PREFACE

The amount of work, subjects, and technicalities to familiarize with involved in this project have been tremendous to say the least, though, the learning-curve has been steep. In the after-math I can definitively see that I could have made the task of accomplishing a graduate thesis much easier, but as noted by my ever-optimistic mentor and supervisor Mr. Hollup: ”The task would not have been nearly so much fun!”. And the ”spin-effects” of acquaintances and experiences that have resulted from this project have been invaluable. But I could never have accomplished the task without the help and guidance from several people. A big thank you is therefore appropriate. To my husband Anders and daughter Ines for your enduring love, patience and sacrifices – you are the best! To my engaging supervisor Stig Hollup, there have been a few cups of coffee, lab re-decoratings, and a fantastic trip to Switzerland. To Mr. Bernhard Weidle, my enthusiastic supervisor Torun Finnanger, and the rest of the very special Nevroteam – there would be no project without you. To Mr. Andreas Mueller for your warm hospitality and excellent lectures in norm-analyzing EEG data, and to his adoring wife for welcoming us in their home. To Venke Arntsberg for interesting conversations and travelling companion. To Jan Brunner for initially inspiring this project. To Mr. Juri Kropotov, for your many enlightening work-shops and encounters. To all the children, adolescents and parents who participated in this study, each and every one of you have made invaluable contributions to this project, and I wish you all the best. And finally, to all my fellow students in the lab, there have been some serious laughs. Thank you all!

CONTENTS

ABSTRACT

This thesis is divided in two parts: *Part I* provides an overview of the basic and clinical QEEG research fields, and is specifically aimed at addressing issues regarding the clinical application of QEEG in childhood disorders. Specific brain oscillations and event related potentials (ERP) have been found to reflect meaningful states, behaviors, and cognitive processes. Clinical studies on neuropsychiatric disorders have demonstrated differences in certain QEEG parameters in clinical populations compared to control groups, however, results have been inconsistent across studies. Studies searching for disorder-specific QEEG profiles in childhood disorders have demonstrated impressive classification accuracies in sorting patients from control groups. But the clinical application of QEEG metrics faces several issues, such as heterogeneity and comorbidity. *Part II* presents a multiple case study of 14 children referred to a neuropsychiatric unit for observation. QEEG analysis was conducted for each individual and provided a wide range of EEG measures that were compared to a normative database. All deviances were analyzed in relation to reported symptoms and problems, and performance measures. Results revealed significant deviances in two or more QEEG parameters for all of the participants, and furthermore, certain problem areas were found to correlate with spectral deviances in the alpha- and theta-bands. A discussion of the results particularly in relation to issues regarding clinical application of QEEG is provided, and suggests that the heterogeneity in childhood disorders are reflected in heterogeneity in the electrophysiological patterns associated with different symptom complexes, and interpretations of deviances faces similar biases as traditional diagnostics.

GENERAL INTRODUCTION

Many children are struggling to cope with everyday chores and tasks. Important venues, such as school, leisure activities, and friendships become sources of negative experiences. This affects not only the child, but also the child's surrounding and family. An estimated 37% of all children and adolescents will at some time have at least one psychiatric disorder before age 16. Furthermore, children with a history of having a psychiatric disorder are significantly more likely to have additional disorders (Costello, Mustillo, Erkanli, Keeler, & Angold, 2003). Many of the childhood disorders are both heterogeneous and partly overlapping "symptom complexes", making differential diagnostics a difficult task (eg. Gillberg et al., 2004; Matson & Nebel-Schwalm, 2007; Pliszka, Swanson, & Carlson, 1999). Quantitative electroencephalography (QEEG) provides a non-invasive and fairly inexpensive method for measuring brain electric activity. While basic research have linked specific QEEG parameters with certain biological, psychological, and behavioral processes (eg. Cochin, Barthelemy, Roux, & Martineau, 2001; Delplanque, Silvert, Hot, & Sequeira, 2005; Jonathan R. Folstein, 2008; Polich, 2007), clinical studies on neuropsychiatric disorders have reported differences in QEEG parameters between clinical populations and control groups (eg. Barry, Clarke, & Johnstone, 2003; Barry, Johnstone, & Clarke, 2003; Brown et al., 2005; Chabot & Serfontein, 1996; Knight, 1990; Lincoln & Courchesne, 1995; Spronk, Jonkman, & Kemner, 2008). This has in turn led to proposals of QEEG as a valuable and objective tool to aid diagnostic procedure (Prichep, 2005). However, a lot of controversy exists regarding the clinical applicability of QEEG in real-life settings, with patients showing a variety of co-existing disorders.

This graduate thesis has two parts. Part I is a presentation of the theoretical and empirical research on the neurobiological and functional properties of QEEG measures,

particularly spectral (i.e. frequency analysis) and event related potential (ERP) components, followed by a selective overview and discussion on the existing QEEG literature on childhood disorders which are relevant for the present patient population, and on some issues regarding the clinical application of QEEG. Part II presents the reportings and results from a multiple case study of fourteen children referred to "Nevroteam", a special psychiatric unit for children and adolescents, for observation and second opinions. This unit receives many children and adolescents with particularly complex symptoms and several co-existing disorders. The main purpose of this project was to explore and report individual QEEG deviances in relation to symptoms and problem description, as well as evaluating the clinical applicability of QEEG in a real clinical setting.

GENERAL QEEG METHODS

The neural basis of EEG

Electroencephalography (EEG) is the registration of field potentials recorded by multiple electrodes on the surface of the scalp, and reflect the electric signaling communication process between neurons and neuronal circuits. The cortical pyramidal cells in particular, play a major role in the generation of the EEG signal. These neurons form excellent dipoles due to their long apical dendrites which are structurally organized perpendicular to the cortical surface. They also form synaptic connections with myriads of other neurons through cortico-cortical and thalamo-cortical nerve fibers. More specifically, the EEG reflects changes in the resting membrane potential inside the cell which leads to the release of excitatory and inhibitory neurotransmitters. This in turn activates specific postsynaptic receptors that generate excitatory and inhibitory postsynaptic potentials (EPSPs and IPSPs). Superficial excitatory or deep inhibitory inputs form the scalp-recorded negative deflections (conventionally recorded upward), whereas deep excitatory or superficial inhibitory inputs form the positive deflections (conventionally recorded downward) that characterizes the EEG. The recorded EEG waves, however, require the summation of a sufficiently large number of synchronized EPSPs and IPSPs. The more synchronously they are evoked, the larger the wave amplitude, which also imply a decrease in frequency (Kirschstein & Köhling, 2009; Niedermeyer & Lopes da Silva, 2004).

Brain oscillations

Isolated neurons have the instrinsic property to display spontaneous oscillations in vitro, even when blocked from synaptic transmission. In the brain, the neurons are influenced by pacemaker ”driving-forces” that tune individual cells into synchronous oscillatory

ensembles which, when large enough, evidently can be recorded by scalp electrodes (Steriade, Gloor, Llinás, Lopes da Silva, & Mesulam, 1990). Cortical neurons in mammals form behavior-dependent oscillating networks of various sizes, expressed in different orders of magnitude and frequency. These characteristics have been preserved during the evolution of the mammal species, suggesting a functional relevance. Indeed, recent findings indicate that network oscillations influence what and how neural information is being processed, by means of biasing input selection, temporally linking neurons into assemblies, facilitating synaptic plasticity, mechanisms that supports temporal representation, and long-term consolidation of information (Buzsáki & Draguhn, 2004). The thalamic neural network form GABAergic, cholinergic, excitatory, and monoaminergic (noradrenaline and serotonin) connections with both brainstem and cortical neural networks, and are thought to mediate the various human EEG regulations (see eg. Lopes da Silva, 1991, for a detailed overview).

Spectral analysis

QEEG is the quantification of the electroencephalogram. Brain activity has multiple frequencies and evolve over time, thus one has to consider both factors when analyzing EEG data. The method of spectral analysis by means of Fourier Transformation, decomposes the EEG data into distinct sinusoidal wave patterns, and produces a power spectrum of the relative dominance of the various frequencies that make up the EEG (Buzsáki, 2006). This method localizes brain waves precisely in frequency, and depicts the intensity and magnitude of brain oscillations in micro volts (absolute power) or in percentage distribution in the spectrogram (relative power). The frequencies of brain oscillations are traditionally divided into five frequency-bands. In this study, the definition of band ranges is consistent with the definition used by the HBI normative database, ranging from; delta δ (1-4 Hz), theta θ (4-8), alpha α (8-13), beta1 β1 (13-21), beta2 β2 (21-30), and gamma γ for frequencies above 30 Hz.

Theta, alpha and beta frequency-ranges can be observed in the normal EEG in wakefulness during rest with eyes open or eyes closed, while delta rhythm peaks in spectrograms are present only during deep sleep. The intensity of specific frequencies can yield information about the metabolic function of the corresponding cortical areas. Alpha, beta and theta oscillations are proposed to reflect different cognitive operations and mental states, as will be discussed briefly in the following sections (Kropotov, 2009).

Alpha oscillations

Alpha oscillations at approximately 10 Hz distributed in occipital and parietal regions is the dominant frequency of the human brain. The alpha frequency range is lower in children, and reaches a mature range of 8-13 Hz between 15 and 20 years (Kropotov, 2009). Different alpha band rhythms can be recorded in different areas of the brain. Eyes closed alpha recorded over occipital areas in the visual cortex when no visual information is processed, is the largest amplitude alpha found during wakefulness (Pfurtscheller, Neuper, Andrew, & Edlinger, 1997). However, about 10 percent of the normal adult population does not show this high amplitude occipital alpha (Kropotov, 2009). Alpha oscillations, the so-called mu rhythm, can also be observed over sensory motor areas when no somato-sensory information is processed and no motor output is generated. Thus, alpha oscillations are considered to be an ”idling” rhythm of the brain. Conversely, when sensory information is being processed, a desynchronization (i.e. suppression) of the alpha rhythm is observed. It is thought that the sensory-motor cortex displays a variety of mu rhythms with specific topographic and functional properties. In fact, rhythmic activity in the alpha-band over supplementary motor area, which plays an important role in the planning and preparation of movements, has also been demonstrated to be phase coupled with the mu-rhythm in primary areas, and accordingly to desynchronize with movement planning and preparation

(Pfurtscheller et al., 1997). Although the mu-rhythm is present in the human brain, it is observed only in about 14% of adults due to anatomical obstacles such as the skull, dura and scalp, and reaches mature levels between age 11-20 years (Niedermeyer, 1997). A more rare variant of the posterior alpha rhythm with maximum peak at Pz has been reported that seems to be independent from the occipital alpha. While the occipital alpha is typically suppressed with task-load, the parietal alpha power increases in task conditions compared to relaxed conditions (Kropotov, 2009).

The neural origins of 10 Hz oscillations have been demonstrated by recordings at a cellular level, and the evidence support that the alpha rhythm is generated in a diffuse and distributed ”alpha system” (Basar et al., 1997). The thalamic neurons display spontaneous activity of several frequencies, like the 7-14 Hz oscillatory modes of the thalamo-cortical relay neurons, centered at 10 Hz. These oscillatory modes are regulated by the interplay between hyperpolarization produced by the GABAergic neurons of the reticular nucleus and the thalamo-cortical relay neurons (Lopes da Silva, 1997). The cortical alpha is not assumed to generate from some sort of thalamic pacemaker, however, but rather to be modulated by the inhibitory action of the thalmo-cortico-thalamic reentrant network (Klimesch, Sauseng, & Hanslmayr, 2007) .

In addition to the spontaneous alpha rhythms that have been described as the rhythm prototype of the brain (Basar, Schürmann, Basar-Eroglu, & Karakas, 1997), phase-locking of alpha activity, as revealed by computation of event-related synchronization and desynchronization, has been linked to cognitive performance, particularly involving memory and attention processes, as well as top-down processing related to the semantic memory system (Klimesch, 1999; Klimesch, Sauseng, & Hanslmayr, 2007). The suppression of alpha band activity (along with increased beta-band activity) have also been demonstrated to be an EEG marker of visual spatial attention (Marrufo, Vaquero, Cardoso, & Gomez, 2001), and

associated with mental calculation (Fernandez et al., 1995). However, in closed head injured patients a reduction of alpha amplitude (together with beta amplitude) correlate with diminished cognitive functioning (Thatcher, Biver, McAlaster, Camacho, & Salazar, 1998). Recently, it has been proposed that alpha activity can result from both a tonic and a burst mode of the thalamic relay cells, which ultimately have different consequences for information processing (Sherman, 2001). It is proposed that the latter ”alpha mode” plays an important role in the timing of neural processes, and thus, account for the event-related functions associated with alpha (de)synchronization (Klimesch et al., 2007). Although several propositions have been made, it should be noted that the physiological basis and functional meaning of brain oscillations in the alpha range is generally little understood.

In the ”tonic mode”, alpha oscillations can only be recorded on the scalp whenever neurons in the suppressed channel is synchronized, i.e. when thalamo-cortical neurons are hyperpolarized due to excess of inhibition or the lack of excitation from nearby channels. For instance, this lack of inhibition happens when we close our eyes, whereby the transfer of visual information to the cortex is limited, resulting in a synchronization that is recognized as the scalp-recorded occipital alpha. The more inhibition, as defined by the level of polarization of the thalamo-cortical neurons, the greater slowing in frequency, which in some cases can be seen in pathological states (Kropotov, 2009). Examples of abnormal alpha phenomena consist of alpha recorded in unusual sites, like the temporal alphoid rhythm in the low alpha/ high theta-range that usually reflects early cerebrovascular disorder, and rhythmic alpha as an expression of ictal epileptic discharge. Also, unusually powerful mu-rhythms capable of reaching scalp-recordings have been linked to conditions such as low thresholds to pain, migraine, neurosis and psychopathic and psychiatric conditions in general (Niedermeyer, 1997).

Beta oscillations

Beta rhythms appear in many brain areas and have been shown to dominate local EEG recordings from olfactory areas in the inferior forebrain. In animals, the most consisting finding of beta oscillations in the neocortex has been associated with high alertness and focused attention on a target, as well as accurate performance in visual conditioned response tasks. Also in humans, cortical beta activity in parieto-temporo-occipital and motor areas has been related to performance in motor tasks and correlated to visual cortical neurons responding to moving objects (light bars) with a precise coupling and synergistic oscillations with neighboring neurons and overlapping receptive fields. This has led to the proposal that such cortical oscillations form a mechanism for the representation of the features of a given stimulus, and interpreted as evidence for this mechanism to form a cell assembly responsible for the extraction of relevant features of a given stimulus configuration (Lopes da Silva, 1991).

A spontaneous 20 Hz rolandic mu-rhythm can be observed in healthy individuals over sensorimotor areas. While the alpha mu-rhythm is generated in the primary somatosensory cortex, the rolandic beta is generated in the motor cortex and is modulated as a result of various motor and cognitive tasks (Hari & Salmelin, 1997). One such beta component has shown a specific pattern of post movement synchronization, interpreted as a correlate of active inhibition or idling of the primary motor area following the execution of movements (Pfurtscheller, Stancák, & Edlinger, 1997). In addition to the rolandic beta rhythm, a frontal beta rhythm three times smaller than the power of the alpha rhythm is usually expressed in spectrograms with a maximum in frontal leads. While the rolandic beta appears in motor-related tasks, the frontal beta rhythm becomes visible in cognitive tasks related to stimulus assessment and decision making (Kropotov, 2009). Different findings

suggest a positive relationship between beta activity and cognitive perfomance, such as mathematical performance (Fernandez et al., 1995), visual spatial attention (Marrufo et al., 2001), and general neuropsychological functioning (Thatcher et al., 1998). In clinical EEG recordings during rest, beta oscillations are found in frontal scalp electrodes in subjects who have taken benzodiazepine drugs known to act as anxiolytic relaxants. Furthermore, this effect has been shown to result from the GABAergic inhibition among inhibitory interneurons which strongly modulate the firing of pyramidal excitatory neurons in the motor cortex (Jensen et al., 2005). However, the precise functional role of this resting motor cortex beta rhythm is unresolved.

Theta oscillations

In children there is generally a shift from dominating lower frequency power to dominating higher frequency power with increasing age, reflecting maturational changes in the growing brain. For example, the suppression of alpha in eyes open condition relative to eyes closed condition is seen solely in the alpha-band in the adult population. This alpha suppression is sometimes termed alpha-reactivity, and in children, this reactivity of alpha have been found to also affect the delta- and theta-bands (Somsen, van't Klooster, van der Molen, van Leeuwen, & Licht, 1997). This has led to the hypothesis that the frequency-bands in children are not fully differentiated from the broad alpha-range, and consequently behaves in an alpha-like way (Klimesch, 1999). This information of maturation in children is stated to be better assessed by investigating the relative proportion of frequency band powers in the EEG power spectrogram.

In the normal adult population, 10-40% displays a frontal midline theta rhythm of 6-7 Hz that is typically induced during periods of mental activity, but can also occur during rest and sleep. This type of theta activity is associated with activation and increase of metabolic

activity in the medial frontal area and anterior cingulate cortex (Inanaga, 1998; Kropotov, 2009). Among findings illustrating this relationship between frontal midline theta and arousal level, are the negative correlation between frontal midline theta and anxiety levels in individuals, personality trait neuroticism, and conversely, the positive correlation with trait extroversion (Inaga, 1998). Moreover, individual differences in reinforcement sensitivity, as reflected in a subject's tendency to be motivated by the neurophysiological behavioral approach system (BAS) or the behavioral inhibition system (BIS) has been linked to levels of frontal midline theta. High BAS scorers are sensitive to reward cues and tend to be impulsive, while high BIS scorers are sensitive to punishment cues and have a tendency for avoidance behavior. Along with increases in high frequency activations (both beta- and gamma-bands), frontal midline theta has been shown to increase in high BAS scorers in anticipation of reward, and to decrease prior to punishment cues. Low BAS scorers show the opposite pattern, with frontal theta power and high frequency increase to punishment cues and decrease to cues of reward (Knyazev & Slobodskoy-Plusnin, 2009).

Evidence from animal studies in rodents has linked the frontal theta with the hippocampal theta rhythms, suggesting a key role in the formation of longterm memory and the neural encoding of places. Invasive EEG recordings in humans have showed similar functional correlates of theta, but in numerous cortical sites over the entire neocortex (Kahana, Seelig, & Madsen, 2001). Associations between theta activity increase during verbal and spatial memory tasks (Kahana et al., 2001), working memory tasks (Tesche & Karhu, 2000), and episodic memory encoding (Klimesch, 1999) have also been demonstrated. However, the notion of a similar hippocampal theta rhythm in humans, as the one found in animals, has been called into question. The rhythmic human theta oscillations that can be observed in anterior temporal-midtemporal regions have been proposed to be confused with the animal hippocampal theta. But unlike animal theta, these rhythmical theta waves increases

during drowsiness and early sleep, and is commonly seen to increase in elderly, as well as in mild or moderate cerebrovascular disorder (Niedermeyer, 2008). Although theta waves normally occur in the EEG, three major pathological types of theta have been distinguished; one that probably represents a slowing of alpha that correspond to decreased blood flow as described by Niedermeyer as ”the third rhythm”, a second of fronto-temporal predominance reflecting disturbances in deep midline structures, and localized theta activity as a mild expression of polymorphic delta activity reflecting metabolic and structural pathology. However, there is little precise knowledge regarding the underlying pathophysiological mechanism of theta (Steriade et al., 1990).

Event related potentials (ERPs) and ERP components

The event related potential technique (ERP) is one of the most informative and dynamic methods for monitoring the information stream in the living brain (Duncan et al., 2009). The method allows the investigation of fast occurring brain activity time-locked to specific events. EPRs derive from small changes in the electrical activity induced by some external or internal event (Otten & Rugg, 2005), and can both precede and follow an event (Kotchoubey, 2006). This electrical activity changes rapidly over time in a spatially extended field, and is recorded on the scalp with a temporal resolution of a few milliseconds from multiple locations. The basic assumption of ERP analysis is that the ongoing (tonic) EEG activity comprises of additive random and systematic noise. Random noise include all task-unrelated EEG signals, while systematic noise concern signals in the EEG that have some degree of correlation with the event of interest. By averaging all electrical potentials in a time window at the occurrence of a stimulus, all random noise will get cancelled, yet all electrical potentials time-locked to the stimulus (systematic noise) will become enhanced (Handy, 2005). Remaining are the ERPs that consists of positive and negative (often denoted with a P

and N) fluctuations of different amplitude and latency, such as P/N100, P/N200, and P300, where the numbers stand for peak latency in milliseconds.

Different interpretations regarding the functional meaning of ERPs have been proposed. Most commonly, ERP studies make assumptions of various stages of sensory and cognitive proccesses reflected in the different ERP waveforms (eg. Evans, Shedden, Hevenor, & Hahn, 2000; Luo, Feng, He, Wang, & Luo, 2010). Studies such as these suggest that ERP components are highly specific to their eliciting conditions, including modality and stimulus paradigm, as well as polarity, latency and scalp distribution. Generally, ERP components can be classified into exogenous (i.e. determined by external stimulus characteristics) and endogenous (i.e. dependent on the subject's intentions and actions) components. Exogenous components are mandatory to a sensory stimulus and thus, given the stimulus situation, relatively stable. Endogenous components, on the other hand, will vary to a great extent according to the subject's internal state and behavior. Consequently, any variance in endogenous components should be explained by the variation of task demand (Näätänen, 1992). Further classification of components is often made on the basis of timing (i.e. latency) into early sensory-related components that reflect the sensory perception of the physical stimulus, and late behavior-related components associated with the execution or suppression of a response. However, complicating matters, behavior has been found to modulate information processing even at an early sensory state by means of attention. For example, studies have demonstrated that serially shifting of attention can operate as fast as 100 ms between visual objects (Luck & Hillyard, 1994), and that spatial attention influence the P1 wave amplitude with a neural generator source in lateral extrastriate cortex (Wijers, Lange, Mulder, & Mulder, 1997). Moreover, invasive recordings in monkeys provide evidence that the attention effect in this area begins already 60 ms post stimulus (Luck, Chelazzi, Hillyard, & Desimone, 1997). Similar effects have also been demonstrated for auditory processing

(Alain & Woods, 1997). This has led some scientists to conclude that attention more specifically seem to mitigate information overload in any cognitive subsystem due to a particular combination of stimuli and task (Luck, Woodman, & Vogel, 2000). Evidence from the above mentioned study on monkeys, suggest that the fashion in which this take place, at least in the visual system, is through modulation of the feedforward transmission of information (Luck et al., ibid).

In line with the notion of feedforward transmission and attention modulation, others have proposed that negative ERP waves can be explained as feedforward processes, whereas positive ERP waves result from feedback processes (for an in-depth overview and discussion, see Kotchoubey, 2006). Kotchoubey argues that the fluctuations of ERPs can be more readily understood from a biological approach than a cognitive one. From a biological perspective, adaptive abilities are essential. To be efficient, we need to be able to form expectancies about what is to come. These feedforward processes can be explained as preparatory activations of pre-existing cognitive or behavioral structures through the formulation of perceptual ”hypotheses”. Behavioral and physiological events accompanying this feedforward mechanism are the selective mobilization of cortical resources in accordance with the information to come, i.e. tuning of specific neuronal assemblies through thalamo-cortical excitation in superficial layers, and inhibition in the deep cortical layers, hence resulting in a negative ERP deflection. To be flexible, we need the capacity to update our expectations with incoming pieces of information from the environment. These feedback processes lead to confirmation or revision of our initial anticipations, and are reflected as positive ERP components. This is associated with performance through the consumption of cortical resources or inhibition of irrelevant sensorimotor coordinations, by depolarization of proximal dendrites of pyramidal cells and possibly GABAergic inhibition in the superficial layers, resulting in a positive ERP deflection. Thus, the biological approach offers a more ”universal”

understanding of the positive and negative fluctuations that comprise the ERPs, and resist the trap of ”explaining-by-naming”, often seen in attempts to apply cognitive theories to experimental ERP data, where different cognitive processes are increasingly being attributed to new and different ERP waves (Kotchoubey, 2006). Thus, from a biological approach, the positive and negative ERP deflections reflect the cyclic interaction of feedforward and feedback processes between an individual and the environment.

Constituents of the ERP have been investigated in various paradigms, like different versions of the Oddball paradigm, the Stop Signal paradigm, the pop-out paradigm, and the Go/ Nogo paradigm. The main focus here is studies from the Go/ Nogo paradigm, however it should be noted that many of the findings and theories also mentioned have resulted or accumulated from studies employing various paradigms. However, presented here is only a highly selective overview of the literature of some components considered to be relevant. Therefore it should be noted that there are several components not mentioned here that have received a great amount of interest in both the scientific and clinical research fields.

The Go/ Nogo paradigm

In our daily lives we rely heavily on our ability to control our behavior according to the goal or task at hand required to adjust adequately in a complex environment. Such goal-directed behavior is enabled by an adaptive cognitive control system. This involves monitoring and comparing ongoing actions and outcomes with internal goals and standards, and subsequent adjustment of behavior accordingly. For example, the active suppression or interruption of an already prepared response. The processes of monitoring and behavioral adjustment are closely related also at a neurobiological level, with considerable activation overlap in frontal areas. However, monitoring processes have been found to elicit activation foci mainly in the anterior cingulate cortex, whereas the regulation of goal-directed behavior

are localized in areas in lateral prefrontal cortex (Ridderinkhof, Ullsperger, Crone, & Nieuwenhuis, 2004). Cognitive control includes processes like selective attention, stimulus or response expectation and preparation, conflict monitoring, and response inhibition (Jonkman, 2006). The Go/ Nogo paradigm has been proved to effectively tap into these cognitive control processes (Falkenstein, Hoormann, & Hohnsbein, 1999). In the cued GO/ NOGO task, a prepotent response is prepared by a cue (eg. the picture of an animal as in the visual continuous performance task, VCPT, or a particular letter or a figure) which has to be executed or inhibited depending on the subsequent stimulus. ERPs elicited in the Go/ Nogo paradigm display several waveforms that are thought to index the specific cognitive control processes involved in this task, some of which will be highlighted in the following sections.

The P300/ P3 component

One of the most studied components is probably the P300, often referred to as the P3, which is measured by assessing its peak positive amplitude 250-600 ms after stimulus onset. However, the range can vary depending on stimulus modality, task conditions and subject age, among other factors (Kok, 2000; Pfefferbaum, Ford, Weller, & Kopell, 1985). The context-updating theory has been one framework of great influence in ERP studies on the P300 (Polish, 2007). According to this theory the P300 is thought be a neural manifestation of the updating of working memory. The initial sensory processing evoke early potentials whereby an attention-driven evaluation of stimulus feature change are followed and either; ”no new stimulus is detected”, which renders only the sensory evoked potentials, or ”a new stimulus is detected”, leading to an updating of stimulus memory representation to produce the P300 (Donchin, 1981). The P3 component is commonly divided into the P3a and P3b components due to their differences in scalp distribution and functional correlates. Careful evaluation of different findings has suggested that the P3a, the novelty component (i.e.

component occurring to perceptually novel distracter stimuli) and the Nogo-P3 most likely are variants of the same ERP (Polich, 2007). The Nogo-P3 is elicited in Nogo trials with a maximum amplitude at Fz and Cz with a latency of 300-500 ms. The P3b (P3 Go) subcomponent of the P300 has a more posterior distribution, with maximum peak at Pz and a somewhat earlier latency (Falkenstein, Hoormann, & Hohnsbein, 1999; Pfefferbaum, Ford, Weller, & Kopell, 1985).

Neural generators of the P300 have been suggested in the anterior cinguli cortex (ACC) and ventromedial frontal cortices (Basinska-Starzycka & Pascual-Marqui, 2002), and inferio-parietal, as well as the parieto-occipital regions (Kiss, Dashieff, & Lordeon, 1989; Smith et al., 1990). When dissociating the P3a and P3b, different cortical sources further separate the components. While generators for the P3a have been targeted to the supra-marginal gyrus, dorsolateral prefrontal cortex (dLPFC), cingulate gyrus and gyrus rectus, generators for the P3b have been found in hippocampus, superior temporal sulcus, posterior parietal lobe, and ventrolateral prefrontal cortex (vLPFC) (Halgren, Marinkovic, & Chauvel, 1998). However, even though an intact P3 is reported to rely on the integrity of these connected brain regions, only lesions in the parieto-temporal junction involve alterations of the P3 component (Duncan et al. 2009).

A robust finding of many ERP studies is a memory load effect on the P3 amplitude, such that an increase of task difficulty is associated with a reduction of amplitude (Gomer, Spicuzza, & O'Donnell, 1976; Kramer, Schneider, Fisk, & Donchin, 1986; Mecklinger, Kramer, & Strayer, 1992; Pelosi, Hayward, & Blumhardt, 1995). Different explanations have been proposed to account for this relationship, including that low memory load produces a greater overlapping of the P3a and P3b component resulting in a larger P3 (Brookhuis et al., 1981; Pelosi et al., 1995), that reduced P3 amplitude index memory loss, which is greater in difficult tasks (Kok, 1986), and due to a trade-off effect of resources in terms of greater

competition between the allocated resources resulting in less recourses dedicated to the target stimuli, and hence a decrease in P3 amplitude (Strayer & Kramer, 1990). However, in his integrative review on the background findings of the P3a and P3b subcomponents, Polich proposes a neural inhibition hypothesis of stimulus processing (Polich, 2007). The hypothesis states that the P300, which comprises of both the P3a and the P3b components, is a signal that reflect rapid neural inhibition of on-going activity to facilitate the transmission of information from attention-related frontal (P3a) to memory-related temporal-parietal (P3b) areas. This minimization of extraneous stimulus processing is needed to enhance focal attention and to efficiently ensure the transference of incoming stimulus information from frontal area working memory to memory operations in temporal-parietal areas. This explanation is consistent with the above mentioned findings in that the more difficult the task, the more limited are the attentional resources to pursue inhibitory control, resulting in a smaller P3 amplitude.

The N2 Nogo component

The Nogo N2 component is a negative deflection that precedes the P3, with a frontal maximum that, similar to the P3, is larger in Nogo compared to Go-trials (Pfefferbaum, Ford, Weller, & Kopell, 1985). This ”Go/ Nogo effect” (Nogo>Go) has consistently been reported in ERP studies in the Go/ Nogo paradigm (eg. Bokura, Yamaguchi, & Kobayashi, 2001; Roche, Garavan, Foxe, & O'Mara, 2005; Thomas, Gonsalvez, & Johnstone, 2009). Two cortical substrates have been suggested, on in the ACC and the other in the dLPFC/ vLPFC (Lavric, Pizzagalli, & Forstmeier, 2004). The N2 component has been showed to be insensitive to task difficulty (Maguire et al., 2009), but to become enhanced when discriminative stimulus features are similar, in the way that a discrimination task between the visual/ auditory letters M and W will yield a stronger N2 Nogo effect for visual stimuli, and

conversely, a visual/ auditory discrimination between the letters F and S will have a larger N2 for auditory stimuli (Smith, Johnstone, & Barry, 2007). In relation to modality, the frontal N2 in visual Go/ Nogo tasks has been shown to display a different topography and to be much larger than the N2 component in auditory Go/ Nogo tasks. Though, N2 in both modalities have been positively correlated to performance, along with earlier latencies for good than poor performers (Falkenstein, Hoormann, & Hohnsbein, 1999). The functional significance of the component has been extensively studied, and evidence has pointed toward an explanation of the component as an index of conflict processes (Bekker, Kenemans, & Verbaten, 2004; Donkers & van Boxtel, 2004; Smith, Smith, Provost, & Heathcote, 2010), inhibitory processes (Falkenstein, Hoormann, & Hohnsbein, 1999; Maguire et al., 2009), neither inhibition nor conflict (Smith et al., 2007), or both (Lavric, Pizzagalli, & Forstmeier, 2004).

The distinction between the Nogo N2 and P3 components and their functional meaning has been a matter of debate. While once regarded to be a single complex (Simson, Vaughan Jr, & Ritter, 1977), the research described above provide strong evidence that support their functional distinction. With the application of independent component analysis (ICA) for ERPs recorded in three different response conditions to manipulate sensory mismatch, action inhibition and conflict monitoring operations in a visual continuous performance task (VCPT), Kropotov and colleagues successfully managed to demonstrate four distinct components that disentangle these inconsistencies (Kropotov, Ponomarev, Hollup, & Mueller, 2011). Two of the ICs were evidently generated in bilateral temporal areas, fluctuated with latencies at P120/ N140, were associated with the visual mismatch operation, and contributed substantially to the anterior N2 wave. The other two Nogo-related ICs were one N240/ P330 coupled with action inhibition that were generated in the supplementary motor cortex, and one N290/ P400 generated in the anterior cingulate cortex and associated with conflict monitoring, that also both substantially contributed to the

conventional Nogo N2 and P3 waves. Their results demonstrate a specific sequence of independent cognitive control operations taking place at different time intervals and in distinct cortical areas.

Early sensory ERP components

In contrast to the abundance of studies and literature on the P300 and N2 components, information about the preceding positivities and negativites, N1, P1 and P2, is more scarce. However, various paradigms investigating effects of selective attention has found evidence that the P1 and N1 reflect different types of modality-specific attentional processing. This is interpreted on the basis of findings that show 1) enhanced component amplitudes to attended stimuli compared to non-attended stimuli, suggesting a sensory gain control (Alain & Woods, 1997; Mangun & Hillyard, 1991), 2) amplitude enhancement, delayed latencies, and shifts in topographic distributions to attended local vs. global stimulus features, suggesting bottom-up vs. top-down early selective attention effects reflected in P1 and N1 dynamics (Han, He, Yund, & Woods, 2001; Wijers, Lange, Mulder, & Mulder, 1997), 3) dissociation of the P1 and N1 components, suggesting that they reflect qualitatively different attentional operations (Luck, Heinze, Mangun, & Hillyard, 1990), and 4) enhanced N1-effect when subjects are required to discriminate between stimuli as opposed to response only, suggesting the N1 component as an index of discrimination processing (Vogel & Luck, 2000). The N1 has also been demonstrated to display a similar ”Go/ Nogo-effect” as the N2 and P3, with enhanced amplitude in Nogo compared to Go conditions, which is compatible with the discrimination proposal, but may also be indicative of early inhibitory processes (Kirmizi-Alsan et al., 2006).

Although findings such as these all point to specific involvement in early attention, the cognitive correlates of the sensory-evoked visual P1 and N1 has been noted to be poorly understood (Vogel & Luck, 2000). In more recent studies, the suppression of a very early

positivity, P50, peaking at about 30-70 ms range generated in fronto-central areas (Weisser et al., 2001) in response to second stimuli (”Go”) relative to first stimui (”probe”), has been linked to efficient sensory gating due to better inhibition control (Liu, Xiao, Shi, & Zhao, 2011). Also, a similar ratio for an N100 component with a latency range of 80-120 ms has been linked to stronger sensory gating due to better stimulus discrimination (Liu et al., 2011; Lijffijt et al., 2009). This early habituation-effect reflected in amplitude reductions to repetitive stimuli, has also been proved to be beneficial to good performance, as Liu and colleagues also found a positive correlation between various performance measures and degree of second stimulus suppression in children.

Interestingly, comparable effects have also been found between the P50 and the somewhat later P200, linking them both to sensory gating with beneficial effects of second stimulus suppression on memory performance (Lijffijt, 2009). Findings such as these have begun to spur ERP research towards the P1-N1-P2 complex, and the proposition that the Go/ Nogo decision occurs already within this early time-window (Filipovic, Jahanshahi, & Rothwell, 2000). One intriguing finding about the P1 amplitude modulation is that both enhancement and suppression of the component has been linked to increased attention. In the first case, a larger P1 to attended as compared to ignored stimuli can also suggest an early inhibition of extraneous information, in line with the ”Nogo P3 effect”-explanation, and has been proposed as a more plausible hypothesis than the ”gating hypothesis” (Klimesch, 2011). However, the same effect can also be accounted for as a suppression of the component to the unattended stimuli, and thus an apparent increase in the attended stimuli component (Hillyard, Vogel, & Luck, 1998).

Independendt component analysis (ICA)

As explained above/ earlier, the ERPs are computed from the summarized and averaged potentials time-locked to certain events, thus reflecting the time-course of sensory evoked changes of electric field potentials. However, since sensory perception and processing occur simultaneously in multiple cortical areas, i.e. parallel processing, the averaged ERPs yield poor information regarding the functionally independent processes that overlap in time and space (Snyder, Abdullaev, Posner, & Raichle, 1995). Independent component analysis (ICA) is a separation technique that decomposes the spatially fixed and temporally independent activations during each response condition, and thus enabling a far better spatial resolution of ERP components. The method is based on assumptions about the linearity of the summarized potentials at the scalp electrodes, and that these components are associated with activities in distinct cortical areas with temporally different and somewhat independent courses of activation (Makeig, Jung, Bell, Ghahremani, & Sejnowski, 1997). Validation studies on of the effectiveness of the ICA method in extracting the specific ERP components have begun to appear. For example, one study evaluated the benefits of ICA in a combined EEG/ fMRI experiment using the Go/ Nogo paradigm, and found superior reliability and validity for ICA compared to conventional ERP analysis in detecting typical experimental-driven ERP modulations (Lavric, Bregadze, & Benattayallah, 2011). In addition, ICA has been reported to provide a natural and powerful measure of the functional connectivity in the brain (Calhoun, Liu, & AdalI, 2009).

Source localization

The EEG method is known for its superior temporal resolution, however, one of its greatest limitations is the poor spatial resolution. The neural signals are subjected to distortions while travelling through brain tissue, blood vessels, brain membranes, skull,

muscles and skin. Averaging, filtering and smoothing techniques are required to yield measurable and readable EEG recordings, but are also causing further distortions (Nunez, 2000). Deriving the location of the cerebral sources from the EEG signal is known as ”the inverse problem”. The problem arises when trying to recover the current sources from the recorded scalp potentials, which mathematically has an infinite number of possible solutions (Ritter & Villringer, 2006). As a consequence of this, there is no direct relationship between the scalp-recorded EEG and the underlying neural generators. However, due to certain electrophysiological and neuroanatomical constraints, an approximate solution to the problem is possible. Various methods have been proposed, often based on equivalent dipole computations (eg. Henderson et al., 1975) and current distributed source models (Hamalainen & Ilmoniemi, 1994). The latter has proven to better deal with expected multiple sources. The low-resolution brain electromagnetic tomography (LORETA) provides a direct 3D solution that has been proved to accurately locate current sources within 1 voxel resolution. The more recent and improved standardized LORETA method (sLORETA) yields even more precise images of standardized current density with allegedly zero location error (Pascual-Marqui, Esslen, Kochi, & Lehmann, 2002; Pascual-Marqui, Michel, & Lehmann, 1994).

Taken together, the sophisticated methods of sLORETA and ICA provide solutions to the spatial limitations facing the EEG. The combination of the two techniques provides information about several independent processes occurring simultaneously at multiple locations, and their neural generators, with high precision.

QEEG IN CLINICAL ASSESSMENT AND THE EVALUATION OF CHILDHOOD PSYCHIATRIC DISORDERS

QEEG in normal development

Evidence from family and twin studies have revealed that EEG parameters have a moderate to high heritability, with estimates for EEG powers in alpha-, beta-, and theta-ranges between 79-89% (Beijsterveldt & Boomsma, 1994). Genetic factors behave in an additive manner to produce EEG variance, such that greater similarity is observed among first-degree relatives (Stassen, Bomben, & Hell, 1998). However, as the brain matures in the course of development through infancy, childhood, adolescence and into adulthood, this is reflected in age-related changes in the EEG.

ERP

A specific developmental trajectory of the Nogo N2 and P3 has been identified in normal children. Young children (6-7 years) display a larger and more fronto-parietal distributed Nogo N2 effect than adults, and a completely absent Nogo P3 effect. The Nogo N2 effect decreases linearly with age, and is comparable to those of adults at about 9 to 10 years of age. From this point in time the Nogo P3 effect starts to develop and reach maturity in young adulthood. Behavioral assessments of attention and inhibition also show that attention processing develops rapidly before age 10 and more gradually from 10 to 13 years, whereas impulsive behavior begins to cease only after about 10 years of age (Jonkman, 2006; Rebok et al., 1997). Considering the role of the Nogo P3 in inhibition and the Nogo N2 in conflict monitoring, this is supported by both developmental behavioral studies that demonstrate that such executive operations undergo a progressive and multistage

development between late childhood and adolescence, and by research in brain development that show simultaneously profound structural development of the frontal cortex (Kanemura, Aihara, Aoki, Araki, & Nakazawa, 2003; Passler, Isaac, & Hynd, 1985). The P2 amplitude on the other hand, increases with age (Johnstone, Barry, & Anderson, 2001). In auditory modality, a reduction in N1, P2, N2 and P3 latencies, as well as N2 and P3 amplitudes, as a function of age and improved task performance have been reported. Additionally, with increasing age a larger parieto-central P3 to Go than Nogo stimuli, with a shift towards a Nogo larger than Go effect (Nogo>Go effect), is observed (Johnstone, Pleffer, Barry, Clarke, & Smith, 2005). However, others have reported an increase in auditory P300 amplitude from early childhood to young adulthood, but reduced visual P300, as well as latency reduction for both modalities (Fuchigami et al., 1995; Katsanis, Iacono, & McGue, 1996).

Spectral EEG

Wide-ranging changes within all frequency-bands and brain areas have been reported in developmental studies. Furthermore, these changes support the notion of growth spurts and plateaus in brain maturing, and coincide with Piagetian developmental stages (Hudspeth & Pribram, 1990). In general, the developmental changes consist of a decrease in lower frequencies and a corresponding increase in higher frequencies. For example, slow alpha decreases from 8 to 10 years of age, while fast alpha increases. Fast alpha activity is at earlier ages more prominent in central than occipital areas, but become increasingly less centralized with advancing age. Also, sex differences in the developmental dynamics of both frequency and distribution over brain regions have been reported. For example, females show a greater age-related decrease in absolute theta power in posterior right hemisphere electrodes compared to males, however, this difference is reduced below significance in relative power (Benninger, Matthis, & Scheffner, 1984; Cragg et al., 2011). Although age-related spectral

changes have been found to coincide with brain maturation, the inter-individual variance has been found to be 2-3 times larger than age-related variance, particularly in the low alpha-band. This suggests that both structural and EEG maturation may occur differently at different ages (Benninger et al., ibid).

EEG sensitivity to cortical dysfunction - the Go/ Nogo paradigm and resting conditions

All the major neurotransmitter systems in the human brain are involved in the generation and modulation of the scalp recorded oscillations, suggesting the potential sensitivity of EEG measures to cortical dysfunction (Steriade et al., 1990). The Go/ Nogo paradigm is ascribed to promise ultimate clinical relevance due to its psychometric properties in assessing specific cognitive control processes (Pfefferbaum, Ford, Weller, & Kopell, 1985). The integrity of the frontal and orbito-frontal areas in particular are crucial to the well functioning of such processes (Stuss & Alexander, 2000). Due to the specificity for Go/ Nogo tests to assess response inhibition, this paradigm is one of choice in studies on neurological conditions involving orbitofrontal cortex and lesions of the frontal and limbic structures (Kirmizi-Alsan et al., 2006). Many of the task instructions involved in the Go/ Nogo task, such as the discrimination of relevant and irrelevant stimuli and the witholding of a response based on this discrimination, as well as fast responding, are known to be impaired in varying degrees in disorders such as ADHD (Pasini, Paloscia, Alessandrelli, Porfirio, & Curatolo, 2007), ASD and AD (Eigsti & Shapiro, 2003), Tourette syndrome (Brand et al., 2002), OCD (Carlsson, 2001; van den Heuvel et al., 2005), and depression (Kaiser et al., 2003).

The eyes closed (EC) condition define a baseline state in the human brain, and have for that reason been termed the ”default mode” of brain states. Even when totally relaxed in the EO condition, our brain is pelted with visual stimuli. In fact, one of the greatest effects on the EEG is the difference between EO and EC resting conditions (Chen, Feng, Zhao, Yin, &

Wang, 2008). As discussed previously, certain resting oscillations reflect trait-like states such as arousal and individual differences in motivation, which have been hypothesized to be involved in the dysfunctional aspects of disorders such as ADHD (Ornitz et al., 1997), anxiety disorders and depression (Clark, Watson, & Mineka, 1994), and autism spectrum disorder (ASD) (Koegel & Mentis, 1985). The resting state EEG is expected to define brain dysfunction during rest and furthermore, to have consequences for sensory, affective and cognitive functioning (Chen et al., 2008).

EEG studies in childhood psychiatric disorders

QEEG research in childhood psychiatric disorders is abundant and has indentified a large number of ERP and spectral correlates ascribed to the etiology, symptoms and behaviors that characterize the different disorders. An exhaustive review of studies and literature in this domain is outside the scope of this thesis, so for the purpose of relevance it should be noted that the following sections represent a highly selective overview of some of the findings and conclusions in the field. In the ERP research field, a main focus of studies conducted in the Go/ Nogo paradigm will be attempted. In the spectral domain the focus is kept in power assessments.

Attention Deficit/ Hyperactivity Disorder (ADHD) and ERP

Attention deficit/ hyperactive disorder (ADHD) is one of the most prevalent childhood disorders, affecting 4% to 7% of children worldwide. The disorder is considered to develop through multiple pathways, with genetic, biologic, environmental and psychosocial risk factors, however, the precise etiology is still unclear (Nigg, 2006; Spencer, Biederman, & Mick, 2007). The disorder is characterized by attentional problems, including inattention and

distractibility and/ or hyperactive and impulsive behavior. Common symptoms include low frustration tolerance, difficulties in sustaining focused attention and frequently shifting between activities, difficulty organizing, and daydreaming (Spencer et al., 2007). It should be noted that while the diagnostic criteria of ADHD is basically similar in the DSM-IV and ICD-10 guidelines, some differences exist. In contrast to the ICD-10, the DSM-IV separates between predominately inattentive and hyperactive/ impulsive types. Also, the ICD-10 guidelines is somewhat stricter than those in DSM-IV (Blikø, 2008).

Behavioral inhibition is proposed to be a core deficit in ADHD, and is linked to impairments in several executive functions often exhibited in the disorder (Barkley, 1997). This makes the Go/ Nogo paradigm particularly suitable in ERP studies of ADHD, with a main focus on inhibitory processes (Barry, Johnstone, & Clarke, 2003). The N2 and P3 Nogo components have been of particular interest in ADHD studies due to their involvement in inhibitory processes. In accordance with this, the N2 amplitude have been reported to be smaller in children with ADHD than controls after both visual and auditory stimuli (Satterfield, Schell, & Nicholas, 1994; Smith et al., 2004; Johnstone et al., 2009). A smaller N2 Nogo effect (Nogo>Go) in ADHD children has been interpreted to reflect stronger inhibitory processing of the prepotent response (Smtih et al., 2004). While a reduced N2 Nogo has been linked to poor inhibition performance (negatively correlated to commission errors) (Falkenstein, Hoormann, & Hohnsbein, 1999; Johnstone et al., 2007), Smith and colleagues interpreted the results as indicating stronger effort to inhibit the response in the clinical group. The Nogo > Go N2 effect in the ADHD group differed also topographically in the Smith study, with larger effect in the left frontal region, or a shift away from right hemisphere processing, which has been reported to be the primary site of inhibition (Casey et al., 1997). They conclude their findings with the proposal that ADHD children have intact prepotent response inhibition, but that in a Go/ Nogo task it needs to be triggered earlier

(reflected in earlier N2 latency) and more strongly (N2 amplitude) to maintain same behavioral performance level as controls.

ADHD children have been shown to display a significant reduction in the parietal P3 component to both Go and Nogo stimuli, with a tendency for an amplitude increase at frontal sites, even with equivalent performance to controls though slower response time (Johnstone, Barry, Markovska, Dimoska, & Clarke, 2009), but also with a concomitant high score of inattention (omission errors) (Overtoom et al., 1998), prolonged P3 latency (Strandburg et al., 1996), as well as a parietal maximum larger for Nogo than Go (Smith, Johnstone, & Barry, 2004). The reduction of the P3 amplitude (parietal) together with a tendency for an anterior shift of the P3 peak has been suggested to reflect different neural generators of this component in children with ADHD related to deficiencies in inhibitory processes (Johnstone et al., ibid).

While some have reported early components in children with ADHD comparable to those of controls, suggesting no differences in preparedness in ADHD (Strandburg et al., 1996), others have reported delays in both P100 and N200 latencies in Nogo compared to Go, and reduced P100 Nogo amplitude source localized in occipital areas in children with ADHD (Nazari et al., 2010). These results suggest an early deficit in visual sensory integration within the occipital cortex in children with ADHD. However, ADHD children aged 10-12 have been shown to display larger P1 and reduced N1 amplitudes at frontal and central sites to warning stimuli (Smith et al., 2004), whereas attenuated P1 amplitude have been reported in 6-7 years old children with ADHD compared to controls (Kemner et al., 1996). Also in the latter study, task performance for children with ADHD were comparable to those of controls. Furthermore, the P2 component amplitude have been reportedly enlarged for warning stimuli, and reduced with earlier latency to Go/ Nogo stimuli in ADHD children compared to controls (Smith et al., 2004), as well as increased with no latency differences regardless of stimulus

type (DeFrance, Smith, Schweitzer, Ginsberg, & Sands, 1996). The P2 warning stimuli >Go stimuli together with the larger P1 and reduced N1 to warning stimuli were proposed to indicate problems with sensory registration and identification of stimuli in children with ADHD. A larger P2 peak in auditory modality has also been associated with hyperactivity and impulsivity in children with ADHD (Oades, 1998). In contrast to this, Johnstone and colleagues reported a reduced P2 amplitude with a parietal central distribution in children with ADHD compared to controls in a visual Go/ Nogo task. Also, the children with ADHD traded off speed for accuracy (longer RT to Go stimuli) which resulted in similar levels of response inhibition performance as controls. While interpreting an increase in P2 amplitude as reflecting better inhibition of irrelevant stimuli from further processing, they propose an underactivation in these processes in the children with ADHD (Johnstone, Barry, Markovska, Dimoska, & Clarke, 2009).

Specific evidence for a deficit in response inhibition in children with ADHD is supported by ERP studies on the effect of methylphenidate (MPH) medication on ERP components. In a cued Go/ Nogo task comparing children with ADHD and controls, the ADHD group made more errors (omission and commission) pre-medication, and continued to make more omission errors than controls post-medication, however, commission errors became ”normalized” post-medication. This suggests that MPH specifically ameliorate deficits in the response inhibition. Furthermore, while children with ADHD displayed enhanced N1 and P2 amplitudes and reduced N2 amplitude relative to controls pre-medication, these differences were not significant post-medication (Broyd et al., 2005). Another placebo-controlled study tested children with ADHD off MPH medication (baseline), at different dose-levels and placebo, and controls in a continuous performance task (CPT). At baseline, the ADHD group was more impulsive and inattentive, displayed shorter P2 and N2 latencies and prolonged P3 latencies. These measures approached that of controls on low

dose-levels, and normalized on higher dose-levels. However, amplitudes remained unaffected (Sunohara et al., 1999).

High variability in response latencies is a typical finding for children with ADHD (eg. Kalff et al., 2005). The proportion of abnormally slow responses, mixed with fast responses at some trials, has been suggested to reflect a state regulation problem (or non-optimal arousal) in children with ADHD, rather than a specific cognitive deficit (McLoughlin et al., 2005). The brain activity underlying arousal and effort, that ultimately affect performance variability, can better be obtained from frequency analysis of the background EEG (tonic EEG).

ADHD and spectral analysis

The majority of spectral studies on childhood disorders available involve those with attention deficit and/ or hyperactivity (Cantor & Chabot, 2009). A variety of frequency abnormalities have been reported in children and adolescents with ADHD, but the most frequently reported include excess of theta, in particular relative theta power. Both reduced and elevated levels of alpha and beta have been reported, as well as increased theta relative to beta (Barry, Clarke, & Johnstone, 2003; Clarke, Barry, Irving, McCarthy, & Selikowitz, 2011; Mucci, Volpe, Merlotti, Bucci, & Galderisi, 2006). Although different spectral measures have been analyzed in ADHD studies, such as frequency coherence, ratios, absolute and relative power, relative power estimates are the most commonly used, and have been shown to yield good test-retest reliability (John et al., 1980). Excess of relative theta power has been associated with processing deficit in ADHD (Clarke et al., 2008). For instance, enhanced frontal resting theta levels (primarily left) along with significantly delayed reaction times and more overall errors in CPT have been demonstrated in children with ADHD compared to controls. Moreover, theta levels was shown to correlate positively with errors in an oddball

task, as well as with false negatives (commission errors) in CPT, but with no relationship with omission errors (Hermens et al., 2004). This may suggest some relevance of theta in response inhibition, and were also suggested to reflect a trait-like biological deficit in ADHD that predict performance in information processing. Note that theta activity specifically has been linked to arousal and motivational states, as described in previous sections. Early work on the synthesis of neuropsychological and psychophysiological data on attention suggests three different ways in which default states may influence performance; 1) arousal affect the individual's physiological response to input, 2) activation influence the physiological readiness to respond, and 3) effort determines how arousal and activation are coordinated to yield efficient task performance (Pribram & McGuinness, 1975). Also elevated theta along with alpha excess (Cantor & Chabot, 2009; Chabot & Serfontein, 1996) or alpha deficiency (Clarke, Barry, McCarthy, Selikowitz, & Brown, 2002) in frontal and central regions have been reported QEEG abnormalities in children with ADHD or ADD. An explanation for the opposite findings of alpha levels in ADHD seems to be unresolved. One study on QEEG correlates of MPH response in children with ADHD showed that the administration of MPH resulted in increased alpha activity in central and parietal regions, both during resting and task conditions (Loo, Hopfer, Teale, & Reite, 2004). Moreover, beta power levels predicted medication responders, such that responders exhibited increased frontal beta activity, whereas nonresponders showed a decrease in frontal beta. Furthermore, increased frontal beta activity was also significantly correlated with medication-related improvements in CPT-performance as well as parent-rated measures of attention and hyperactivity, whereas decreases in right frontal theta activity correlated with parent-rated measures of attention only. Indications also exist that increased theta activity reflects the impulsivity component in ADHD, while decreased beta activity reflect hyperactivity (Bresnahan, Anderson, & Barry, 1999). In line with Loo et al. (2004), increased beta power with stimulant administration has also been

reported by others (eg. Clarke, Barry, Bond, McCarthy, & Selikowitz, 2002; Clarke et al., 2003). The increase in alpha activity with stimulant medication is in some sense a paradoxical effect, since alpha levels have been reported to be suppressed with certain cortical functions (eg. Marrufo et al., 2001; Fernandez et al., 1995), and is considered an ”idling” rhythm brain state. Although reports on improvement of both EEG and behavior after MPH medication are convincing, the relationship is not necessarily straightforward. For instance, in a study evaluating the effect of MPH by measuring computed tomography (regional cerebral blood flow, rCBF), QEEG, neuropsychological tests, and clinical symptoms in children with ADHD, they found that the majority (57%) of the children had no changes in EEG activity after treatment, about 24% had improvements, and 19% displayed a worsening of activity. Although there was an association between test performance and clinical improvement for those patients who had improved or no difference in EEG after MPH treatment, they found no significant spectral differences after treatment, however rCBF normalized in those children with low pre-treatment rCBF (Yildiz Oc et al., 2007).

Different QEEG subtypes have been differentiated on the basis of cluster findings involving combinations of theta-, alpha-, and beta-power levels. In particular, children with predominantly inattentive ADHD (or ADD) have shown increased theta activity and deficiencies in alpha and beta power. However, a small subset of children with ADHD show excess beta in their spectrogram which has been linked to the ADHD combined type (i.e. both inattentive and impulsive). Although allegedly similar in their behavior, the excess beta sub-group tended to be more prone to temper tantrums and to be emotionally labile. Despite these corresponding traits, the two subtypes were independent of current diagnostic categories (Clarke, Barry, McCarthy, & Selikowitz, 2001; Clarke, Barry, McCarthy, Selikowitz, & Brown, 2002). Others have yet failed to demonstrate such differences within ADHD groups (Hermens et al., 2004).

To clarify on the findings of excess theta centrally in ADHD, Niedermeyer and Naidu have compared EEG findings in Rett syndrome (RS) with those found in ADHD (Niedermeyer & Naidu, 1998). Electrophysiological findings in patients with RS resemble in some respects those found in ADHD patients, with a prominent central theta activity. These EEG findings together with the clinical phenomenology in RS (eg. stereotypic hand-movements) have led to an assumption of a hyper-excitability of the motor-cortex, or motor cortex dyscontrol caused by disturbed prefrontal or premotor function. Niedermeyer and Naidu theorize that such motor dyscontrol may also exist in ADHD, resulting in a ”lazy frontal lobe” that is reflected in excess theta activity in these brain regions.

Autism Spectrum Disorder (ASD) and Asperger Syndrome (AS) – spectral analysis

Similar to those with ADHD, children with autism spectrum disorder (ASD) and Asperger syndrome (AS) are a highly diverse and heterogeneous group with multiple possible etiologies (Folstein & Rosen-Scheidley, 2001). While viewed as a set of disorders involving a wide spectrum of functioning, ASD and AS are included in the definition of pervasive developmental disorders (PDD) along with Rett syndrome (RS), childhood disintegrative disorder, and pervasive developmental disorder not otherwise specified (PDD/ NOS). Core characteristics of them all are early onset of social and communicational deficits. However, for ASD, problems regarding social reciprocity, inadequate language and communication skills, stereotyped behaviors, and a strikingly ”jagged” profile across subscales of mental abilities (eg. Wechsler Scales), with typical strengths in visuospatial and perceptual organization tasks, are also typical (Eigsti & Shapiro, 2003). AS share several of the impairments that characterizes ASD, though often in a milder form and with the absence of mental retardation and language delay (WHO, 1992). Also noted is the poor emotional regulation often displayed in children and youngsters with ASD and AS, with sudden

outbursts and sometimes extreme anger over what others would describe as trivialities (Thompson & Thompson, 2010). There is an ongoing debate whether ASD and AS represent two qualitatively different syndrome entities, or quantitative differences on the same continuum, though evidence do exist that support the latter notion (Kamp-Becker et al., 2010).

EEG studies of ASD have generally been troubled by issues of defining ASD and certain technological differences across studies, making conclusions difficult. For instance, low functioning autistic individuals have difficulties with being cooperative in testing conditions and many are simply unable to give informed consents. As a consequence of this, studies have mostly been limited to include higher functioning autistic individuals (Cantor & Chabot, 2009). A somewhat common spectral finding in ASD seems to be the suppression of alpha activity and increased slow wave activity in delta and/ or theta-bands. For instance, one study comparing children with ASD and controls, found significantly less relative alpha and more relative delta in the ASD group, with a 91% sensitivity and 73% specificity for the relative alpha (Chan, Sze, & Cheung, 2007). Another study examined EEG activity across several groups of children with different disorders (children with Rett's syndrome, autism, fragile X-syndrome, and also elderly with Alzheimer-type dementia), and found suppressed alpha activity and enhanced theta activity. The elevated theta activity was specific to parietal regions and was suppressed during visual stimulation and motor tests. The authors maintain that the theta activity appeared in the visuomanual coordination system which is a physiological correlate of decreased functional status of the frontal lobes, thus indicating frontal lobe dysfunction (Iznak et al., 2001). In an earlier study spectral differences between autistic children aged 5 to 18 and age-matched controls were measured, and revealed that the autistic group displayed reduced alpha power in frontal and temporal regions, but not parietal areas. However, in this study, also a reduced slow wave power in both delta (frontal and

temporal) and theta-band (frontal, temporal and parietal) were found. Furthermore, the spectral differences were more robust for the left hemisphere. Due to the regional findings and to the lack of fast-wave differences, the authors cast doubt to the notion of a selective impairment in frontal lobe functioning in ASD, and propose that autistic children are likely to have abnormal limbic lobe functioning and reduced left hemisphere activity in particular (Dawson, Klinger, Panagiotides, Lewy, & Castelloe, 1995). Yet another study compared EEG in low functioning autistic children with age-matched controls, age-matched mentally handicapped children, and mentally age-matched normal toddlers, and found reduced alpha activity and increased slow wave (delta) activity in the autistic and toddler groups compared to controls. In contrast to the Dawson study, autists and toddlers also showed greater hemispheric coherence (i.e. less amplitude asymmetry) than the control groups. The similarity between the autistic children and toddlers suggest severe developmental delay as a component of autism (Cantor, Thatcher, Hrybyk, & Kaye, 1986). The difficulties with social interaction and imitation often seen in subjects with ASD and AS have been linked to the dysfunction of cortical mirror neurons (MN), particularly to the imitation-related cortical activation sequences in the frontal and parietofrontal circuitries (Nishitani, Avikainen, & Hari, 2004). MNs are activated both during observation of conspecific others', and during execution of one's own motor actions. Interestingly, the suppression of mu rhythm (8-13 Hz) has been demonstrated in adults and children in response to the performance and observation of human actions, suggesting a possible electrophysiological correlate between mu rhythm and MN activation (Lepage & Theoret, 2006; Pineda, 2005). Furthermore, mu rhythm deficiencies have also been observed in individuals with ASD. While control subjects show mu rhythm suppression both during action observation and execution, autistic subjects display suppression only during self-performed actions and not to observed actions (Oberman et al., 2005).

ERP in ASD and AS

ERP studies in ASD and AS have predominantly been conducted in the auditory modality, and in a large variety of paradigms and task protocols, such as oddball, language tasks, and missing stimulus paradigm. Although a few studies have focused on the visual modality as well, these have generally been conducted using oddball paradigms (see Jeste & Nelson III, 2009, for a review). Children with autism have been found to show greater autonomic responsitivity to all environmental stimulation, which make them vulnerable to hyper arousal (Hirstein, Iversen, & Ramachandran, 2001). This can be linked to their impaired capacity to modulate sensory input effectively, and explain why they sometimes can be unusually reactive to visual and auditory stimulation (Kootz, Marinelli, & Cohen, 1982). One ERP study investigating this in children with autism, receptive developmental language disorder (RDLD) and controls on the clinical influence of N1 and P2 auditory ERP components, found that children with autism and RDLD failed to display an N1 amplitude increase to increases in stimulus intensity. The auditory N1 is normally sensitive to stimulus intensity, thus, their findings provide support to the notion that these clinical groups exhibit ineffective sensory input regulation. No differences were found between the groups for the P2 component (Lincoln & Courchesne, 1995). One study of relevance investigating executive functions, although with high functioning *adults* in a visual CPT, found that the N1 and P3 components were enhanced in the autism group compared to controls, despite no differences in performance measures. The results were suggested to indicate more effortful processing required for the autism group to sustain performance (Strandburg et al., 1993). However, reduced auditory P3a amplitude in children with AS compared to controls have also been reported, interpreted as diminished involuntary orienting to changes (Lepistö et al., 2006).

EEG studies in anxiety and affective disorders

Anxiety disorders include a broad class of specific anxieties, like specific phobias, panic disorders, obsessive compulsive disorder (OCD), post-traumatic stress disorders (PTSD), separation anxiety, and generalized anxiety disorder (GAD), according to the DSM-IV and ICD-10 diagnostic classification manuals. Most common in children are specific phobias, OCD, and separation anxiety in young children and social phobias with a later onset in adolescence (Cartwright-Hatton, McNicol, & Doubleday, 2006). Common to all anxiety disorders are the main feature of anxiety, although the anxiety-provoking conditions and their phenomenology vary to a great extent (WHO, 1992).

OCD is characterized by recurrent obsessions manifested through intrusive thoughts accompanied with or without compulsive ritualized behavior or avoidance. The disorder causes significant stress and impairment for those affected, estimated to be around 2 to 4% of the population (Merlo, Storch, Murphy, Goodman, & Geffken, 2005). Though onset of the disorder typically occur during childhood and adolescence (WHO, 1992), most EEG studies available have been conducted with adults due to the chronicity and prevalence into adulthood. QEEG studies in OCD patients have reported a wide variety of spectral findings, including decreased delta and beta power in frontal and right hemisphere regions (Kuskowski et al., 1993), excess delta in frontal and parietal regions along with decreased alpha power at parietal sites during rest (suggested to reflect greater right-sided inhibition due to elevated low frequency) (McCarthy, Ray, & Foa, 1995), increased global theta and beta power, as well as increased delta power in right temporal and frontal regions (alterations reduced with serotonergic treatment) (Molina et al., 1995), relative delta and theta power, with female patients showing decreased alpha- and beta activity as well as increased theta activity in left frontal regions (Tot, Özge, Cömelekoglu, Yazici, & Bal, 2002), elevated levels of delta and reduced high alpha power (10-12 Hz) in temporal regions (temporal recordings only)

(Locatelli, Bellodi, Grassi, & Scarone, 1996), and elevated beta activity source localized in the middle cingulate gyrus by means of LORETA (Sherlin & Congedo, 2005). These findings pretty much involve all spectral deviations possible, except maybe for the reduced alpha activity. However, interesting correlations between spectral measures and OCD symptoms and symptom severity have been documented, suggesting some applicability in this heterogeneous disorder. For instance, while increased delta- and decreased alpha- and beta-powers were shown to discriminate OCD patients from controls in one study, these power measures correlated positively with sub-scores of obsession (i.e. Yale-Brown obsessive-compulsive scale, Y-BOCS) and negatively with scores of compulsive behavior (Pogarell et al., 2006). Another study found that increased theta- and decreased beta power in fronto-temporal regions significantly separated OCD patients from controls. Furthermore, OCD patients were classified into ”doubters” and ”checkers”, and while the ”doubters” showed decreased alpha and increased delta- and theta-power in fronto-temporal regions, the ”checkers” displayed decreased alpha- and beta-power and increased theta power in the same brain areas. The severity of OCD symptoms were associated with similar EEG patterns as the ”doubters”, with decreased alpha and increased delta-power in fronto-temporal areas (Karadag et al., 2003). Also, spectral differences have been found between medication responders and non-responders suggesting that OCD includes pathophysiological subgroups sharing a common clinical expression. One of the studies found that increased left frontal delta activity was associated with moderately decreased beta activity in the right parietal region in treatment responders (Tot et al., 2002). Another study found that treatment responders (clomipramine or fluoxetine) displayed excess relative alpha power, while non-responders showed excess theta power, both groups in frontal and temporal regions (Prichep et al., 1993). Taken together, spectral deviances in OCD pertain predominantly reduced alpha

power and increased slow wave activity in theta and/ or delta band-ranges in fronto-temporal regions, which generally suggests fronto-temporal dysfunction in OCD.

ERP studies in the Go/ Nogo paradigm can be of particular interest in patients with OCD due to the assumption that intrusive thoughts and compulsive behaviors may result from a failure to inhibit prepotent motor responses, but have only recently started to gain interest (Myung-Sun, Young Youn, So Young, & Jun Soo, 2007). However, the results have been inconsistent. One study found enhanced N1 and P3 amplitude for targets (Go) in frontal sites in OCD patients, and no differences in the Nogo components (Di Russo, Zaccara, Ragazzoni, & Pallanti, 2000), while others found less pronounced anteriorization of the Nogo P3 for the OCD group compared to controls, and no other significant differences (Herrmann, Jacob, Unterecker, & Fallgatter, 2003). Using a balanced Go/ Nogo task (50/50 ratio of Go and Nogo stimuli), Myung-Sun and colleagues found significantly smaller Nogo N2 amplitudes in the OCD group, and furthermore, that obsession scores (Y-BOCS) were negatively correlated with amplitude and positively correlated with latency. This was suggested to indicate inferior prefrontal cortex dysfunction in patients with OCD, including orbitofrontal and cingulate cortices (Myung-Sun et al., ibid). Despite some inconsistencies in regard to Go/ Nogo component differences displayed in the OCD groups, they suggest impairment in the frontal inhibitory system in OCD. Differences in the P3, and specifically the P3b (P3 Go) component, between patients with OCD and controls have been reported in other auditory ERP paradigms however (eg. Gohle et al., 2008; Mavrogiorgou et al., 2002).

In contrast to the more abundant EEG studies in OCD, studies in GAD and other anxiety disorders (maybe except for post traumatic stress disorder) are generally non-existing (Clark et al., 2009). However, one ERP study investigating the N1/P2 auditory component found indications of an altered auditory processing in the disorder (Senkowski, Linden, Zubrägel, Bär, & Gallinat, 2003). In social phobia, a general spectral finding have been a

marked increase in right-sided activation in temporal prefrontal regions when patients are facing an anxiety-provoking social situation (eg. Davidson, Marshall, Tomarken, & Henriques, 2000). A study of children with at least one parent diagnosed with social phobia showed that these children had a higher frontal resting activity and greater relative activity in right frontal areas compared to children with healthy parents (Campbell et al., 2007). Activations in the left frontal hemisphere is associated with approach-related and positive emotional experiences, while the right frontal hemisphere is associated with avoidance behavior and negative emotions (Davidson, 1994). It is important to note, however, that greater right-sided activation is operationalized as decreased alpha power in that area. However, for posterior regions, decreased right-sided activity is associated with low levels of emotional arousal, and a reduced capacity to accurately evaluate the affective significance of stimuli, which has been associated with depression (Bruder et al., 2008). Accordingly, similar EEG asymmetry has also been reported in adults with depression (Funk & George, 2008), and to predict future development of anxiety symptoms (Blackhart, Minnix, & Kline, 2006). In a recent meta- analytic review this particular EEG-asymmetry pattern was concluded to be common in both anxiety and depression (Thibodeau, Jorgensen, & Kim, 2006). Although the majority of studies have been conducted with adult subjects, one early study with computerized tomography showed CNS dysfunction, particularly right-sided, in adolescents with OCD similar to those found in patients with frontal lobe lesions, thus suggesting fronto-temporal dysfunction in line with many of the findings in anxiety and mood disorders (Behar et al., 1984). Also, alpha asymmetry has been found in young children (5-6 years) with low scores of positive emotions, although only in posterior regions (decreased right-sided activation = higher alpha power) (Shankman et al., 2005). This finding is not surprising, however, considering the later structural and functional development of frontal brain areas.

EEG studies in other specific phobias are also scarce (Clark et al., 2009), and are limited to examining differences in EEG in phobic situations, like the findings of EEG dynamics in patients with social phobia. Generally, faster response-time and increased ERP component amplitudes have been reported, interpreted as evidence for a general behavioral hypervigilance in specific phobias (Kolassa, Musial, Kolassa, & Miltner, 2006; Miltner et al., 2005; Straube, Kolassa, Glauer, Mentzel, & Miltner, 2004).

EEG studies in Tourette Syndrome

Tourette Syndrome (TS) is a disorder of childhood onset categorized under Tic disorders (Tic) (F95) according to the ICD-10 (WHO, 1992). The syndrome is characterized by a combination of simple and/ or complex vocal and motor tics, defined as involuntary repetitive, stereotyped movements or vocalizations (Singer & Walkup, 1991). The diagnose occurs in about 1 in 1500 children, and is three times more common in males than females (Sheppard, Bradshaw, & Pantelis, 1999). Although the cause of TS is unknown, it is generally accepted to have a complex genetic basis with a pathophysiology involving the basal ganglia (BG) and frontocortical circuits. The BG is involved in the focal selection and inhibition of competing motor pattern programs. Overactivity in discrete sets of striatale neurons of the BG is thought to be the cause of the multiple tics characterizing the disorder (Mink, 2001). Additional problems are also common in TS, like anger management problems, sleep disturbances and self-harming behavior, particularly in those with other co-existing disorders (Freeman et al., 2000).

Despite high rates of co-existence between TS and other common disorders, like OCD (eg. Termine et al., 2006) and ADHD (eg. Banaschewski, Neale, Rothenberger, & Roessner, 2007), few EEG studies have addressed TS either in combination with other disorders or in isolation. In fact, apart from a few spectral studies, these are generally non-

existing in TS. In one such study, elevated alpha coherence between sensorimotor areas and the prefrontal and mesial frontal cortices during the acute voluntary suppression of tics was found in TS subjects. Also, the same frontomesial network was shown to be overactive during the voluntary withholding of responses in a Go/ Nogo task compared to controls, though behavioral performance was equal, suggesting an adaptive inhibitory enhancement of the same neural networks during both voluntary movements and the voluntary suppression of tics (Serrien, Orth, Evans, Lees, & Brown, 2005). A more early study of resting EEG in TS patients, reported that nearly half (47%) showed abnormalities in their EEG, most commonly sharp waves and EEG slowing. Subjects with an earlier onset of the disorder were also more likely to display these abnormalities (Volkmar et al., 1984).

Inhibitory processes have been of interest in TS using ERP method, despite the general dearth of such studies. One line of research conducted by Johannes and collegues have investigated ERPs in patients with TS in various task paradigms in both visual and auditory modality, however, all tasks involved instructions to respond to a target (Go) and to withold response to non-targets (Nogo). In one of their studies, subjects with TS showed increased visual N2 amplitudes to targets, and increased P3b latencies in some of the tasks, although reaction times (RT) were similar to controls, suggesting a stronger attentional effort in the TS subjects to obtain similar behavioral performances (Johannes et al., 1997). In another visual oddball task they found no difference in P3b components between TS and controls, but higher amplitude for an event-related negativity component (ERN), a negative component peaking between 0-100 ms post stimulus which is known to serve as indicator of action monitoring. This was suggested to reflect an abnormal action monitoring system in TS due to a hyperactive frontal-striatal-thalamic-frontal circuit (Johannes et al., 2002). In a third study be the same researchers, task difficulty in a combined visual/ auditory stimulus detection task was manipulated. This resulted in a suppressed P3b amplitude in both controls

and TS subjects when opposite modality difficulty was high (visual target P3b decreased when auditory stimuli competed and vica versa). Yet again, despite equal performance, this suppression-effect was more pronounced in the TS group, suggesting an altered attentional resource allocation processing that was speculated to be related to deficient inhibitory functions in TS (due to the competing stimulus requiring stronger inhibition to maintain task-performance) (Johannes, Wieringa, Nager et al., 2001). It has also been suggested that whereas stimulus evaluation occurs later in TS subjects, the overlapping pre-motor response selection processes is faster, as demonstrated in faster RT, delayed P300 component latency to Go, and a more pronounced anteriorization of the P3 Nogo component in subjects with TS compared to controls (Thibault, O'Connor, Stip, & Lavoie, 2009).

EEG studies in developmental learning disorders

Learning disorders are categorized as specific developmental disorders (F81) and are characterized by a disability to acquire certain academic skills, such as reading (dyslexia) and/ or calculation (dyscalculia), a mix of specific learning disabilities or unspecified (WHO, 1992).

A variety of EEG abnormalities has been demonstrated also in different learning disorders, though the majority of QEEG studies have been conducted with children with reading disorders (Chabot, Michele, Prichep, & John, 2001). Compared to controls, children with learning disabilities have been shown to display excessive absolute delta-, theta-, as well as relative theta-power, and reduced alpha power in resting conditions compared to controls (Byring, Salmi, Sainio, & Örn, 1991; Fonseca, Tedrus, Chiodi, Cerqueira, & Tonelotto, 2006). Moreover, verbal performance and total IQ values in children with learning disabilities have been shown to be positively correlated with relative high alpha power (Fonseca et al., ibid). The most replicated findings in children with developmental learning disabilities have

been reported to include excessive theta and alpha deficiency, which has been interpreted to reflect a maturational lag underlying the disorder. However, the clinical utility of these findings has been questioned due to the lack of specificity (Chabot et al., ibid).

ERP components in visual CPT have been shown to yield a significantly reduced P3 amplitude and prolonged latency for adolescents with developmental dyslexia compared to controls (Taroyan, Nicolson, & Fawcett, 2007). This study also reported that while the component was lateralized in the control group, the dyslexic group showed a symmetrical component. Although this component has not been reported to be lateralized in normal controls elsewhere, the finding support those from earlier research on evoked potential differences in learning disabled children and controls in passive tasks (for example simple visual or auditory stimulation). This has been initerpreted as reflecting a lesser degree of interhemispheric specialization in children with learning disorders (see Dool, Stelmack, & Rourke, 1993, for a review). Children with reading disabilities have been reported to show the same pattern of late component differences from controls also in linguistic tasks, with smaller P3 amplitude and longer latency. Furthermore, a fronto-central negative wave (N450) has been shown to successfully distinguish between learning disorder subtypes in several paradigms from healthy controls (Stelmack, Rourke, & van der Vlugt, 1995). Although Stelmack and colleagues reported that children with developmental dyslexia display ”normal” early sensory-related components, a longitudinal auditory ERP study (oddball and block) found a slower fronto-central P1 response in the dyslexic group compared to controls. Additionally, the dyslexic group showed different amplitude modulations to different tone-conditions (i.e. rise-time and intensity), with smaller amplitude to higher tone intensity than controls, as well as differences in amplitude modulations for an N1 component (decrease to slower tone rise-time) for the dyslexic group. This was suggested to reflect that neuronal

responses underlying some aspects of auditory sensory processing may be impaired in dyslexia (Stefanics et al., 2011).

Co-existing childhood psychiatric disorders

Comorbidity is stated to be one fundamental issue in ADHD, which is one of the most prevalent childhood disorders. With reports of comorbidity as high as 80%, this has increasingly been acknowledged to be one of the most important aspects of the disorder. As a consequence of this, so-called ”pure” cases of ADHD are rather the exception than the rule in clinical practice (Pliszka, Swanson and Carlson, 1999). The same is true for many of the associated disorders, like ASD, anxiety disorders, affective disorders, and disruptive disorders, (oppositional defiant disorder, ODD, and conduct disorder, CD), learning disorders (Kaland, 2009; Ollendick, Jarrett, Grills-Taquechel, Hovey, & Wolff, 2008), and TS (Sheppard, Bradshaw, & Pantelis, 1999). The term ”comorbidity” is controversial, however, with some arguing that the term refer to common underlying etiologies that can lead to two or more different disorders, while others use the term when describing two etiologically separate disorders occurring together (Caron & Rutter, 1991). Also, ”comorbidity” implicates the existence of disease conditions, whereas the behaviors and problems listed in childhood disorders primarily represent clusters of symptoms and functional impairments whereby the underlying etiologies are not very well understood. Therefore, in line with these arguments, the term ”co-existing disorders” will preferably be used in this thesis (Gillberg et al., 2004). Some of the most common co-existing childhood disorders include ADHD, disruptive-, and learning disorders, anxiety, depression, autism spectrum disorders (ASD) and Asperberger syndrome (AS), Tourette syndrome (TS), obsessive compulsive disorder (OCD), and more (eg. Pliszka et al., 1999; Gillberg et al., 2004; Simonoff et al., 2008). The high rates of co-existing childhood disorders make differential diagnostics a complicated matter.

While heritability in many of the disorders have been found to be somewhat high, which has motivated the search for specific endophenotypes underlying the different disorders, they are all characterized by a high degree of heterogeneity and broad constellations of more or less overlapping symptoms, as well as several neurobiological candidates proposed to underly the disorders (eg. Banschewski, Neale, Rothenberger, & Roessner, 2007; Brieber et al., 2007; Carlsson, 2001; Castellanos, Giedd, Hamburger, Marsh, & Rapoport, 1996; Eigsti & Shapiro, 2003; Sheppard et al., 1999; Hattori et al., 2006; Jarrett & Ollendick, 2008; Kamp-Becker et al., 2010; Neilson, Piek, & Hay, 2006; Nigg, 2005; Simonoff et al., 2008; Singer, 1997). Symptom-overlap may be ”arteficial”, or a consequence of diagnostic criteria overlap (Pliszka et al., 1999). However, some findings exclude such an explanation (Milberger, Biederman, Faraone, Murphy, & Tsuang, 1995), supporting a view that overlap in symptoms rather may result from both shared, and the presence of two or more distinct etiologies, as would be the case in ”true” comorbid conditions, with likely candidates being common impairments especially in frontal and subcortical circuits. For instance, a review on the wealth of neuroimaging, lesion, and neurochemical literature in TS, OCD and ADHD conclude that the three disorders overlap considerably also at a neuropathological and neurochemical level, particularly involving the basal-ganglia thalamocortical (BGTC) pathways and irregularities in the catecholaminergic system, in slightly different ways. Furthermore, evidence point toward the TS gene(s) as being responsible for the higher degree of comorbidity of OCD and ADHD in TS patients, which explain why TS patients are much more predisposed to develop OCD and ADHD, although not the other way aorund (Sheppard et al., 1999). Also, dimensional perspectives, opposing a categorical one, have been proposed, suggesting quantitative differences rather than qualitative distinctions accounting for the heterogeneity in some childhood disorders, such as OCD (Ivarsson, Melin, & Wallin, 2008), ASD and AS (Kamp-Becker et al., 2010), and ADHD (Pliszka et al., 1999). On the other

hand, one approach does not necessarily rule out the other one, as a categorical or a dimensional approach can be a matter of choice depending on the nature of a disorder and the use of diagnoses. For example, describing the duration and severity of a disorder along a continuum (axis V), and categorize diagnoses based on cut-points along the dimensional phenomena (axis I or II) (Kraemer, Shrout, & Rubio-Stipec, 2007). Arguably, this may also be the case in co-existing conditions, such that different ”forms” of comorbidity may exist. Nonetheless, the co-existence of two disorders have been associated with heavier comorbidity, i.e. the co-existence of even more disorders, and greater psychosocial impairment, and to cause a great deal of stress to the child and its environment (Masi et al., 2006).

EEG studies in co-existing childhood disorders

The high degree of co-existence among the childhood disorders is one of the main arguments for more objective aids in differential diagnostics in the assesment of childhood psychiatric disorders (Quintana, Snyder, Purnell, Aponte, & Sita, 2007). QEEG methods can potentially provide such a tool, and EEG studies, at least in ADHD, have reported promising diagnostic classification accuracy above 90 % correct classification of normals and of children with ADHD (see eg. Barry, Clarke, & Johnstone, 2003; Barry, Johnstone, & Clarke, 2003, and also; Cantor & Chabot, 2009, for reviews; Chabot & Serfontein, 1996; Monastra, Linden, & Lubar, 2001). Others have reported somewhat lower and different precision regarding to age, with a 73% accuracy for younger children aged 8-12, and a 59% accuracy for adolescents aged 13-18 years (Smith, Johnstone, & Barry, 2003). However, studies adressing classification accuracy have predominately assessed highly selected, or ”pure” ADHD samples and normal age- and gender-matched controls, thus less is known about the effect of comorbidity or co-existing disorders in modulating EEG parameters (Barry et al.,

2003). A few studies have adressed this issue, particularly in ADHD with or without a secondary disorder. Due to the general lack of such studies, no selection based on visual Go/ Nogo paradigm is possible, and basically, presented are any studies available. One such study compared auditory ERPs (P1, N1, P2, N2 and P3) in children with ADHD with/ without Tourette and tic symptoms (TS) and healthy controls. The major effects reported were 1) shorter latencies as early as 100 ms in ADHD, 2) larger P2 in both ADHD and TS groups, and 3) topographical differences in late components with right hemisphere topography in ADHD and more posterior in TS. The findings were interpreted as an unusually marked early inhibitory processing in both ADHD and TS, and a frontal impairment in TS and right hemisphere impairment in ADHD in later stimulus processing (Oades, Dittmann-Balcar, Schepker, Eggers, & Zerbin, 1996). Another ERP study assessed the effect of four different groups (males), one group with dyslexia, one with ADHD, a combined ADHD + dylexia-group and control-group, in a so-called valid, invalid and no-cue condition-task. The results revealed that both the dyslexic and the combined group displayed a smaller cue-related N2 and larger target-related N2 in the valid condition. The smaller N2 cue-related component was localized to the superior parietal lobe and precuneus by LORETA, and was related to spatial cue processing and attention shifting problems in dyslexia, since there were no target N2 amplitude differences evident in the ADHD only group. Also, the dyslexic-groups showed a right-sided suppression of the P3 component across conditions. A longer latency to target N2 and a prominant enhanced amplitude difference was displayed in the ADHD only group, interpreted as reflecting an increased responsitivity and arousal in response to relevant stimuli. The authors concluded that the dyslexic group was impaired in early processing, while the ADHD group differed in later processing stages. Taken together, in this study differences related to dyslexia seemed to be evident in both the combined and dyslexia only group, while effects of ADHD were limited to this group only (Dhar, Been, Minderaa, &

Althaus, 2008). In a study with main focus to investigate ASD in relation to different controls on the P300 component, one control group consisted of subjects with dyslexia, a second with ADHD, and healthy controls. The ASD group were reported to display a significantly smaller P300 to novels (novelty component) (resembling the P3a) measured at Pz than all other groups, as well as an unexpected P3 task effect in occipital region in the ASD group. Unfortunately, the effects of the clinical controls-groups were not reported (Kemner, Verbaten, Cuperus, Camfferman, & van Engeland, 1995). Further, two different studies examined the P3 component in ADHD only and different combined groups with disruptive disorders (conduct disorder, CD and oppositional defiant disorder, ODD), and one with Tic disorder. The first study (Rothenberger et al., 2000), reported no difference between groups in the auditory P3b component, while the second study (Yoon, Iacono, Malone, Bernat, & McGue, 2008) reported that that the comorbid group (ADHD + CD/ ODD) displayed a significant reduction in the visual P3 amplitude, as well as poorer task performance than all other groups. This was suggested to indicate that the observed deficits reflected the effects of co-existing childhood disruptive disorders and not ADHD. In the Rothenberger-study, however, they found some differences in earlier auditory components between the different groups that they were unable to provide any explanation for, and concluded that comorbidity deserves particular scrutiny in the future due to the different manner in which different associated psychopathologies may modulate brain dynamics (Rothenberger et al., ibid).

In another study, effects of TS and OCD were examined in a visual ”stop-signal” task that resembles the Go/ Nogo task. All groups showed equal performance, however, while Go and stop (Nogo) stimuli elicited enhanced frontal negative activity in both TS and OCD compared to controls, Nogo stimuli were associated with a Nogo-anteriorization selectively in the TS group (Johannes, Wieringa, Mantey et al., 2001). In a later study by the same researchers, TS, OCD subjects and controls were tested in a visual Stroop paradigm. This

protocol evoked an enhanced frontal N450 component with prolonged latency for incongruent stimuli (Nogo), enhanced N2 and P3b compnent amplitudes for targets (Go) in both patient groups, however, the OCD group displayed the largest P3b amplitude (Johannes et al., 2003). While the first study was suggested to indicate somewhat differently altered sensorimotor inhibition processes (stronger) in both TS and OCD, the second study was suggested to reflect that frontal inhibitory mechanisms are altered alike in TS and OCD.

Spectral studies in patient groups with co-existing disorders have also mainly focused on ADHD, with a few exceptions. One of these investigated frequency-bands in male children with ADHD with/ without ODD, and healthy controls. The ADHD groups showed more absolute and relative theta, less relative alpha and more relative delta in posterior regions, and less relative beta in frontal regions. They found only two significant topographic differences between the ADHD and ADHD+CD groups, namely greater absolute theta power in right hemisphere for the ADHD group. Their findings are consistent with previous spectral research findings in ADHD, and, in contrast to the ERP study by Yoon et al. (2008), it was suggested that the differences from controls mainly were due to the ADHD and not the co-existing CD (Clarke, Barry, McCarthy, & Selikowitz, 2002a). The same research group has also investigated spectral differences in ADHD in relation to autistic symptoms and reading disorder (RD). The first one revealed qualitatively different spectral results for the ADHD groups with (ADHD+) or without autistic symptoms (ADHD-). In relative powers, the ADHD- group displayed somewhat higher relative theta activity, and decreased relative delta activity compared to age-matched healthy controls, while the ADHD+ group had significantly more beta power across the entire scalp, enhancement in central theta, and a relative right frontal reduction in beta compared to the ADHD- group (Clarke, Barry, Irving, McCarthy, & Selikowitz, 2011). The second study suggests, on the other hand, that spectral EEG differences may behave in an additive or accumulative manner in ADHD with co-existing

RD. Specifically, both children with ADHD with and without reading disorder (RD) displayed elevated slow wave activity (delta and theta) and decreased fast wave activity in alpha- and beta-ranges globally in relative powers compared to controls. Analyzed by region, both clinical groups had less delta, theta, and alpha at posterior sites, and less frontal beta, than the control group. Further, ADHD + RD showed more global theta- and less alpha-power than the ADHD group, elevated levels of posterior delta, and more theta relative to alpha in frontal regions. Thus, spectral differences in both clinical groups were pertained to the same frequency-bands and in similar directions, however, the group with co-existing ADHD and RD had quantitatively larger spectral deviances than the ADHD only group (Clarke, Barry, McCarthy, & Selikowitz, 2002b).

Spectral studies on co-existing mood disorders and anxiety are also scarce, particularly in children. However, one study of interest investigated adolescents (females) with depression (major depressive disorder, MDD) with/ without co-existing anxiety disorders and healthy controls. The group with MDD only showed alpha asymmetry similar to those demonstrated in younger children, with greater alpha power (less activation) in right posterior region compared to left. Also, this alpha asymmetry was less pronounced for adolescents with co-existing anxiety disorder, and absent in all subjects without MDD. This suggests that alpha asymmetry in posterior sites can serve as an indicator of depression in young children (note that similar results have been reported in young children with depressive symptoms, as described in earlier sections) and adolescents, and furthermore to differentiate between depression and anxiety disorders in young subjects (Kentgen et al., 2000). However, there are also indications for a different spectral pattern in secondary depression, as demonstrated in a study mentioned earlier with adults with OCD with/ without depression (Karadag et al., 2003). In contrast to the more common alpha asymmetry finding in depressed patients, the OCD patients with secondary depression showed a globally increased alpha

power, suggesting a different underlying pathophysiological process of depression secondary to OCD than for primary depression.

Normative comparison of QEEG

Assessment of neuropsychological functioning is traditionally based on the behavioral performance on tests that has been proved to be sensitive measures of certain functions and abilities. For instance, the widely recognized Wechsler Intelligence Scale for Children-III (WISC-III) provide several subscales for assessing verbal and performance abilities in children (Spreen & Strauss, 1998). The evaluation of individual scores on the WISC-III, however, depends on the known distribution of scores in the normal population. This allows any score to be expressed in relation to the population mean, and thus, to what level of confidence the results are obtained (i.e. standard error of measurement). Basically, the scores are evaluated on the two-dimensional scale or continuum that characterizes the normal distribution, whereby the ”value” is implicated. A negative value (eg. poor verbal skills) is implied whenever scores fall considerably below the mean, whereas a positive value (eg. good verbal skills) is implied for scores considerably above the mean. EEG metrics, on the other hand, can be said to provide a multidimensional scale where ”scores” may very well behave like dependant variables that can vary over several dimensions, like frequency, location, time and amplitude or power. For example, the relative alpha power have been shown to significantly account for the variability of the P300 amplitude in visual detection tasks (Ergenoglu et al., 2004). Moreover, even if EEG metrics are normally distributed in the population, the value of any deviance is not implied. Both enhanced and reduced ERP and spectral components can potentially reflect good or poor performance or no difference at all. In fact, validation studies on QEEG databases have established that they are both reliable and approximately gaussian (Thatcher, Walker, Biver, North, & Curtin, 2003). Yet again, the

value of deviant components may in turn depend upon some other dimension, like location or distribution of activity. The profound changes in EEG parameters that have been documented in developmental studies underscore the necessity for age-matched normative comparisons when assessing these parameters in children. But statistically significant deviances provide no basis to evaluate whether the differences are clinically significant. The clinical significance is determined by the content validity of EEG measures which are empirically founded by the correlations between statistical deviations and clinically significant conditions, exemplified by some of the presented EEG studies in childhood disorders (Thatcher et al., 2003). The content validity also depend on the psychometric properties of QEEG measures, for instance like when basic research is trying to pinpoint the cognitive processes underlying certain ERP components. However, the majority of QEEG studies in childhood disorders have mainly been conducted for research objectives, and not for diagnostic purposes. For example, task protocols have been varied and manipulated to elaborate on the specific cognitive processes that are hypothesized to be impaired in a given disorder.

There has been a search for distinctive QEEG patterns in different disorders and attempts to develop statistical analysis for the diagnostic classification of individual QEEGs, such as discriminant analysis and cluster analysis, featured in certain available databases (Johnstone & Gunkelman, 2003). In discriminant analysis, a subject is categorized according to membership probability in each of two or more different groups included in the discriminant function. Cluster analysis have been used to differentiate between different subtypes depending on the similarity of QEEG profiles between all possible pairs of subjects (Prichep, 2005). Even though there have been reports of successful applications of the discriminant approach in the ability to classify different groups of psychiatric patients, which sometimes exceeds 90% accuracy (although sensitivity and specifisity estimates vary greatly across studies and disorders) (eg. Coburn et al., 2006, for a review), the approach has been

criticized for not being legitimately usable in real-life clinical settings with patients exhibiting multiple possible comorbidities and co-existing disorders, as well as excessive drowsiness (Johnstone & Gunkelman, 2003). This concern is supported by the lack of knowledge about the influence of co-existing disorders on QEEG measures. Although reports of reasonably high discrete differential diagnostics of QEEG in disorders such as dementia (ex. Alzheimer's disease and fronto-temporal dementia), the Report by the Committee on Research of the American Neuropsychiatric Association cautions against the use of automatic diagnostic classification, and stresses the importance of using QEEG as diagnostic adjuncts similar to any other laboratory test that inform clinical judgment (Coburn et al., 2006). However, due to the considerable variation in results across EEG studies in many of the disorders, regarding medication status, control group selection, inclusion and exclusion criteria, as well as recording conditions and task protocols, a general optimism is held towards the trend of using QEEG databases in combination with investigating a wider range EEG measures and disorders (Clark et al., 2009).

GENERAL CONCLUSION

Brain oscillations in the beta-, alpha-, and theta-ranges have been found to reflect meaningful states, behaviors, and cognitive processes, while ERP analysis, together with sophisticated separation techniqes (ICA ERP) and standardized current density (sLORETA) can target the specific cognitive operations taking place with a resolution of miliseconds, source localized with zero location error. These advantages with QEEG method have resulted in numerous studies trying to pinpoint the brain processes involved in different psychiatric disorders, as well as searching for disorder-specific profiles based on QEEG deviances in children with disorders compared to control groups. Several studies have demonstrated abnormal QEEG in clinical populations. However, results have been inconsistent across

studies. In ADHD, excess relative theta power is the most common finding, though alpha and beta deviances (both elevated and reduced) have also been reported. Both theta and delta excess and deficiency have been found in autistic disorders, along with decreased alpha levels. QEEG deviances in OCD resembles both some of the reported deviances in ADHD, with elevated beta- and increased theta-powers, and some of the reported deviances in autistic disorders, such as decreased alpha- and increased delta-powers. In mood and anxiety disorders, mostly differences in hemispheric alpha coherence have been reported, although also a variety of reduced and enhanced power in delta, theta, alpha, and beta-bands. Generally there are also great variations in reported brain regions where deviances have been found, although frontal and parietal sites most commonly are reported for alpha and theta deviances, and frontal sites for deviant beta. Similar inconsistencies pertain to results from ERP-studies, with smaller and larger amplitudes, shorter and longer latencies, in different components thought to reflect the underlying processing deficits in the studied disorders. The inconsistencies across many of the studies may partly be due to technicalities, such as diagnostic procedures, sampling of clinical and control groups, differences in task protocols, recording procedures, and analysis. Wide-ranging age-related changes, as well as inter-individual variance in QEEG parameters have been documented in developmental studies, that underscore the necessity for age-matched normative comparisons when assessing these parameters in children. The search for distinctive QEEG patterns have revealed promising precision in terms of sensitivity and specificity. However, the applicability of QEEG in clinical practice with real-life comorbidity is debated. Particularly, the method has been criticized for not being legitimately usable in real-life clinical settings with patients exhibiting multiple possible co-existing disorders.

OBJECTIVES OF THE PRESENT STUDY

The objectives of the present study are threefold:

1. An exploratory approach will be undertaken by means of QEEG methodology (spectral analysis and ERP) to map the deviances in EEG parameters sampled from a population of children in a real-life clinical setting.
2. To explore and report the nature of any deviance in relation to component description and location, and behavioral measures and problem descriptions, including a mental health screening, a more in depth clinical interview, as well as diagnostic information, and
3. to evaluate any deviance in individual QEEG parameters in relation to existing literature on the neural and functional basis of the ERP and spectral components, and reported QEEG findings in clinical populations (relevant childhood disorders) in order to a) gain further insight into the clinical applicability of QEEG in psychiatric childhood disorders, and b) to assess the course for the future project concerning clinical application of QEEG.

METHODS

Subjects

Fourteen children and adolescents (seven boys and six girls) aged 7-15 years referred to a special psychiatric unit for children and adolescents participated in the study (M= 11.43, SD= 2.56). All the children were referred on the basis of different concerns regarding their daily functioning and underwent ongoing clinical evaluation at the psychiatric unit concurrently while they (and their parents) were asked to participate. The parents and adolescents from 11 years answered a mental health screening questionnaire. In addition the parents and children took part in a qualitative interview to elaborate their concerns regarding the child's daily functioning, and main reason for seaking help for the child.

Diagnostic information

The children were in the clinic for observation and the majority was referred to the special psychiatric unit for second opinions. Thus, the diagnostic status of the children was available mainly after they participated in this study. Three children were diagnosed with Tourette syndrome only, one of these had been diagnosed with separation anxiety and elective mutism previously. One child had Asperger syndrome (AS) only, three children had ADHD only, one child had main (M) diagnose ADHD with other secondary diagnoses (O) unspecified behavioral and emotional disorder. One child had ADHD (M) and mixed developmental disorders of school abilities (O). One child had unspecified emotional disorder (M), and unspecified learning disorder of school abilities (O). One child had social fobia (M) and mixed specific developmental learning disorder (O). One child had pervasive developmental disorder, not otherwise specified (PDD NOS) (M), and developmental disorder of motor skills, mild mental retardation, unspecified depressive disorder, and ADHD (O). One

child had indiscriminative attachment disorder in childhood (M), and mixed developmental disorder of school abilities, dissociative motor disorder, ADHD and unspecified emotional disorder in childhood (O). And finally, one child was still under observation and had not been diagnosed. None of the children used medication, however, two of the participants were currently using melatonin for sleep disturbances.

The qualitative interview

The qualitative interview was conducted in an unstructured manner in order to obtain information about the parent's main concerns regarding their child's daily functioning, and main reason for seaking help for their child. 3 open questions and 2 follow ups were used as an interview guide:

1. Can you in your own words describe your main concerns regarding your child's health and functioning?
2. Do you have any additional concerns regarding your child? (eg. less severe problems, problems which are not so pervasive or are not so chronic? Problems that is a consequence of main problems)
3. For how long has these problems persisted, when was the onset for these described concerns?
4. Is your child currently on any medication?

Follow-up questions used when required:

1. Are these concerns the main reason for seeking help for your child?
2. Have your child been diagnosed before? If so, what diagnose did he/ she get, and when was he/ she diagnosed?
3. Follow-up questions were mainly focused on specification, description and exemplification of how problems and symptoms manifested themselves in the child's life.

Thematic analysis

A thematic analysis was chosen to reduce the qualitative material according to a pragmatic thematic approach (Aronsen, 1994). This approach is commonly adopted for research clinicians as a way to structure the information that is provided in therapy sessions or during interviews. The thematic analysis focuses on identifiable themes and patterns that

emerged during the interview. Usually data is collected through audiotapes, however, detailed notes were written during the interviews in the present study. All the topics, descriptions and examples given by the parents and children were first listed, than categorized into sub-themes, and finally into main themes (problem domains) by the support from the detailed symptom-descriptions and related problem areas provided by the work of Mash and Barkley on the assessment of childhood disorders (Mash & Barkley, 2007).

The Strengths and Difficulties Questionnaire (SDQ)

The SDQ is a brief behavioral screening questionnaire which is comprised of 25 items on psychological attributes for screening of mental health in children and adolescents, originally developed from the Rutter scales (Goodman, 1997). The SDQ is divided into 5 subscales; emotional symptoms, conduct problems, peer problems, hyperactivity and attentional problems, and prosocial behavior. The extended version of the questionnaire also includes an impact screen, that asks if the respondent thinks the young person has a problem, and if so, enquires further about chronicity, distress, social impairment and burden for others (Goodman, 1999). The SDQ has repeatedly been validated in studies with populations across different countries, and has demonstrated acceptable levels of internal consistency, test-retest stability, specificity (>.60) and sensitivity (>.90) (Goodman, Ford, Simmons, Gatward, & Meltzer, 2000), parent-youth agreement of the five scales, and good concurrent validity (Goodman, 2001; Goodman & Scott, 1999; Hawes & Dadds, 2004; Koskelainen, Sourander, & Kaljonen, 2001; Mathai, Anderson, & Bourne, 2002; Muris, Meesters, Eijkelenboom, & Vincken, 2004; Muris, Meesters, & van den Berg, 2003; van Widenfelt, Goedhart, Treffers, & Goodman, 2003). Furthermore, the diagnostic predictive validity has shown to be moderate to high, with a stable five-factor structure (Goodman, Renfrew, & Mullick, 2000; Mathai, Anderson, & Bourne, 2004). The instrument has presently not been normed in a Norwegian

population, however, such norms exist for Swedish and Dutch populations among others (Smedje, Broman, Hetta, & von Knorring, 1999; Woerner et al., 2002). Thus, the SDQ has demonstrated great usefulness in assessing child psychiatric disorders and sound psychometric properties.

The SDQ responses were scored online at www.sdqscore.org, a site that allows for anonymous entry of the data from paper versions. The five subscales are scored from 0 to 10, indicating low vs. high level of symptoms (prosocial behavior scale is reversed). A maximum total score of difficulties is 40. The scores are then grouped into four level bands according to how the general population of young people typically score; from ”close to average” to ”very high”/ ”very low”. The diagnostic predictions are set as the risk for having emotional, behavioral or attentional problems severe enough to warrant a diagnosis according to the ICD-10 or DSM-IV classifications. There are three possible levels predictions for each diagnostic grouping, namely ”low”, ”medium” and ”high” risk.

While the interviews allowed for more detailed descriptions regarding how the problems and symptoms manifested themselves in the children’s lives, the SDQ confirmed the significant impact and overall stress of problems (severity and chronicity) for the children and surroundings.

Procedure for EEG recordings

EEG was recorded from 19 tin electrodes attached with conductive gel and placed on the scalp embedded in an ElectroCap (Electro-Cap International, Inc.) The electrodes were distributed on the scalp according to the international 10-20 system (see figure 1). Electrodes Fp1 and Fp2 corresponds to prefrontal areas, F3 and F4; frontal, F7 and F8; fronto-temporal, Fz; frontal midline, C3 and C4; central, Cz; central vertex, P3 and P4; parietal, Pz; parietal midline, T3 and T4; temporal, T5 and T6; posterior temporal, and O1 and O2; occipital areas.

All sites were referenced to linked earlobe electrodes (A1 and A2), and a ground electrode was placed at Fpz. Electrode impedance was kept below 5*K*Ω. The signal was amplified using a Mitsar 201 multi-channel digital EEG system (Mitsar Co. Ltd.) with a sampling rate of 250Hz. EEG data was processed using WinEEG 2.81.25 Software (V. A. Ponomarev, Institute of the Human Brain, St.Petersburg, Russia). A notch filter from 45-55 Hz was used, and data was bandpass filtered offline at low cut; 0,53Hz to high cut; 50 Hz. Visual and audio stimulus presentation was programmed in PsyTask (Mitsar Co.Ltd.) and communicated to the subjects through a 19" PC screen and a stereo speaker system (60 dB SPL). The subjects were placed in a comfortable chair, at a distance of approximately 1 meter from the PC screen, which yielded a visual angle of 9 degrees for the images.

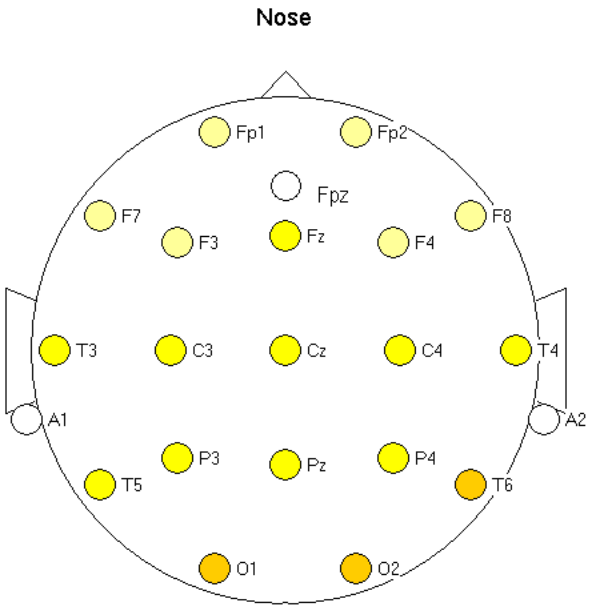

Figure 1 Positioning of the 19 electrodes according to the 10-20 international system.

All EEG recordings were corrected for muscle and eye movement artifacts by the method of spatial filtering of independent component analysis (ICA), in accordance with the standard artifact correction procedure applied by the HBI reference database (see below).

Recording conditions and task protocols

The data was recorded during 3 different conditions. Two resting state conditions whereby the subjects were instructed to relax and avoid any muscular movement while recording a minimum of 3 min. with the eyes open (EO), and a minimum of 3 min. with the eyes closed (EC). Further on the subjects were exposed to the task condition consisting of an approximately 25 min. visual continuous performance task (VCPT).

VCPT

The VCPT is a modification of the visual two-stimulus Go/ Nogo paradigm, where 3 different categories of visual stimuli are presented in series of 400 visual pairs, as well as an artificial ”novel” sound stimuli. The trails consisted of the presentation of pairs of stimuli presented in a random order with equal probability (see figure 2): Animal-animal (Go trials), animal-plant (Nogo trials), plant-plant (p-p, ignore trials), and plant-human + novel sound (p-h, novel trials). The duration of stimuli presentation was 100 ms., the inter stimulus interval in a pair was 1000 ms., and the interval between trials was 3100 ms.. The novel sounds consisted of five 20 ms fragments filled with tones of different frequencies (500, 1000, 1500, 2000, and 2500 Hz). The task was to press the left mouse button as fast as possible in response to a series with two subsequent animals, avoid pressing the button whenever an animal was followed by a plant, and ignore all other stimulus sequences.

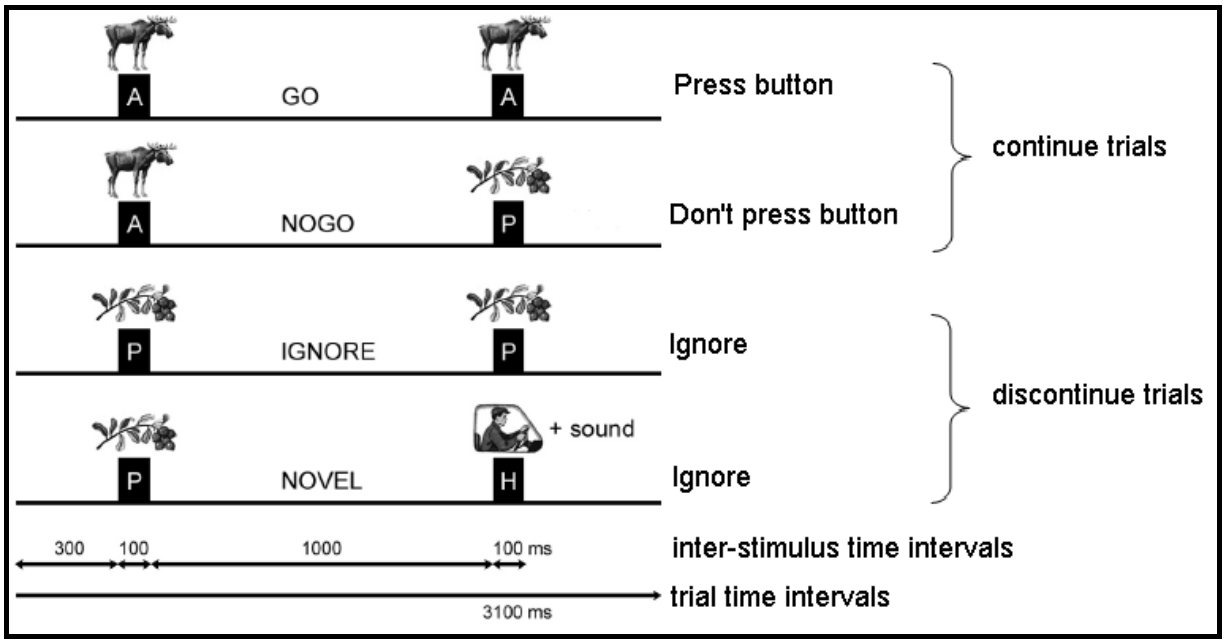

Figure 2 Schematic representation of the VCPT GO/ NOGO task. A, P and H refer to the stimulus-pictures of animals, plants and humans. GO trials requires the subject to press a button as fast as possible, NOGO trials require the subject to suppress the prepared response, IGNORE and NOVEL trials require no response. In the NOVEL trials, the picture of a human is coupled with a novel sound. Continue trials are defined as preparatory sets, i.e. whenever the first stimulus is a picture of an animal and the subject is supposed to prepare a response. Likewise, the discontinue trials are defined as whenever the first stimulus is a picture of a plant, and thus no response is prepared.

The normative database

The HBI database includes the results of more than 3000 processed EEG recordings collected from ~1000 healthy subjects, ranging from age 7 to 89. The database selected for this study was for ages from 7 to 18, with a total of ~350 subjects. All the EEGs recorded in this study were recorded under exactly the same test- and task-conditions and montage setup as included in the database. The recordings are also matched according to age, and corrected for time of the day. For further specifications of the HBI database see appendix 1 (Human Brain Institute HBI, 2007).

Statistical analysis

Statistical analysis was performed in the Mitsar WinEEG 2.80.30 software, and the SPSS 17.0 software package. The Mitsar WinEEG 2.80.30 allows estimations of statistical significance of the deviances of EEG parameters, found by comparing the spectral, conventional ERPs and ICA ERP component files with the HBI reference database. Statistical significance was accepted at the level of $p<0.05$. Spearman's rho (r) and Kendall's tau b (τ) correlations were calculated in SPSS to look for any association between significant deviances in spectral EEG parameters and the level of reported problems and symptoms, impact and predicted diagnose risk, as well as problem domains and behavioral performance in the VCPT. The EEG spectral variables for correlation analysis were frequency (theta, alpha and beta) and region (frontal, central, parietal, temporal and occipital). Only relative power values (i.e. percentage of frequency distribution) and not absolute values, were subjected for analysis and DB comparison, as this eliminates many potential errors due to changing bone thickness, skull resistance and impedance in children (Benninger, Matthis, & Scheffner, 1984). Analysis were performed for EO and EC condition separately, and for for the two conditions together.

Source localization

Significant deviances of spectra and ERPs detected when compared to the reference database are depicted in certain electrodes by WinEEG, with "bars" indicating a statistical deviance and p-values. Deviances can show up at only one, a few, or several electrodes. As discussed in earlier sections, the neural generators of the EEG components can not be inferred by electrode positioning. A more useful approach is the application of source localization techniques that has been proved to improve the spatial resolution of scalp-recorded EEG (Pascual-Marqui et al., 2002). In order to precisely locate the sources of the EEG parameters,

overlapping activations in multiple cortical areas must be separated by means of Independent component analysis. All significant deviances in spectra and ERP components where therefore localized by first computing Independent component spectra and Independent component ERPs, respectively, by the WinEEG software. The separated components were then subjected to sLORETA analysis to compute the standardized current density distributed over cortical grey matter.

Conventional ERP components

ERPs were analyzed from the VCPT task for each subject in the following discontinue trials: visual (p-p), visual/ auditory (p-h), and the difference-wave between the discontinue trials, (p-h) – (p-p) to extract better indices for auditory processing. ERPs were analyzed in the following continue trials: Go (a-a), Nogo (a-p), and the difference-wave between Go – Nogo to provide the ”N2 motor inhibition”-wave and the ”P3 Nogo”-wave (Kropotov, Ponomarev, Hollup, & Mueller, 2011). The ERP components were extracted from the electrode positions revealing the largest amplitudes. For visual (p-p) from occipital (O1, O2) and temporal (T6, T5) electrodes; for visual/ auditory (p-h) from occipital (O1, O2), temporal (T6, T5) and central (Cz) electrodes; for (p-h) – (p-p) difference wave from the central (Cz) electrode; for Go (a-a) from parietal electrode (Pz); for Nogo (a-p) from the central (Cz) electrode; for the ”N2 motor inhibition”-wave at frontal (Fz) electrode; and for the ”P3 Nogo”-wave at central (Cz) and frontal (Fz) electrodes.

Independent ERP components

The following 10 distinct components from the VCPT task were analyzed: P1N1 visual occipital, left and right temporal components, the N1P2 auditory component, the left

and right temporal visual comparison components, the P3b parietal and P3 frontal suppression components, and the two P4 frontal monitoring and working memory components. Component names with descriptions and localization in terms of Brodmann's areas for the ICA ERP components extracted from the DB and compared to the individual ERPs of the subjects in the study are provided in table 1. Figure 3 provides an illustration of the source distribution by sLORETA of one of the early visual components. The sLORETA also suggests the best fit for Brodmann's area.

Independent ERP components		
Component name	Description of IC ERP indexes	Localization of IC from the DB by sLORETA
P1N1 visual occipital	Visual sensory processing	Ba19
P1N1 visual left temporal	Visual processing in the left ventral ("what") pathway	Ba22
P1N1 visual right temporal	Visual processing in the right ventral ("what") pathway	Ba39
N1P2 auditory central, P3b parietal, P3 suppression frontal (P3 Nogo)	Orienting response, Memory operations and inhibitory processing	Ba6
Visual comparison right and left temporal	Change detection of the current stimulus with the memory trace stored in working memory	Ba21
P4 working memory frontal	Working memory operations	Ba11
P4 monitoring	Monitoring operations	Ba25

Table 1: Component name, description and best fit localizaiton in Brodmann's area (Ba) for the IC ERPs extracted from the database (DB).

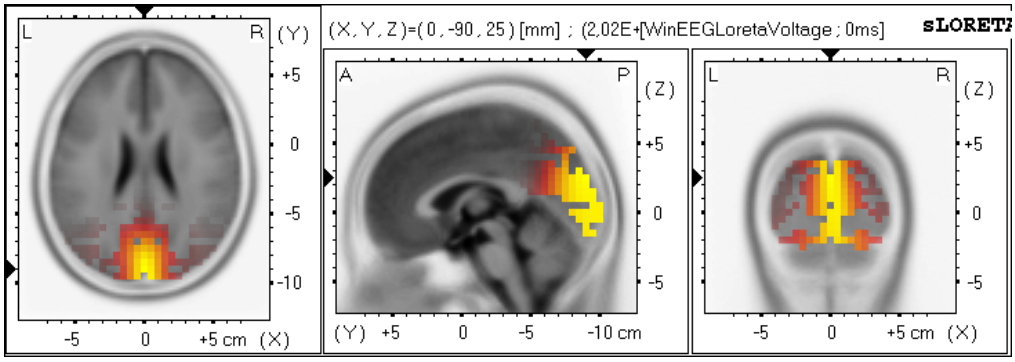

Figure 3 Example of source distribution of ICA ERP by sLoreta, showing the source of the P1N1 component in Ba19 visual occipital cortex.

The ICA ERP components can largely be classified into early sensory components reflecting early visual and auditory processing, and later occurring components reflecting higher order information processing. The P1N1 visual independent component (IC) is

generated in the occipital cortex corresponding to Brodman's area 19 (Ba19). The P1N1 visual left and right components are generated in the corresponding ventral pathways, the "what"-pathway, where physical and semantic features of the stimulus is processed (Goodale, 1993). The three above mentioned components are the ICs of early sensory processing in the visual discontinue task. The N1P2 auditory IC is a component resulting from the auditory discontinue tasks, whereby an irrelevant sound occurs at different frequencies delivered in a random fashion. This triggers an exogenous orienting respons, as the subjects are instructed to ignore the sound (Mulckhuyse & Theeuwes, 2010; Kropotov et al., 2011). The source of the component is localized in Ba6, along with the P3b and the P3 suppression ICs. The P3b is the IC associated with responding to the target in the Go condition, and indexes memory updating operations. Two ICs are derived from the Nogo condition; the P3 suppression component (P3 Nogo) that reflects inhibitory processes in the 250-400 ms time-window, and the P4 monitoring component reflecting monitoring operations in the 325-500 ms time-window. The two bilateral temporal visual comparison ICs reflect the mismatch operation, and are derived from the difference-wave between the Nogo and the Go conditions.

Schematic representation of the stepwise analysis

All individual EEG recordings were subjected for a stepwise analysis that consisted of five steps. 1) Pre-processing of EEG record-file by artifact removal, 2) manual inspection of preprocessed raw EEG to check for obvious contaminations of the EEG (eg. muscle artifacts, movements etc. not removed in the pre-processing of the data), 3) Analysis of power spectrum and ERPs, 4) Comparison of spectra and ERP files with the normative DB, and 5) IC analysis and source analysis by sLORETA of any deviant components (see appendix 2 for a more detailed schematic representation of the stepwise analysis of the individual preprocessed EEG data from the three different conditions EO, EC and VCPT task condition).

RESULTS

Comparison of power spectrum

QEEG comparison analysis of the individual power spectrums with the HBI normative database showed significant deviances with power excess in the alpha, theta and beta bands ($p < 0.05$) for all but one of the subjects (N=14). Deviances appeared for most of the subjects primarily in the alpha (21 %) and theta bands (29 %), or both alpha and theta (29 %) (see table 2). None of the subjects had significant deviances solely in the beta band. A total of 64 % of subjects had significant deviances in alpha, with or without combinations of deviances in the other frequency bands. A total of 57 % of the subjects had different combinations of deviances in the theta band, and 14.2 % in the beta band.

Frequency bands	Deviances
Alpha only	21.4 %
Beta only	0 %
Theta only	28,6 %
Alpha & beta	7.7%
Alpha & theta	28.6 %
Theta & beta	0 %
Alpha, theta & beta	7.7 %
Alpha total	64.2 %
Theta total	57.1 %
Beta total	14.2 %

Table 2 Percentage of subjects with deviances when compared to the HBI normative database.

Statistical analysis for spectrum

Statistical analysis in SPSS using Kendall's tau b (τ) and Spearman's rho (r) correlations revealed a significant negative correlation between theta deviance and symptoms score for behavior difficulties ($\tau = -0.567$, N=14, $p < 0.05$; $r = -0.639$, N=14, $p < 0.05$, two-tailed), as well as parents score of overall stress ($\tau = -0.474$, N=14, $p < 0.05$; $r = -0.556$, N=14, $p < 0.05$,two-tailed), and for the prediction of having a behavioral diagnosis ($\tau = -0.626$, N=13,

$p < 0.05$; $r = -0.637$, N=13, $p < 0.05$,two-tailed). The analysis also revealed a significant positive correlation between alpha deviance and symptoms score for hyperactivity and attention difficulties ($\tau = 0.506$, N=14, $p < 0.05$; $r = -0.569$, N=14, $p < 0.05$,two-tailed). Correlations between deviant frequency-bands and all of the other symptoms scores; emotional, peer problems, prosocial behavior, and impact score, were not significant.

Correlational analysis conducted for symptom domains and spectra deviances revealed no significant correlations. However, correlations approach significance for a positive association between attentional problems and alpha deviance ($\tau = 0.501$, N=13, $p = 0.083$; $r = 0.501$, N=13, $p < 0.081$,two-tailed), emotional problems and theta deviance ($\tau = 0.527$, N=13, $p = 0.068$; $r = 0.527$, N=13, $p = 0.064$,two-tailed), and a negative association between social problems and theta deviance ($\tau = 0.501$, N=13, $p = 0.083$; $r = 0.501$, N=13, $p = 0.081$,two-tailed).

Additionally, analysis revealed significant positive correlations within all deviant frequency bands between both resting conditions (EO and EC); for alpha ($\tau = 0.708$, N=14, $p < 0.05$; $r = 0.708$, N=14, $p < 0.005$,two-tailed), for beta ($\tau = 0.679$, N=14, $p < 0.05$; $r = 0.679$, N=14, $p < 0.01$, two-tailed), and for theta ($\tau = 0.708$, N=14, $p < 0.05$; $r = 0.708$, N=14, $p < 0.005$, two-tailed).

Comparison of ERP and ICA ERP components

ERP and ICA ERP comparison analysis of each of the individual potentials with the HBI reference database showed significant deviances in at least one ERP and ICA ERP component (see table 3). Deviances appeared for most of the subjects in early visual and auditory components, 67% in P1/ P2 for the visual condition (p-p) and 58% in P2 visual/ auditory (p-h) component. Three distinct ERP components from the discontinue waves (p-p – p-h) revealed significant deviances in several of the participants when compared with the DB:

An N100 peaking at approximately 136 ms was significantly enhanced in 43% of the children, and a P200 peaking at 212 ms deviated in 50% of the subjects (6 with enhanced amplitudes, 1 with shorter latency). Significant deviances (enhanced) in early ICA ERP components were evident in 50% of the subjects in the P1N1 visual occipital component, 17% in the P1N1 left temporal and 25% in the right temporal visual components, and 67% in the N1P2 central auditory component. Two subjects showed elevated left temporal comparison components and one had elevated right-sided comparison component. Later ERP component deviances as revealed when compared with the DB were two (17%) reduced P3 Go components, one participant showed significantly enhanced P3 Nogo component, 42% had deviances in the P3 Nogo-wave; two were reduced, one showed a shorter latency, and one showed a delayed latency. No significant deviances were revealed for the N2 motor inhibition wave. Significant deviances in later ICA ERP components consisted of two enhanced and one reduced P3b parietal components and P4 working memory frontal components, 43% had deviances (3 enhanced, 2 reduced) in the P3 suppression frontal component, and one participant showed enhanced P4 monitoring frontal component.

A simple sorting of ERP deviances by diagnose and subject (table 4), as well as by ERP deviant components and type of deviances (table 5), revealed no apparent correspondence between ERP deviances and diagnoses.

ERP components (condition)	Deviances
P1 visual (p-p)	67 % (8e)
P2 visual (p-p)	67% (8e)
N2 visual (p-p)	8% (1e)
P1 auditory (p-h)	17% (2e)
N1 auditory (p-h)	33% (4)
P2 auditory (p-h)	58% (7e)
N2 auditory (p-h)	8% (1e)
P3 Go	17% (2r)
P3 Nogo	8% (1e)
Missing data	14% (2)
ERP difference wave components	Deviances
Nogo-Go N2 motor inhibition wave	0%
Nogo-Go P3 (P3 Nogo wave)	43% (2r, 3s, 1del)
Ph-pp N100 (auditory)	50% (7e)
Ph-pp P200 (auditory)	57% (7e, 1s)
Missing data	14% (2)
ICA ERP components*	Deviances
P1N1 visual occipital	50% (6e)
P1N1 visual left temporal	17% (2e)
P1N1 visual right temporal	25% (3e)
N1P2 auditory central	67% (8e)
Left temproal visual comparison	17% (2e)
Right temproal visual comparison	8% (1e)
P3b parietal +	25% (2e, 1r)
P4 working memory frontal	25% (2e, 1r)
P3 suppression frontal	42% (3e, 2r)
P4 monitoring frontal	8% (1e)
Missing	14% (2)
VCPT behavioral measures	
Omission errors	42% (5)
Commission error	17% (2)
RT	0 %
RT var	25% (3)

Table 3 Percentage and number of subjects with significant deviances in ERP and ICA ERP-components when compared to the HBI reference database. *See tableX for description and localization of Component. e= enhanced; r= reduced; ER= reaction time; RT var.= reaction time variability.

Diagnose	Subj.	ERP component	Deviance
ADHD	12	P3 Nogo wave	S
ADHD	12	Right temp visual comparison IC	E
ADHD	14	Left temp visual comparison IC	E
ADHD, LD	10	P3 suppression IC	R
ADHD, LD	10	P4 working memory IC	E
Emotional disorder, LD	9	P3 Nogo wave	R
Emotional disorder, LD	9	P3b IC	E
PDD NOS, Depression/ ADHD	6	P3 Nogo wave	S
Social phobia, LD	1	P3 Go	R
Social phobia, LD	1	P3b IC	R
Social phobia, LD	1	P3 suppression IC	E
TS	2	P3 Nogo wave	R
TS	2	P3 Go	R
TS	2	P3b IC	R
TS	2	P3 suppression IC	R
TS	2	P4 working memory IC	E
TS	2	P4 monitoring IC	E
TS	4	P3 Nogo wave	S
TS	4	P3 Nogo	E
TS	4	Left temp visual comparison IC	E
TS, separation anxiety in childhood, elective mutism	7	P3 suppression IC	E
TS, separation anxiety in childhood, elective mutism	7	P4 working memory IC	R
Z	13	P3 Nogo wave	Del
Z	13	P3 suppression IC	E

Table 4 ERP deviances sorted by diagnose and subject. Abbreviations: E=enhanced; R=reduced; S=short latency; Del=delayed latency; IC=independent Component; TS= Tourette Syndrome; Z=under observation/ no current diagnose; LD= learning disorder; PDD NOS=Pervasive Developmental Disorder/ Not Otherwise Specified.

ERP component	Deviance	Subj.	Diagnose
Left temp visual comparison IC	E	4	TS
Left temp visual comparison IC	E	14	ADHD
P3 Go	R	1	Social phobia, LD
P3 Go	R	2	TS
P3 Nogo	E	4	TS
P3 Nogo wave	Del	13	Z
P3 Nogo wave	R	2	TS
P3 Nogo wave	R	9	Emotional disorder, LD
P3 Nogo wave	S	4	TS
P3 Nogo wave	S	6	PDD NOS, Depression/ ADHD
P3 Nogo wave	S	12	ADHD
P3 suppression IC	E	1	Social phobia, LD
P3 suppression IC	E	7	TS, separation anxiety in childhood, elective mutism
P3 suppression IC	E	13	Z
P3 suppression IC	R	2	TS
P3 suppression IC	R	10	ADHD, LD
P3b IC	E	9	Emotional disorder, LD
P3b IC	R	1	Soc fobia, LD
P3b IC	R	2	TS
P4 monitoring IC	E	2	TS
P4 working memory IC	E	2	TS
P4 working memory IC	E	10	ADHD, LD
P4 working memory IC	R	7	TS, separation anxiety in childhood, elective mutism
Right temp vis comp IC	E	12	ADHD

Table 5 ERP deviances sorted by component and type of deviance. (See table 4 for abbreviations.)

Localization of deviant spectra components and ERP components

A separation of the deviant spectral components as revealed when compared with the HBI DB, by means of Independent component spectra computation and source localization via sLORETA, suggest that the sources differed somewhat between subjects and to a lesser extent between conditions (see table 6).

	alpha		beta		theta	
Subj	EO	EC	EO	EC	EO	EC
1	4f	4f		8f		
2	7p	7p			9f	9f
3		22t	8f	11f	6f	
4						
5	40p,3p				7p	7p
6					9f	9f
7	21t, 3p*	21t,3p				
8	6f	6f				
9					7p	7p
10						4f
11					10f	6f
12	1p,2	3p				
13	-**	-**			21t	21t
14	-***	-***			6f	40p

Table 6: sLoreta's best match in Brodmann's areas when localizing the significant deviances in the respective frequency-bands by means of Independent component spectra in the resting conditions (EO, EC).
* two different deviant alpha components; one temporal, one parietal. ** reduced alpha in parietal electrodes. ***reduced alpha power globally.

Distributions of the deviant frequencies over the cortex were for alpha mainly in parietal areas, for five of the nine subjects showing alpha abnormalities. Four of these displayed alpha excess, and one showed alpha deficiency in this region. Two subjects had excessive alpha activity located frontally, two had temporally located excess alpha components, and one showed a global alpha deficiency. Deviant theta components were mainly located in the same regions as the deviant alpha components. However, all theta deviances consisted of excessive activity; five out of eight subjects displayed deviant theta in frontal areas, two in parietal area, one subject had excess theta localized in frontal region during EO condition and parietal region during EC condition. Finally, one subject showed

deviant temporal theta. Only two of the subjects showed any deviance in the beta-band, both with beta excess located in frontal areas.

Brodmann areas and the associated functions localized via sLORETA of the deviant spectra components by frequency and ERP components are summarized in table 7 according to Brodmann's Interactive Atlas, with cross referenced PubMed sites (Bernal & Perdomo, 2008). Deviances found in the frequency-bands and the ERP components corresponding to the Brodmann areas are also listed. Brodmann's areas are depicted below (figure 4).

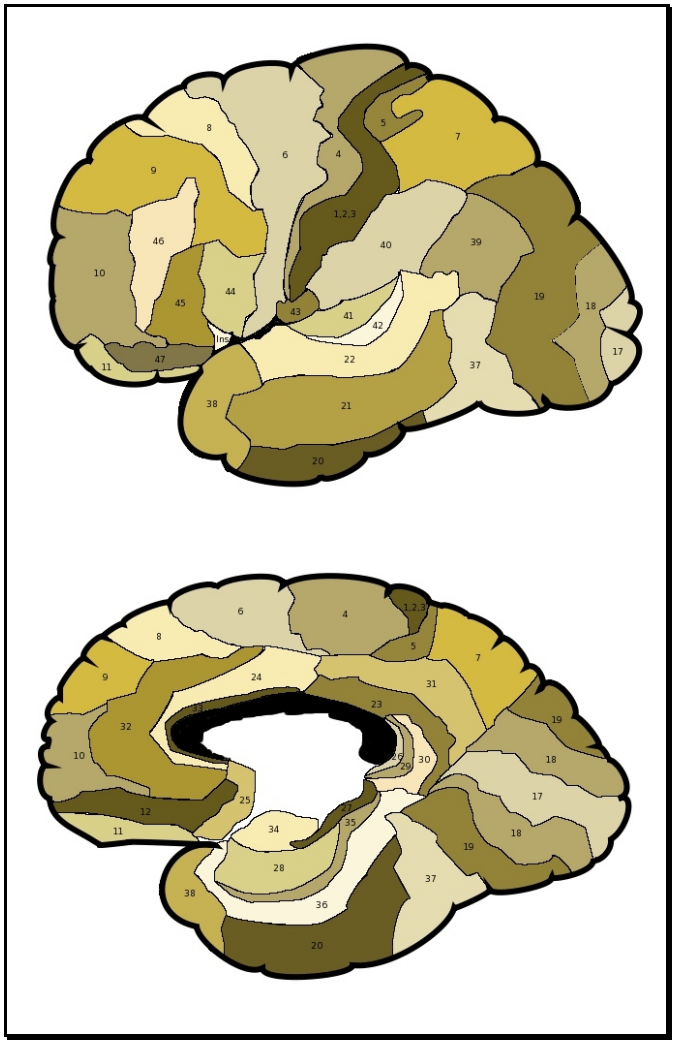

Figure 4 Brodmann's areas (Bernal & Perdomo, 2008).

BA	Localization	Function	Freq.	ERP comp./ (ICA)
1	Parietal; postcentral gyrus	Primary somatosensory cortex; somatosensory perception, organization of movements; volentary movements and perception of movements (mirror neurons).	α	P3Nogo
2	Parietal; postcentral gyrus	Primary somatosensory cortex.	α	N2 (p-p)
3	Parietal; postcentral gyrus	Primary somatosensory cortex.	α	
4	Frontal; precentral gyrus	Motor execution, somatosensory perceptions, certain aspects of verbal encoding, attention to action, and motor memory.	α	P2 (p-h)
5	Parietal; superior gyrus	Secondary sensorymotor cortex; visuospatial processing.		N1 (p-h)
6	Frontal; middle gyrus	Motor sequencing and planning of movements are basic functions; also involved in a vast array of functions incl. language production, memory and attention.	α θ	P2 (p-h)/ N1P2aud, P3b, P3 supp.
7	Parietal; superior gyrus	Secondary sensorymotor cortex involved in visuo-spatial processing; spatial system of goal-directed behavior; attention shift; visual imagery; self processing; temporo-occipito-parietal integration area.	α θ	P1 (p-p) P1 (p-h) P2 (p-p) N1 (p-h)
8	Frontal; dorsolateral prefrontal	Involved in motor learning, saccadic eye movement control, language production, executive functions, memory and attention.	β1	
9	Frontal; dorsolaterale prefrontale	Memory encoding, retrieval and working memory; executive functions.	θ	P3 (Go)
10	Frontal; middle gyrus, prefrontal	Memory encoding, retrieval and working memory; executive functions.		
11	Frontal; orbito-medial prefrontal	Association cortical areas; involved in cortical networks controlling executive functions, and association integration processes, as well as decision making involving rewards.	β1	P3 (Go)/ (P4WM)
18	Occitpital; inferior gyrus	Secondary visual cortex; visual processing.		P2 (p-h) P2 (p-p)
19	Occipital; middle gyrus	Secondary visual cortex; visual processing.		P1 (p-p)/ P1N1vo. P2 (p-p) N2 (p-p)
21	Temporal; middle gyrus	Multimodal area; complex language processing; involved in complex sound processing.	α θ	P1N1 l/ r comp.
22	Temporal; superior gyrus	Part of Wernicke's area; receptive language; language-related attention. In visual processing (right); remembered saccades. Semantic processing.	α	
25	Limbic; anterior cinguli	Emotional, motivational processing; executive functions.		P4 monitoring
39	Parietal; angular gyrus	Cross-modal association among somatosensory, auditory and visual information; involved in arithmetic- and reading-related tasks, as well as in the executive function brain circuitry.		P1 (p-p)/P1N1vr.
40	Parietal; supramarginal gyrus	Semantic representation, spatial orientation.	α	N1 (p-h)
41	Temporal; superior gyrus	Auditory processing, including auditory memory.		P2 (p-h)
42	Temporal; superior gyrus	Auditory processing, including auditory memory.		P2 (p-p)

Table 7 The positioning of deviant spectra components by frequency and ERP components provided by sLORETA, with best mach in Brodmann's area (BA), brain localization of areas and functional descriptions (Bernal & Perdomo, 2008).

Statistical analysis for region of deviant spectra components

The statistical analysis for region of deviant spectra components revealed significant positive correlations between alpha deviance and frontal and parietal areas ($\tau = 0.598$, N=14, $p< 0.05$; $r= 0.598$, N=14, $p< 0.01$, two-tailed). For theta, the correlation was significant for frontal areas ($\tau = 0{,}556$, N=14, $p< 0.05$; $r= 0.556$, N=14, $p< 0.05$, two-tailed). Correlations investigated for region and SDQ measures revealed no significant results.

Thematic analysis of qualitative data

A thematic analysis based on the parents' and children's problem-descriptions was conducted to reduce the qualitative material with the support from the detailed symptom-descriptions and related problem areas provided by the work of Mash and Barkley on the assessment of childhood disorders (Mash & Barkley, 2007). The analysis resulted in the following specific problem-domains: 1) *Emotional problems* – included problems with affect regulation, such as temper tantrums and frequent aggression outbursts, as well problems related to the child being overly depressed (sad) or anxious. 2) *Attention problems* – included difficulties sustaining attention, distractibility, and poor concentration. 3) *Executive function problems* – included difficulties organizing themselves or tasks, initiating, enduring, and/ or finishing tasks, as well as poor flexibility (ex. the child being extremely rigid). It should be noted, however, that such difficulties often are described as being related to attention problems. 4) *Social problems* – included poor social skills and competence, problems with peer relationships. 5) *Hyperactivity/ impulsivity* – included reports of the child being excessively overactive, restless and low impulse control. 6) *Academic problems/ learning difficulties* – included problems with learning and poor academic skills not thought to be due to attentional deficits or other problems "getting in the way" for learning. 7) *Sleep*

disturbances – included problems with "night terror" and difficulties falling asleep. 8) *Thought problems* – included obsessional thoughts and "weird" ideas, as well as compulsions to act on these. 9) *Tolerance to bodily sensations* – included reports of excessively high or low tolerance for pain and/ or sensory stimulations (sound, touch, smell, etc). There were remarkably many reports on children being overly sensitive (hyper-reactive) or overly insensitive (hypo-reactive) to certain sensory stimulations. This "theme" was analyzed by the support of the conceptual work of Dunn (Dunn, 1997), and by the informative review and case reports on the phenomenon by Reynolds and Jane (Reynolds & Lane, 2008). 10) *Motor control problems* – included poor fine and/ or gross motor control and coordination. 11) *Tics* – included simple and complex motor and vocal tics.

The majority of the children (N=14) were described as having significant problems in several of the domains, however, attentional problems (9/14) and emotional problems (9/14) were the most prevalent, followed by executive function problems (7/14), hyperactivity/ impusivity (6/14), social problems (6/14), learning/ academic problems (6/14), sleep disturbances (5/14), Low/ high tolerance for bodily sensations or sensory hyper reactive (4/14), motor control problems (3/14), tics (2/14), and thought problems (1/2). The main problem areas described in the interviews with the parents and children were mainly in agreement with the reported problem ratings from the SDQ. However, while the interviews allowed for more detailed descriptions regarding how the problems and symptoms manifested themselves in the children's lives, the SDQ confirmed the significant impact and overall stress of problems (severity and chronicity) for the children and surroundings.

SDQ descriptives

Descriptive analysis of parent reports (N=14) on overall stress of difficulties on the SDQ screening showed that ratings varied from close to average (28,6%), slightly above

average (21,4%), high (21,4%) to very high (28,6). Impact scores of any difficulties showed that one (7,1%) reported high, and twelve (85,7%) rated very high impact of any dificulty on life (N=14, 1 missing). 57,1% reported problems indicating medium risk and 28,6% reported problems indicating high risk to warrant a diagnosis according to the ICD-10 or DSM-IV (emotional, attentional or behavioral disorder) (N=14, 1 missing). Reported problems that were scored above average from the SDQ are listed for each individual in table 8.

MULTIPLE CASE REPORTINGS

An overview of all the subjects' main problem areas with descriptions reported by the parents and children in interviews and SDQ reportings, information regarding diagnoses, along with deviances in spectra, conventional ERP components, and ICA ERPs is provided in table 8. Reported results from SDQ are scales scored above average for each individual.

1) SUBJ. (AGE)	2) PARENTS REPORTED CONCERNS	3) DESCRIPITION	4) SDQ RATED PROBLEMS and DIAGNOSTIC PREDICTION	5) QEEG, ERP, ICA ERP DEVIANCES and VCPT PERFORMANCE	6) DIAGNOSE ICD-10* and MEDICATION
1 (13)	• Emotional problems • Attention problems • Executive function problems • Thought problems	• Sad, depressive • Distractibility/ easily distracted • Diff. organizing, initiating tasks, enduring and finishing tasks (due to problems knowing where to begin, when to end, prioritize, seeing "the big picture"; grasping the connection between the little details in forming a whole). • Obsessive compulsive thoughts and actions	Emotional distress Peer problems Prosocial behavior Overall stress Impact of any diff. on life High risk for emotional disorder	Frontal alpha+ (EO & EC) Ba4 – Frontal beta+ (EC) Ba8 - P2+ (p-h) Ba41- temporal P1+ (p-p) Ba 7 - parietal P2+ (p-p) Ba19 - occipital P3- (GO) Ba11 - frontal ph-pp P200 (auditory) s P1N1 vis. occipital + N1P2 aud. central + P3b parietal – P3 supp. Frontal + Omission errors Commission errors	M: F401. Social fobias. F83. Mixed specific developmental disorder; nonverbal learning disorder (NLD) No medication
2 (10)	• Attention problems • Academic problems/ Learning difficulties • Sleep disturbance	• Difficulties concentrating/ sustain attention • Diff. reading • Including night terror, difficulties falling a sleep	Hyperactivity/ attention diff. Impact of any diff. on life Medium risk for hyperactivity or attention disorder	Parietal alpha+ (EO & EC) Ba7 Frontal theta+ (EO & EC) Ba9 P1+ (p-h & p-p) Ba7 - parietal P2+ (p-h) Ba18 - occipital P2+ (p-p) Ba19 - occipital P3- (GO) Ba9 - frontal Nogo-Go P3 (P3 Nogo wave) - P1N1 vis. occipital + N1P2 aud. central + P3b parietal – Commission errors	F952. Tourette Syndrome Medication: Melatonin
3 (12)	• Emotional problems • Social problems • Hyperactivity/ impulsive • Executive function problems	• Aggression/ temper tantrums • Poor social skills and competence •Restless/ hyperactive • Rigid/ poor flexibility • High tolerance for pain; reckless, often	Hyperactivity/ attention diff. Peer problems Prosocial behavior Impact of any diff. on life	Temporal alpha+ (EC) Ba22 - temporal Frontal beta+ (EO & EC) Ba 8,11 Frontal theta+ (EO) Ba6 N1+ (p-h) Ba7 - parietal	F845. Asperger syndrome No medication.

	• Tolerance for bodily sensations	injured without taking precautions	Medium risk for hyperactivity or attention disorder	P2+ (p-h) Ba4 - precentral P1+ (p-p) Ba7 - parietal N2+ (p-p) Ba19 - occipital ph-pp N100 (auditory) + ph-pp P200 (auditory) + P1N1 visual occipital IC + (Ba19) N1P2 auditory central IC + (Ba6)	
4 (12)	• Emotional problems • Social problems • Hyperactivity/ impulsive • Sleep disturbance • Tics	• aggression/ temper tantrums • poor social skills and competence • restless/ hyperactive • diff. falling a sleep. • including simple and complex motor and vocal tics	Emotional distress Behavioral diff. Peer problems Overall stress Diagnostic prediction – missing data	No deviances in power spectrum N1+ (p-h) Ba5 - parietal P1+ (p-p) Ba7 - parietal P2+ (p-p) Ba18 - occipital Nogo P3+ Ba1 - postcentral Nogo-Go P3 (P3 Nogo wave) s+ ph-pp N100 (auditory) + P1N1 visual occipital IC + N1P2 auditory central IC + Vis. comparison left temporal IC + P4 working memory frontal + P3 suppression frontal IC – P4 monitoring IC +	F952. Tourettes Syndrome No medication.
5 (10)	• Attention problems • Hyperactivity/ impulsive • Academic problems/ Learning difficulties	• difficulties concentrating/ sustain attention • restless; low impulse control • diff. with reading, writing, math. (Parents think problems with reading is caused by the diff. concentrating/ focusing at the task at hand)	Hyperactivity/ attention diff. Impact of any diff. on life Medium risk for hyperactivity or attention disorder	Parietal alpha+ (EO) Ba40 & 3 Parietal theta+ (EO & EC) Ba7 P2+ (p-p) Ba19 - occipital ph-pp N100 (auditory) + P1N1 visual occipital IC + Omission errors	F900. Activity and attentional disorder; primarely attention deficit (ADD). No medication.
6 (13)	• Emotional problems • Social problems • Executive function problems • Academic problems/ Learning difficulties	• sad/ depressive ; anxious • problems with peers; diff. with eye contact • rigid/ poor flexibility • nonverbal learning diff.; diff. learning time (analogue/ digital), poor sense of direction, can't differentiate left/ wright.	Emotional distress Peer problems Prosocial behavior Impact of any diff. on life Low risk for any diagnosis	Frontal theta + (EO & EC) Ba9 N1+ (p-h) Ba5 - parietal P2+ (p-h) Ba6 - frontal P1+ (p-p) Ba7 - parietal P2+ (p-p) Ba 7 - parietal Nogo-Go P3 (P3 Nogo wave) s.	M: F849 Pervasive developmental disorder; not otherwise specified (PDD NOS) F82. Developmental disorder; specified motor skills. F700. Mild mental retardation

	• Tempo problems	• slow tempo in information processing, need long time to finish tasks		ph-pp N100 (auditory) + ph-pp P200 (auditory) + N1P2 auditory central IC + (Ba6)	 O: F329. Depressive episode; unspecified. F900. Activity and attentional disorder (ADHD)
7 (7)	• Emotional problems • Attention problems • Hyperactivity/ impulsive • Executive function problems • Sleep disturbance • Tics • Motor control problems • Tolerance for bodily sensations	• aggression/ temper tantrums; anxious • difficulties concentrating/ sustain attention; absent-mindedness • restless/ hyperactive; low impulse control • rigid/ poor flexibility • difficulties falling a sleep • including simple and complex motor and vocal tics • Poor motor control and coordination; poor fine- and gross motor control • High tolerance for pain; reckless, often injured without taking precautions	Behavioral diff. Hyperactivity/ attention diff. Prosocial behavior Impact of any diff. on life Overall stress Medium risk for hyperactivity or attention disorder, and behavioral disorder	Temporal alpha+ (EO & EC) Ba21 Parietal alpha+ (EO & EC) Ba3 P2+ (p-h) Ba6 - frontal P1+ (p-p) Ba7 - parietal ph-pp P200 (auditory) + P1N1 visual right temporal IC + N1P2 auditory central IC + P3 suppression frontal IC + P4 working memory frontal IC -	M: F952. Tourettes Syndrome. O: F930. Separation anxiety in childhood. F940. Elective mutism Medication: Melatonin.
8 (8)	• Emotional problems • Social problems • Attention problems • Hyperactivity/ impulsive • Academic problems/ Learning difficulties • Sleep disturbance • Motor control problems • Tolerance for bodily sensations	• aggression/ temper tantrums • problems with peers (gets rejected) • difficulties concentrating/ sustain attention • restless/ hyperactive; low impulse control • nonverbal learning diff.; diff. learning time (analogue/ digital), poor sense of direction • difficulties falling a sleep • poor motor control and coordination; poor fine- and gross motor control • high tolerance for pain; reckless, often injured without taking precautions; overly sensitive to certain bodily sensations; sounds, smell, touch.	Emotional distress Behavioral diff. Hyperactivity/ attention diff. Peer problems Prosocial behavior Impact of any diff. on life Overall stress Medium risk for hyperactivity or attention disorder	Frontal alpha+ (EO & EC) Ba6 Subject did not perform the VCPT, thus no ERPs or ICA ERPs available for analysis.	M: F900. Activity and attentional disorder; primarely attention deficit (ADD). O: F989. Behavioral and emotional disorder; unspecified.
9 (12)	• Emotional problems • Attention problems	• sad, depressive • distractibility/ easily distracted; diffi. concentrating/ sustain attention; absent-	Hyperactivity/ attention diff. Peer problems	Parietal alpha+ (EO & EC) P2+ (p-p) Ba19 - occipital	F939 Emotional disorder in childhood; unspecified. F818. Other developmental

	• Executive function problems • Academic problems/ Learning difficulties • Sleep disturbance • Motor control problems	mindedness • diff. organizing; initiating tasks, enduring and finishing tasks • nonverbal learning diff.; diff. learning time (analogue/ digital), poor sense of direction • diff. falling a sleep • poor motor control and coordination.	Prosocial behavior Overall stress Impact of any diff. on life Medium risk for hyperactivity or attention disorder	Nogo-Go P3 (P3 Nogo wave) - ph-pp P200 (auditory) + P1N1 visual occipital IC + P1N1 visual left temporal IC + P1N1 visual right temporal IC + Visual comparison right temporal+ P3b parietal + Omission errors RT variability	disorders of school abilities; unspecified.
10 (15)	• Academic problems/ Learning difficulties	• struggles with school subjects (math, language, reading, writing) No symptoms otherwise– described as a normally functioning girl according to parents.	Emotional distress Peer problems Prosocial behavior Overall stress Impact of any diff. on life Medium risk for emotional disorder	Frontal theta+ (EC) Ba4 P2+ (p-h) Ba6 - frontal P2+ (p-p) Ba18 - occipital ph-pp P200 (auditory) + N1P2 aud. central + P3 suppression frontal IC - P4 working memory frontal IC + Omission errors RT variability	M: F900. Activity and attentional disorder; primarely attention deficit (ADD). F813. Mixed developmental disorders of school abilities; dyslexsia, dyscalculi, characteristics similar to NLD.
11 (8)	• Social problems • Attention problems • Executive function problems • Motor control problems • Tolerance for bodily sensations	• Poor social skills and competence • Absent-mindedness • Difficulties organizing him/ herself, initiating tasks, enduring and finishing tasks • Poor motor control and coordination; poor fine- and gross motor control • High tolerance for pain; reckless, often injured without taking precautions	Emotional distress Hyperactivity/ attention diff. Peer problems Prosocial behavior Overall stress Impact of any diff. on life High risk for emotional disorder, medium risk for hyperactivity or attention disorder	Frontal theta+ (EO & EC) Ba* Subject did not perform the VCPT, thus no ERPs or ICA ERPs available for analysis.	M: F942. Indiscriminate attachment disorder in childhood F813. Mixed developmental disorders of school abilities O: F444. Dissociative motor disorder. F900. Activity and attentional disorder (ADHD) F938. Other emotional disorders i childhood; unspecified. No medication

12 (15)	• Emotional problems • Social problems • Attention problems	• Sad, depressive • Poor social skills and competence • Difficulties concentrating/ sustain attention (Poor motivation; loses interest in things easily (tasks, activities etc)	Emotional distress Behavioral diff. Hyperactivity/ attention diff. Peer problems Prosocial behavior Overall stress Impact of any diff. on life High risk for behavioral disorder, medium risk for emotional disorder and hyperactivity or attention disorder.	Parietal alpha+ (EO & EC) Ba1,2,3 N1+ (p-h) Ba40 – parietal/ supramarginal P1+ (p-p) Ba39 – parietal/ angular Nogo-Go P3 (P3 Nogo wave) del. ph-pp N100 (auditory) + P1N1 visual right temporal IC +	F900. Activity and attentional disorder (ADHD) No medication
13 (11)	• Emotional problems • Attention problems • Hyperactivity/ impulsive • Executive function problems	• Low tolerance for frustration/ stress • Distractibility/ easily distracted • Restless/ hyperactive • Difficulties organizing him/ herself, initiating tasks, enduring and finishing tasks	Emotional distress Hyperactivity/ attention diff. Peer problems Overall stress Impact of any diff. on life Medium risk for hyperactivity or attention disorder.	Alpha – (parietal electrodes)** (EO & EC) Temporal theta+ (EO & EC) Ba21 P1+ (p-h) Ba7 - parietal N2+ (p-p) Ba2 - postcentral P1+ (p-p) Ba19,7 – occipital, parietal Nogo-Go P3 (P3 Nogo wave) s. ph-pp N100 (auditory) + ph-pp P200 (auditory) + N1P2 aud. central + P3 supp. frontal+	Z032. Observation; suspicion of mental and behavioral disorder. No medication.
14 (14)	No qualitative interview was conducted	-	Emotional distress Behavioral diff. Peer problems Prosocial behavior Overall stress Impact of any diff. on life High risk for emotional disorder	Alpha – (globally)** (EO & EC) Frontal theta (EO) and parietal theta (EC) Ba6, 40 P2+ (p-h) Ba5 – parietal superior P2+ (p-p) Ba19 - occipital ph-pp N100 (auditory) + ph-pp P200 (auditory) + ph-pp N400 (auditory) s P1N1 visual left temporal IC +	F900. Activity and attentional disorder; primarely attention deficit (ADD) No medication

				Visual comparison left temporal IC + Omission errors RT variability	

Table 8 Overview of information from each subject participating in the study. First column 1) with subject number and (age), 2) main themes from qualitative interview with parents and children, 3) description of problem domains, 4) results from SDQ report with scores above average (more than normal problems reported) and diagnose prediction, 5) QEEG deviances, first; spectral deviances, second; deviances in conventional ERP components, and third; deviances in independent component analysis (ICA) ERPs, all with sLORETA location estimated by Brodmann's areas, and 6) Diagnoses for all subjects. Abbreviations: Diff.= difficulty/ ies; M= main diagnoses; O= other diagnoses; Ba= Brodmann area; Ba*= no clear results for Brodmann area by sLORETA; + =excess/ component enhanced; - = deficit/ component reduced; s= short latency; del.= delayed latency; Omission errors=sign.number of missed targets (Go); Commission errors=sign. many responses to non-targets (Nogo); RT variability=sign. variability in reaction time during the test (VCPT); *All subjects were diagnosed by professional and clinically experienced personnel at the special psychiatric unit for children and adolescents according to ICD-10. The diagnose labels have been translated from Norwegian. **deficiency in any given frequency band does not provide a component for source analysis, thus electrodes where significant deviances occurred are reported instead.

DISCUSSION OF RESULTS

The purpose of this pilot study was to examine and report deviances in spectra and ERP components in relation to reported symptoms and problems causing impaired daily functioning in a sample of fourteen children (age 7-15) referred to a special psychiatric unit for observation, many of them for second opinions. Particularly, the study was aimed at addressing issues regarding the application of QEEG in a real clinical setting with children exhibiting both overlapping and different symptoms and co-existing disorders. Reports on high classification accuracies in classifying clinical groups based on QEEG metrics have spurred both optimism (Prichep, 2005) and skepticism (Coburn et al., 2006) regarding the clinical utility of QEEG for diagnostic purposes. In addition, detailed descriptions of symptoms and behaviors of concern were reported by the parents and children, both in a psychometric screening (the SDQ) and an open-ended qualitative interview. Information of current diagnoses set by professionals in the psychiatric unit was also obtained. First, the symptoms and problems reported by the parents and children in relation to spectral deviances and correlational analysis will be discussed. Second, a discussion on the ERP deviances will be provided, followed by two sets of selected cases that will be more thoroughly evaluated to elucidate some of the challenges in the clinical application of QEEG, as well as a general discussion on the subject. Third, a more general discussion on methodological issues will be followed by a section on limitations and implications of the present study with future recommendations.

The symptom overlap, as revealed by the SDQ screening and the thematic analysis of the qualitative interviews with parents and children was profound, regardless of the differences in diagnostic categories, and support several reports on the common

phenomenology of the different childhood disorders (eg. Sheppard et al., 1999; Thompson & Thompson, 2010; Ollendick et al., 2008; Pliszka et al., 1999). Attention and emotional problems were main problem areas for the majority of the children, followed by hyperactivity/ impulsivity, social problems and learning difficulties (see table 8 for details).

Spectral deviances and correlations

All but one of the participants in the present study showed significant deviances from the normative database (DB) in relative power in one or more of the frequency-bands ranging from theta-, alpha- and beta-ranges. Alpha and theta discrepancies were most prevalent, and evident in respectively 64% and 57% of the children, whereas beta deviances were displayed in only two of the children. Five of the children also showed deviances in both alpha- and theta-powers. These results support numerous previous studies reporting theta and alpha deviances in clinical samples (eg. Cantor & Chabot, 2009). Deviances in the alpha-range consisted mainly of excess activity, however, one exhibited reduced alpha activity at parietal sites, and one showed reduced alpha globally (subject 13 and 14 respectively). Regionally, the deviant alpha activity was predominantly source localized in parietal areas involved in somatosensory processing, however, alpha deviances were also localized at frontal and temporal areas involved in more "higher-order" mental functions such as language, planning of movements, memory and attention (see table 4). Furthermore, abnormal alpha activity (regardless of excess or deficiencies) was positively correlated with parent ratings of hyperactivity and attention difficulties. Correlation analysis between alpha deviances and problem domains revealed no significant results. However, results approached significance for an association specifically with attention problems. Such an association between alpha and attention problems could lend support from the notion of alpha as an "idling" rhythm (Pfurtscheller, Stancák, & Neuper, 1996), suggesting insufficient attention processing due to

excess of alpha. However, the view is expanding regarding the functional relevance of alpha, particularly its role in memory and attention processes. Specifically, alpha has been linked with inhibitory processes, and in healthy adults, larger tonic alpha power during rest has been positively correlated with better task performance. Alpha power during task performance, on the other hand, shows an opposite relationship, with low levels corresponding to good performance (Klimesch et al., 2007). This has also been linked with findings of diminished alpha power reported in schizophrenic patients and interpreted to reflect a dysfunction in the thalamo-cortical circuits that is associated with an impaired ability to inhibit irrelevant information (Sponheim, Clementz, Iacono, & Beiser, 2000). The question remains thus, how will "too much" alpha activity, as reflected in the finding of alpha excess, relate to attention? Although EEG findings in adults not readily can be applied to children, this suggest that alpha in certain ways can modulate attention through inhibitory processes. Interestingly, inhibitory dysfunction has (also) been proposed as a common "link", both pathophysiologically and phenomenologically, between TS, OCD and ADHD (Sheppard et al., 1999). The role of inhibition in ADHD is stated to be important due to its fundamental relevance in attention. Inhibitory operations are prerequisite in a variety of attentional functions, for example the ability to inhibit irrelevant information in selective and sustained attention (Friedman et al., 2007). Abnormal alpha activity has commonly been reported in ADHD and OCD, while in TS there is a general lack of such studies. While the abnormal alpha usually involves excess power in ADHD, alpha deficiencies are a more robust finding in OCD. Again, EEG studies in OCD have predominantly been conducted with adult subjects. At a neurobiological level alpha oscillations are regulated by inhibitory actions in the thalamo-cortical feedback network system (Klimesch et al., 2007). Also, paradoxical effects on alpha power have been reported, with increases in alpha activity (parietal) in response to MPH medication (Loo et al., 2004). Thus, although purely speculative, deviances in alpha, regardless in which direction, may

reflect sub-optimal or inadequate inhibitory processing that ultimately can be expressed as various difficulties related to attention.

Deviances in the theta-range consisted of excessive activity, mainly located in frontal areas (see table 4). Partly overlapping with some deviances in frontal alpha (Ba 6), deviant theta was also found in dorsolateral prefrontal region (Ba9), an area particularly involved in a variety of executive functions (ex. working memory). Two of the children displayed excessive theta activity in parietal areas (Ba 7, 40), and one had deviant temporal theta. One explanation for the alpha/ theta deviant overlap may be that deviant theta actually represents a "slowing" in the alpha rhythm, or conversely, alpha deviances may in some of the cases represent high frequency theta. As noted previously, the frequency-band in children are not fully differentiated from the broad alpha band (Klimesch, 1999). Also, children generally display slower frequencies in their power spectrograms (eg. Benninger et al., 1984). However, all of the children were compared to an age-matched normative database, thus, such age-related differences should be accounted for. Deviances in theta activity correlated negatively with parent ratings of behavior difficulties and scores of overall stress in the present study. This finding is somewhat surprising, since frontal theta excess is one of the most common findings in behavioral disorders, such as ADHD (eg. Barry et al., 2003). Although results revealed no significant correlations between problem domains and theta deviance, also here results approached significance for a negative association of theta deviance and social problems, although a positive association between theta excess and emotional problems. The negative correlation between theta deviances and social problems can be expected in the light of the negative correlational finding between theta deviance and behavioral difficulties and overall stress, as behavioral problems, such as acting out, often may lead to social rejection. Again, these negative correlations of theta deviances are surprising, as an opposite association could be expected on the basis of excess theta often found in behavioral disorders. A tendency for a

positive association between theta and emotional problems is interesting, since there is considerable evidence for the critical role of the anterior cingulated cortex (ACC) in the generation of theta oscillations. In fact, theta oscillations have been recorded in numerous regions in the entire limbic system which is crucial for the processing and regulation of emotions, and consequently for emotional self control and adaptive behaviors (Allman, Hakeem, Erwin, Nimchinsky, & Hof, 2001). These areas include the ACC, entorhinal cortex, the hypothalamus, superior colliculus, the medial septum, mammilary bodies, anterior thalamus, and the amygdala (Bland & Oddie, 1998; Buzsaki, 2002; Pizzagalli, Oakes, & Davidson, 2003). For this reason, "limbic theta oscillations" has been proposed as a more appropriate term for the so-called "hippocampal theta" (Buzsaki, 2002). Theta has been shown to be generated in multiple areas in the human brain, and to functionally coordinate the integration across distributed networks in the limbic system and neocortex (Kirk & Mackay, 2003). Theta oscillations in animal studies have been coupled with emotional arousal and fear responses (Pare & Collins, 2000). In experimental studies of emotional reactions in humans, higher theta synchronization (event related) have been observed in reaction to emotional stimuli compared to neutral stimuli (Aftanas, Varlamov, Pavlov, Makhnev, & Reva, 2001). The role of theta oscillations in emotions is also supported by studies linking arousal levels and motivational states to theta activity (Inaga, 1998; Knyazev et al., 2009). However, emotional, attentional and memory processes are all closely related and interdependent (Knyazev, 2007; Vinogradova, 1995). Thus, a "simplistic" relationship between specific brain oscillations, such as theta, and brain processes is very unlikely. For instance, considerable evidence also exist for the functional relevance of alpha in memory processes (Klimesch, 1999), as well as for theta in selective attention and memory (see eg. Vinogradova, 1995, for a comprehensive review). Although theta oscillations correlate with a variety of behavioral, cognitive and emotional variables, they seem to play a particularly important role in memory

and emotional regulation (Knyazev (2007). However, it should be noted that the problem domains that resulted from the qualitative interview reflect broad categories of domain-related problems. For example, "emotional problems" could reflect problems in a wide variety of affective dysregulations, like anger problems and low frustration tolerance, as well as sadness and anxiety. Additionally, when going through the individual cases, theta deviances appeared also where no emotional problems were reported, and conversely, alpha deviances were present in the absence of reported attentional problems. Despite these limitations, the spectral results in the light of the relevant studies mentioned so far may suggest that statistical deviances in certain frequency-bands can be better understood in relation to their associated functional meaning than as a "marker" of certain disorders or diagnose categories.

ERP deviances

Early component deviances

Enhanced P1 and P2 visual components were displayed in 67% of the children and were the most common ERP deviant findings in the present study. Nearly half of the children also showed enhanced N100 and P200 auditory components. Deviances in the difference-waves between the visual and visual/ auditory conditions (N100, P200) and the N1 and P2 auditory components correspond to a great extent, as would be expected. This difference wave is the subtraction of the visual (p-p) and the visual/ auditory (p-h) discontinue-trials. Thus, since there will be some overlap between visual and auditory processing in the N1/ P2 visual/ auditory (p-h), the N100 and P200 are more likely to only reflect the auditory processing (contributions of visual perception to the components have been subtracted). There were some differences in the frequency of deviances between the N1/ P2 visual/ auditory and the N100/ P200 auditory difference waves. The N1 component was enhanced in 33%, while the N100

difference wave was deviant in 50% of the children. The P2 auditory and P200 difference-waves showed more deviances for the P2 (58%) than for the P200 (50%). This is probably due to a generally larger P2 in visual than auditory modality, and conversely, a larger N1 for auditory than visual modality. Deviances in early IC ERPs corresponded largely with the deviances in early conventional ERP components. The advantage of separating ERP components into ICs was apparent when considering the wide variety of localizations suggested by sLORETA for the deviances in early conventional ERP components (see table 4 for an overview of the cerebral sources of deviant ERP components in Brodmann areas with a functional description of the associated areas). For example, while the visual conventional P1 was localized in Ba39, Ba19, and Ba7, the corresponding IC is the P1N1 occipital localized in Ba19. Thus, when evaluating deviances in the conventional visual P1 component (and other conventional ERPs), an important aspect is that they may actually reflect different operations taking place simultaneously at different locations.

A detailed description or attempts to explain these deviances for each individual will not serve the purpose of this study. In general, the results revealed that all participants showed two or more deviances in early sensory-related components, and furthermore, that all deviations in early components were due to enlarged components. Furthermore, as exemplified with the visual P1 component above, the cerebral generators for the deviant conventional ERP components were widely distributed in different brain areas across subjects. However, as indicated by both conventional ERPs (visual P1 and P2, auditory N1/ N100 and P2/ P200 components) and IC ERPs (P1N1 visual occipital IC and N1P2 auditory central IC), early visual processing (primarily in occipital areas) and central/ parietal auditory processing were deviant in 50% or more in the subjects. Except for the Nogo N2 component, little interest has been paid in examining or reporting early sensory components in childhood disorders. However, both enhanced and reduced P1 and N1 amplitudes have been reported in

ADHD in frontal and central sites in auditory modality (Smith et al., 2004; Kemner et al., 1996; Broyd et al., 2005). These differences have also been shown to cease after MPH medication (Broyd et al., 2005). A larger visual N1 amplitude has been reported in high functioning adults with autism (ASD) (Strandburg et al., 2003) and OCD patients (Di Russo et al., 2000), although results have been inconsistent with others failing to show such effects (eg. Herrmann et al., 2003). In ADHD, delayed latency and reduced amplitude of the visual P100 have been reported in occipital areas. Typically for studies reporting altered early components, is that deviances have been measured relative to stimulus conditions. For exmple, reduced or enhanced P1 amplitude to non-targets (Nogo) compared to targets (Go) (or the other way around) for the clinical group compared to controls. In the present study, all deviances in early components were more pronounced in passive conditions (discontinue trials). Although deviances appeared in early components also in both Go and Nogo conditions, they were only reported in the discontinue trials. Additionally, other clinical studies have often reported QEEG deviances between clinical and control groups measured as differences in modulation-effects to changing stimulus conditions. For instance, altered processing has been interpreted on the basis of the failure of clinical groups to show adequate modulation of the auditory N1 component to stimulus intensity. In children with ASD this has been interpreted to reflect ineffective sensory input regulation (Lincoln & Courchesne, 1995), and in a study with adult diagnosed with GAD, this has been suggested to reflect insufficient processing in the primary auditory cortex due to enhanced serotonergic activity in GAD (Senkowski et al., 2003). Such modulation effects could not be analyzed and compared with the normative DB in the present study, which makes it difficult to compare such findings with the present results.

Similar inconsistencies as described for the P1 and N1 components also exist for clinical findings of P2 and N2 differences. For example, a larger auditory P2 amplitude have

been reported to reflect hyperactivity and impulsivity in children with ADHD (Oades, 1998), while reduced amplitude has been interpreted to reflect under-activation of inhibitory processes (Johnstone et al., 2009). The N2 "motor inhibition wave" resembles the Nogo N2 often reported to be smaller in children with ADHD (eg. Satterfield et al., 1994; Smith et al., 2004). Although not widely reported in OCD patients, one study reported a similar small Nogo N2 amplitude, and furthermore, that smaller amplitude along with longer latency was associated with the degree of obsessions. However, none of the children in the present study displayed any deviances in the Nogo N2 inhibition wave.

Generally, the N1 and P1 components are thought to reflect different types of modality-specific attention processing, and the N2 and P2 components have been interpreted in terms of discriminatory and inhibitory functions, respectively. The functional and clinical significance of amplitude enhancement and reduction are still debated and unresolved. However, in clinical studies they tend to be interpreted as confirming early sensory or attentional deficits in clinical groups displaying deviances in the P1, N1, P2 and/ or N2 components. The role of sensory performance for social, emotional, cognitive, and sensorimotor functioning and development has received increasing attention in recent years. In a conceptual model, Winnie Dunn has proposed that children differ in their neurological thresholds to various sensory stimulation (eg. touch, visual, olfactory, or auditory) (Dunn, 1997). The model states that a child's ability for sensory modulation (ie. the ability to monitor and regulate sensory information) greatly affects the child's ability to generate an appropriate response to certain stimuli. A high threshold indicates poor registration and a hypo-reactiveness, whereas a low threshold indicates high sensitivity and a hyper-reactiveness to certain sensory stimulations. A sensory modulation dysfunction has been found to be much more common in children with other disabilities than in children without disabilities (Dunn & Westman, 1997; Mangeot et al., 2001). Given the sensitivity of early sensory processing and

modulation effects on early ERP components, individual differences in sensory regulation should be expected to affect these in various ways. The high prevalence of deviant sensory-related components in the present study, with no specificity regarding to diagnostic belonging, along with the inconsistencies reported in early component discrepancies within certain sampled clinical groups compared to controls, as well as the similarities of such deviances (although inconsistent) across clinical groups, could potentially be explained by the high prevalence and differences in sensory modulation dysfunction, not accounted for in clinical ERP studies.

Late ERP component deviances

Deviances appeared to a lesser extent in later ERP components in the present study, and consisted of both reduced and enhanced amplitudes, as well as shorter or delayed latencies (frequencies and details on all deviances in ERP components are provided in table 3). All of the analyzed late ERP components showed one or more deviances in the present study. These included three different Nogo-related components; the conventional P3 Nogo, the P3 Nogo-wave (P3 Nogo-Go), and the P3 suppression IC, the two Go-related components; the conventional P3 Go component and the P3b parietal IC, and furthermore, the left and right temporal visual comparison ICs, the P4 monitoring IC, and the P4 working memory IC. Five of the children (43%) showed deviances in the P3 Nogo-wave (Nogo-Go), five deviances were shown in the P3 suppression IC, while only one of the children showed deviance in the conventional P3 Nogo component (enhanced). The deviances in these three different P3 Nogo-related components did not correspond, such that a subject could display a significant deviance when compared to the DB in any one of these, without necessarily showing deviances in the other two. This indicates that these three Nogo-related components measure

somewhat different processes and/ or that the normal variation is different in the three components, making them more or less "sensitive" for deviances.

A simple sorting of different deviances in the late conventional ERP components and ICs revealed no apparent correspondence between certain types of deviant components or type of deviance (ex. reduced or enhanced amplitude) and diagnose for the subjects in the present study (table 4). In fact, when sorting by type of deviant component, the diagnose categories are listed in what seems to be a random fashion (table 5). In clinical studies, alterations of the P3 component are one of the most commonly reported deviances in clinical groups when compared to control groups, although findings have been somewhat inconsistent across studies. In children with ADHD, a reduced amplitude of the P3 Go and/ or Nogo components, longer latency, and a parietal maximum larger for Go than Nogo stimuli, as well as increased amplitude (both Go and Nogo) at frontal sites, have been reported (Johnstone et al., 2009; Smith et al., 2004; Strandburg et al., 1996). This has been suggested to reflect altered inhibitory processing in ADHD, often seen as a trade off of response-speed for the benefit of accuracy, resulting in similar performance, longer reaction times, reduced P3 amplitude and longer P3 latency (eg. Johnstone et al., ibid). In aults with ASD, enhanced P3 amplitude in visual CPT has been suggested to reflect more effortful processing required for ASD-subjects to sustain performance (similar to controls) (Strandburg et al., 1993), while a reduced auditory P3a amplitude in children with AS has been interpreted as diminished involuntary orienting to changes (Lepistö et al., 2006). In OCD patients, a larger P3b component compared to controls was suggested to reflect a hyper activated cortical state in OCD (Gohle., 2008). In children with TS, increased P3b latency with equal performance compared to controls were interpreted to reflect stronger attentional effort (Johannes et al., 1997), while a more suppressed P3b amplitude with increasing task difficulty than controls were suggested to reflect altered attentional resource allocation processing due to deficient

inhibitory functioning in TS (Johannes et al., 2001). And finally, a reduced P3 amplitude and longer latency (and symmetric as opposed to asymmetric P3 reported for the control group) in adolescents with dyslexia was interpreted to reflect abnormal information-processing in the right parietal lobe and less interhemispheric specialization in dyslexia (Taroyan et al., 2007). Results in the present study revealed that performance measures were poorer or average in subjects showing a variety of late component deviances and non-deviances, and generally, there were no apparent correspondence between type of deviance(s) and diagnose, parent-rated problems, and/ or behavioral performance. In the following section, some selected cases in the present study will be presented and compared to elucidate some of the challenges regarding the clinical evaluation of individual QEEG deviances.

Selected cases evaluated

Three cases of QEEG deviances in TS

Three of the subjects (S) were diagnosed with TS, two had TS only (S2 and S4), and one had additional diagnoses separation anxiety and elective mutism (S7) (see table 9 below for summary of QEEG and performance deviances for S2, S4 and S7). These three children showed strikingly different power spectra when compared with the DB, with S4 showing no deviances, S2 showed parietal alpha excess and frontal theta excess, while S7 displayed a distinct temporal alpha excess (left sided) and parietal alpha excess. The general lack of spectral studies in TS makes any reference to previous findings a difficult task. One study found elevated alpha coherence in sensorimotor areas (Serrien et al., 2005), whereas an early study reported EEG slowing in nearly half of TS subjects (Volkmar et al., 1984). The parietal alpha excess of S7 was localized more centrally in somatosensory area, while the alpha excess for S2 was localized more posterior in parietal cortex. With an association between alpha and

attention problems, this could be hypothesized to explain the alpha excess in S2 and S7, both reported to have attentional problems, and the lack of alpha deviance in S4 were no attention problems were reported. The distinct temporal alpha component in S7 was unusual. Could this represent the abnormal temporal alphoid rhythm in the low alpha/ high theta-range (Niedermeyer, 1997)? This is unlikely, since the temporal alpha-component peaked at about 10 Hz. One other subject (S3) diagnosed with AS showed a similar temporal alpha component. Both S3 and S7 were reported to have a "hot temper", low frustration tolerance, to be restless and hyperactive, rigid with poor flexibility and with high tolerance for pain. However, all of these complaints were also true for S4, except he was not reported to be rigid nor to have a high tolerance for pain. Again, others were reported to also have a high pain tolerance (S8) and to be rigid (S6) without showing this temporal alpha component. Further, reported symptoms and problems (as well as impact) were more similar for S4 and S7 than S2. The question remains thus, how to interpret the spectral deviances in these particular individuals.

Great similarities in deviances in early components (increased P1, P2 visual and auditory, and N1 auditory) were evident for S2, S4 and S7, as for the majority of all of the children in the present study. Do they indicate early attention and/ or stimulus discrimination deficits in over half of the children? Or are they indicative of sensory dysregulations? Generally, interpretations regarding amplitude-differences are complicated, since both reduced (eg. Johnstone et al., 2009) and enhanced (eg. Broyd et al., 2005) amplitudes have been interpreted to reflect poor performance or indications of deficiencies. It can be speculated whether the enhanced P1N1 right temporal visual IC for S7 is due to the excess left temporal alpha, however, the remaining deviant components are difficult to explain. In regard to performance, commission errors above normal levels have generally been viewed as a sign of impulsivity due to impaired inhibitory control. Impaired inhibitory processes are

thought to underlie the symptoms characterizing TS (Sheppard et al., 1999). S2 had significantly more commission errors than normal, whereas S4 and S7 scored within normal levels. Thus, S2 tended to be more impulsive than S4 and S7. Is this reflected in ERP component deviances? Nogo-related ERPs have been proposed to specifically index inhibitory processes (Smith, Johnstone, & Barry, 2006, 2007). The P3 Nogo-wave was significantly reduced for S2, while S4 showed a shorter latency and somewhat enhanced P3 Nogo-wave. This could be explained as stronger inhibitory processing for S4 to maintain normal levels of performance. However, looking at S7, no deviances were apparent in the P3 Nogo-wave or the P3 Nogo component. On the other hand, S7 showed an enhanced P3 suppression IC. Maybe this reflects stronger inhibitory functioning for S7 to maintain performance, although not evident in the other Nogo-related components? Again looking at S4, this same P3 suppression IC was reduced. The P3 Go component and P3b IC were significantly reduced in S2, but not in S4 and S7. Can this be explained by more commission errors for S2? Looking at the literature, suppressed P3b amplitude has been suggested to (indirectly) reflect deficient inhibitory functioning in TS. What then about the inhibitory functioning of S4 and S7, both with TS? Both S4 and S7 showed deviances in the P4 working memory ICs. However, while S4 had increased amplitude, S7 displayed reduced amplitude of the same component. In addition to this, S4 showed a significantly enhanced P4 monitoring IC, not displayed in S2 and S7. Action monitoring in TS has been studied in oddball paradigms based on the hypothesis that TS subjects display hyperactive striatocortical dynamics reflected in hyperactive error signals (Johannes et al., 2002). The P4 monitoring IC component should be sensitive to hyperactive error-monitoring, and thus, differences in this component could be predicted in TS subjects.

	Subject 2 (age 10)	Subject 4 (age 12)	Subject 7 (age 7)
Spectral deviances	Parietal alpha+ (EO & EC) Ba7 Frontal theta+ (EO & EC) Ba9	No deviances in power spectrum	Temporal alpha+ (EO & EC) Ba21 Parietal alpha+ (EO & EC) Ba3
ERP deviances:			
Early components	P1+ (p-h & p-p) Ba7 - parietal P2+ (p-h) Ba18 - occipital P2+ (p-p) Ba19 - occipital P1N1 visual occipital IC + N1P2 auditory central IC +	N1+ (p-h) Ba5 - parietal P1+ (p-p) Ba7 - parietal P2+ (p-p) Ba18 - occipital ph-pp N100 (auditory) + P1N1 visual occipital IC + N1P2 auditory central IC +	P2+ (p-h) Ba6 - frontal P1+ (p-p) Ba7 - parietal ph-pp P200 (auditory) + P1N1 vis. right temporal+ N1P2 auditory central IC +
Late components	P3 (Go) - Ba9 - frontal Nogo-Go P3 (P3 Nogo wave) - P3b parietal IC –	Nogo P3+ Ba1 - postcentral Nogo-Go P3 (P3 Nogo wave) s+ P3 supp. frontal – Vis. comp. left temporal + P4 working mem. frontal IC+ P4 monitoring IC +	P3 suppression frontal IC + P4 working mem. frontal IC -
Performance deviances	Commission errors	No deviance in perfomance	No deviance in perfomance

Table 9 QEEG deviances shown for subject 2, subject 4, and subject 7. Remaining information is provided in table 8. Abbreviations: += significantly enhanced component; - = significantly reduced component; IC= independent component; s= shorter latency; del=delayed latency.

Three cases of QEEG deviances in ADHD

Three of the participants were diagnosed with ADHD only (S5, S12, and S14), primary concerns were attentional difficulties, although several problem areas were described as well (see table 10 below for summary of QEEG and performance deviances for S5, S12 and S14). Remarkable differences in spectra deviances were evident between these subjects as well. S5 showed parietal alpha excess in eyes open (EO) condition, and theta excess in both EO and eyes closed (EC) condition, S12 displayed parietal alpha excess in both EO and EC localized somewhat more centrally, whereas S14 showed a global alpha deficiency in both EO and EC with additional frontal theta excess in EO that was localized at parietal areas in EC condition. Relative theta excess is widely reported in ADHD, and resting theta excess has

been associated with processing deficits (Clark, 2008). Along with theta excess, both reduced and elevated alpha power has been reported in ADHD (eg. Barry et al., 2003). As such, the different spectra deviances reported in the disorder seem represented in these three selected cases. However, alpha and theta deviances were seen in 64% and 57% respectively, of the children in the present study, displaying a variety of different disorders. Again, apart from the fact that clinical populations display differences in their spectrogram when compared to healthy controls, specific explanations for the functional and clinical significance of spectral deviances, such as the excess and deficiency in alpha found in these particular individuals, is not an easy task. One hypothesis could be proposed that they are related to attention problems, which is a common problem area in many different disorders, although the "hallmark" of ADHD. Attention problems were indicated by poor task performance for S5 and S14, who showed significantly more omission errors (missed responses for Go stimuli) compared to normal levels. S14 also showed greater variability in reaction time, which frequently have been reported in children with ADHD (Kalff et al., 2005). Could this be explained by deviances in alpha or the elevated theta power displayed in S5 and S14? Theta excess was also evident in subjects showing no deviances in performance (S3, S6), and poor performance was evident in other children without theta deviances (S1, S9). Although poor performance in attention tasks is commonly reported in children with ADHD (eg. Kalff et al., ibid), also common are reported QEEG abnormalities even with equal performance as control groups (eg. Johnstone et al., 2009). S12 showed a delayed P3 Nogo-wave latency, no deviances in late ERP components were evident in S5 and S14. Could the poor performance be explained by the deviances in early ERP components? Again, early ERP component deviances were common for the majority of the children, with or without poor task performance. Although subjects in the present study generally were very similar in regard to deviances in early components, these three selected cases, all with ADHD only, seemed to

differ somewhat more. Hemispheric differences in certain ERP components have been reported in children with ADHD. For instance, Smith et al. (2004) found a larger N2 for Nogo stimuli compared to Go stimuli particularly in the right frontal region, that was explained as being due to the involvement of the right frontal hemisphere in inhibitory processing. No such effects (deviances in the N2 motor inhibition wave) were evident in any of the children in the present study. Different hemispheric effects in temporal areas were found for S12 and S14 in the early visual ICs. However, while S12 showed enhanced P1N1 visual *right* temporal IC, S14 showed enhanced P1N1visual *left* temporal IC.

	Subject 5 (age 10)	Subject 12 (age 15)	Subject 14 (age 14)
Spectral deviances	Parietal alpha+ (EO) Ba40 & 3 Parietal theta+ (EO & EC) Ba7	Parietal alpha+ (EO & EC) Ba1,2,3	Alpha – (globally)** (EO & EC) Frontal theta (EO) and parietal theta (EC) Ba6, 40
ERP deviances:			
Early components	P2+ (p-p) Ba19 - occipital ph-pp N100 (auditory) + P1N1 vis. occip.+	N1+ (p-h) Ba40 – parietal/ supramarginal P1+ (p-p) Ba39 – parietal/ angular ph-pp N100 (auditory) + P1N1 vis. right temporal+	P2+ (p-h) Ba5 – parietal superior P2+ (p-p) Ba19 - occipital ph-pp N100 (auditory) + ph-pp P200 (auditory) + P1N1 vis. left temporal + Vis. comp. left temporal +
Late components		Nogo-Go P3 (P3 Nogo wave) del.	
Performance deviances	Omission errors	No deviance in perfomance	Omission errors Reaction time variability

Table 10 QEEG deviances shown for subject 5, subject 12, and subject 14. Remaining information is provided in table 8. Abbreviations: += significantly enhanced component; - = significantly reduced component; IC= independent component; s= shorter latency; del=delayed latency.

Issues in the clinical application of QEEG metrics

The cases discussed above were selected on the basis of their common diagnoses. The comparison of three children diagnosed with TS and three children diagnosed with ADHD illustrate some similarities, but also differences and "conflicting" QEEG deviances.

For example, one subject showing an increased component amplitude, the second showing a reduced amplitude of the same component, whereas the third showing no deviance. A general focus on studying a limited set of QEEG variables in clinical studies makes comparison of the wide range of QEEG measures reported in the present study a difficult task. Differences in spectral components and certain ERP deviances may fit the reported abnormalities for a given disorder, while other ERP deviances do not, and vica versa. With the amount of inconsistencies in QEEG deviances reported in the literature on childhood disorders, similarities can easily find some support while differences can readily be explained. Several pitfalls have been described that can influence and potentially interfere with clinical judgment in providing valid diagnosis. These include illusory correlations, covariations and confirmatory bias (de Mesquita & Gilliam, 1994). Confirmatory bias is the tendency to emphasize information that confirms preconceived assumptions. For instance, let us say that the present study focused primarily on analyzing early ERP components in a selected clinical group. Considering the high degree of similarities in early ERP deviances for all of the subjects, these deviances could easily serve to explain the impairments or dysfunctions assumed to underlie the given disorder. On the other hand, any difference could be explained by the heterogeneity that characterizes the majority of childhood disorders, or differences in task protocols. The cases also serve to illustrate the issues when attempting to apply group differences found in clinical QEEG studies when evaluating individuals. Aggregated QEEG group differences between clinical and control groups may not necessarily be "true" for any individual patient. Also, the deviances that appear when comparing individual data with a normative DB may not be equal to the group differences reported in clinical studies.

For QEEG to provide a clinically useful tool for diagnostic purposes, deviances in QEEG measures should be able to reliably differentiate between different clinical populations, or alternatively, in some way be associated with clinically meaningful conditions, such as

specific symptoms, problem areas, or dysfunctions. However, as noted by Cantor and Chabot (2009), there are no studies to date that have provided distinctive QEEG clusters specific to childhood disorders. Furthermore, due to the commonality of co-existing disorders, they claim that distinctive QEEG clusters not likely will be established for distinctive childhood disorders as defined by current diagnostic criteria. The question of etiology is fundamental in QEEG studies on psychiatric disorders, however, disorders are classified based on diagnostic criteria. Diagnostic criteria are typically clusters of symptoms and certain behaviors. The question of evidence for diagnosis or etiology is relevant in this case (Buchsbaum, 2009). Moreover, several of the studies outlined in previous sections report correlations between specific symptoms (and symptom severity) and certain QEEG measures. For example, power measures have been demonstrated to correlate with specific symptoms and symptom severity in OCD (Pogarell et al., 2006; Karadag et al., 2003), and performance measures and parent-rated problems in ADHD (Bresnahan et al., 1999). Also motivational and arousal states and traits have been found to correlate with theta levels (eg. Knyazev et al., 2009). Evidence for specific cognitive operations reflected in the different ERP components and their dynamic have been widely established in basic ERP research. The point to be made here, is that if QEEG parameters are reflected in certain symptoms, problem behaviors and mental operations that so often are reported to both differ to a great extent in heterogeneous disorders, and to overlap in co-existing disorders, great variations in QEEG measures should be expected both in selected clinical samples (based on diagnoses) as well as in mixed clinical samples. The profound symptom overlap demonstrated between children in the present study across diagnose categories provide an illustrative example of this point. A greater similarity in QEEG deviances was expected for children with similar diagnosis and no co-existing disorders than for children with different and/ or secondary diagnoses. However, both the variability as well as the similarities in QEEG deviances between all the children, regardless

of diagnostic belonging, was both unexpected and quite striking. It has been noted that diagnostic categories and individual symptoms are not necessarily associated with similar brainwave patterns (Hammond, 2009). Hammond provides examples from clinical practice where anxiety have been associated with generalized-, midline-, parietal-, and right fronto-temporal beta excess, as well as frontal alpha excess. This suggests a large heterogeneity also in the electrophysiological patterns associated with different symptom complexes.

Methodological issues

Several methodological issues should be addressed both in regard to the different results reported in other studies, as well as for the present study. As outlined in previous sections, the QEEG abnormalities reported in similar patient groups vary considerably across studies. Such differences may partly be explained by methodological differences, such as differences in diagnostic procedures, in the sampling of clinical and control groups, different task protocols, recording conditions, and differences in analysis. For instance, some of the studies reporting high classification accuracies (sensitivity and specificity) in ADHD used only a single electrode at the vertex (Cz) (eg. Monastra et al., 2001). Moreover, positioning of QEEG deviances have often been reported by electrodes. However, brain imaging techniques, such as sLORETA, show that the brain sources of QEEG components not necessarily are located in the tissue immediately below the electrode. Also, definitions of frequency-bands vary somewhat across studies, which can affect particularly the "cut-off point" for the alpha and theta ranges, and thus low alpha can be reported as theta whereas high theta can be reported as alpha. Additionally, there are some findings that suggest that a narrower division in the frequency-bands can provide more precise measures of brain processes. For example, beta activity source localized in the middle of ACC has been shown to be more precisely localized in anterior parts of the cingulate gyrus in the low beta-band, whereas higher beta

was localized more posteriorly (Sherlin & Congedo, 2005). Also, low alpha (alpha1) and high alpha (alpha2) have been demonstrated to show different developmental changes, as well as inter-individual variations. For instance, while the percentage of alpha2 increases steeply before age 7, levels off, and finally decreases after age 12 to 13, alpha1 percentage remains stable during these ages. This suggests that the alpha-band can be differentiated in a meaningful way as these changes reflect brain maturation, thus indicating different functional meanings for alpha1 and alpha2 frequency-bands (Benninger, Matthis, & Scheffner, 1984).

ERP studies have adopted a variety of different paradigms, task protocols, and task modulations that eventually can yield different experimental effects. For instance, early ERP components have been interpreted as reflecting the sharpening of cognitive functions by protecting early perceptual operations from extraneous interference, and thus serve as a filtering mechanism, or gating of information, for more elaborate higher-order processing (Lijffijt, 2009). Amplitude and latency ratios between second and first stimuli (S2/ S1) have proven to be a useful measure for the effectiveness of this filtering mechanism, such that a low ratio reflects strong gating (Liu, 2011; Lijffijt, 2009). Such ratio measures could potentially yield better indices for sensory reception and regulation than only first or second stimulus amplitudes. Typically, there were far more deviances apparent in conventional ERPs. Since conventional ERPs are more susceptible for the "contamination" of several overlapping neural processes taking place more or less simultaneously, impairments in any of these processes can theoretically yield deviances in several ERP components. ICA ERP tackles this obstacle by separating the ERP components into spatially fixed and temporally independent activations during each response condition. This technique is particularly promising in terms of the clinical application of ERPs, and could make it easier to compare findings in the future.

Limitations

The present study has been conducted as a set of multiple cases of a ”convenient” sample from a real clinical psychiatric unit. The small sample size and diversity of symptoms and problems represented in the sample poses great limitations for the generalization of results, and restricted the statistical methods that could be used when analyzing results. For instance, correlational analysis of ERP deviances was not possible due to the large amount of variables (ERP deviances) revealed when comparing each individual to the normative DB. Non-parametric bivariate factor correlations together with the relatively small sample size could also lead to spurious positive findings in the present study. Further, although an attempt has been made to report a wide range of QEEG deviances, no coherence, frequency ratios, or task modulation effects were able to be analyzed with the HBI normative DB. Several of the outlined studies have reported such measures, which limits the possibility for comparing the results in the present study. Also, the Go/ Nogo paradigm (VCPT protocol) used in the present study is not traditionally used in ERP studies on childhood disorders such as ASD, AS, dyslexia and mood disorder. These have typically adopted task protocols to assess functions assumed to be impaired in the respective disorders, such as face perception in AS, emotional vs. neutral stimuli in mood disorder and anxiety disorders and reading and word perception in dyslexia.

Implications and future recommendations

This study ”overcome” many of the confounding variables that have been explained to account for many of the inconsistencies in previous QEEG findings across studies, like differences in task and diagnostic procedures, and other methodological issues discussed above. In this study, individual QEEG parameters such as spectral components, conventional ERP components, and ICA ERPs have been mapped and evaluated in 14 children using

similar task and diagnostic procedures, identical behavioral data were collected, all were age- and gender-matched to the same normative DB, and the sample consisted of both ”pure” and co-existing disorders. However, the results in the present study seem to reflect the inconsistencies reported in many of the studies outlined in this thesis. The individual QEEGs revealed complex patterns of deviances in both spectral and ERP components. This suggests altered underlying neurophysiological processes in a wide variety of childhood disorders that can be measured at an individual level. Moreover, correlational analysis revealed associations between certain spectral deviances and parent-rated symptoms and behaviors. Such correlations have also been reported in other studies searching to answer the functional significance of brain electric oscillations and potentials. Despite reports on high classification accuracies when classifying selected clinical groups and healthy controls, inconsistencies in QEEG literature keep being reported, and no distinctive QEEG clusters specific to childhood disorders have been reported to date. The proposition here is that if, a) QEEG measures correlate with certain symptoms and behaviors, b) childhood disorders are heterogeneous in terms of symptoms and behaviors, c) symptoms are greatly overlapping in childhood disorders, and d) childhood disorders are commonly co-existing, the quest for an objective method that can classify individual patients like a ”filtering machine” and with a high degree of clinical validity may be an Utopian idea. As for now, there seem to be a ”jungle” out there with numerous nuances in spectral and ERP component differences between various clinical and control groups that is cumbersome to navigate. While clinical QEEG studies largely have been designed to investigate impaired brain functioning in certain disorders by means of QEEG method, the results reported in such studies (group differences) cannot readily be applied in clinical settings when evaluating individual data, nor necessarily be reflected in the individual QEEG deviances when compared to a normative DB. Future investigations are highly needed to elaborate on the functional and clinical properties of QEEG measures in

relation to statistical deviances in QEEG parameters, not only by means of QEEG, but for the sake of QEEG method.

Summary and conclusions

The purpose of this pilot study was to examine and report deviances in spectra and ERP components in relation to reported symptoms and problems causing impaired daily functioning for children referred to a special psychiatric unit for observation. The individual QEEGs revealed complex patterns of QEEG deviances, and all of the children showed two or more deviances in spectra and/ or ERP components. A positive correlation was found between alpha deviances and parent ratings of hyperactivity and attention difficulties that might specifically be related to attention problems. A negative correlation was found for theta deviances and parent ratings of behavior difficulties and scores of overall stress, a finding that in some sense runs counter to other studies that have often reported theta excess (deviances) in behavioral disorders. There was a tendency for a positive association (although not significant) between theta deviances and emotional problems, which is consistent with other studies linking theta to emotional regulation. A greater similarity in QEEG deviances was expected for children with similar diagnoses and no co-existing disorders than for children with different and/ or secondary diagnoses. However, results revealed both differences and similarities in QEEG deviances between all the children, regardless of diagnostic belonging.

The study was also aimed at addressing issues regarding the clinical application of QEEG. Reports on high classification accuracies in classifying clinical groups based on QEEG metrics have spurred both optimism and skepticism regarding the clinical utility of QEEG for diagnostic purposes. Despite reports on high classification accuracies in some childhood disorders, particularly in ADHD, no studies to date have defined distinctive QEEG clusters specific to childhood disorders. However, in real clinical practice, the challenge is not

to sort a sample of ”clear-cut” cases that easily fit into a diagnose category from healthy controls. The challenge is to deal with complex heterogeneity in multiple co-existing disorders. The high degree of co-existing childhood disorders have been an argument for a more objective tool in adjunct to traditional diagnostic procedures. Although providing an objective tool, subjectivity comes into play when interpreting QEEG deviances. Thus, QEEG seems to face similar challenges regarding biases, such as confirmatory bias, as traditional diagnostic procedures. The proposal in this thesis is that the heterogeneity in childhood disorders are reflected in heterogeneity in the electrophysiological patterns associated with different symptom complexes. This forms the basis for proposing the need for a different ”line” of research designed to investigate the functional and clinical properties of QEEG measures in relation to statistical deviances in QEEG parameters. It is believed here that the endeavours in constantly refining and detailing the knowledge and expertise in the field of QEEG provides good reason for optimism for the viewpoint that QEEG metrics potentially have an important place in the clinic.

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APPENDICES

Appendix 1

	Spectra condition		Spectra task-condition	ERP task-condition
Age	Eyes opened*	Eyes closed*	VCPT*	VCPT*
7-9	40	43	61	50
10-11	49	49	61	58
12-13	65	61	65	63
14-15	50	47	54	50
16-17	59	59	58	57
18-19	62	64	65	63
Total	325	323	364	341

(*all montages in ”Average referent”). Specifications of the HBI reference database for number of subjects according to age distribution in all conditions.

Appendix 2

Figure 1-3 provides a schematic representation of the stepwise analysis of the individual preprocessed (artifact-corrected) EEG data from the three different conditions EO, EC and task condition. Figure 1 shows a short segment (~2-3 sec.) of the online recorded EEG from all electrodes and conditions. A manual inspection of the preprocessed raw EEG data is superficial, however important to check for obvious contaminations of the EEG (eg. muscle artifacts, movements etc. not removed in the preprocessing of the data). Figure 2 and 3 depict the stepwise analysis of power spectrum and ERPs respectively. Each of the subjects (N= 14) underwent similar analysis of the recorded EEG data. Presented is the data analysis from a subject (subject n) only for selected electrode locations and individual ERPs and ERP components with a statistical deviance indicated when compared with the database (DB). Indeed, most of the subjects showed a ”mixture” of several significant deviances in both power spectrum, several ERPs in different trials, and independent ERP components.

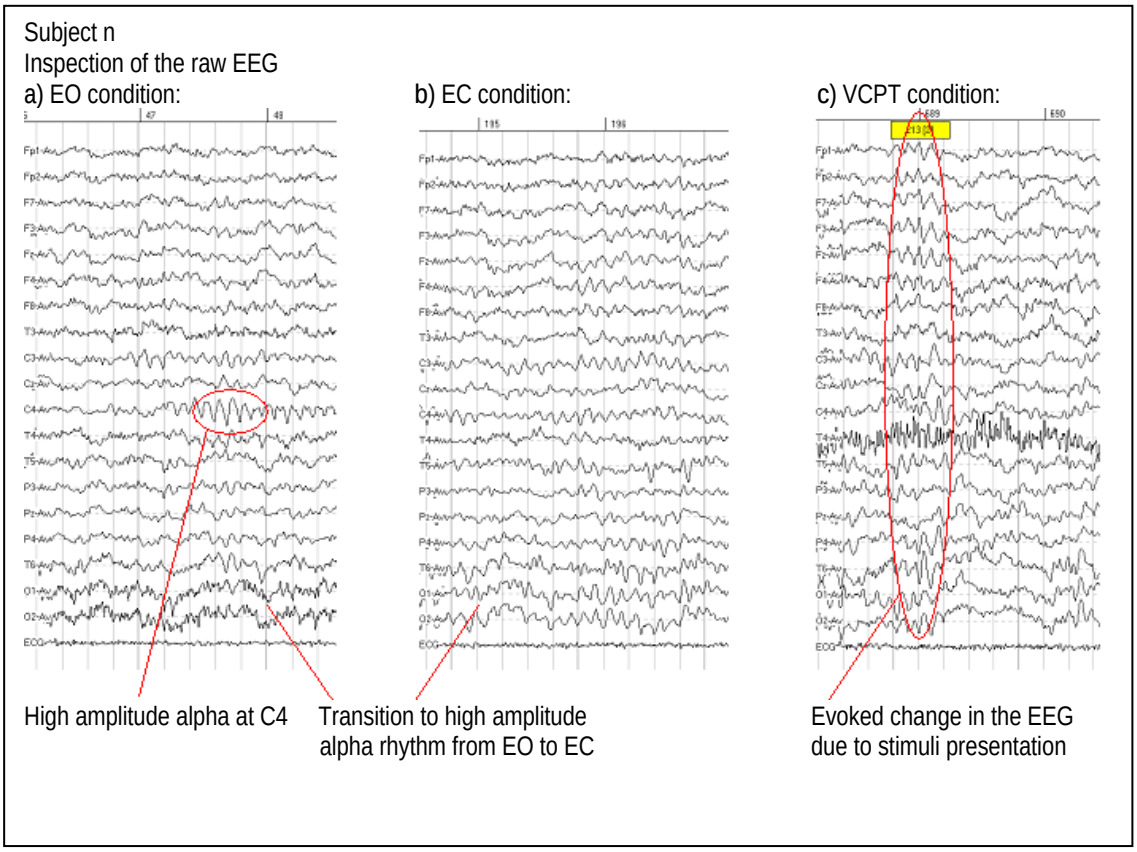

Figure 1: The preprocessed EEG of subject n was manually inspected for possible irregularities, as well as for normal wavepatterns. **a)** A periodic increase of high amplitude alpha was evident at electrode C4 during EO condition. **b)** Subject n showed a transition from low frequency, low amplitude wave pattern to a syncronized high amplitude alpha (”eyes closed alpha”) in occipital electrodes from EO to EC condition. **c)** Section showing a visible change in the EEG amplitude and frequency after the presentation of a stimulus (yellow lable), trial number 213 (a NOGO trial) in the VCPT condition. Also visible is some muscular artifacts on T4 (thicker line) that can render any deviance in power spectrum, especially in the beta band, difficult to interpret for this electrode.

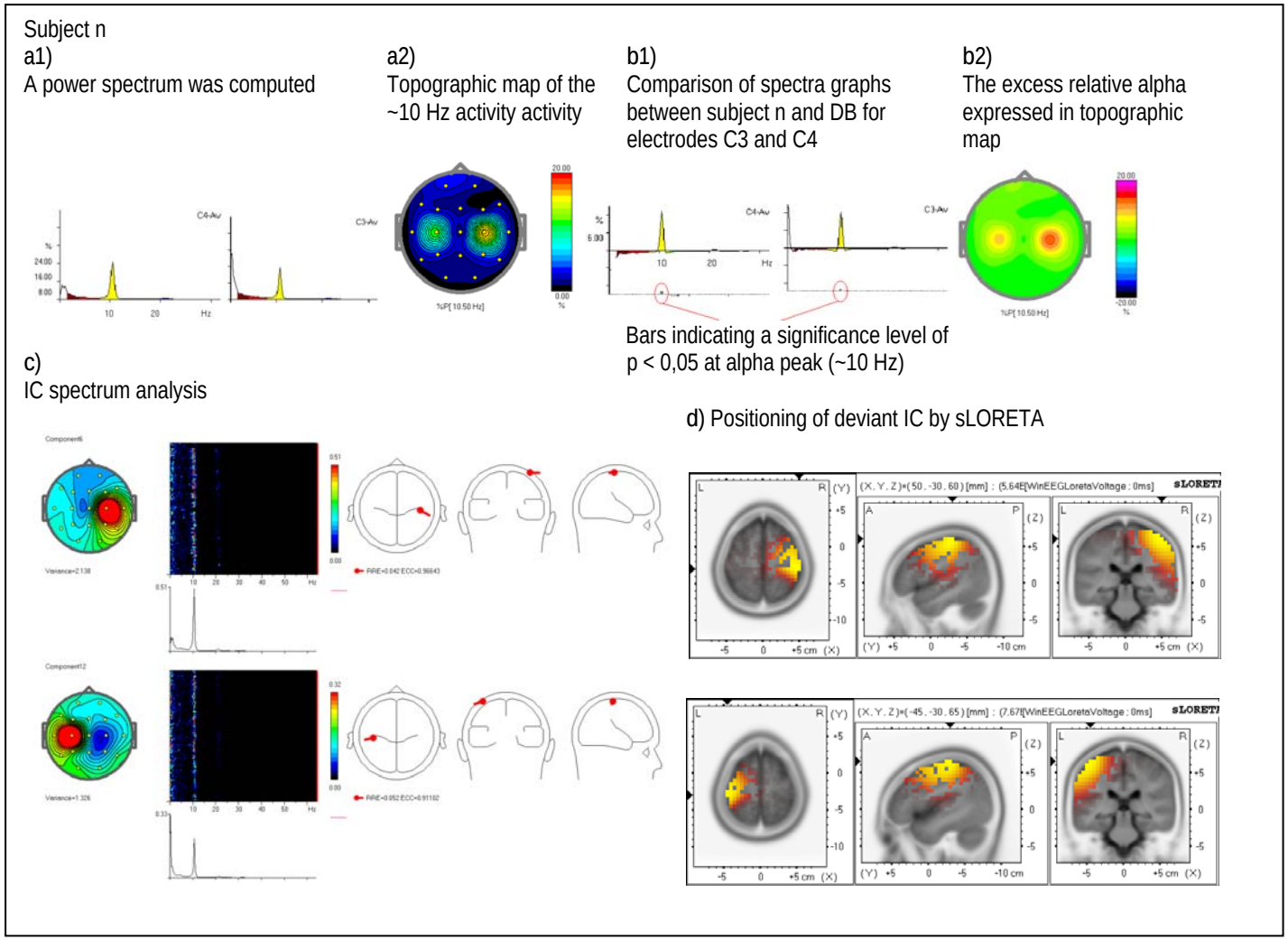

Figure 2 Schematic representation of the stepwise analysis of spectrum of individual EEG data. **a1)** Section showing the relative power spectrum of subject n expressed by graph and **a2**) topographic map for electrodes C4 and C3 selected on the basis of a statistical deviant relative alpha peak of 16,84 % (excess) in ~10 Hz shown in **b1)** and **b2)** as indicated when compared with the database (DB). Relative alpha power differed between subject n and DB with 13,54% **c)** An independent component (IC) spectrum analysis was computed for source localization of the excess alpha. The IC in C4 is depicted in the figure on top, and the IC in C3 below. **d)** Further analysis by sLORETA enabled a positioning of the excess alpha activity in Brodmann areas 2 and 1 in the postcentral gyrus for electrodes C4 and C3 respectively.

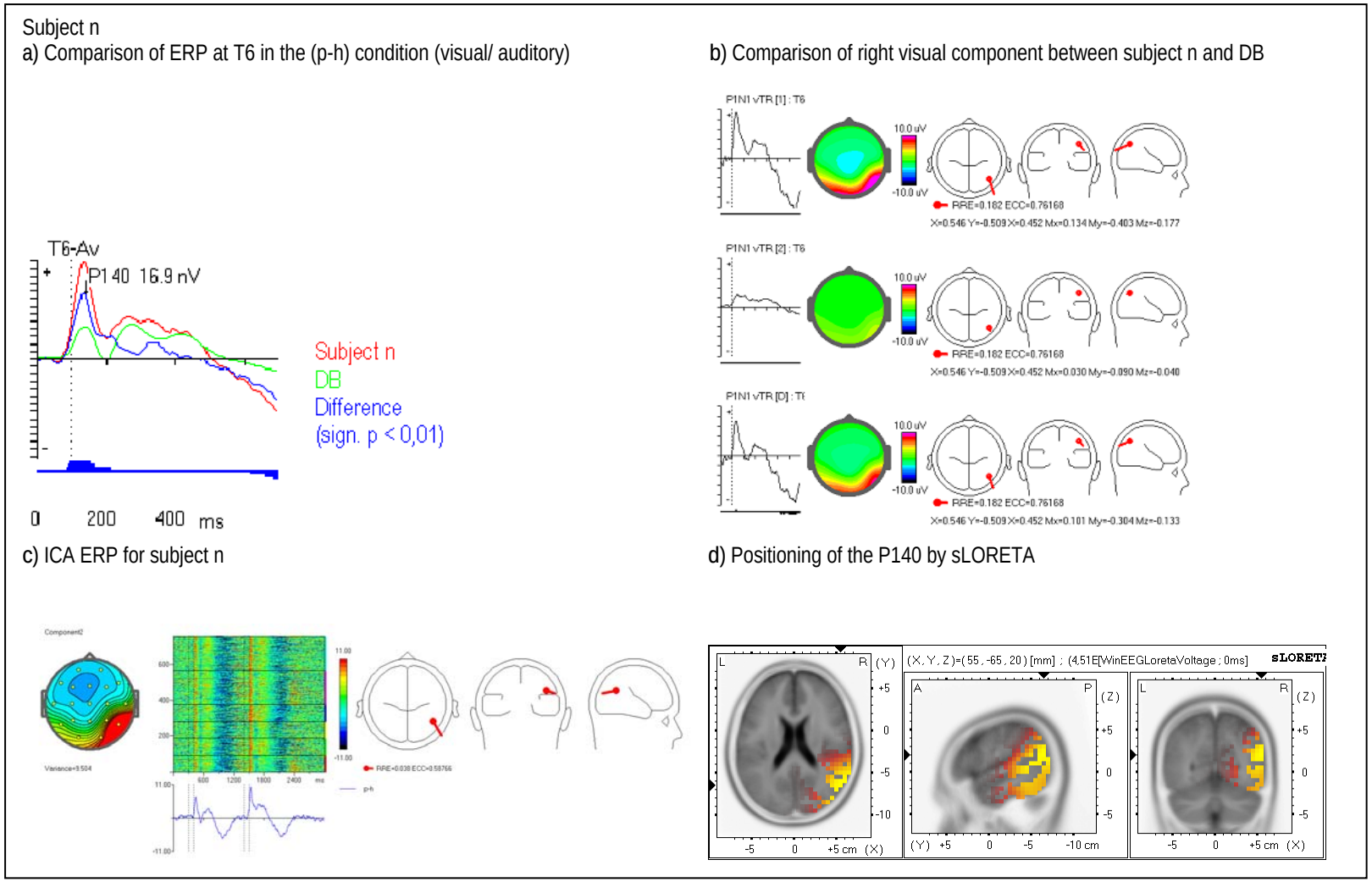

Figure 3: Schematic representation of the stepwise ERP analysis of individual EEG data. **a)** Comparison analysis of subject n with database (DB) showing a 25,84 uV positive amplitude at 140 ms post stimulus (P140) (difference of 16,9 uV from the DB), yielding a significant deviance (p< 0,01) in the plant-human (p-h) condition in electrode T6. **b)** Comparison analysis for ERP components indicated a statistical significance

($p<0,05$) for the early P1N1 right visual component. [1]=Subject n; [2]= DB; [D]= difference [1-2]. Significance bar (below) indicating sign. Deviance ($p>0.05$) **c)** Independent component analysis of single trials ERP in the p-h condition; ERP (blue line)
after the first two dotted lines represent post plant-stimulus; ERP after the second two dotted lines post human-stimulus (with sound). **d)** Further analysis by sLORETA shows that the component is generated in Ba 39, located in the superior temporal gyrus.