., Higa, J., Harper, R., Guthrie, D., 1996. Continuous-processing–related event-related potentials in children with attention deficit hyperactivity disorder. Biol Psychiatry 40 (10), 964–980.

Strelets, V. B., Garakh, Z. V., Novototskii-Vlasov, V. Y., 2007. Comparative study of the gamma rhythm in normal conditions, during examination stress, and in patients with first depressive episode. Neurosci Behav Physiol 37 (4), 387–394.

Strüber, D., Başar-Eroğlu, C., Hoff, E., Stadler, M., 2000. Reversal-rate dependent differences in the EEG gamma-band during multistable visual perception. Int J Psychophysiol 38 (3), 243–252.

Summerfield, C., Mangels, J. A., 2006. Dissociable neural mechanisms for encoding predictable and unpredictable events. J Cogn Neurosci 18 (7), 1120–1132.

Swanson, J. M., Flodman, P., Kennedy, J., Spence, M. A., Moyzis, R., Schuck, S., Murias, M., Moriarity, J., Barr, C., Smith, M., Posner, M., 2000. Dopamine genes and ADHD. Neurosci Biobehav Rev 24 (1), 21–25.

Swanson, J. M., Kinsbourne, M., Nigg, J., Lanphear, B., Stefanatos, G. A., Volkow, N., Taylor, E., Casey, B. J., Castellanos, F. X., Wadhwa, P. D., 2007. Etiologic subtypes of attention-deficit/hyperactivity disorder: brain imaging, molecular genetic and environmental factors and the dopamine hypothesis. Neuropsychol Rev 17 (1), 39–59.

Swartwood, J. N., Swartwood, M. O., Lubar, J. F., Timmermann, D. L., 2003. EEG differences in ADHD-combined type during baseline and cognitive tasks. Pediatr Neurol 28 (3), 199–204.

Tallon-Baudry, C., Bertrand, O., 1999. Oscillatory gamma activity in humans and its role in object representation. Trends Cogn Sci 3 (4), 151–162.

Tallon-Baudry, C., Bertrand, O., Delpuech, C., Pernier, J., 1996. Stimulus specificity of phase-locked and non-phase-locked 40 Hz visual responses in human. J Neurosci 16 (13), 4240–4249.

Tallon-Baudry, C., Bertrand, O., Peronnet, F., Pernier, J., 1998. Induced gamma-band activity during the delay of a visual short-term memory task in humans. J Neurosci 18 (11), 4244–54.

Tamm, L., Menon, V., Reiss, A. L., 2006. Parietal attentional system aberrations during target detection in adolescents with attention deficit hyperactivity disorder: event-related fMRI evidence. Am J Psychiatry 163 (6), 1033–1043.

Tanaka, J. W., Curran, T., Porterfield, A. L., Collins, D., 2006. Activation of preexisting and acquired face representations: the N250 event-related potential as an index of face familiarity. J Cogn Neurosci 18 (9), 1488–1497.

Tannock, R., 1998. Attention deficit hyperactivity disorder: advances in cognitive, neurobiological, and genetic research. J Child Psychol Psychiatry 39 (1), 65–99.

Thapar, A., Hervas, A., McGuffin, P., 1995. Childhood hyperactivity scores are highly heritable and show sibling competition effects: twin study evidence. Behav Genet 25 (6), 537–544.

Thapar, A., O'Donovan, M., Owen, M. J., 2005. The genetics of attention deficit hyperactivity disorder. Hum Mol Genet 14 Spec No. 2, R275–R282.

Thompson, L., Thompson, M., 1998. Neurofeedback combined with training in metacognitive strategies: effectiveness in students with ADD. Appl Psychophysiol Biofeedback 23 (4), 243–263.

Thorell, L. B., 2007. Do delay aversion and executive function deficits make distinct contributions to the functional impact of ADHD symptoms? A study of early academic skill deficits. J Child Psychol Psychiatry 48 (11), 1061–1070.

Tiitinen, H., Sinkkonen, J., Reinikainen, K., Alho, K., Lavikainen, J., Näätänen, R., 1993. Selective attention enhances the auditory 40-Hz transient response in humans. Nature 364 (6432), 59–60.

Toga, A. W., Thompson, P. M., Sowell, E. R., 2006. Mapping brain maturation. Trends Neurosci 29 (3), 148–159.

Tripp, G., Alsop, B., 2001. Sensitivity to reward delay in children with attention deficit hyperactivity disorder (ADHD). J Child Psychol Psychiatry 42 (5), 691–698.

Uhlhaas, P. J., Roux, F., Singer, W., Haenschel, C., Sireteanu, R., Rodriguez, E., 2009. The development of neural synchrony reflects late maturation and restructuring of functional networks in humans. Proc Natl Acad Sci U S A 106 (24), 9866–9871.

Uhlhaas, P. J., Singer, W., 2006. Neural synchrony in brain disorders: relevance for cognitive dysfunctions and pathophysiology. Neuron 52 (1), 155–168.

van Deursen, J. A., Vuurman, E. F. P. M., Verhey, F. R. J., van Kranen-Mastenbroek, V. H. J. M., Riedel, W. J., 2008. Increased EEG gamma band activity in Alzheimer's disease and mild cognitive impairment. J Neural Transm 115 (9), 1301–1311.

van Mourik, R., Oosterlaan, J., Heslenfeld, D. J., Konig, C. E., Sergeant, J. A., 2007. When distraction is not distracting: a behavioral and ERP study on distraction in ADHD. Clin Neurophysiol 118 (8), 1855–1865.

Vles, J. S. H., Feron, F. J. M., Hendriksen, J. G. M., Jolles, J., van Kroonenburgh, M. J. P. G., Weber, W. E. J., 2003. Methylphenidate down-regulates the dopamine receptor and transporter system in children with attention deficit hyperkinetic disorder (ADHD). Neuropediatrics 34 (2), 77–80.

Volkow, N. D., Swanson, J. M., 2003. Variables that affect the clinical use and abuse of methylphenidate in the treatment of ADHD. Am J Psychiatry 160 (11), 1909–1918.

Volkow, N. D., Wang, G., Fowler, J. S., Logan, J., Gerasimov, M., Maynard, L., Ding, Y., Gatley, S. J., Gifford, A., Franceschi, D., 2001. Therapeutic doses of oral methylphenidate significantly increase extracellular dopamine in the human brain. J Neurosci 21 (2), RC121.

Waldman, I. D., Rowe, D. C., Abramowitz, A., Kozel, S. T., Mohr, J. H., Sherman, S. L., Cleveland, H. H., Sanders, M. L., Gard, J. M., Stever, C., 1998. Association and linkage of the dopamine transporter gene and attention-deficit hyperactivity disorder in children: heterogeneity owing to diagnostic subtype and severity. Am J Hum Genet 63 (6), 1767–1776.

Weiler, M. D., Bernstein, J. H., Bellinger, D., Waber, D. P., 2002. Information processing deficits in children with attention-deficit/hyperactivity disorder, inattentive type, and children with reading disability. J Learn Disabil 35 (5), 448–461.

Weiss, R. H., 1997. Grundintelligenztest Skala 2 (CFT 20). Göttingen: Hogrefe.

Weissman, D. H., Roberts, K. C., Visscher, K. M., Woldorff, M. G., 2006. The neural bases of momentary lapses in attention. Nat Neurosci 9 (7), 971–978.

Werkle-Bergner, M., Shing, Y. L., Müller, V., Li, S.-C., Lindenberger, U., 2009. EEG gamma-band synchronization in visual coding from childhood to old age: Evidence from evoked power and inter-trial phase locking. Clin Neurophysiol.

Whitham, E. M., Pope, K. J., Fitzgibbon, S. P., Lewis, T., Clark, C. R., Loveless, S., Broberg, M., Wallace, A., DeLosAngeles, D., Lillie, P., Hardy, A., Fronsko, R., Pulbrook, A., Willoughby, J. O., 2007. Scalp electrical recording during paralysis: quantitative evidence that EEG frequencies above 20 Hz are contaminated by EMG. Clin Neurophysiol 118 (8), 1877–1888.

Wienbruch, C., Paul, I., Bauer, S., Kivelitz, H., 2005. The influence of methylphenidate on the power spectrum of ADHD children - an MEG study. BMC Psychiatry 5, 29.

Woldorff, M. G., Gallen, C. C., Hampson, S. A., Hillyard, S. A., Pantev, C., Sobel, D., Bloom, F. E., 1993. Modulation of early sensory processing in human auditory cortex during auditory selective attention. Proc Natl Acad Sci U S A 90 (18), 8722–8726.

Yordanova, J., Banaschewski, T., Kolev, V., Woerner, W., Rothenberger, A., 2001. Abnormal early stages of task stimulus processing in children with attention-deficit hyperactivity disorder–evidence from event-related gamma oscillations. Clin Neurophysiol 112 (6), 1096–1108.

Yordanova, J., Heinrich, H., Kolev, V., Rothenberger, A., 2006. Increased event-related theta activity as a psychophysiological marker of comorbidity in children with tics and attention-deficit/hyperactivity disorders. Neuroimage 32 (2), 940–955.

Yordanova, J., Kolev, V., 2008. Event-Related Oscillations in Normal Development. In: Schmidt, L., Segalowitz, S. (Eds.), Developmental Psychophysiology - Theory, Systems, and Methods. Cambridge University Press, New York, USA, pp. 15–68.

Yordanova, J., Kolev, V., Demiralp, T., 1997. The phase-locking of auditory gamma band responses in humans is sensitive to task processing. Neuroreport 8 (18), 3999–4004.

Yordanova, J., Kolev, V., Heinrich, H., Woerner, W., Banaschewski, T., Rothenberger, A., 2002. Developmental event-related gamma oscillations: effects of auditory attention. Eur J Neurosci 16 (11), 2214–2224.

Yuval-Greenberg, S., Deouell, L., 2009. The Broadband-Transient Induced Gamma-Band Response in Scalp EEG Reflects the Execution of Saccades. Brain Topogr.

Yuval-Greenberg, S., Tomer, O., Keren, A. S., Nelken, I., Deouell, L. Y., 2008. Transient induced gamma-band response in EEG as a manifestation of miniature saccades. Neuron 58 (3), 429–441.

Zaehle, T., Fründ, I., Schadow, J., Thärig, S., Schoenfeld, M. A., Herrmann, C. S., 2009. Inter- and intra-individual covariations of hemodynamic and oscillatory gamma responses in the human cortex. Front Hum Neurosci 3, 8.

Zschocke, S., 2002. Klinische Elektroencephalographie. Springer-Verlag, Berlin.

ANHANG A

Curriculum vitae

Persönliche Angaben

Name	Daniel Lenz
Adresse	Otto-von-Guericke-Str. 47, 39104 Magdeburg
Geburtsdatum	8. Dezember 1979
Geburtsort	Magdeburg
Familienstand	ledig, keine Kinder
Staatsangehörigkeit	deutsch

Berufserfahrung

Seit 10/2005	wissenschaftlicher Mitarbeiter am Lehrstuhl für Biologische Psychologie des Instituts für Psychologie II / Otto-von-Guericke-Universität Magdeburg
02/2004 - 04/2004	Praktikant, Klinik für Kinder- und Jugendpsychiatrie / AMEOS Fachkrankenhaus für Psychiatrie und Neurologie Haldensleben
02/2003 - 04/2003	Praktikant, Arbeitsgruppe MEG / Max-Planck-Institut für Kognitions- und Neurowissenschaften Leipzig

11/2002 - 09/2005	studentische Hilfskraft am Lehrstuhl für Biologische Psychologie des Instituts für Psychologie II / Otto-von-Guericke-Universität Magdeburg

Ausbildung

Seit 10/2008	Weiterbildung zum Kinder- und Jugendlichenpsychotherapeuten (Schwerpunkt Verhaltenstherapie) / Akademie für Psychotherapie und Interventionsforschung Potsdam
10/2000 - 09/2005	Studium der Psychologie (Schwerpunktfächer Klinische Psychologie und Pädagogische Psychologie) / Otto-von-Guericke-Universität Magdeburg Abschluss: Diplom-Psychologe (Note: 1,3) Thema der Diplomarbeit: 'Das hab ich doch schon mal gehört - Auditorische Langzeitgedächtnisprozesse realer Alltagsgeräusche modulieren die Gamma-Aktivität im menschlichen EEG'
10/1999 - 09/2000	Studium der Humanmedizin / Otto-von-Guericke-Universität Magdeburg
09/1991 - 07/1998	Hegel-Gymnasium Magdeburg, Abitur (Note: 1,4)

Ersatzdienst

09/1998 - 09/1999	Station 8 der Kinderklinik des Universitätsklinikums / Otto-von-Guericke-Universität Magdeburg

Ehrenamtliche Tätigkeiten

Seit 10/2003	stellvertretender Projektleiter der 'Kinder-Uni Magdeburg' für Kinder zwischen 8 und 12 Jahren und Projektentwicklung und Betreuung des 'Studium Schnupperale' als Nachfolgeprojekt der Kinder-Uni für Schüler ab 13 Jahren / Prorektorat der Otto-von-Guericke-Universität Magdeburg
07/2003 - 06/2004	studentisches Mitglied im Fakultätsrat der Fakultät für Naturwissenschaften / Otto-von-Guericke-Universität Magdeburg

07/2002 - 06/2005	Mitglied im Fachschaftsrat der Fakultät für Naturwissenschaften / Otto-von-Guericke-Universität Magdeburg

Auszeichnungen

05/2009	'Best Poster Award' auf dem 2^{nd} International Congress on ADHD / Wien, Österreich

Gutachtertätigkeit

	European Journal of Neuroscience
	International Journal of Psychophysiology
	BMC Neuroscience
	MRC Medical Research Council, UK

Mitgliedschaften

Seit 11/2008	Bundesvereinigung Verhaltenstherapie im Kindes- und Jugendalter

ANHANG B

Eigene Publikationen

Publikationen in begutachteten internationalen Fachzeitschriften

1. Lenz D, Krauel K, Flechtner HH, Schadow J, Hinrichs H, Herrmann CS (under review)
   Altered evoked gamma-band responses reveal impaired early visual processing in ADHD children
   Biological Psychiatry

2. Herrmann CS, Fründ I, Lenz D (in revision)
   Human gamma-band activity: A review on cognitive and behavioral correlates and network models
   Neuroscience and Biobehavioral Reviews

3. Schadow J, Lenz D, Dettler N, Fründ I, Herrmann CS (2009)
   Early gamma-band responses reflect anticipatory top-down modulation in the auditory cortex
   Neuroimage 47(2):651-658

4. Krauel K, Duzel E, Hinrichs H, Lenz D, Herrmann CS, Santel S, Rellum T, Baving L (2009)
   Electrophysiological correlates of semantic processing during encoding of neutral and emotional pictures in patients with ADHD
   Neuropsychologia 47(8-9):1873-1882

5. Schadow J, Naue N, Paramei GV, Lenz D, Fründ I, Sabel BA, Herrmann CS (2009)
   Impairments of Gestalt perception in the intact hemifield of hemianopic

patients are reflected in gamma-band EEG activity
Neuropsychologia 47(2):556-568

6. Lenz D, Krauel K, Schadow J, Baving L, Duzel E, Herrmann CS (2008)
Enhanced gamma-band activity in ADHD patients lacks correlation with memory performance found in healthy children
Brain Research 1235:117-132

7. Lenz D, Jeschke M, Schadow J, Naue N, Ohl FW, Herrmann CS (2008)
Human EEG very high frequency oscillations reflect the number of matches with a template in auditory short-term memory
Brain Research 1220:81-82

8. Jeschke M, Lenz D, Budinger E, Herrmann CS, Ohl FW (2008)
Gamma oscillations in gerbil auditory cortex during a target-discrimination task reflect matches with short-term memory
Brain Research 1220:70-80

9. Thaerig S, Behne N, Schadow J, Lenz D, Scheich H, Brechmann E, Herrmann CS (2008)
Sound level dependence of auditory evoked potentials: Simultaneous EEG recording and low-noise fMRI
International Journal of Psychophysiology 67(3):235-241

10. Schadow J, Lenz D, Thaerig S, Busch NA, Fründ I, Herrmann, CS (2007)
Stimulus intensity affects early sensory processing: Visual contrast modulates evoked gamma-band activity in human EEG
International Journal of Psychophysiology 66(1):28-36

11. Schadow J, Lenz D, Thaerig S, Busch NA, Fründ I, Herrmann CS (2007)
Stimulus intensity affects early sensory processing: Sound intensity modulates auditory evoked gamma-band activity in human EEG
International Journal of Psychophysiology 65(2):152-61

12. Lenz D, Schadow J, Thaerig S, Busch NA, Herrmann CS (2007)
What's that sound? Matches with auditory long-term memory induce gamma activity in human EEG
International Journal of Psychophysiology 64(1):31-38

13. Demiralp T, Bayraktaroglu Z, Lenz D, Junge S, Busch NA, Maess B, Ergen M, Herrmann CS (2007)
Gamma amplitudes are coupled to theta phase in human EEG
International Journal of Psychophysiology 64(1):24-30

14. Busch NA, Herrmann CS, Müller MM, Lenz D, Gruber T (2006)
A cross-laboratory study of event-related gamma activity in a standard

object-recognition paradigm
Neuroimage 33(4):1169-117

15. Bayraktaroglu Z, Demiralp T, Lenz D, Junge S, Busch NA, Maess B, Ergen M, Herrmann CS (2006)
Interactions of gamma and theta oscillations in the electroencephalogram (EEG) during memory processes
IEEE Signal Processing and Communications Applications 14:1-4

16. Herrmann CS, Lenz D, Junge S, Busch NA, Maess B (2004)
Memory-matches evoke human gamma-responses
BMC Neuroscience 5:13

Buchbeiträge

1. Lenz D (2008)
Hochfrequente EEG-Aktivität bei Wahrnehmungsprozessen und ADHS
In: Gruss M, Braun K (Hrsg.) Magdeburger Tage der Erziehung (3. erweiterte Auflage) S. 31-43
ISBN 978-3-940961-13-6

ANHANG C

Danksagung

> Begegnet uns jemand, der uns Dank schuldig ist, gleich fällt es uns ein. Wie oft können wir jemand begegnen, dem wir Dank schuldig sind, ohne daran zu denken.
>
> *Johann Wolfgang von Goethe*

Aus, Schluß, vobei - der letzte Satz im Projekt 'Dissertation' ist geschrieben und die Doktorarbeit gedruckt und gebunden. Nicht unerheblich war dabei die unermüdliche und fortwährende Unterstützung, die ich in den letzten Jahren von meinen Kollegen, Freunden und Familienangehörigen erfahren habe. An dieser Stelle möchte die Gelegenheit gerne nutzen, dafür ein paar besonderen Menschen DANKE zu sagen.

Wem, wenn nicht ihm, gebührt mein besonderer Dank - meinem Doktorvater Prof. Christoph S. Herrmann. Er hat mich vor inzwischen fast 7 Jahren als studentische Hilfskraft in die Weisheiten der EEG Analyse mit all ihren Tricks und Kniffen eingeführt und mich schon damals außerordentlich eigenständig das inzwischen legendäre Experiment 'GAMMAMEM' bearbeiten lassen, was zu einem festen Grundstein für eine Reihe weiterer Experimente wurde, die sich unter anderem auch in dieser Dissertation wiederfinden. Außerdem möchte ich mich dafür bedanken, dass er mir im Rahmen meiner Promotion die Möglichkeit gegeben und mich darin unterstützt hat, eine Fragestellung zu verfolgen, die primär nicht in das eigentlich von mir zu bearbeitende Forschungsprojekt über das ak-

tive Hören fiel – sicher keine Selbstverständlichkeit! Schlussendlich möchte ich auch noch die extrem ausgeglichene Arbeitsatmosphäre hervorheben, die geprägt war vom wissenschaftlich motivierenden Austausch auf der einen Seite und einem angenehmen, entspannten Umgang auf der anderen. Die kleinen Schwätzchen zwischendurch über seine Windows-Probleme, den letzten Segel-Törn, die kleineren oder größeren Erfolge seiner Tennismannschaft oder unsere inzwischen traditionelle Weihnachsfeier im Frühjahr sowie die gemeinsame Teilnahme beim Drachenboot-Rennen werden mir fehlen.

Da zu jedem Vater auch eine Mutter gehört, möchte ich mich an dieser Stelle bei meiner Doktormutti Dr. Kerstin Krauel bedanken. Durch die Zusammenarbeit mit ihr erhielt ich die Möglichkeit, in ein sehr spannendes und faszinierendes Thema eintauchen und dieses in meiner Promotion untersuchen zu können. Dabei unterstützte sie mich fortwährend in vielerlei Hinsicht und hatte auch immer ein aufmunterndes Wort parat, wenn es vielleicht mal gerade nicht so lief (ich sag nur: DFG-Antrag). Ich freue mich, dass sich dabei ein sehr freundschaftliches Verhältnis entwickelt hat!

Ganz besonders möchte ich mich außerdem bei den Kollegen der Abteilung für Biologische Psychologie bedanken, allen voran Steffi Thärig, Jeanette Schadow und Nicole Dettler. Mit Steffi hab ich inzwischen hier so einiges erleben dürfen, seit wir beide damals zusammen als Hiwis erste Wissenschaftsluft schnupperten. Ihr danke ich dafür, dass sie ein Mensch ist, mit dem ich unwahrscheinlich viel lachen konnte, der immer ein offenes Ohr hat und der Nino De Angelo, ich geb es gerne zu, besser singt als ich. Jeanette war für mich ebenfalls eine wichtige Stütze, mit der ich zusammen in die Tiefen der Auditorik eintauchen durfte und gemeinsam mit ihr immer wieder auch scheinbar unlösbare Probleme doch in den Griff bekommen habe. Ihr danke ich auch dafür, dass sie mir bis zum letzten Wort dieser Arbeit mit ihren Korrekturen und hilfreichen Rückmeldungen zu meinen Schachtelsätzen zur Seite stand und ebenfalls immer ein aufmunterndes Wort parat hatte. Und Nicole danke ich dafür, dass auch sie gerade im letzten Jahr als Diskussionspartnerin immer zur Verfügung stand und dass sie außerdem Brötchen zum Mittag und eine nachmittägliche Kaffeepause genauso schätzt wie ich. Gleiches gilt auch für Tino Zähle, dessen Meinung ich im letzten Jahr auch sehr zu schätzen gelernt habe und der durch die Einführung eines gemeinschaftlichen Abteilungs-After-Work-Beisammenseins ebenfalls für etwas Freizeitausgleich gesorgt hat. Weiterhin möchte ich mich noch bei Niko Busch und Ingo Fründ für ihre fachliche Unterstützung bedanken, sowie bei Franzi Bauch, Susi Fischer und Toralf Neuling – den besten Hiwis, die man sich wünschen kann, sowie bei Christina Thaun – der weltbesten Sekretärin!

Einen besonderen Dank möchte ich noch den Kindern, Jugendlichen sowie deren Eltern aussprechen, die sich freiwillig für die Untersuchungen im Rahmen

dieser Doktorarbeit zur Verfügung gestellt haben und dafür eine Menge Zeit und Geduld aufbringen mussten. Auch das ist keine Selbstverständlichkeit!

Ebenfalls ganz herzlich bedanken möchte ich mich bei meinen Freunden, insbesondere Janett Els, Steffi Marx, Judith Deutloff, Nicole Boxberger, Romy Jahnke und Rene Wendel, die oft für den notwendigen Freizeitausgleich sorgten und dabei jede Menge Verständnis zeigten, wenn ich mich gerade in den letzten Monaten etwas rar gemacht habe.

An dieser Stelle bleibt mir nur noch eine Person, der ich meinen Dank aussprechen möchte – meine Mutti. Ich kann gar nicht oft genug sagen wie froh ich bin, dass sie mich in allem unterstützt hat, was ich mir so in den Kopf gesetzt habe. Sie war immer für mich da und ist das bis heute – DANKE!

ANHANG D

Selbstständigkeitserklärung

Hiermit erkläre ich,

Daniel Lenz, geboren am 08.12.1979 in Magdeburg,
wohnhaft in der Otto-von-Guericke-Str. 47 in 39104 Magdeburg,

dass ich die vorliegende Dissertationsschrift

'Behavioural and cognitive relevance of evoked gamma-band responses in ADHD patients and healthy children'

selbstständig verfasst und keine anderen, als die angegebenen Quellen und Hilfsmittel verwendet habe sowie wörtlich oder inhaltlich übernommene Stellen als solche gekennzeichnet habe.

Weiterhin erkläre ich, dass ich weder diese, noch eine andere Arbeit zur Erlangung des akademischen Grades doctor rerum naturalium (dr. rer. nat.) an anderen Einrichtungen eingereicht habe.

Magdeburg, am 28. Juli 2009 Daniel Lenz