EEG Analysis in Adults with Attention-Deficit-Hyperactivity-Disorder

Resting state and behavioural data analysis

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"So long- and thanks for all the fish" (Adams, 2014)

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Abbreviations

ADHD – attention -deficit/ hyperactivity disorder

ANCOVA – analysis of Covariance

AP – action potential

CNS – central nervous system

EEG – electroencephalography

ERD – event related desynchronisation

ERP – Event related potential

FFT – fast Fourier transform

IC – independent component

ICA – independent component analysis

ISV - intra-subject variability

IPSP/EPSP – inhibitory/ excitatory postsynaptic potentials

(f)MRI – (functional) magnetic resonance imaging

PES – Post error slowing

RT – response time

SD – standard deviation

Summary

Introduction: Adults with attention- deficit/ hyperactivity disorder (ADHD) are examined by electroencephalography (EEG). EEG is a non-invasive method to measure brain activity indirectly, by measuring voltage changes on the scalp. This thesis focuses on EEG signals from relaxed resting, recorded with closed eyes. 8-12Hz alpha is the predominant signal and is analyzed, and we hypothesize that Alpha power is lower and more variable in ADHD. ADHD is a common childhood onset mental disorder (prevalence of about 3-7 % of school children) with symptoms of inattentiveness, impulsivity and hyperactivity. Between 50 – 70 % of patients continue to have symptoms in adulthood. Numerous behavioural studies showed that participants with ADHD have slower response times (RT) compared with control participants. In EEG/event related potentials (ERP) studies, the most consistent EEG findings have been an increased theta/beta ratio.

Methods: EEG recordings were performed in three different conditions, during resting state, Flanker task and Oddball task on 59 participants, equally distributed between ADHD patients and controls. The EEG data were analyzed in MATLAB® with EEGLAB by Independent component analysis (ICA) which separates multichannel data and projects it into a source space. The source time series were transformed into power spectra by fast Fourier transform (FFT). The alpha peak was analyzed and correlated with the behavioural data. T-tests were performed in Statistica® for most analyses.

Results: Behavioural results showed significant longer maximum RT and slightly lower accuracy for incompatible trials in participants with ADHD. Further, we found trend-significant post error slowing (PES) in participants with ADHD. EEG results showed a marginally but significantly lower parietal alpha frequency in ADHD participants while power did not show significant differences. Significant

correlations between EEG and flanker behaviour were found positive for right occipital region between alpha frequency and incompatible RT and incompatible error RT in controls. In the oddball task in the frontal region alpha frequency and RT correlated positively in controls. In the central region incompatible RT and alpha power related negatively in controls. The only correlation for ADHD was negative, in the central region compatible RT and alpha frequency correlated.

Discussion: Overall, there were only few and small differences in the resting EEG between normally developed adults and adults with ADHD. The paucity of significant differences might indicate recruitment bias, the participants that manage to meet and finish the scheduled experiments might belong to a high functioning group of ADHD cases in this study.

Conclusion: RT slowing, as found in most studies, was not replicated here, similar with Woltering et.al.(Steven Woltering, Jung, Liu, & Tannock, 2012) Less PES in ADHD was not as obvious as expected from the literature, where the majority of studies find less PES. Alpha power decrease was not found either. More research is needed on ADHD to develop robust EEG markers. Future analyses of behavioral and EEG data from Oddball and Flanker might help understand the questions on the underlying biology of adults with ADHD.

1. Introduction

1.1 Electroencephalography

Electroencephalography (EEG) is a neurophysiologic method to measure the brains' electrical activity on the scalp. It is used for diagnostics in e.g. epilepsy, encephalopathy, coma and a variety of different cognitive neuroscience research. Summation potential from active neuronal populations spread through the scull, reaching the surface of the scalp, where these can be measured non-invasively. EEG is primarily considered a functional method, in contrast to magnetic resonance imaging (MRI), because it by itself does not yield images of the brain. EEG has a low spatial resolution, about 1 cm, but on the other hand it has a very good temporal resolution, about 1 ms. (Carter, Shieh, & ScienceDirect, 2010) The German Neuropsychiatrist (*'Nervenarzt')* Hans Berger was the first to perform an EEG on humans in 1929. (Alois Ebner, 2011; Cacioppo, Tassinary, & Berntson, 2000; T Eichele, 2007)

1.1.1 EEG Generation

EEG is generated by excitatory and inhibitory postsynaptic potentials (PSP). Action potentials (AP) produce the biggest potential difference over the cell membrane in the central nervous system (CNS) (80-100 mV), but the field potential outside the cell is a lot weaker (a few 100μV). (Zschocke & Hansen, 2011, p. 2) Therefore it is generally considered that AP are too brief (1-2 ms) and produce too little current, to be measurable by EEG on the scalp. On the other hand, PSP are slower potentials, that elicit a greater current of positive charged ions into the cell and negative charged ions into the extracellular space, than AP. PSP occur when an AP arrives in the synapse and depolarizes the end head of the synapse (presynaptic membrane). This makes calcium, Ca^{++} ions stream into the synapse which leads to vesicle

migration towards the presynaptic membrane. These vesicles contain neurotransmitter substances, which are released into synaptic space by exocytosis. The neurotransmitters diffuse towards the postsynaptic membrane, of the soma or dendrite, where they bind to their receptors. This binding of transmitter and receptor leads to a brief structural change in the postsynaptic cell membrane, which opens channels for specific ions for milliseconds. An ion movement will be initiated through the channels and lead to concentration and charge differences, which change the membrane potential of the postsynaptic membrane. In most excitatory synapses the neurotransmitter is glutamate and the ion channels it opens are sodium, Na^+ and potassium, K^+ channels. Na^+ flows into the postsynaptic cell and the results in a short decrease of electric membrane potential, a depolarization. In relation to EEG measurements it can simply be said that the outside of cells become more negative. In inhibitory synapses the main transmitter is GABA which leads to the opposite net effect, more positive ions on the cell surface, hence hyperpolarisation. (Zschocke & Hansen, 2011) When a synapse is excitatory, the area outside of the postsynaptic membrane will have less positive charges, as mentioned above. This makes the area negative in comparison to other postsynaptic membrane areas. In terms of electricity, the outside of this neuron, under the excitatory synapse, is now a negative pole and the postsynaptic area a positive pole, this is called an electrical dipole. Each neuron has many synapses (pyramidal cells up to 10.000), and each forms such a dipole. These dipoles add up to a sum, which is strong enough to be measured at the skull. Therefore synchronization is important to generate measurable EEG.(Zschocke & Hansen, 2011, p. 7) When PSP occur in many million pyramid cells of the cortex simultaneously, it will be measurable by EEG. Another pre-requisite for obtaining an EEG is that the neurons involved are in an open field, arranged in parallel. This is the case in the cortex, where EEG is able to record more easily. Deeper, subcortical grey matter often has closed field structure and is therefore difficult to record on the scalp (see figure 1). (Alois Ebner, 2011)

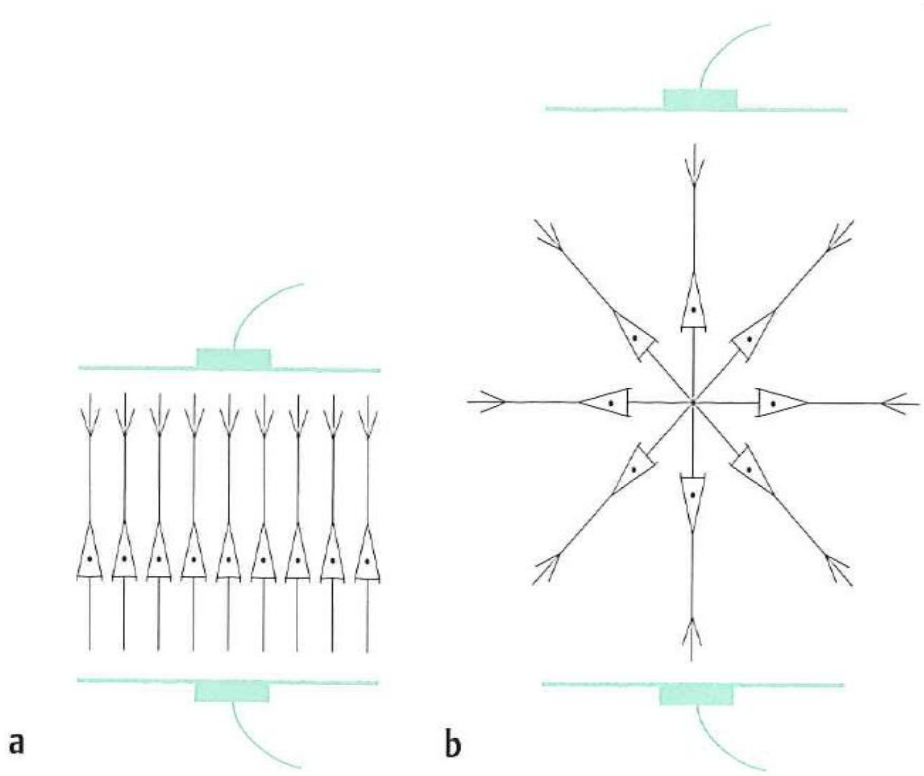

Figure 1 shows open (a) and closed (b) fields neurons can form. Only the open field form will give a clear EEG signal, while the signals in the closed field formation cancel each other.(Alois Ebner, 2011, p. 4)

Figure 2 shows how the origin of the PSP affects the polarity shown on the EEG. Notice that both a negative event and positive events in the cell can lead to negative measurements in EEG.

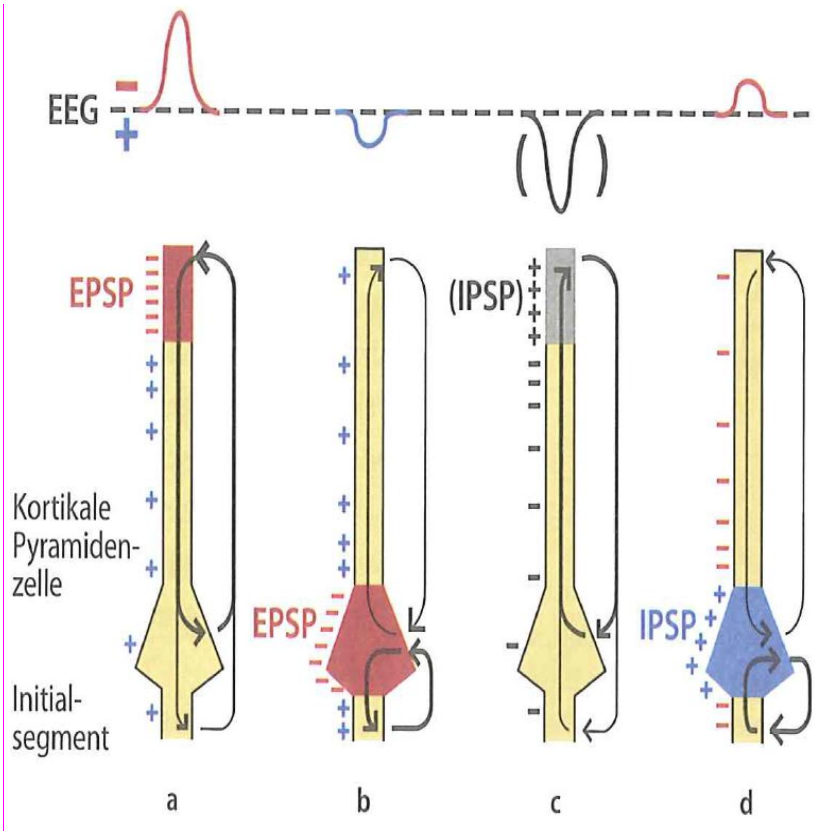

Figure 2 shows a schematic overview of the polarity of electrical dipoles in cortical pyramidal cells, depending on their synaptic activation and the voltage change in the EEG provoked through this. (a) EPSP in dendrites gives negative EEG. (b) EPSP close to soma gives positive EEG result. (c) IPSP in dendrites, very rare, would give positive EEG and (d) IPSP close to soma gives small negative EEG.(Zschocke & Hansen, 2011, p. 10)

It is generally agreed that glial cells also can contribute to slow changes in the electrical activity, but that they do not contribute to measurable EEG waves (Cacioppo et al., 2000). When interpreting dipolar structures of an EEG, one cannot always assume that the actual highest activity in the cortex is where the biggest signal is measured. If the firing neurons are on the top of a gyrus, then there will be a radial dipole at the same place on the scalp and signal and origin of signal will match. If the active neurons are tangential in the sulci a tangential dipole will be formed. In this case maximal activity will not correspond to the maximal signal measurement position; the signal will be strongest shifted left/right to the activity in cortex, like seen in figure 3. (Alois Ebner, 2011)

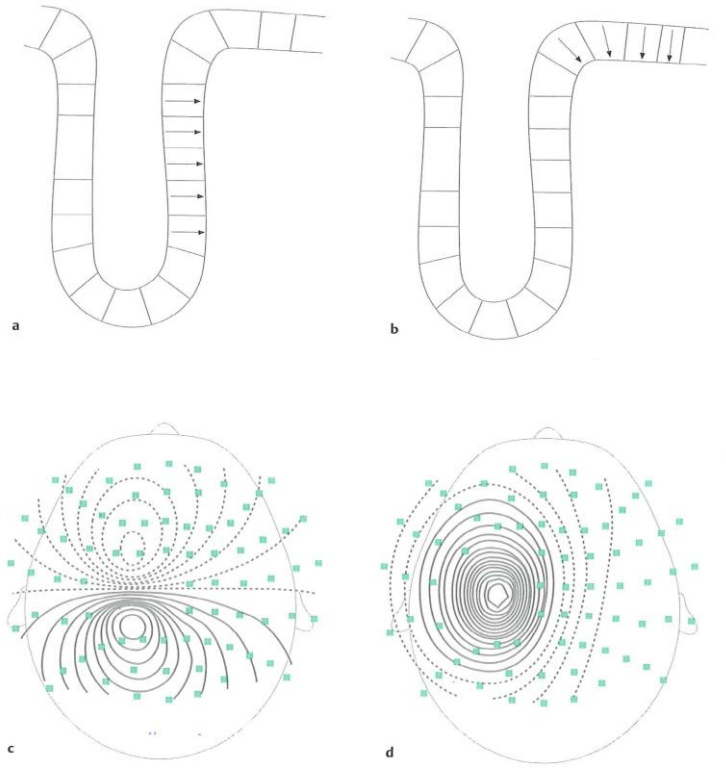

Figure 3 shows schematically how the dipole on the head depends on where in the gyrus there is activation. Activation in tangential (a) and radial (b) columns (oriented to calotte; bottom of sulci) and their respective distribution on head (c) and (d). (Alois Ebner, 2011, p. 6)

It can be difficult to correctly interpret an EEG because of the complexity of the firing in the cortex. A single source of electrical activity is unlikely to be detected, rather one sees a mixture of many sources that are simultaneously active. An EEG electrode can compared with a microphone hanging over a big crowd. This microphone will not be able to pick out one single person speaking, but will determine big events, like everyone in the crowd cheering. The full broadband and amplitude of electrical activity in the brain is only measurable in a neurosurgical setting after crainiotomy , while the non-invasive measurement is only measuring weakened signals after the penetration of both scull and skin.(Sand, 2008)

Spatial sampling

To obtain an EEG, the potential between two electrodes needs to be measured. A reference is inevitable to measure voltage, therefore a reference electrode on the head or referencing by averaging is needed. (Sand, 2008) At least 19 electrodes are needed to create reasonable spatial resolution in EEG for clinical purposes; this is reflected in the international 10-20 system, which operates with 21 electrodes including ground and reference electrode. High resolution EEG is increasingly used in research and varies between 64-256 channels samplings. Even with 128 channels, the spatial resolution of EEG will only be around 2 – 2.5 cm, which is an order of magnitude larger than what can be measured with MRI. The head is divided into 5 general zones: frontal, central, temporal, parietal and occipital, loosely representing the underlying lobar anatomy (Cacioppo et al., 2000)

Temporal sampling

In EEG one can usually sample activity in the frequencies from 1 to 30 Hz.(Zschocke & Hansen, 2011, p. 70). The Nyquist theorem states that any measurement rate should be at least twice the highest frequency of the signal to be investigated, for example if the analog –to-digital- conversion is 250 samples/sec the highest signal frequency that can be resolved is 125 Hz (Srinivasan, Tucker, & Murias, 1998). If the Nyquist theorem is not followed, false low frequency components in the signal may be the result, so called aliasing. As EPSP occur with extremely brief intervals in neurons, almost constantly in the cortex, a high temporal resolution is needed in EEG, with at least 200 points recorded per second per channel and digitalized to 12 or 18 bits. (Sand, 2008) The moderate cost of EEG and the fact that it has nearly no risk makes it a good choice of method (Carter et al., 2010).

Contributions of each frequency of the entire EEG spectrum are contained in the obtained power spectrum, (Cacioppo et al., 2000) as we can see illustrated in figure 4. Figure 4 shows the relation from the wave itself to the frequency spectrum, which will be further explored in the result section.

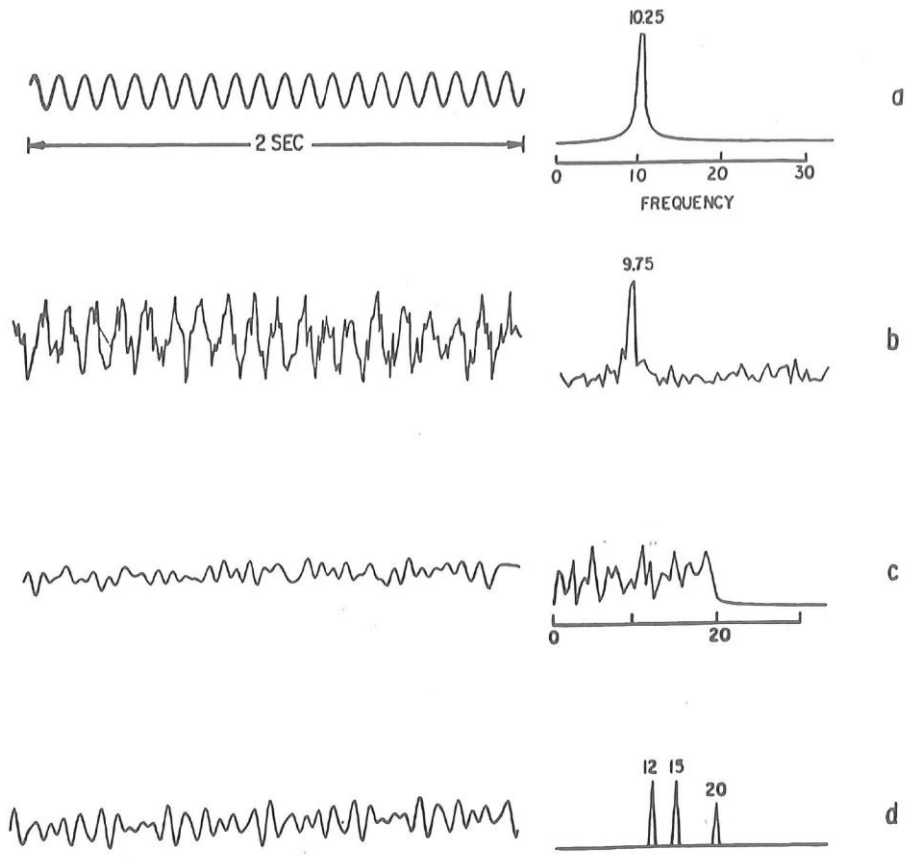

Figure 4 shows the raw signal to the right with the corresponding power spectra to the left for different mathematical functions. (a) A sine wave with a frequency of 10.25 Hz, sampled over 2 second. (b) Oscillations at 9.75 Hz with noise added. (c) Noise only, with frequency components only below 20 Hz. (d) Shows a mixture of three sinusoidal oscillations with frequencies of 12, 15 and 20 Hz. (Cacioppo et al., 2000, p. 39)

1.1.2 Alpha Band And Other Waveforms

The activity in the cortex measured by EEG is generally not considered purely spontaneous, it needs constant afferent signals from deeper subcortical nuclei. The thalamus has a central role in this signalling, specifically its reticular subnuclei, which generate rhythms in EEG (Zschocke & Hansen, 2011). Activation in the thalamus is associated with desynchronization of the EEG. Desynchronization can be event related desynchronisation (ERD). ERD means that the oscillations switch out of their idling state at rest and this is represented by amplitude decrease, in

relation to an event.(Klimesch, 2012) EEG waves show different frequencies, which are connected to various states of consciousness and age. Brain activity differs greatly between infants, children, adolescent and adults. There are both structural and electrical activity changes from the brain of a fetus to the brain of elderly. (Başar, 2012) Usually there are five classifications used for wave bands: Delta bands range from 0.5-3.5 Hz, Theta bands from 4-7 Hz, Alpha bands from 8-13 Hz, Beta bands above 13 – 30 Hz and the highest frequency is found in gamma bands, 30+ Hz. (Ebe, 2002) Delta bands are dominant in children up to two years, and they are related to deep slow-wave sleep in adults. An increase in delta bands in adults can indicate lesions or metabolic imbalance in the brain. Theta band oscillations have variable functions and can indicate drowsiness, but also executive function, attention and memory process (Cavanagh, Frank, Klein, & Allen, 2010). Conscious and aware humans with open eyes usually display a mixture of beta and gamma activity. Gamma bands are related to attention, arousal and object recognition. (Alois Ebner, 2011)

Alpha bands occur during relaxed wakefulness, with closed eyes and mental concentration. (Alois Ebner, 2011) Alpha activity increases in amplitude and frequency during maturation of the human brain and the high amplitude alpha activity moves from the posterior towards the frontal brain. This maturation needs to be taken in account when studying cognitive functions. (Başar, 2012) The alpha band is complex, since it is apparent when the subject is awake and relaxed, but it becomes instable when one gets drowsy. Drowsiness is quite likely to occur, during EEG recording or else, when ones' eyes are closed. In the vast majority of people normal EEG activity shows alpha band activity, in particular the posterior dominant rhythm. We do not know the exact function of the alpha rhythm today, but there are models that account for a variety of the observed phenomena. One is the suggestion that Alpha rhythm is a general phase-locker for the brain, but it is not global, which is why the theory is not fully embraced. (Zschocke & Hansen, 2011, p. 28) The alpha

rhythm shows a lot of variation between people, but very little intraindividual variability and e.g. slowing of alpha later in life is considered a sign of cognitive ageing, while excess slowing to <8 Hz is a hallmark in encephalopathies such as dementia. Aurlien et al. found that alpha rhythm increases up to 10 Hz until the age of 20 and remains stable until age 45, from where it starts to decline again. They found the alpha rhythm amplitude to vary a lot between age groups. The mean alpha amplitude declined from 50 μV in very young to 30 μV in 35-40 year olds, from where it was stable throughout life. (Aurlien et al., 2004) Alpha rhythm occurs mostly postcentrally, in the occipital and parietal region. The posterior dominant rhythm is desynchronized by mental activity, especially if activation is of visual character.(Zschocke & Hansen, 2011, pp. 27-29) Stress leads to desynchronization of the alpha band. ERD can be observed after stimuli, like mentioned or cognitive demands without stimulation. A hint toward alpha band activity function is the finding that the magnitude of ERD varies as a function of the semantic content of information that is retrieved, during retrieval from long term memory. Klimesch argues that event related synchronisation represents inhibition, while ERD is release from inhibition, where the increase in amplitude induces timing. Klimesch proposes that the two functions of inhibition and timing may be elementary for cognitive functions that require both suppression and selection. When seeing meaningful objects, the EEG alpha frequency band coherence, in the occipitotemporal region, is strengthened. Mental calculation is associated with stronger frontoparietal alpha and beta band phase synchrony. This shows cognitive tasks involve pronounced large-scale alpha frequency band phase synchrony. (Klimesch, 2012) (Herrmann, Strüber, Helfrich, & Engel, 2015)

Palva and Palva conclude with several points: top-down modulation is mediated by alpha frequency band phase interactions, alpha frequency band oscillations can phase lock between widely separated cortical regions and therefore functional networks. In response to cognitive demands alpha oscillations can be synchronized

with theta, beta and gamma oscillations, which might be essential to coordination and communication. (Palva & Palva, 2007) Alpha oscillations exhibit an inverse correlation with cognitive performance, thus suggesting an inhibition of task-relevant cortical structures. (Herrmann et al., 2015; Jensen & Mazaheri, 2010). There remain fairly different conclusions from these models, there is therefore uncertainty about the alpha wave and its function.

Several alpha bands have been suggested, 9-10 HZ and 11-13 Hz. (Cacioppo et al., 2000) Also there are different alpha variants that lie outside of the typical alpha range, like fast alpha variant in beta spectrum 16-18(-20) Hz and slow alpha variant in the theta spectrum, 5-6 Hz. These are very similar to alpha in several ways and it is suspected that they are from the same generators. In children and adolecents there is also a slow 4/s variant and a delta variant in EEG, which is also called "posterior slow waves of youth".

The μ - (Mu- or my-) activity is, after occipital alpha, the most frequently occurring form of a local specialized rhythm. μ stands for motoric and it occurs mostly in the precentral region. The frequency lies dominantly between 10-11/s and is distributed individually between 8-12 /s. μ rhythm is mostly 1/s frequency faster than alpha and has a different dynamic. μ is uninfluenced by visual stimuli and disappears when vigilance is reduced. (Zschocke & Hansen, 2011)

Silva et al. (1991) found that pyramidal neurons of layer 5 can fire unstable rhythmic patterns at 5 to 12 Hz. Fragments of cortex only containing layer 5 could generate oscillations at 4 to 7 Hz, while cortex without layer 5 does not oscillate. The conclusion was drawn that some neurons have intrinsic attribute to oscillate. Groups of these neurons may interact synaptically to produce synchronous patterns. But rhythms can also occur by a network of neurons, which as individuals are non-rhythmic. Alpha rhythms are found at cellular level, in 10 Hz oscillations, so the alpha rhythm represents a basic physiological property of the brain. In contradiction

to earlier suggestions, Alpha does not reflect "passive states" of the brain. (Başar, 2012):

1.1.3 Artefacts

EEG recordings are easily affected by artefacts. Artefacts may be divided into biological artefacts and non-biological artefacts. Most of the biological artefacts, like eye-blinking, eye movement and ECG are not possible to avoid during recording. Artefacts due to eye movements appear more distinct in the frontal electrodes, and are easy to detect with an additional electrode beneath the eye. Similarly, by using an additional electrocardiography (ECG) electrode, the related electric and pulse artefact are easy to detect. Muscle artefacts are possible to minimize to a certain degree, by instructing the participant well. Still, they are quite common, especially in children and in patients with movement disorders as e.g. Parkinson's disease or Tourette syndrome. Most commonly they appear in frontal and temporal electrodes from jaw clenching or frowning. There are also possible muscle artefacts in the occipital electrodes from the muscles in the neck. (Cacioppo et al., 2000)

Non-biological artefacts are technical artefacts, such as poor electrode contact, faulty equipment, and interference from other electrical devices close to the EEG recording, which lead to noise on the recordings. For this reason, it is of great benefit to do EEG recordings in an electro-magnetically shielded chamber. (Alois Ebner, 2011; Ebe, 2002) The electrical noise has 50 Hz frequency and is easy to detect, but not as easy to eliminate. 50 Hz stop-band/notch filters may be used. (Cacioppo et al., 2000)

1.1.4 Independent Component Analysis

Independent component analysis (ICA) is a powerful method to separate multichannel signal sources, e.g. in order to separate artefact from EEG activity of interest. ICA belongs to a class of blind source separation algorithms, and can be

compared to the cocktail party problem in order to illustrate its function: many people are talking at the same time in a room and a set of microphones, installed in that room, will pick up a mixture of all these voices. How to filter out one voice from the mixture of voices the microphone records? ICA will identify the individual signal components (voices) that are unrelated from the mixture (microphone output) based on the spatial distribution such that the sources are maximally independent over time. (Stone, 2002) Independence is meant here in the information-theoretic sense, i.e. that knowing the value of one signal provides no information about the value of the other signal. The assumption is that statistically independent signals are derived from different physical processes. In EEG, each electrode output is a temporal mixture and gives a mixture of temporal independent components (IC), ICA is used to estimate these temporal IC's. (Stone, 2002). EEG signals from different cortical sources are highly temporally independent. However, due to properties of signal propagation and volume conduction, scalp recorded signals are mixed and highly correlated. Which means that scalp EEG measured at one place, at a given time, allows no inferences of EEG activity in other sources at the same time. The ICA separates the data matrix (X) based on that the source time courses (U) are independent and finds the "unmixing" matrix (W). When unmixing matrix (W) is multiplied with the original data (X), the matrix (U) of IC is calculated:

Eq. 1 $U=WX$

Rearranging the formula:

Eq 2. $X=W^{-1}U$

The portion of the original data (X) that forms the *i*th IC (X_i) is the products of two vectors, the *i*th column of W and the *i*th row of U;

Eq. 3 $X_i=W_i^{-1}U_i$

ICA is powerful in separating electrooculography (EOG), electromyography (EMG) and ECG and pulse artefact. IC usually fall into one of four categories, cortical brain sources, biological artefacts like eye- or muscle movement, cardiac pulse artefact or external artefact. (Onton, Westerfield, Townsend, & Makeig, 2006). In a typical recording, one can expect about 10-20 temporally and dynamically distinct EEG sources in data from normal subjects. (T. Eichele, Calhoun, & Debener, 2009; Onton et al., 2006)

1.2 Attention -Deficit/ Hyperactivity Disorder

ADHD is a mental disorder that has its onset in childhood, with various behavioural symptoms, the main problems being inattentiveness, impulsivity and hyperactivity. Examples of symptoms for inattention are "does not seem to listen when spoken to", "often has difficulty sustaining attention in tasks or play activities", "often easily distracted" "makes careless mistakes" and "often has difficulties organizing tasks and activities". Symptoms of hyperactivity are "fidgets with hands or feet or squirms in seat", "often talks excessively" and many more. To diagnose ADHD, impairment from the symptoms must be present in two or more settings such as school and home, symptom onset must be before age of 7 and they must persist for at least 6 months. Also, six or more of nine symptoms for either inattentiveness (predominantly inattentive subtype) or hyperactivity/impulsivity (predominantly hyperactive-impulsive subtype) or both categories (combined type) must be present. (American Psychiatric Association . Task Force on DSM-IV, 1995)

Although the numbers vary in different publications prevalence of ADHD is estimated to be 3-7% of all school aged children. ADHD is more common in males, than in females. (Halmøy, 2011) In some studies it has been reported that boys are nine times more likely to have ADHD than girls. In adulthood the ratio shifts to 2:1, which could indicate that especially girls are under- diagnosed in

childhood.(Carlson, 2007), in particular since inattentiveness is more predominant in girls.

ADHD in adults is less studied than in children and it was earlier believed that symptoms lessen significantly or disappear in early adulthood. In the last decades, studies have shown that between 50-70% of adults continue to have symptoms later on in life.(Barry, Clarke, & Johnstone, 2003) The symptoms often change. While the hyperactivity is reduced, inattention can worsen. Impulsivity, organization struggle, little focus and emotional dysregulation can lead to difficulties in having sustainable work and private relationships. The inability to relax, the intolerance of boredom and impulsive decision making might even lead to socially inacceptable behaviour. (Ginsberg, Hirvikoski, & Lindefors, 2010; Pinhard & Dovi–Akue, 2004) In addition to the core symptoms, patients might experience a variety of other problems, due to additional disorders. In adults with ADHD approximately 80% have been reported to have one comorbid disorder and about 50 % qualify for two or more comorbid diagnoses. Most common comorbid disorders in adult ADHD are anxiety, learning disabilities, depression, bipolar disorder and substance abuse. (Halmøy, 2011)

Genetic findings underlying ADHD biological cause are inconsistent, even though there are several candidate genes. ADHD is considered to be highly heritable, with a heritability of approximately 75%. (Halmøy, 2011)

On average, the brain volume is reported to be reduced by 3- 4% in ADHD children compared to age-matched controls. (Halmøy, 2011; Solanto, 2002) Affected brain areas in ADHD that are reported to be affected include the caudate nucleus, globus pallidus, anterior frontal cortex , cerebellar vermis, anterior cingulate cortex and corpus callosum (Kasparek, Theiner, & Filova, 2013; Solanto, 2002). Kasparek et.al. find the main anatomical difference to control brains is that the regions are smaller in ADHD. The caudate nucleus, vermis, prefrontal cortex and anterior cingulate

cortex all show a reduction in grey matter volume. Loss of integrity is shown in the prefrontal and anterior cingulate cortex.(Kasparek et al., 2013)

There are different theories on underlying cause of ADHD, the first being that there is a developmental lag in CNS function in ADHD children. This means that they behave as younger children normally would do. The second theory states that ADHD is an abnormality in the function of CNS, so the measured EEG would not be considered normal in children of any age. Finally, there is the hypoarousal model of ADHD, which suggests that the disease results from cortical underarousal. All three theories have some support. (Barry et al., 2003)

Treatment for ADHD can be psychological training and therapy or medication. The most common ADHD medication prescribed today is methylphenidate (Ritalin®), which is a phenethylamine (Felleskatalogen; Markowitz, Straughn, & Patrick, 2003) Methylphenidate has varying effect, studies showed that the response rate, rated by physicians are between 19% - 78% in short term studies. Amphetamines are also used as ADHD treatment, the effect lies between 34% -70%. Overall there is strong evidence for effectiveness of methylphenidate and amphetamines on reducing core ADHD symptoms in both short term and long term studies. (Fredriksen, Halmøy, Faraone, & Haavik, 2013; Torgersen, Gjervan, & Rasmussen, 2008) Methylphenidate works by inhibiting the reuptake of dopamine and noradrenaline into the presynaptic terminal. Therefore, it is defined as a dopamine agonist. (Carlson, 2007) The neurotransmitter dopamine is involved in the regulation of movement, cognition and motivation, while noradrenaline has an important role in arousal. These aspects are part of ADHD psychopathology. (Halmøy, 2011)

Apart from the defining clinical symptoms, people with ADHD will also perform differently in simple behaviour experiments and have different behavioural outcomes. Response time (RT) varies in different age groups, which is important to keep in mind during this research. Children between 8-10 have a typical slow RT,

which keeps accelerating until the age of 17-20,when people are at their fastest, with 350-400 ms. After that age, one can estimate to slow down 25ms per decade, in the 30th 375-425 ms, 400-450 ms in the 40th and so on. (Fozard, Vercruyssen, Reynolds, Hancock, & Quilter, 1994) Some studies show that patients with ADHD have greater variability in RT than controls and overall somewhat slower RT. This means that that increased intra-subject variability (ISV) for RT is one of the strongest findings in ADHD. (Andreou et al., 2007; Hervey et al., 2006; Saville et al., 2014; Thissen et al., 2014) However, Woltering et.al. could not find significant differences in measures related to RT. (S. Woltering, Liu, Rokeach, & Tannock, 2013) A participant who is very tired will have longer and more variable RT, as vigilance is important during RT measurements.

One of the cognitive domains that can be tested is cognitive control/performance monitoring. A number of psychological tests can be used, one of them being the Eriksen Flanker task. The Eriksen Flanker task activates the anterior cingulate cortex,(Davelaar, 2012) which is also involved in emotional regulation and decision making (Bush, Luu, & Posner, 2000; Bush et al., 2002). It is used to study brain activity while making errors. Immediately after an error has occurred, there will be time and phase locked waves in an EEG called ERP, event-related-potentials.

Post error slowing (PES) is another phenomenon connected to errors that can be measured by the Flanker task. While people usually commit fast error responses, RT are slow after they committed an error and adapt then to their own baseline RT after a post error trial. The current understanding is that PES is an outcome of cognitive control that provides signals to optimize the behaviour to avoid more errors.(H. Eichele, Juvodden, Ullsperger, & Eichele, 2010) However, other theories have also been proposed, like PES being an orienting response. (Dutilh et al., 2012; Notebaert et al., 2009) Balogh and Czobor published a metanalysis of all studies that include PES in ADHD in 2014. They found that out of 24 studies 19 stated that ADHD patients have less PES than controls where the whole standard deviation (SD) is

above 0 effect size. They stated both groups slow down, but "PES in ADHD is markedly diminished compared with PES in control group". (Balogh & Czobor, 2014)

1.3 EEG Research in ADHD Patients

There has been a lot of research with EEG in ADHD patients, especially in children but also in adults. Predominantly inattentive ADHD patients have less posterior Alpha suppression during Flanker task when giving response preparing cue on trials. Posterior alpha suppression has been linked to behavioural attention benefit, where ADHD patients also have slower RT. (Mazaheri et al., 2014) EEG studies have found increased delta and theta power and activity in ADHD. Also decreased beta and gamma power was found. Theta/beta ratio is one of the most prominent and consistent findings in EEG oscillations in patients with ADHD. The theta power has been found to be increased, while beta power is decreased. (Barry et al., 2003; Basar & Guntekin, 2013, p. 28; Calderone, Lakatos, Butler, & Castellanos, 2014) In 2011, Arns et. al. published a meta-analysis of research done on the theta/beta ratio and found that the effect size of findings in this research has gone down in a linear manner throughout the years in which the studies were done. This is known in statistics as the decline effect or generalizations decay, and hints at weak initial findings. (Arns, Conners, & Kraemer, 2012) People with ADHD have lower power in their alpha bands and lower percentage time of alpha than controls. (Barry et al., 2003)

Several studies that assessed ADHD with an Oddball paradigm (see below) found that ADHD patients showed reduced N1, P2 and P3 (specific ERPs) amplitudes. The P3 is important in decision making, among many other things, like information processing (Polich, 1997) and attention switching (Friedman, Cycowicz, & Gaeta, 2001). N2 and P3 also showed reduced latency. Different studies found varying

effects on ERP components and differ in study setup, so conclusions are inconsistent, but many studies interpret the results as deficit in ADHD to process stimuli and attention allocation. Many EEG ADHD studies have small sample sizes and they often do not take comorbidity and subtypes in ADHD into account. Flanker task studies have found mostly a reduced N2, which could indicate issues with conflict resource and processing allocation. (Johnstone, Barry, & Clarke, 2013) Distraction tasks indicate attention switching problems in ADHD patients. Helps and co-workers showed in 2010 that ADHD patients have a different very-low-frequency-network at rest, compared to controls and suggest deficits in "switch from rest to task" situations for ADHD. (Helps et al., 2010) Vollebregt et.al found a relationship between the theta/beta power ratio and ADHD core symptoms. They also point out that low alpha peak frequencies can affect, "leak" in a way, the theta band power and that this needs to be taken in account. (Vollebregt, van Dongen-Boomsma, Slaats-Willemse, Buitelaar, & Oostenveld, 2014) Mazaheri et.al. found that children with ADHD don't have the same pattern of anticorrelation between posterior alpha and frontal theta, as control children do. They concluded that children with ADHD might not fully utilize top-down attentional control on sensory processing. (Mazaheri et al., 2010) There is a lot more to be said on ERP studies in ADHD, but it would exceed the frame of this introduction.

2. Aims

This study is part of the University of Bergen K.G Jebsen Centre for research on neuropsychiatric diseases. The project started in 2004 and is ongoing. The main goal of this study is to gain knowledge about adults with ADHD and ultimately improve diagnostics and treatment, since there is a lack of diagnostic criteria, based on an organic/biological marker, in both adults and children. The underlying biological processes of ADHD need to be more studied. The project has established a national bio-bank of blood/salvia samples and other information on health and symptoms from both ADHD and control persons. Every subject is diagnosed according to ICD10 and DSM IV criteria, and questionnaires with ADHD symptoms and other information are filled out. Molecular genetic studies and protein analysis are also performed. Some participants were asked to participate in clinical interviews, neuropsychological testing and EEG and fMRI recordings. The EEG/fMRI part "Adults with ADHD cognitive function and brain imaging" is an add-on part with data collection from March 2012- December 2015. (Haavik, 2015) This thesis comprises the EEG data collected in the study. The first 60 participants of the study were included in the analyses with following aims:

1. Statistically evaluate behavioural parameters collected during a modified Flanker task and an Oddball paradigm.

2. Analysing the resting state dataset of the EEG – data to be able to use artefact clear data for further statistical analysis and analyse the alpha band. Examine resting EEG collected before behavioural data for correlations between alpha frequency/power and response speed and accuracy. The hypothesis was that participants with ADHD have lower alpha wave power and frequency, less accuracy, slower RT and less PES. We also expect correlations between alpha and behaviour data from Flanker task and Oddball paradigm to be low,

Connectivity in the frontal and occipital region was hypothesized to be different between ADHD and controls.

3. Materials and Methods

This study was conducted at the K. G. Jebsen Centre for research on neuropsychiatric disorders at the University of Bergen and it is part of the main project "ADHD in Norway". Participants were recruited through an ongoing study (http://www.uib.no/kgj-npd). The data collection is ongoing and the first 60 participants (male n = 30, female n = 30) were included in the statistical analyses.

The main and add-on study were approved by the Regional Committee for Medical Research Ethics, West-Norway (REK) and written consent was obtained from all participants (REK numbers are 2012/95 for the MR/EEG study and 2013/543 for the ADHD in Norway study.)

Patients met the criteria in Diagnostic and Statistical Manual of Mental Disorder, fourth edition (DSM IV) and were confirmed by a specialist in psychiatry. ADHD symptoms were determined in adult ADHD self- report Scale, along with a neuropsychological test battery (data not shown here)(Kessler et al., 2005). Exclusion criteria for the control group were a life time history of ADHD, or a current DSM-IV axis I disorder. Additional exclusion criteria for all groups were epilepsy, head trauma with loss of consciousness, suspicion of Autism spectrum disorder, prematurity (gestational age < 36 weeks), or an IQ below 75, measured by the Wechsler Intelligence Scale for Adults-IV (WAIS). (Wechsler, 1955)

After verbal and written instruction and a training sequence, participants performed three different tasks - a five minute resting phase and two psychological tests, the oddball and the Eriksen flanker task in a randomized order, EEG was recorded during all three tasks.

3.1 Resting state

During resting state task the participant was asked to sit as still as possible with closed eyes for 5 minutes. This is done to get a baseline EEG. This part of the study is analysed in this thesis.

3.2 Oddball

In the Oddball task three different sounds were presented one frequent standard sound, that is low pitched (500 Hz) (70% of all trials), a target sound, to which participants are required to respond to, it is higher pitched, with 750 Hz (15%) and a distracter sound (white noise), presented 15% of the trials. All stimuli were presented at 80 dB and for 75 ms. The interstimulus – interval was 1 s and the sounds are presented randomly. In total 500 trials were collected per participant 250 being standard and 250 being 100 standard, 75 target and 75 noise trials.

3.3 Eriksen Flanker Task With Feedback

The Eriksen flanker task is a visual forced choice task. Participants were presented 6 horizontally orientated flanker arrows appearing below a fixation point. A centre target arrow was presented 100ms after flanker arrows pointing either in the same direction as the flanker arrows (compatible: <<<<<<< or >>>>>>>) or pointing in the opposite direction as the flanker arrows (incompatible: <<< > <<< or >>> < >>>) Participants were instructed to press either the right or left mouse button following the direction of the central target arrow. Target and flanker arrows remained on screen until response was registered followed by a fixed 800 ms interval before onset of the next trial. Compatible and incompatible trials as well as right and left responses were kept on a 0.5 probability, respectively. Response feedback was given when RT or error rates increased. Response feedback was given either as an “x” to

indicate that the participant had made an error or as an exclamation mark, "!", to indicate slower answers (adaptive threshold , mean plus 1.5 standard deviations), these were shown for 800 ms. Stimuli were presented in two blocks, 260 trials that were pseudorandomized, a total of 520 trials were collected per participant. The target arrow appears later than the flanker to provoke a pre-response and post-response conflict, which means that the brain locks itself on the arrows that for example point in the right direction and then has to shift to left, if the trial is incompatible and the target arrow points left. (H. Eichele et al., 2010)

3.4 Practical Protocol For Jebsen-Study – EEG Recordings

To ready the EEG-equipment; turn on lights in EEG chamber and two PC's in the lab. On one PC open "Vision recorder"-program (Brain-Products-GmbH, 2015). Open the check screen for impedance for all electrodes. Open "E.prime" studio-program, to track responses/behavioural data (Psychology Software Tools, 2015). If the circumference of the participants head is known, prepare the electrode cap (BrainCap-MR3 64Ch from EASYCAP GmbH, 82211 Herrsching, Germany) with electrodes before the participant arrives, if not measure the head with a measuring tape. Find the right sized cap and put it on a Styrofoam head for easy handling. Put the 64 + 2 (ground and reference) Ag electrodes ends in electrode-input-box – 64 channels (Cat No. EIB64-A, EASYCAP GmBH, 82211 Herrsching, Germany) and the electrode contacts in the plastic mounts in the cap. In figure 5 the arrangement of the electrodes on the scalp can be seen.

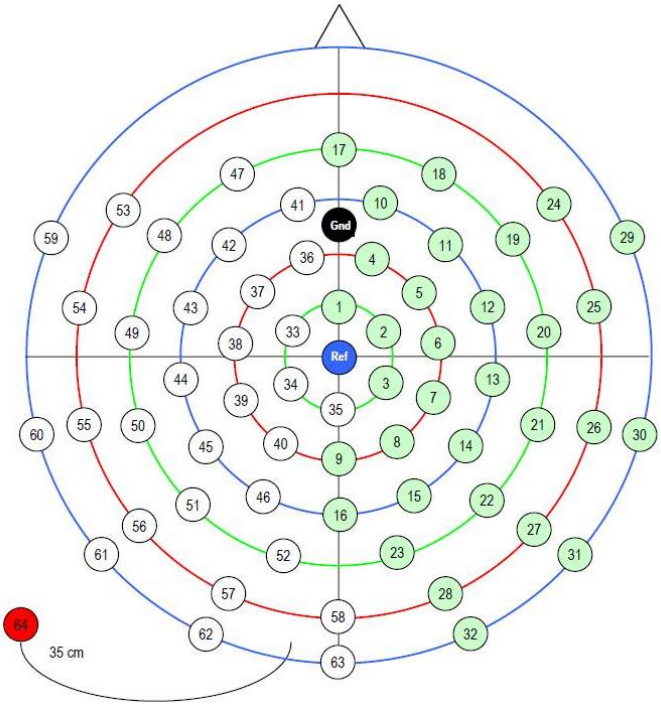

Figure 5 shows equidistant electrode distribution on head for study. 64 electrodes are indicated. Black shows ground electrode and blue shows reference which is recorded from the middle of the head. The red electrode indicates the ECG which is attached to participants left chest.

Show the participant the recording chamber and let them take place in electro-magnetically shielded chamber. Place the cap on head, check that it sits correctly, i.e. reference in the midpoint between nasion and inion, and on midpoint between ears (Cz). Fill about 20 ml Isopropyl alcohol 70% in a plastic cup. Inspect and wash the skin in the electrode mounts with a swab drenched in Isopropyl alcohol 70%. Fill a new plastic cup with about 20 ml conductive and abrasive gel (Abralyt 2000,EASYCAP GmbH, 82211 Herrsching, Germany). Apply the gel on the scalp beneath the electrodes. Apply some paste on the ECG electrode and tape it on the participants left chest, lateral to the mammillary line intercostal 5-7. All the 64 electrodes need to be adjusted to reduce skin impedance (<10 kΩ).

Before starting the recording, instruct participants how artefacts affect the signal by showing the online EEG trace on screen and asking participants to generate typical artefacts (eye blinking, chewing). Motivate them to sit as relaxed and as still as possible, as this is important to get good EEG data. Start a recording where the participant sits still for 5 minutes with closed eyes. To start the oddball or flanker test open the correct file on the PC that runs E.prime. Push "run" and fill out all the information the program asks for: Subject Number, Session Number, Age, Gender, Handedness and Researcher ID. The order of the experiments is counterbalanced.

Explain the first task, either flanker or oddball, to the participant, let the participant do the training and start the task. Look at the EEG recording and E.prime program to see if the participant has understood the task and that the EEG looks correct. Save on vision recorder before recording and E.prime after recording.

3.5 Descriptive Statistics of Behavioural Data

The descriptive statistics were done in MATLAB® (Mathworks, Natick, MA, USA) software. For the **oddball,** we computed: accuracy, minimum RT, maximum RT, the mean for RT, the SD, variance, skewness and kurtosis. This was done to evaluate individual performance of participants and detect outliers, as well as reviewing the data and preparing for correlation with EEG data (This is true for Flanker task as well).

For the **Flanker** task the accuracy was computed to see if participants had high enough accuracy. The minimum RT and maximum RT were computed and plotted, for compatible trials, incompatible trials and incompatible errors, because this is a feature where we suspected differences between groups ADHD and control. Mean RT and SD were computed and plotted, for all three different conditions as well, to look for differences.

PES was calculated and plotted for flanker data, by finding all errors between 100 and 1000 ms and the error RT (error speed) and the trials -2, -1, +1 and +2 from error, to see how RT differs through the time course of making a mistake in Flanker task.

In addition a multiple linear Regression was done on PES, it models RT. The linear regression equation is shown:

$$\text{Eq. 4} \qquad y_i=\beta_0+\beta_1 X_{i1}+\beta_2 X_{i2}+\cdots+\beta_p X_{ip}+\varepsilon_i, \quad i=1,\cdots,n,$$

Where, yi is the i^{th} response. β is the coefficient, where $\beta 0$ is the constant term in the model. Xij is the i^{th} observation on the j^{th} predictor variable, j = 1, ..., p.εi is the i^{th} random error.(http://se.mathworks.com/help/stats/what-is-linear-regression.html). The regression model allows a more exact calculation of PES because it takes error sources, for example two errors in a row, into account.

The statistics described below were performed in Statistica® (StatSoft, Tulsa, OK, USA). A Chi-Square test was conducted to check if gender and handedness was distributed equally in groups. For **PES,** correlations between error speed, PES and pre error speed were done as well as a T-test between ADHD and control. Analysis of covariance (ANCOVA) was done for PES with covariates gender and age.

For **Flanker incompatible** trials, correlations were performed between mean RT on error responses, SD RT error, min /max RT error responses and accuracy. A T-test was done for the same parameters between groups. ANCOVA was done for age and gender. For **Flanker compatible** trials the same correlations, ANCOVA and T-test were done. For **Oddball** task correlations between mean RT and SD RT, min/max RT and accuracy were done. T-test between groups for mean RT, SD RT, min/mas RT and accuracy was done. ANCOVA for age and gender was done.

3.6 EEG Resting State Analysis

To analyze EEG data "EEGlab", an interactive MATLAB® toolbox for processing event-related EEG data and other electrophysiological data, was used. (Delorme & Makeig, 2004) The datasets were imported into MATLAB®. A filter was applied to the data to remove frequencies of no interest, with a high-pass filter of 0.5 Hz and a low-pass filter of 40 Hz. The data was decimated to 500 Hz sampling rate. (Widmann, Schroger, & Maess, 2014)

EEG signals of interest are obscured by a variety of artefacts, like mentioned in the introduction. In order to identify and remove known artefacts we used a template matching approach similar to CORRMAP and COMPASS (Viola et al., 2009; Wessel & Ullsperger, 2011). To retrieve the hidden data, ICA was used and 30 IC were estimated. Initially, we visually identified a component in three single subjects, that best matched across all subjects and used it as a template in order to automatically identify and create a group template (step 1) and reject one independent component per dataset (step 2). The outline of the method can be seen in figure 6.

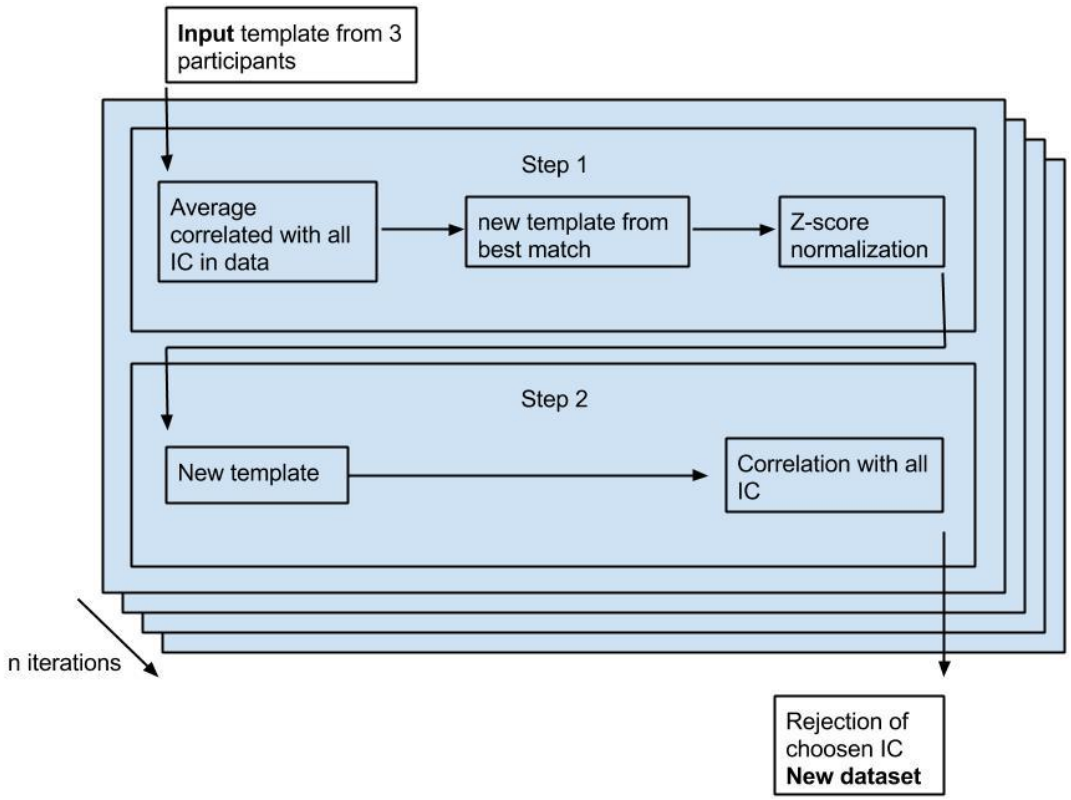

Figure 6 shows the method used for IC selection schematically. N iterations is the number of participants the method ran through.

COMPASS retrieves IC with help of outliers in the voltage pattern of the spectrum, but is also operates with two passes like done in this study. (Wessel & Ullsperger, 2011)

The IC selection was repeated for lateral eye movements and ECG artefacts. Lateral eye movements were found in all datasets even though the resting state task was performed with closed eyes. Other components with sparser topographies and little overall contribution to the variance of the EEG signal were identified using z-statistics.

ICA is powerful for separating data in a time course, but not on spectral aspect of the data, this is why one also needs Spectral analysis. In this study fast Fourier transform (FFT) was used, to convert data into frequency domain. Which means it decomposes the complex EEG signal into underlying sine wave components and

computes the amount of power at different frequencies, like shown in figure 4 in introduction. The spectral time information is lost during FFT, but one gets good information about the frequencies contained in the data. The FFT computes the discrete Fourier transform faster. Fourier transform takes the time signal as input and computes the amplitudes of the sine waves, which one would need to add, to recreate the waveform which was put in. The biggest advantage of FFT is that it is faster than comparable methods and it is good for processing of stationary signals, a disadvantage is that it does not have good spectral estimation and cannot be employed for short EEG signals. (Al-Fahoum & Al-Fraihat, 2014; Cacioppo et al., 2000; Cochran et al., 1967; Luck, 2005) Like with the electrode artefacts, the data are sorted by power and the weakest are rejected. After the spectral analysis 9 IC per dataset were left.

Five templates were then generated for alpha- band components: 1. Left occipital, 2. Right occipital, 3. Central, 4. Frontal, 5. Parietal. The remaining 9 IC were analyzed according to these five templates. These data were used to correlate to behavioural data and find the alpha peak, which will be further explored in the result section.

To visualize the progress in the analysis of EEG data there is figure 7 below. Figure 7 a) shows the data raw, like it was imported into MATLAB®. The data improves tremendously through filtering (b) and ICA (c).

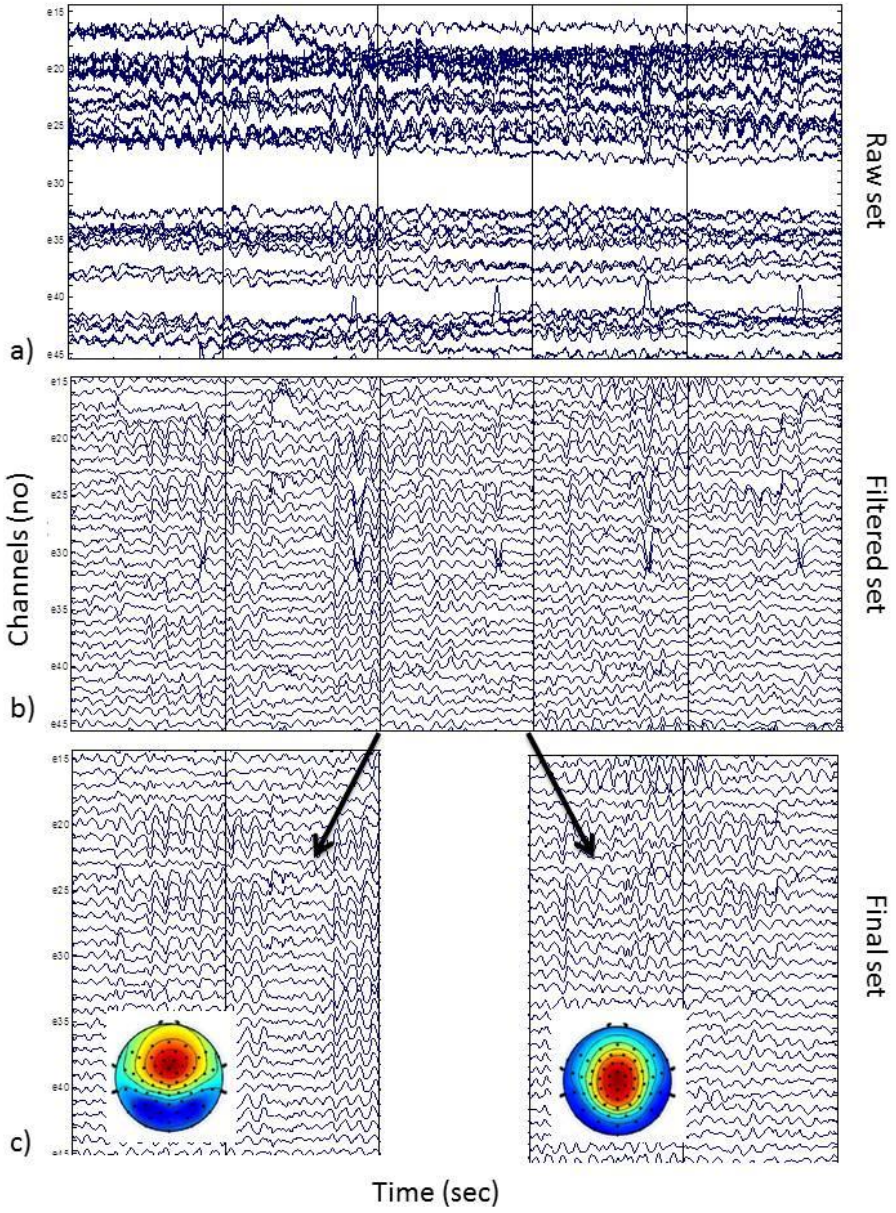

Figure 7 shows an example of one participant with a 30 channel EEG recording to visualize analysis of EEG data. a) The raw data is shown. Seconds 20-25 from the recording are shown. The alpha waves can be glimpsed but nothing is clear. The heartbeat artefact can be detected throughout all channels. b) The same participant and same timeframe is shown again after filtering the raw data. All the very high (and very low) frequencies were filtered out, the alpha waves can be seen more clearly. The heart artefact can still be observed over the whole recording. c) The data has been cleared by ICA and IC selection. Alpha waves are clearly detectible and there are no more artefacts, like the heartbeat. The selected IC's are shown.

Mean Alpha peak power and frequency were computed by group and found manually for all participants. The mean was computed for all 5 brain regions by group and a t-test was done to check for group differences in alpha power and frequency. A global alpha peak for power and frequency mean was computed and a t-test was done to check for differences between ADHD and control.

The correlation between the 5 EEG spectra for alpha peak frequency and power and the behaviour was done in MATLAB®. The behaviour data for both Oddball and Flanker were correlated to the frequency and the power of the alpha peak for left occipital, right occipital, central, frontal and parietal region to obtain r- coefficients and p-values. The variance in the spectra, SD spectra was calculated and t-test was done to check how stable the signal was over time. The alpha EEG was checked for connectivity by computing the correlation coefficients between regional estimates.

4. Results

The study originally had 60 participants, but one was rejected because of incomplete raw data. Finally, there were data from 28 ADHD participants and 31 controls available for analysis. The mean age of all 59 participants in the analysis was 33 ± 7 years. There were 30 females and 29 males and 8 left handed and 51 right handed participants, equally distributed between groups.

4.1 Behavioural Data

4.1.1 Oddball

In the oddball task, ADHD participants had 5.4 ± 7.3 % omission errors (not responding to target stimuli) and controls 4.3 ± 8.1 % errors, the difference was not significant ($t = 0.58$, $p = 0.56$, $df = 57$). Commission errors, i.e. responding to non-target stimuli (noise and standard sound) were 3.4 ± 8 % in ADHD and 3.4 ± 11% in controls (n.s. $t = 0.01$, $df = 58$, $p= 0.99$). Mean RT for ADHD participants was very similar in both groups with 377.5 ± 34 ms and 376 ± 55 ms for controls (n.s. $t = 0.095$; $df=57$; $p= 0.92$). The SD or ISV for RT in the oddball was 95 ± 31 ms for ADHD and 91 ± 28 ms for controls (n.s. $t= 0.53$, $df= 57$, $p= 0.61$). Figure 8 shows a sorted distribution of the mean RT for each participant, separated by group. Figure 9 shows a scatterplot showing the relation between RT and RT SD for all participants in the Oddball dataset, there is little difference between groups.

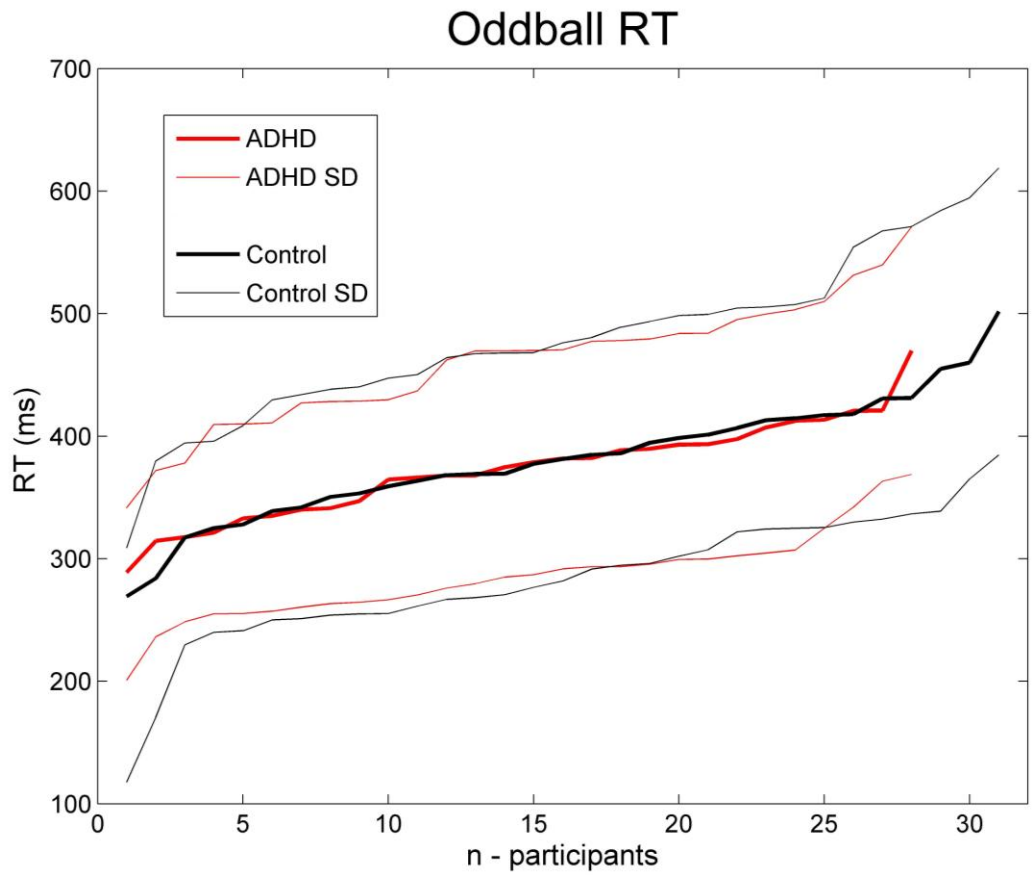

Figure 8 shows the sorted mean RT for all participants, red lines represent ADHD and black depict controls. Lines proceed very similar, as the mean RT for both groups (ADHD 377 and control 376) also confirms. The RT SD is also very similar for both groups.

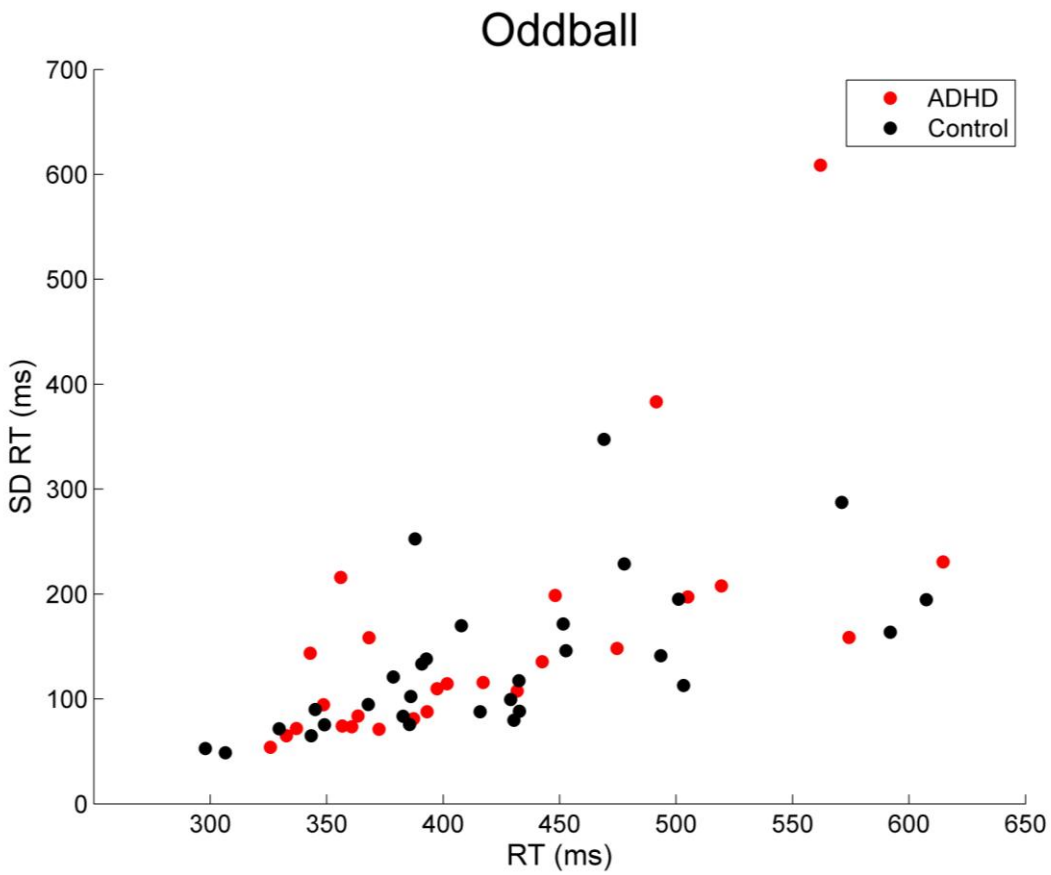

Figure 9 shows a scatterplot for oddball datasets, red dots are ADHD participants, black dots are controls. One can appreciate the marginal difference between groups, but one can see that participants with longer mean RT, on average, have greater SD of RT as well.

4.1.2 Flanker Task

For Flanker analysis, data from three additional participants had to be removed from the dataset, because of outlier datasets, with low accuracy under 0.3 or large mean RT with very high SD.

Compatible trials

The mean RT of compatible trials for ADHD was found to be 426 ± 71 ms and 418 ± 86 ms in controls (n.s. t = 0.33, df= 54, p= 0.74). ANCOVA showed a non-significant group effect (F = 0.1; p= 0.75). In ANCOVA, age had a significant effect on mean RT in compatible trials ($F_{1,53} = 4.95$, p = 0.03) with a positive correlation between older

age and longer RT (r = ,29). Gender showed a significant effect ($F_{1,53}$ = 6.4, p = 0.01), with lower compatible RT in males (396± 14 ms) than in females (446 ± 13 ms). The ISV of RT in compatible trials for ADHD was 167 ± 122 ms and for control 123 ± 57 ms, and showed a trend-significant result (t= 1.74; p= 0.09; df= 54). ANCOVA revealed that gender influenced the result ($F_{1,53}$ = 4.27; p = 0.04), with lower ISV for males (120 ±18 ms) than females (165 ± 17 ms). Maximum RT for compatible trials in ADHD was 1870 ±1263 ms and control 1333 ± 741 ms, this is a significant result (t= 1.97; p= 0.05 ; df = 54). The ADHD participants had a mean accuracy of 97.4 ± 3 % and controls had 98.2 ± 2 % (n.s. t= -1.36; p= 0.18; df=54). Compatible errors in ADHD and controls were 2.6 ± 3 % and 1.8 ± 2 %, respectively (n.s. t= 1.36, df= 54 p= 0.18)

In figure 10 the data is shown in a scatterplot to visualize the broadness of RT and SD of RT in ADHD and controls.

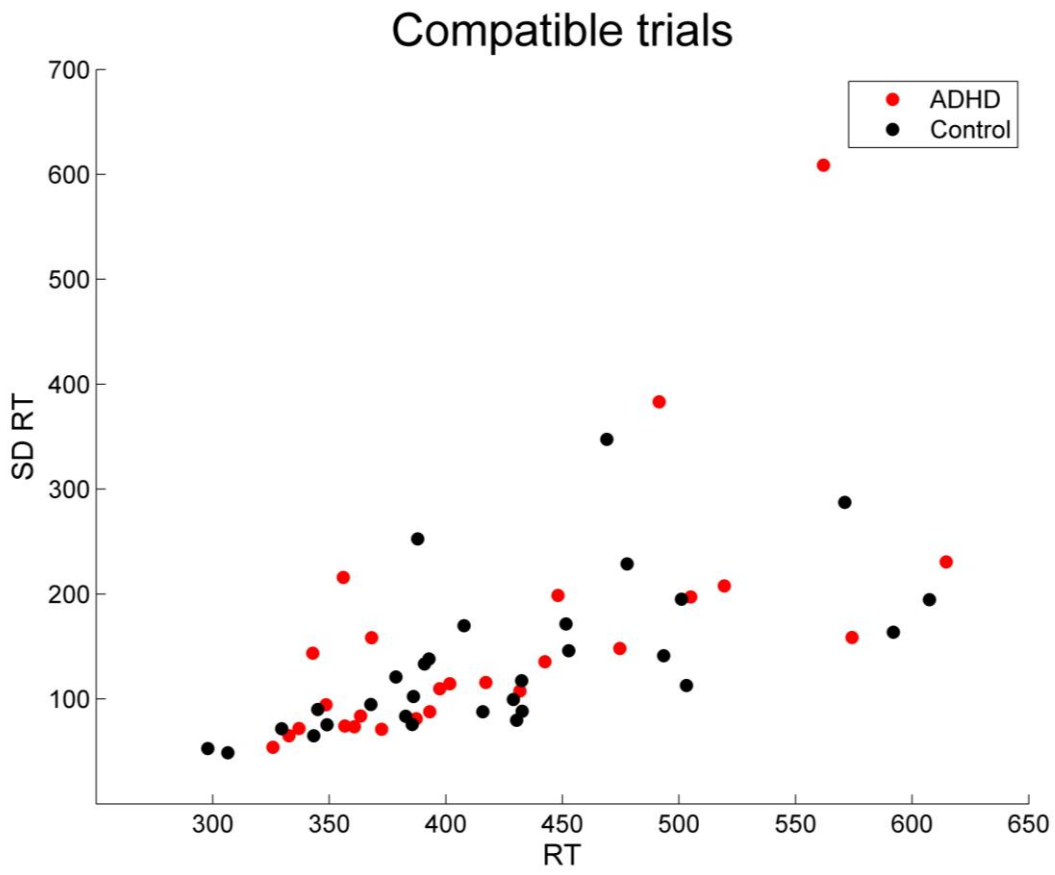

Figure 10 shows the distribution of data for RT and SD RT, ADHD shown as red dots, and control as black dots. In line with the statistics above is there little difference to be seen between groups. Participants with longer mean RT also have more SD deviation.

Incompatible trials

The mean RT for incompatible trials was 543 ± 106 ms for ADHD and 526 ± 118 ms for controls (n.s. t = 0.58, df= 54, p= 0.57). ANCOVA showed no group effect ($F_{1,53}$ = 0.73, p= 0.40), gender had significant effect on mean RT for incompatible trials ($F_{1,53}$ = 5.8; p = 0.02), with lower RT for males (499 ± 20ms) than females (566 ± 19ms). Minimum RT incompatible trials for ADHD was 283 ± 94 ms and control 314 ± 70 ms (n.s. t= -1.4; p= 0.16; df = 54). Maximum RT incompatible trials for ADHD was 2053 ± 1454 ms and control 1803 ± 1493 ms (n.s. t= 0.63 ; p= 0.53 ; df = 54). The accuracy in incompatible trials for ADHD was 87.0 ± 8 % and 90.5 ± 7 % for controls, this difference is a trend result (t = -1.8; p= 0.07; df= 54). ANCOVA showed age had

a significant effect ($F_{1, 53} = 6.61$; $p = 0.01$), higher age correlates ($r = 0.3$) with higher accuracy.

Incompatible errors

In the Flanker task ADHD participants had 13 ± 8 % and controls 9.4 ± 6 % incompatible errors, a trend level difference ($t = 1.84$, $p = 0.07$, $df = 54$). Age did have a significant effect here ($F_{1,53} = 6.6$; $p = 0.01$), with older age giving higher accuracy ($r = -.32$).

The mean RT for incompatible errors was 379 ± 205 ms for ADHD and 409 ± 221 ms for controls (n.s. $t = -0.52$, $df = 54$, $p = 0.61$). The minimum RT on incompatible errors was 193 ± 93 ms for ADHD and 237 ± 72 ms for control, this is a significant difference ($t=-1.99$; $p= 0.05$; $df=54$). Both age and gender had a significant effect on the minimum RT in incompatible error trials ($F_{1,53} = 5.04$; $p= 0.03$ and $F_{1,53} = 4.36$; $p = 0.04$ respectively).Where older age gave higher RT ($r= .28$) and females (225 ± 15ms)having longer RT than males (209 ±16ms). Maximum RT incompatible errors was 994 ± 1045 ms for ADHD and 866 ± 759 ms, this is not significant ($t= 0.53$; $p= 0.60$; $df= 54$).

Post error slowing

As we can see in figure 11, ADHD showed about 50 ms slower RT than controls in PES (trial after an error).

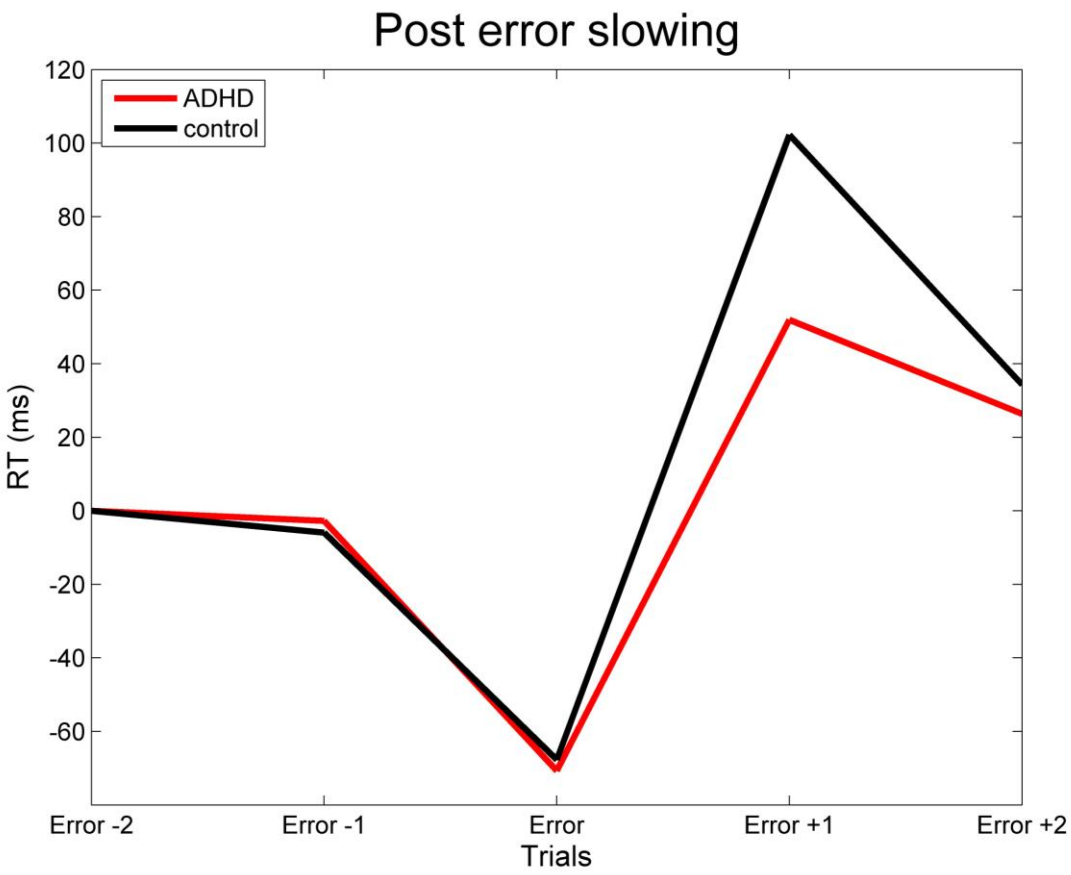

Figure 11 shows post error slowing in by group, ADHD red line and control in black. The x-axis represents single trials in the Flanker task. One can see that there is some speeding before the error trial occurs compared to baseline RT. The error itself has a fast RT for both groups. On the trial after an error, error +1, we see the slow down after the error. PES is less in ADHD than in controls.

The regression showed that erroneous RT are -123 ± 93ms faster than baseline for ADHD, while they are -98 ± 125 ms in control (n.s. t = -0.48 ; p = 0.63). PES has 48 ± 55 ms compared to baseline in ADHD and 96 ± 120 ms in control, which is a trend result (t = -1.89, p = 0.07). Compatibility is 106± 53 ms for ADHD and 107± 52 ms for controls (n. S., t = -0.1 ; p = 0.9). The pre error trial had -13 ± 39 ms for ADHD and -12 ± 49 ms for controls (n.s. t = -0.11, p = 0.9). Lapses >2000 ms were 2.5 ± 4 in ADHD and 1.2 ± 3 in controls (n.s. t= 1.37, df = 54, p = 0.18) Error RT correlates to PES by 0.35 and to Pre error speed by 0.43. ANCOVA with age and gender did not show any relations.

4.2 EEG

Here the results of the EEG analysis will be presented, especially regarding the alpha peak, as well as the correlation between EEG spectra and the behavioural data.

4.2.1 Alpha Peak Analysis

In figure 12 the topographies for the 5 analysed brain regions are shown. One can observe clear dipoles representing alpha activity in red and blue in all five regions.

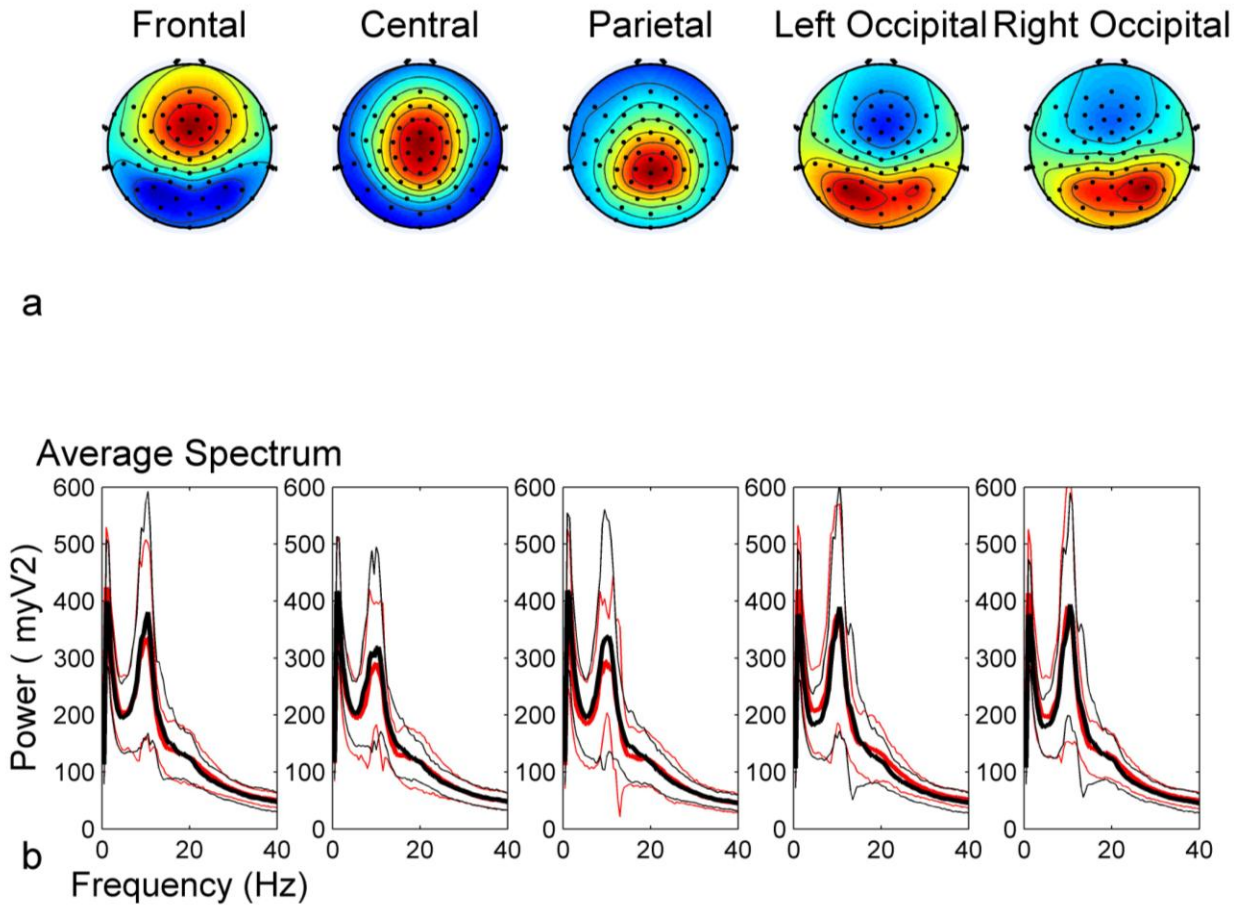

Figure 12 shows a) Average EEG topographies for the five brain regions: frontal, central, parietal left and right occipital. Nose indicated on top of each head circle and ears on the side. Electrodes are indicated by black dots. Clear dipoles, that represent alpha activation, can be seen in all regions, red areas. b) Average spectra for the five brain regions. ADHD in red,

control in black, thin lines are SD. Clear alpha peaks are visible around 10 Hz in all five regions, but none are significantly different in between groups. Note: power in μV^2.

Alpha peak power was calculated, we did not find any significant difference by groups ADHD and controls in power. In figure 13 we can see the alpha frequencies and power for each participant divided by group for the left occipital region, as an example. This was done for all five brain regions. One can see that most participants have strong power peaks for alpha frequencies and some have power peaks for theta too, but there is little difference in ADHD compared to control.

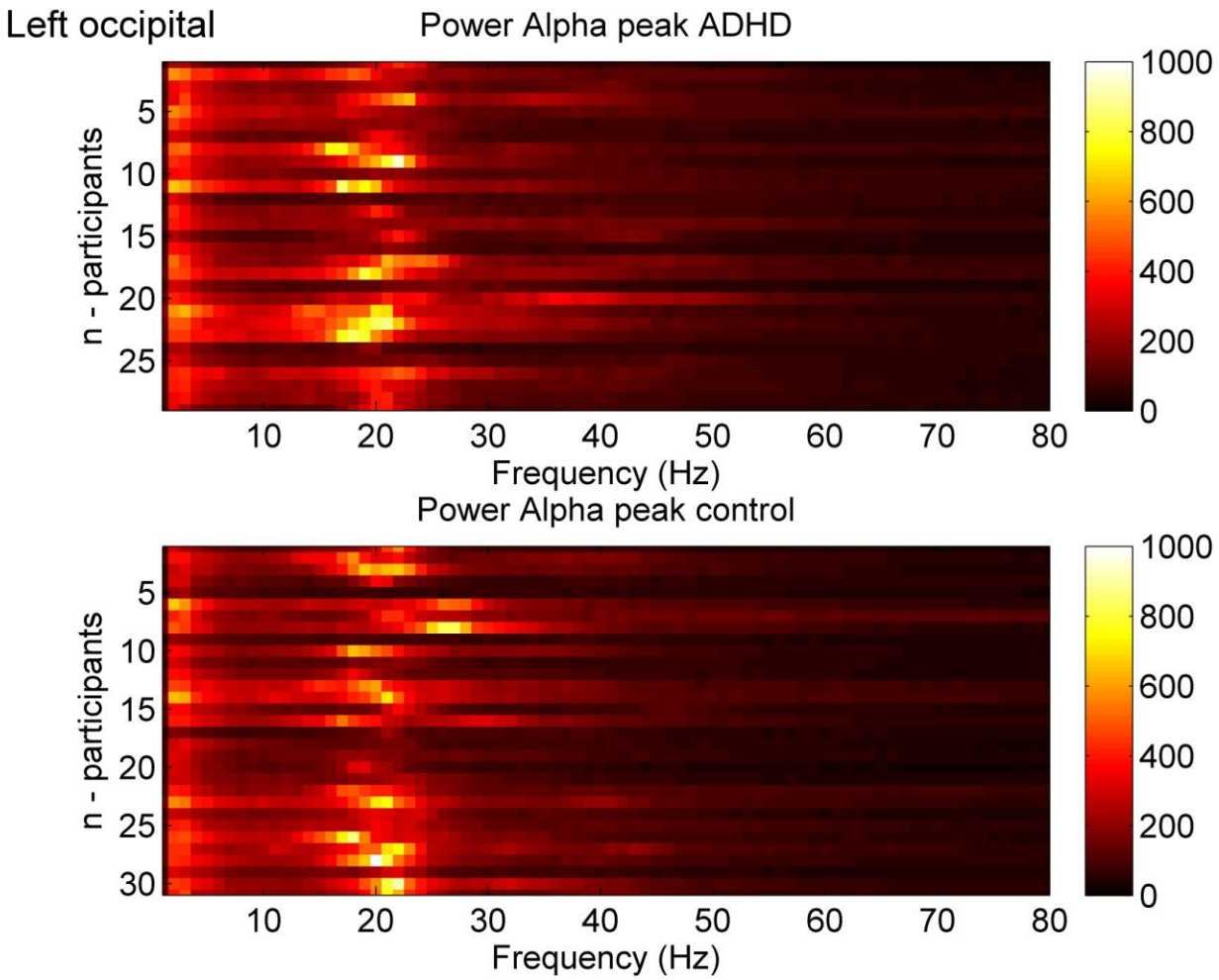

Figure 13 shows power by frequency of Alpha peaks for each participant, divided into group (ADHD and control) for the left occipital region. Some participants have strong alpha peaks while others are weaker. The whole range is represented in both ADHD group and control.

The **global alpha peak frequency** mean was found to be 10.01 ± 0.88 Hz for ADHD participants and 10.20 ± 0.81 Hz for control (n.s, t = -0.82, df = 54, p= 0.42). **Frontal** alpha frequency for ADHD was 9.88 ± 1.2 Hz and 10.17 ± 1.0 Hz for control (n.s t= -0.97, df= 54, p=0.33). **Central** alpha frequency for ADHD was 9.78 ± 1.1 Hz and 10.04 ± 1.1 Hz for control (n.s. t= -0.90, df= 54, p=0.37). **Parietal** alpha frequency for ADHD was 9.80 ± 1.1 Hz and 10.39 ± 1.1 Hz for control, this difference was significant for this one t-test (t= -2.07, df= 54, p=0.04). However, since there were 5 tests done, one would require that significance has to lie around 0.05/5=0.01 and that

is not the case (see discussion). **Left occipital** alpha frequency for ADHD was 10.31 ± 1.3 Hz and 10.19 ± 0.8 Hz for control (n.s. t= 0.44, df= 54, p=0.66). **Right occipital** alpha frequency for ADHD was 10.31 ± 1.2 Hz and 10.22 ± 0.95 Hz for control (n.s. t= 0.30, df= 54, p=0.76).

The **global alpha peak mean power** for ADHD was 464 ± 153 μV^2 and for control 472 ± 188 μV^2 (n.s. t = -0.18, df = 54, p = 0.86). Alpha power for **frontal** region was 467 ± 203 μV^2 for ADHD and 467 ± 252 μV^2 for control (n.s. t= 0.00 , df= 54, p=0.99). Alpha power for **central** region was 430 ± 194 μV^2 for ADHD and 395 ± 187 μV^2 for control (n.s. t= 0.68, df=54, p=0.5). Alpha power for **parietal** region was 397 ± 158 μV^2 for ADHD and 463 ± 264 μV^2 for control (n.s. t= -1.1; df=54; p=0.26). Alpha power for **left occipital** region was 513 ± 225 μV^2 for ADHD and 519 ± 241 μV^2 for control (n.s. t= -0.11, df=54, p=0.92). For the **right occipital** region it was 512 ± 198 μV^2 and 516 ± 270 μV^2 respectively (n.s. t= -0.07, df=54, p=0.95).

Variance in the spectrum, spectrum SD was calculated and a T-test was done, no significant differences between ADHD and control were found.
Correlations between the 5 spectra were performed in MATLAB® to check **connectivity**. 5 electrodes corresponding to the maxima of the topographies seen in figure 12 were selected to calculate the correlation. The data was divided into epochs by two seconds. T-tests were done. The correlation did not decrease in ADHD compared to controls. Overall, the power correlations between the 5 regions were high, with means from 0.47 to 0.70, but no significant group differences were found.

4.2.2 Correlation Behaviour and EEG

The EEG spectra and behavioural parameters were correlated. For flanker either incompatible, compatible or incompatible error RT were correlated to either alpha peak frequency or alpha peak power divided by the 5 brain regions analysed. For oddball the RT where correlated to either alpha peak frequency or power. All correlation coefficients and p-values can be seen in the table below. There are 2 negative and 3 positive correlations.

The analysis of the EEG dataset was successful and the alpha band has been investigated. Global alpha frequency was found to be 10 Hz for ADHD and control. A significant difference in parietal alpha frequency, with 9.80 for ADHD and 10.39 for control, was found. Global alpha power was 464 μV^2 and 472 μV^2 for ADHD and control respectively. The correlations on Alpha power and frequency and behavioural data was conducted.

Table 1 shows the correlation between alpha peak frequency or power and behavioural data by group for EEG spectra from 5 brain regions: frontal, central, parietal, left and right occipital. Significant values are marked in red. The correlation coefficients and p-values are given for all correlations. Incom = incompatible; com= compatible; freq = frequency; RT = response time

	Frontal		**Central**		**Parietal**		**Occipital left**		**Occipital right**	
Flanker	r[1.]	p[2.]	r	p	r	p	r	p	r	p
Incom RT freq ADHD	-.31	.13	-.36	.07	-.21	.30	-.11	.59	-.21	.31
Incom RT freq control	.19	.32	.14	.45	-.10	.60	-.26	.16	.38	.04
Incom RT power ADHD	-.02	.94	.02	.91	-.24	.25	.10	.60	.16	.43
Incom RT power control	-.33	.07	-.38	.04	-.26	.16	-.19	.33	-.21	.31
Com RT freq ADHD	-.35	.08	-.43	.03	-.28	.16	.13	.54	-.37	.07
Com RT freq control	.16	.38	.14	.47	.04	.84	-.23	.23	.34	.07
Com RT power ADHD	.06	.79	.11	.60	-.11	.59	.12	.55	.20	.32
Com RT power control	-.30	.11	-.29	.12	-.15	.43	-.14	.46	-.16	.39
Incom error RT freq ADHD	-.05	.80	-.06	.76	-.02	.91	-.04	.82	-.06	.78
Incom error RT freq control	.05	.78	.24	.21	-.12	.54	-.22	.23	.36	.05
Incom error RT power ADHD	-.26	.19	-.04	.84	-.20	.32	-.13	.54	-.10	.62
Incom error RT power control	-.18	.34	-.22	.24	-.13	.48	-.14	.45	.04	.82
Oddball										
RT freq ADHD	-.25	. 19	-.32	.09	-.14	.46	-.00	.99	-.25	.19
RT freq control	.37	.04	.24	.20	.25	.17	-.19	.32	.15	.42
RT power ADHD	.01	.95	-.21	.26	-.02	.91	.06	.77	.10	.62
RT power control	.15	.43	.11	.55	-.14	.44	.13	.48	-.00	.99

1. Value r= Pearson correlation coefficient 2. Value: p = p value

5. Discussion

In this study, two datatypes were analyzed, the EEG data and the behavioural data of 59 adults with ADHD and controls. These datatypes were correlated after the analysis. The behavioural dataset was analyzed for RT parameters and PES. The EEG data was analyzed for alpha peak power and frequency, connectivity and spectrum SD by ICA. Here, we will discuss the methods and outcome of the results. Finally, reviewing the literature and our results on alpha peak frequency and power and linking EEG alpha together with the behavioural data, to bring the different parts of the study together.

5.1 Methological Discussion

The practical methodology of EEG recording has been basically the same for almost a century, but of course with the advances in computing, analysis of EEG has become easier and more sensitive. New algorithms have been developed to automate most of the steps in the analysis. Here some methodological advances and drawbacks are discussed.

Filtering of EEG data is an important step in the analysis process, because if it is done wrong, one can filter out the actual data and wash out the effects in the EEG. The goal is to reduce noise, without deleting the real EEG. The reason filtering can distort the EEG is, as Luck states, *"precision in the time domain is inversely related to precision in the frequency domain"*. (Luck, 2005) By filtering out frequencies, the waveform will become spread out in time. This means low pass filters can cause waves to start earlier and stop later and high pass filters can cause artificial oscillations. The relevant data in EEG recordings lie between frequencies from 1 to 30 Hz.(Luck, 2005) Therefore, a low pass filter can be applied up to about 40 Hz and a high pass filter under 1 Hz, which was done in this study. (Luck, 2005)

As described in the introduction, the ICA model assumes independent sources. How can we assume EEG signals to be independent when they come from the same brain? In this case one is looking for statistical independence and ICA helps us to separate multichannel data into unrelated IC, so after the ICA we have independent IC's. The EEG itself is never really independent but the functional dependent sources are independent in time, which is the aspect the ICA exploits. It separates two sources by their temporal structure, which is an easier solution than trying to separate by frequency or content of the source (example: like voices, it is easier to divide two voices by temporal start/stop than by what they are actually saying). The hypothesis of temporal independence is supported by the long known fact that the cortex is divided into compact regions with specializes function. (Onton et al., 2006) Since the ICA separated the time variable and not the spectrum, was the spectrum separated by FFT algorithm. It can be argued that FFT is not of advantage for EEG analysis, since it is not well suited for non-stationary signals, like the EEG. FFT is better suited for stationary signals and it is the fastest of all available methods in real time applications. Its disadvantage is that it suffers from noise sensitivity and that it does not have a good spectral estimation. (Al-Fahoum & Al-Fraihat, 2014) However, if short timeframes are used (here 2 seconds), the EEG will be pseudo -stationary in that time period and FFT will be applicable, therefore it is a common, widely used method.

We used a template matching approach to remove artefacts. This is similar to CORRMAP and COMPASS, and provides and effective and robust method because it offers a uniform largely user independent approach to artefact rejection. However, one might argue that expert visual judgement provides a more sensitive and ultimately superior approach in individual cases. Other error sources in the methods are manual alpha frequency and power determination when there are multiple peaks. If only first or last peak is picked all the time, we have consistency but also a falsely low or high results. The manual determination still appears to be more

straight forward than the computed version. If one sets the computed window from 10-12 Hz, then particular peaks in participants with for example 9.5 Hz will fall outside the analysis. The result shifted wrongly to higher Hz numbers.

5.2 Behaviour

In this study, the ratio between men and women with ADHD was 4:3, which is fairly similar to the ratio reported by Carlson, 2:1, so we can see that there are fewer females with ADHD, but that the ratio is much more normalized in adults compared to children (9:1 in clinical samples, 4:1 in epidemiological studies), which could indicate over diagnosing in boys and under diagnosing in girls. (Barry et al., 2003) The behaviour data is divided into the two tasks:

5.2.1 Oddball

For the oddball task one would suspect an increased ISV and higher error rate for ADHD, this could not be replicated in this study. Omission errors (where participants failed to answer a stimulus) do not give any RT to analyse. RT had no significant difference in commission errors (answered to the noise or standard sound, the non-target stimuli) in the Oddball task. Hervey et. al. did not find difference in errors of commission either, but they found a higher rates in errors of omission in ADHD than in controls. They used a Conner's continuous performance test. In contrast to our study, the study included children, which might point to that the increased ISV measurement is even less accurate in adults than in children with ADHD. (Hervey et al., 2006) Castellanos et. al. and Klein et. al. found ISV to be increased in ADHD, here it was found increased once, in the flanker task (see below). (Castellanos et al., 2005; Klein, Wendling, Huettner, Ruder, & Peper, 2006) That there are no group differences found in Oddball task, can have several reasons. One might be that the ADHD participants, in this study, are highly functioning.

They are often employed and the fact that they are able to come to the study shows that they are not the most severe ADHD cases, because not being able to organize and show up to appointments is part of ADHD symptomatic.

5.2.2 Flanker

When comparing compatible trials, incompatible trials and incompatible errors, one expects the compatible trials to be faster than incompatible ones and errors to be the fastest. These expectations were met, incompatible trials showed slower RT than compatible RT ($t = 12$, $df=2$; $p= 0.007$) with fastest RT in erroneous trials ($t= 8$, $df= 2$, $p = 0.01$) The hypothesis was that ADHD participants are slower in their general RT's than controls. (Andreou et al., 2007; Hervey et al., 2006; Thissen et al., 2014) All the three studies shown in references were conducted in children, there is not as many studies on adults yet, but Oberlin et.al. found the same effect in adults. (Oberlin, Alford, & Marrocco, 2005) Here, we did not see slower RT in ADHD. In none of the three conditions of the flanker task did ADHD participants have significantly slower RT than control. Woltering et. al. did not find differences for measures related to reaction time either, that study was conducted with a go/nogo task . (S. Woltering et al., 2013) Slower RT in ADHD is a fairly consistent finding in the literature. Reasons we did not find it are outlined in the discussion of bias in the study further below.

What we did see, are some trend differences in RT related parameters. In compatible trials the SD of RT was higher in ADHD than in controls, that is in accordance to literature. We did see this effect only on one of four conditions (1 oddball, 3 flanker). ADHD participants do not necessarily have different RT by terms of mean, but since their attention varies up and down, the RT will vary a lot more over time, so the SD is higher. (Castellanos et al., 2005; Oberlin et al., 2005) In compatible trials the maximum RT of ADHD was significantly higher than in controls, which is in accordance with the hypothesis of ADHD having slower RT (being skewed towards

right in RT distributions). For compatible mean RT, age did have a positive correlation where older age gave slower RT, this is in accordance to literature which shows that people slow down with age. (Fozard et al., 1994) The accuracy in incompatible trials was lower for ADHD than for controls, by trend result, this means ADHD made more errors. More errors are expected for ADHD, because of concentration difficulties, even though some studies in adults do not get significant accuracy differences. (McLoughlin et al., 2009; Saville et al., 2014; Wiersema, Van Der Meere, & Roeyers, 2009) The accuracy in incompatible trials was influenced by age, where older age gave more accuracy. This could be part of the speed-accuracy trade off which is observed in age, the RT goes down in order to keep accuracy high. (Uemura, Oya, & Uchiyama, 2013) The minimum RT for incompatible error trials was significantly faster in ADHD than in controls. This shows that ADHD might work more impulsively and more often click on the mouse guessing, not taking time to consider the trial. This fast, impulsive answering might be part of the inattention/impulsivity problem of the ADHD symptomatic. Age played into incompatible error minimum RT with older age giving longer RT, this is due to slowing of RT with age. Maximum and minimum RT are measures that are prone to outliers since they measure extremes. ISV is more robust, but we had only one group result to show there. For compatible mean RT, incompatible mean RT, minimum RT for incompatible errors and compatible ISV in RT gender did have a significant effect, with males being faster than females and females having larger ISV than men. This is in accordance with literature, which shows that females have longer reaction times than men. (Clayson, Clawson, & Larson, 2011; Upadhayay & Guragain, 2014) This goes especially for incompatible trials in Flanker task, as Stoet found. (Stoet, 2010) Tamnes et. al. did not find sex differences in ISV though. (Tamnes, Fjell, Westlye, Østby, & Walhovd, 2012)

The regression analysis of errors trials showed, as a trend result, that ADHD had less PES than controls in our study, this is in consistency with the literature. Balogh

and Czobor showed in their meta-analysis of PES studies, that most studies concluded that ADHD have less PES than control groups. (Balogh & Czobor, 2014) Van de Voore et. al., Jonkman et.al. and others found less PES in ADHD with a very small effect size and SD that pushes into the result towards zero like in this study. (reviewed in(Balogh & Czobor, 2014) In our group the PES in healthy participants was confirmed in a study in 2010, where Eichele et.al. found PES to be about 40 ms from baseline. (H. Eichele et al., 2010). PES is a measure of cognitive control and it makes good sense that ADHD lack this regulation to an extent, which is why one would suspect the trend result would be stronger in a larger sample size. Numeric differences in error RT are found in PES analysis, with ADHD having faster error trials. ADHD participants also had twice as many lapses over 2000 ms as controls, but SD was high in both groups and obscured significance, one could say this is expected, because of ADHD participants have more frequent lapses of attention.

5.3 EEG

The global alpha mean frequency was found to be around 10 Hz for both controls and ADHD in this study; this is in consistency with the literature. (Aurlien et al., 2004; Klimesch, 2012) There was found one alpha peak frequency difference between groups here. The parietal alpha frequency was significantly different in a single t-test, ADHD had less alpha frequency than control ($p=0.04$). 5 tests were run, so technically one has to increase threshold on p-value, by numbers of tests done, to make sure of significance, $0.05/5= 0.01$. A larger number of participants would be needed, therefore, to check the robustness of this result. Other studies that find difference in parietal alpha in ADHD patients are Heinrich et.al., but they found the parietal alpha frequency to be increased in ADHD vs. control (Heinrich et al., 2014) There are few new studies on alpha frequency, but it is suspected that alpha frequency can vary between ADHD and control, if the alpha rhythm is unstable in ADHD(Santamaria & Chiappa, 1987). Alpha frequency is an important tool in

clinical diagnostics, but has not received much attention in scientific studies now, in contradistinction to alpha power.

No differences were found in Alpha peak power. This is not in consistency with literature, Barry and Clarke found decreased alpha power and Barry finds that most power studies found lower alpha power for ADHD in his review. (Clarke, Barry, McCarthy, & Selikowitz, 1998) However, most studies use longer data, or pre-selected artefact free data segments, both of which would render it more likely to find drowsiness related EEG changes, which may occur more frequently in patients. Hutt finds in her extensive meta-analysis that externalizing behaviour has a small effect less alpha power than controls. (Rudo-Hutt, 2015) Woltering et. al. found significantly decreased oscillatory power, particularly in fast frequencies, like alpha power, in eyes closed condition (Steven Woltering et al., 2012). This is in accordance with Barry and Hutt but not supported by our data. Diamond did not find any EEG differences in ADHD and controls, like in this study of power analysis (reviewed in (Barry et al., 2003). Fonseca et.al. did not find any differences in absolute alpha power between ADHD and control either. (Fonseca, Tedrus, Bianchini, & Silva, 2013) Koehler found increased alpha power in frontal, central and especially posterior regions in adults (Koehler et al., 2009). In line with Koehler, Vollebregt et.al. found the alpha power to be increased significantly more for ADHD than for controls from eyes closed to eyes open condition. (Vollebregt et al., 2014) There are many studies on this and the conclusions are very diverse and effect sized are often small. The majority of studies discussed here is on adults, but a lot of the research, included in Hutt for example, is on children, which might affect the outcome of meta-analysis given that there is an age effect on the alpha power. (Aurlien et al., 2004)

Even though participants were asked not to take their ADHD medicine 48 hours prior to EEG recording in this study, one cannot exclude the possibility of medication affecting the EEG. Loo et.al. found that mean alpha power increased

with medication. (reviewed in (Becker & Holtmann, 2006) There was only one effect found in this power and frequency analysis, as described above. There might be more group differences in the tasks EEG, but not in the resting state analysed here.

Some studies report lateralization in ADHD in the occipital region, we did not see any significant differences in our analyses between left occipital and right occipital region. (ter Huurne et al., 2013) The analysis of connectivity did not show any results here, the expectation was to see less Frontal- occipital connectivity in ADHD. Mazaheri found the frontal and visual cortex to be relatively less connected disconnected in ADHD. (Mazaheri et al., 2010) Mazaheri also proposed that adolescents with ADHD have a lot less RT benefit of getting shown cues before the trials and that suppression in alpha power is more inefficient than in typical adolescent after cueing. (Mazaheri et al., 2014) Variance in the spectrum, spectrum SD, did not show any differences between groups in this study.

5.3.1 Alpha peak and behaviour correlation

There are two negative correlations, one is between incompatible trials RT and alpha peak power in controls in the central region ($r = -.38$, $p = .04$). The other negative correlation is between compatible trials RT and alpha peak frequency in ADHD in the central region ($r = -.43$, $p = .03$). Negative correlation means that faster RT gives bigger power in the alpha wave and higher frequency of alpha. (Loo et al., 2009)

There are three positive correlations. Incompatible trials RT and alpha peak frequency correlate positively in control group in the right occipital region ($r = .30$, $p = .04$). Incompatible error trials RT correlated positively to alpha peak frequency in the control group in the occipital right region ($r = .36$, $p = .05$). The oddball RT correlated positively to alpha peak frequency in control group in the frontal region ($r = .37$, $p = .04$). Again, since multiple tests are performed, the significance threshold would need to be adjusted to a more conservative level. One has to bear in mind

that the resting EEG data are collected in a different state before the collection of behavioural data, therefore, weak and few correlations are not surprising as behaviour and brain EEG activity is not in direct correlation. Here one would expect to see a lot more correlation in the tasks EEG and behaviour. Loo et. al. found correlations between frontal and parietal region and behaviour data mainly in controls and one in ADHD, they interpret them as increased alpha power being associated with fast response style and ADHD having higher levels of cortical arousal to maintain the same level of performance as controls.(Loo et al., 2009)

5.4 Conclusions and Future Perspectives

The moderate differences between cases and controls could be explained by the recruitment strategy in the study. All the participants are relatively young (mean 33 years) and are by- and large well functioning. The ADHD participants meeting up for the study appointments, are obviously not the ones who have the most unorganized live. So one has to assume, that the most severe cases of ADHD are not in the study. The ADHD might have heterogeneity in their symptoms, which makes the behavioural and EEG data unclear. Some of the younger participants might be experienced computer gamers. Gaming has shown to heighten eye-hand coordination and giving faster RT. (Green & Bavelier, 2006) Since gaming requests "jumping of thoughts" and is highly stimulating it might be popular in the ADHD group, so it might influence the results towards faster RT for ADHD. Another considerable reason for fewer results is that ADHD participants have a personal interest in the study and are therefore more motivated. This difference in endogenous incentive may reduce differences between ADHD and control. But personal interest might also be the case for controls and produce an error type 1 in the study. The vigilance of participants is of utmost importance in behavioural and EEG studies, it might be argued that ADHD or control group were too tired or getting tired because of intensive testing and long tasks. Especially for ADHD this

might play a role, because the attention lessens quickly. That is why at least resting stage was kept as short as possible (5 minutes) even though more time might have given stronger results, but then the risk of alpha wave falling apart during drowsiness is higher.

Participants had not been on medication for 48 hours while recording EEG for this study. Still it cannot be certain medication didn't have an effect on EEG. The effect of medication might last longer than 48 hours if it is used regularly and dosed well in accordance to the need of the participant. Half-life of methylphenidate in Ritalin® form is 2 hours, duration of action is estimated to 3-4 hours and elimination time is 20 hours or more depending on doses. For methylphenidate in Concerta® form elimination time is 48-96 hours (2-4 days). If the ADHD participant was still medicated and treated for ADHD symptoms in a way, this might reduce differences between ADHD and control in the EEG. Even though the time of action for the medication is shorter, there will still be something left in the blood 2-4 days after intake and one cannot be sure it does not affect the body anymore. It is probably not a major factor with the shorter elimination time of Ritalin®, but for participants on Concerta® a longer wash out time of medication should be considered. (Coghill & Seth, 2006; Felleskatalogen)

All the planned **aims** were carried out in the thesis, but many of the hypothesis expectations could not be confirmed. RT times did not differ greatly between ADHD and controls, even though they were suspected slower. The accuracy was only found to be less in ADHD in one condition (incompatible trials flanker).The lower PES effect in ADHD was only close to significance. Alpha peak frequency differed only marginally between groups, to my knowledge there is little other material on alpha frequency in ADHD adults, but it can vary between groups if alpha rhythm is unstable due to drowsiness (Santamaria & Chiappa, 1987). No lower alpha power, which one would expect according to literature, was found in ADHD. The correlations between behaviour and alpha EEG were low with few

significant correlations, this is similar to Loo et.al. and as expected (Loo et al., 2009). Connectivity in EEG was high within groups, but no differences were found between groups or the frontal – occipital region in ADHD.

In **conclusion**, we find few differences between ADHD and control in resting EEG and behaviour in simple tasks, according to our findings. This would have to be considered good news for ADHD patients. It means that: they are high functioning, the symptomatic of ADHD is relatively soft compared to other mental diseases and they are not very different from everyone else. This on the other hand leaves open questions about why many ADHD patients struggle in daily life, how one can identify them early and how to help them.

For the **future** it would be of benefit to repeat the study with a larger sample size to see if the parietal alpha difference gets stronger and earlier common findings from literature on differences in RT get more distinct. Work that needs to be done to finish this study is the analysis of the EEG recordings during Flanker and Oddball tasks and correlate them to the behaviour dataset analysed here. Here, one would do ERP studies to see if ADHD ERP differs from control. Especially the P3 and N2 have earlier been found important in ADHD. It would be highly interesting to see if earlier results can be replicated. There are yet relatively few studies on adults with ADHD, therefore this is important work that we wish to continue in the near future. (Johnstone et al., 2013)

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