Local neuronal dynamics in planning during Wisconsin card sorting test in ADHD

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Tiivistelmä:
Jotta tehokkaiden ja tuotteliaiden päätösten tekeminen on mahdollista, ihmisen tulee suunnitella toimintaansa läpi elämän oleellisen tiedon ylläpitämisen ja päivittämisen avulla. Tällaiset tavoitteelliset tilanteet vaativat joustavaa käyttäytymisen hienosäätöä ja epäoleellisen tiedon vaimentamista. Toiminnanohjauksessa vaadittava kognitiivinen joustavuus, työmuisti ja inhibitio, on liitetty poikkeavaa etuaivokuoren toimintaan. Etuaivokuoren on aiemmin havaittu toimivan taaemmilta alueilta tulevan aistitiedon prosessoijana. Rakenteellisia ja toiminnallisia poikkeavuuksia on löydetty aktiivisuuden ja tarkkaavuuden häiriössä (ADHD) liittyen toiminnanohjauksen aivoalueisiin. Perustana oleva syy toiminnanohjauksen häiriöön ja vaikeuksiin suunnittelussa sekä päätöksenteossa saattaa löytyä yllä mainituista poikkeavuuksista. On silti epäselvää, miten aivojen oskillaatiot muokkaavat erilasia kognitiivisia toimintoja suunnitteluun ja päätöksentekoon liittyen. Tämän tutkimiseksi aivotoimintaa mitattiin MEG-laitteella koehenkilöiden (21 ADHD, 28 kontrolliosallistujaa) suorittaessa Wisconsin korttienlajittelutehtävää (WCST). WCST on nopeatempoinen tehtävä, jossa lajitellaan kortteja muuttuvien sääntöjen mukaan palautetta apuna käyttäen. Tämän tutkimuksen tarkoituksena oli tutkia ADHD-aikuisia ja kontrolliryhmää WCST-suunnitteluvaiheen aikana verraten kokeen suorittamista aiemmin saadun oikean tai väärän palautteen mukaan. ADHD ja kontrolliryhmän välillä odotettiin eroa paikallisessa hermosolutoiminnassa etuaivokuorella ja taaemmilla alueilla. Data-analyysi sekä lähdemallinnus ja -rekonstruktio tehtiin neuronaalisten (MEG) mittausten ja aivojen rakenteellisten (MRI) mittausten perusteella. Tilastolliset analyysit tehtiin selvittäen paikallisten hermosolujen amplitudidynamiikkaa ja visualisoitiin ryhmien sisällä ja välillä. Reaktioajat ja osumatarkkuus eivät osoittaneet merkittäviä eroja ryhmien välillä. Kuitenkin kontrasti suunnittelun aikana verraten oikeita-vääriä vastauksia, ilmensi tehostunutta ja vaimentunutta aivotoimintaa delta-, theta-, alfa- ja beta-oskillaatioissa. Kontrolliryhmä osoitti aktiivisuutta etuaivokuoressa-, parietaalisessa, temporaalisessa ja näköaivoalueilla. Nämä alueet on aiemmin liitetty ns. oletustilan verkostoon sekä somaattis-liikkeelliseen verkostoon. Tehostunutta aktiivisuutta havaittiin beta- ja alfa -oskillaatioissa. ADHD -ryhmässä suurin positiivinen aktiivisuus havaittiin etuaivolohkossa ja parietaali- sekä kuuloaivoalueella, jotka on liitetty kahteen huomioverkostoon ja somaattis-liikkeelliseen, mutta myös oletustilan ja näköaivoalueiden verkkoon. Ryhmien välisessä vertailussa havaittiin vaimentunutta delta-, theta- ja alfa -oskillaatioiden aktiivisuutta aivojen lateraalisilla alueilla temporaalilohkolla. Nämä alueet liittyivät ventraalisen huomion ja somaattis-liikkeelliseen verkkoihin. Heikentynyttä aivotoimintaa havaittiin ADHD -ryhmässä vaimentuneissa positiivisesti aktivoituneissa betaoskillaatioissa verrattuna kontrolliryhmään ja kokonaan puuttuvista positiivisesti aktivoituneissa alfa -oskillaatioissa. Tulevien tutkimusten tehtäväksi jää näiden värähtelyiden toiminnan roolien tulkitseminen. Suuntaa-antavia tuloksia ADHD potilaiden aivotoiminnan poikkeavuudesta voitiin löytää aivoalueista ja toiminnasta jotka liittyvät joustavuuden ja työmuistin rooleihin suunnittelussa ja päätöksenteossa. Tulokset viittaavat myös siihen, että WCST:n suunnittelu edellyttää monien kognitiivisten toimintojen ja prosessien joustavaa organisaatiota, joita moduloivat tehostuneet alfa- ja beta -oskillaatiot sekä vaimentuneet delta- ja theta -värähtelyt.

Abstract

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Abstract:

To make fast and efficient decisions in changing environments, humans must plan their actions throughout their lives by maintaining and updating relevant information. Such goal-directed situations demand flexible adjustment of behavior and the suppression of task-irrelevant details. Executive dysfunctions in cognitive flexibility, working memory and inhibition have been related to aberrant prefrontal cortex functioning. The prefrontal cortex has previously been found to have an important role in these executive functions as a supervisory modulator and processor of information from posterior sensory brain areas. Structural and functional abnormalities in these brain areas have been found in attention deficit/hyperactivity disorder (ADHD). These impairments may be the underlying reason for problems in decision making and planning for people with ADHD. However how the brain's oscillatory activity modulates different cognitive functions in areas relating to planning and decision making is still unclear. To investigate this the brain's activity was measured with MEG while participants (21 ADHD patients, 28 controls) performed in Wisconsin card sorting test (WCST). WCST is a fast-paced task, where cards are sorted according to changing rule categories with the direction of feedback. The aim of this study was to investigate planning in adults with ADHD and a control group during WCST planning period and compare trials with previous feedback being correct or incorrect. Difference in the local neuronal activity in prefrontal and posterior areas were expected between the ADHD and control groups. Data-analysis and source modelling and reconstruction were conducted on the neuronal (MEG) data and structural (MRI) data. Statistical analyses were run for local neuronal amplitude dynamics and visualized within and between groups.

The behavioral results of reaction times and hit rates did not show significant differences between groups. Clinical questionnaire scores did not correlate with reaction times. However, contrast of planning in correct-incorrect feedback trials within groups showed increased and decreased brain activity in delta, theta, alpha and beta oscillations. The control group showed activity in frontal, parietal, temporal, and occipital regions related to default mode, somatomotor with increased activity in the beta and alpha bands. For the ADHD group greatest positive activity was seen in beta band in frontal and parietal areas, but also in occipital regions. These activation sites were mostly related to dorsal and ventral attention and somatomotor networks but also to default mode and visual networks. Mostly temporal activity of suppressed delta, theta and alpha oscillations in the lateral areas was seen in the between groups comparison. These areas related to ventral attention and somatomotor networks. Impaired neuronal activity in the ADHD group was seen in weaker increased beta than the control group and the missing increased alpha oscillations. It remains for the future studies to interpret the roles of this oscillatory activity but direction towards impairments in cognitive functions like flexibility, working memory and inhibition in planning in ADHD. These data also suggest that planning in the WCST needs the flexible modulation of many cognitive functions and processes that are modulated by increased alpha and beta oscillations and the suppressed delta and theta oscillations.

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Abbreviations

Abbreviation	Term
ADHD	Attention deficit hyperactivity disorder
ASRS	Adult attention deficit hyperactivity disorder self-report scale
BADDS	Brown Attention Deficit Disorder Scales
BIS	Barratt Impulsiveness Scale
DAN	Dorsal attentional network
DLPFC	Dorsolateral prefrontal cortex
DSM	Diagnostic and Statistical Manual of Mental Disorders
EEG	Electroencephalography
EF	Executive functions
EMG	electromyography
EOG	electro oculography
ERD	Event related desynchronization
FEF	frontal eye fields
fMRI	Functional magnetic resonance imaging
HR	Hit rate
ICA	Independent component analysis
IPS	intraparietal sulcus
MEG	Magnetoencephalography
MNE	Minimum norm estimates
NCM	Noise covariance matrix
PFC	Prefrontal cortex
RT	Reaction time
SOA	Stimulus onset asynchrony
SQUID	Super conducting quantum interference device
TFR	Time-frequency representations
WCST	Wisconsin card sorting test
WM	Working memory

Abbreviations of brain areas

CS	central sulcus
paC	paracentral lobule and sulcus
poCG	posterior central gyrus
poCS	posterior central sulcus
prCG	precentral gyrus
prCN	precuneus
sFG	superior frontal sulcus
sPG	parietal supplemental gyrus
sprCS	precentral supplemental sulcus

1. Introduction

1.1. Executive functions

Executive functions (EF) are the abilities of adaptive and flexible environmental engagement in independent, purposeful, and inner-directed manner (Lezak, 1983, Chiaravalloti, et al., 2003). In the early cognitive theories, executive functioning was thought to be built on the central executive (Baddeley, 1992). It was a simplistic, single unity working memory model that had not been studied to extent. In Baddeley's own criticism executive functioning was judged to be as well explained by a homunculus, a human miniature version sitting inside one's head (Baddeley, 1996). The central executive model of the mind has since been broadened towards modular form where each executive function depends on various control processes and is separable from each other (Jurado, 2007). In Luria's model from 1960s (Luria, 1966), planning is the process of encoding, regulating and verification of information to form decisions. According to the model these processes would be represented in different parts of human brain and the damage to the prefrontal cortex would cause problems in regulating and verifying consequences of behaviour. According to the theory of supervisory attentional system (Norman & Shallice, 1986), there are two processing systems, one for automated routine actions and one for supervisory use of attention for novel information. Planning is one of the cognitive processes that was thought to be dependent on the non-routine supervisory attention.

Executive functions are often thought to be built on inhibition of irrelevant information, flexible use of surrounding information, control of attention, and working memory. (Gratton et al., 2018) Higher executive functions such as planning and problem solving need all these processes. Some EF models use the terms executive functions and cognitive control interchangeably. In their review of cognitive control, Gratton and companions (2018) have interpreted cognitive control to be related to functioning in task-specific timeline. Executive functions are thought to overlap with cognitive control and to appear in longer periods of time. The executive functions support each other in multiple levels of processing. Orchestration of many executive functions is needed for example in decision making. Planning, working memory, cognitive control and flexibility are needed in modulating fast-paced decision-making. Inhibition is also fundamental in situations that demand these cognitive functions.

In the hierarchical executive functions model (Diamond, 2013), planning is described as higher-level EF alongside of reasoning and problem solving. In the core of executive functions are inhibitory control and working memory. The core functions would contribute to higher-level functions through cognitive flexibility especially when the goal is to switch from one strategy to another. Processing of EF are manifolded and need different cognitive functions to be able to flexibly use the surrounding information. Miyake et al (2000), have made a distinction between shifting (choosing from information learned in the near past) and updating (choosing from novel information). Although adaptive behaviour and inhibition of irrelevant information is needed in both processes, shifting represents the faster processing of online information that is needed in the daily lives of humans.

Planning has been studied in different tasks such as the Tower of London/Hanoi, Porteus Mazes and Rey–Osterreith Complex Figure Test. In 59% of 27 studies using these tasks, the group differences for ADHD and control group have been reported significant. (Lazeron et al., 2000, Wagner et al., 2006, Baker et al., 1996, Morris et al., 1993, Goethals et al., 2004). However, in Tower of London/Hanoi and Porteus Mazes and Rey–Osterreith Complex Figure Test there is no demand for quick test performance. In Porteus Mazes, the participant can decide the pace of performance by themselves.

In fast-paced planning, attention must be directed, distractions inhibited and previously learned information remembered simultaneously. Careful pondering of things with unlimited access of information resources and time is not possible for humans, as some models of executive functioning seem to present. In Diamond's model working memory and inhibition contribute to each other but cognitive flexibility seems to be only a conveyer between the core functions and higher functions. However, all situations cannot be acted upon in a feed-forward hierarchical manner because human behaviour is prone to errors and biases. Flexible adjustment of behaviour is needed to evaluate the environment efficiently. When there's not enough information, top-down processing takes place to make use of the information that is available. Unlike automatic bottom-up processing, top-down processing actively uses feedback from environmental information that is selectively assessed to achieve goals (Gilbert & Burgess, 2008). Planning is needed in expected and unexpected situations, to maintain information and shift between attention on different information. The top-down processing takes place when decisions have been made in uncertain situations.

1.2. Wisconsin card sorting test

One of the neurocognitive tasks demanding fast planning and decision making is the Wisconsin card sorting test (WCST) (Grant & Berg, 1948). The test was developed to provide an objective technique for measuring "human abstraction and shift of set". (Buchsbaum, et al., 2005) In the test the participant sees four cards in the top row and one card in the bottom row (See Figure 1.). The target cards on the top row stay always the same and the bottom card changes in each trial. The bottom row card needs to be sorted to one of the top row's cards according to changing task rules. There are usually three rule categories determined by the cards' shape, colour, or number.

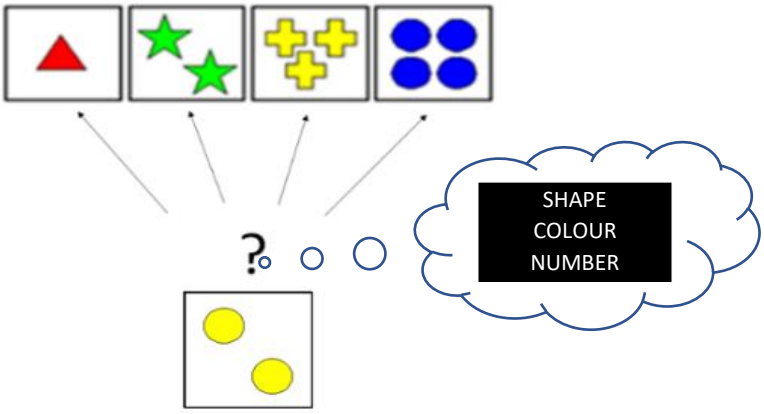


Figure 1. Illustration of the decision-making process of the participant in one trial where the bottom row card must be sorted to one of the top row's cards by their colour, number, or shape.

WCST is based on implicit sorting rules and correct-incorrect feedback. The task is to maintain (stay trial) one rule or flexibly change (shift trial) previously chosen strategies to new ones. In WCST, there is always a level of uncertainty since the next sorting category following a rule shift is not known in advance. Thus, when the sorting rule changes, the participant often leans on trial and error to find the correct rule. In some versions of the test, the sorting rules change in predictable series, e.g.,

after every 10 trials but the series length might be varied within test. In the varied series length versions cognitive flexibility and control are especially needed.

In the test's implementation part, the participant acts upon external (feedback) and internal (remembering rules) cues. Perseverance errors in WCST means the inability to shift to a new rule by sticking to using the previous rule. Set shifting in WCST means the flexible cognitive process of changing between different sorting categories. Some research on preparatory/planning processing in WCST has been done previously, like set-shifting (Periáñez et al., 2004) or feedback processing but rarely in the context of maintaining of the rule set information (Drover-Roig & Barceló, 2010).

1.3. ADHD

Meta-analytic reviews have found the worldwide prevalence to range between 2,5-5 % in adults diagnosed with attention deficit hyperactivity disorder (ADHD) by the DSM-IV criteria (Simon, et al., 2009, Willcutt, 2012, Fayyad, et al., 2017). The worldwide prevalence for children and adolescents has been reported to be 5-7% (Polanczyk, et al., 2014, Willcutt, 2012, Polanczyk, 2007). In a recent review (Dobrosavljevic, et al., 2020) the prevalence in adults 50 years and above was found to range between 1.49-2.18 %.

1.3.1. Symptoms

ADHD was first described by Still (1902) as an inability to sustain attention and control behaviour. (Barkley, 2015) Medical doctor Anthony Weikard called ADHD as an 'attention problem' in his 1775 research (Barkley & Peters, 2012). He described symptoms like distractibility and hyperactivity. More recently the DSM-IV (Diagnostic and statistical manual of mental disorders: DSM-IV, 1996) diagnostic criteria for ADHD introduced three main types of predominantly inattentive, hyperactive-impulsive or a combination of these types. Inattention is the failure of paying and directing attention as well as maintaining specific information needed to perform tasks. Hyperactivity means restlessness and producing excessive movements. Impulsivity means fast and unplanned reactivity. These symptoms manifest to an extent that may cause problems for the individual and people around them. (The National Institute of Mental Health, 2019, Moeller, et al., 2001)

Although ADHD is strongly characterized with an inability to concentrate it is not uncommon that these individuals can have a deep and long-lasting ability to concentrate on tasks. This deep

concentration state, called hyper focus, emerges from activities where the individual might get an instant reward of. Hyper focus can lead to positive outcomes like learning new things, but it can also be problematic. In hyper focus state, people tend to lean on preservative strategies that are characterized by repetitive and inflexible behaviours. These strategies lead to difficulties in shifting attention from one task or detail to another which is fundamental for executive functioning.

1.3.2. Diagnostics

ADHD diagnosing is subjective since it relies mainly on clinicians', parents', or other caregiver's observations. Despite the long history of research on the disorder, there is no unified diagnostic measure of ADHD. Clinical interviews and self-questionnaires are used, but they are not always similar, let alone identical with each other. This makes diagnosing and treatment planning uncertain and difficult.

One criterion for the diagnosis is the age-of-onset at seven but sometimes earlier manifestation of symptoms of inattention may arise before the age of seven (Diagnostic and statistical manual of mental disorders: DSM-IV, 1996). The age-of-onset was broadened until the age of 12 in DSM-5 (American psychiatric association, 2013). In 1798 a physician Alexander Crichton predicted ADHD to be mostly a disorder of childhood. However, in the more recent times Barkley, et al., (2002) reported that the childhood diagnosis for ADHD is persistent to adolescence. Furthermore, the persistence to adulthood has been found to be ranging from 30-70% for the young-age-diagnosed (Biederman et al., 2000, Kessler et al., 2005, Faraone et al., 2006). The differing views of persistency are explained by the studies' emphasis on different aspects of cognitive functions and other ADHD symptoms. Comorbidity with depression, anxiety and mood disorders, substance abuse and dependence, and personality disorders have also been linked to ADHD. (Biederman, 2004, Katzman, et al., 2017)

In a recent study by Rovira et. al. (2020) the genetic background for different traits were seen in children and adults with ADHD. Crichton had presumed of the possible heritability of the disorder already in 1798 (Crichton, 1798). In the more recent times heritability measures have ranged from 30-90% in twin gene studies. The wide range of heritability estimates stems from differing ways of studying it. The higher estimates in the young-aged-studies were found by measuring the occurrence of ADHD in the children's and adolescent's parents. The lower estimates from adult studies were found by self-reporting of the twins. (Brikell, Kuja-Halkola, & Larsson, 2015)

There has been raised a concern about over diagnosing ADHD, especially in children. On the contrary, under diagnosing has been reported for children and adults. The heterogeneity of the disorder symptoms between individuals raises its own kind of issues for the diagnostics. Other reason could simply be related to how visible the symptoms in different subtypes of ADHD are. Although the most common type of ADHD is the mainly inattentive type, the individuals with the combined type are directed to medical care more often (Willcutt, 2012). Yet another possible explanation for over- and underdiagnosing could also be found in the unestablished diagnostic criteria.

1.4. Brain anatomy and structure

It is important to find out how the meaningful representations of the surrounding world are formed in the brain to better understand how the mind works. The biology of the mind has emerged as one of the governing subjects of study in cognitive neuroscience in the 21st century. The whole human brain has around 86 billion neurons and 16 billion neurons only in the cerebral cortex i.e., the brain's folded surface. The shape of cerebral cortex is characteristic of its grooves, called sulci, and ridges called gyri (Figure 2.). The main parts of the brain are cerebellum in the back of the head, brainstem, connecting brain to the spine, and cerebrum that consists of cerebral cortex and subcortical areas. The largest part of cerebral cortex is neocortex consisting of six layers (Figure 2.) that withhold massive amounts of information and connections. The neocortex is comprised mostly of grey matter. Grey matter is rich in neuronal and glial cell bodies. The neuronal cells convey information and glial cells support the work of neurons. Neurons are connected by branched dendrites that have synapses in their endings. The dendrites' branches continue from the grey matter cells to the white matter consisting of myelin covered axons in subcortical areas.

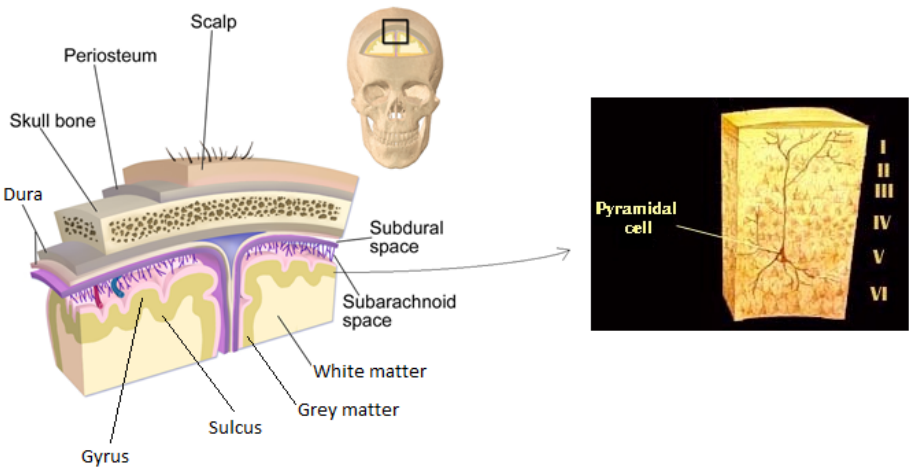


Figure 2. Illustration of the human head's layers from skull to pyramidal cells in grey matter to the white matter. Figures from Blausen.com staff, (2014) and Consenza, (1998).

1.4.1. Functional networks of the brain

The brain's connections can be examined in different scales from the level of individual cell to large-scale connections between clusters of cells and throughout the brain's layers from the surface to the innermost areas. Structural connectivity (SC) networks are the anatomically distributed areas of the neural or white-matter connections in brain. In humans, white matter tracts forming the SC networks can be estimated using diffusion tensor imaging (DTI) and with magnetic resonance imaging (MRI).

Cognition is based on dynamically organized networks of the brain. The network theories aim to explain the functioning of the complex systems such as the brain (Sporns, & Betzel, 2016). Brain is thought to operate through functionally distributed neural networks (Zanto & Gazzaley, 2013). Brain's functional connectivity (FC) is thought to be modular in their nature which means that they can appear as dense connected brain areas or regions with scarcer connections. The modules co-localize with different sensory modalities and attentional networks (Sporns, & Betzel, 2016).

Attempts of localizing the brain activity in certain areas stems to the 19th century. Although the structural and functional connectivity are not corresponded in a straightforward manner several approaches have been formed to divide brain to subareas and networks. The different areas of designated brain source spaces are called parcels. An automated parcellation (Figure 3 A) of generally accepted sulco-gyral division, have been built by Destrieux et al. (2010) based on the brain's anatomical reconstruction process of Dale & Fischl (1999). The brain's named and color-coded subsystems (Figure 3 B) by Yeo et al. (2011) were estimated from 1000 participant's brain and illustrate brain areas that are functionally coupled during brain spontaneous activity across subjects. In addition to these, there are tens of other parcellations based on different brain measures and more is being developed for different purposes.

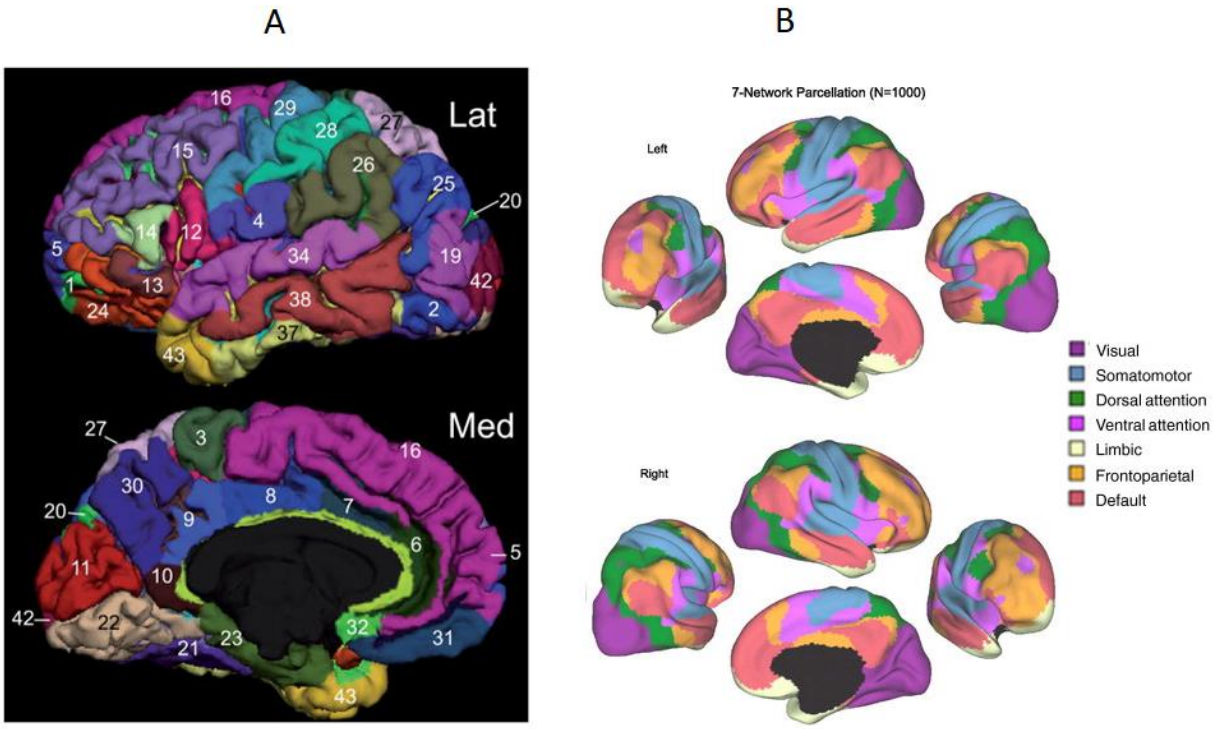


Figure 3. A. Sulco-gyral division of brain's left hemisphere from lateral (side) and medial (inner) pial views (Destrieux, 2010). B. Functional subsystems in left and right hemispheres according to 7-network parcellation (Yeo et al., 2011).

Brain's functional networks important for planning and decision making are dorsal and ventral attentional networks (DAN, VAN) (Corbetta & Shulman, 2002, Posner & Petersen, 1990) as well as the default mode network (DMN). The role of DAN and VAN is thought to be an active part of attentional processing during task execution. Both areas reach to the frontal and parietal brain lobes and are convey information for example towards and away of the visual areas in occipital lobe. The DAN is located more towards the superior direction (the top of the brain) and VAN more towards the medial direction (middle part of the brain). DAN consists of frontal eye fields (FEF) and intraparietal sulcus (IPS). VAN consists of inferior frontal gyrus (IFG), inferior parietal lobe (IPL), middle frontal gyrus (MFG), temporo-parietal junction (TPJ) and superior temporal gyrus (STG). (Vossel et al., 2014) Despite its suggested role in idling, automatic type of processing the DMN has also been related to higher cognitive functioning. DMN has been observed to activate in the processing outside the task execution period for example in planning and decision making. DMN has been linked to visual imagery processing that is partially overlapping with DAN and VAN (Pearson, 2019). DMN consists of medial prefrontal, posterior cingulate and left and right lateral parietal areas.

1.5. Measuring brain activity from humans

Functional magnetic resonance imaging (fMRI) can be used to measure events within second time scales, and it can locate the activation site in the human brains within millimetres. fMRI measures the changes in blood oxygenation levels which is increased during task performance. They can hence be used to give direction in analysing the most probable activation sites.

Electro encephalography (EEG) measures brain's electric activations from the surface of the scalp. The source of the measured EEG signal emanates from the activated postsynaptic receptors in widespread pyramidal cells (See above Figure 1.) that have suitable perpendicular orientation towards the skull for measuring its signal. (Singh, 2014, Hämäläinen & Hari, 2002) Spatial resolution is 7-10 mm in EEG. (Singh, 2014)

The electrical signalling in brain generates very small magnetic fields that can be measured with magnetoencephalography (MEG). The brain's magnetic fields arise from current flow in the pyramidal cell's dendrites. Unlike in EEG measurements where the activation source is suppressed by the skull, in MEG the magnetic fields are not interfered by skull's structures. MEG is measured with highly sensitive magnetism detectors called SQUIDS (super conducting quantum interference device). The magnetic fields are captured with gradiometers and magnetometers that send the signal to the device's helmet of SQUID sensors array. The temporal resolution of MEG is close to sub millisecond and has a spatial resolution 2-3 mm. (Singh, 2014, Hämäläinen & Hari, 2002)

1.5.1. Neuronal activity can be recorded with electrophysiology

In electrophysiological recordings the brain activity is characterized by rhythmicity in all spatial scales from single neurons to global neuronal populations. The neuronal oscillations reflect fluctuations in neuronal excitability. Oscillatory activity can be measured from at least 10^5 active group of synapses. Oscillations act as temporal filters in dynamically organizing brain's processing. A wide range of frequencies from 0.05-500 Hz have been recorded in mammalian brain (Buzsáki, et al., 2004). Oscillations have been divided to delta (1-3 Hz), theta (3-5 Hz), alpha (8-15 Hz), beta (15-30 Hz) and gamma (30 - 120 Hz) bands. They can be characterized in frequency, amplitude, and phase.

Delta (δ) band has been found to reflect behavioural inhibition as well as attention and motivation. Theta (θ) band reflects behavioural inhibition and have been found to be suppressed through gating when working memory is no longer needed for maintaining information. (Raghavachari, et al., 2001) θ activity has also been linked to working memory maintenance and retrieval in episodic encoding. (Hsieh, et al., 2014) θ have been linked to increasing cognitive control processes in error related situations. Cohen et al., (2009) have recorded increased θ power after error.

The role of alpha (α) band oscillations has traditionally been linked to the sensory suppression in active memory processes. has also been observed to strengthen during imaginary and mental calculation processes and in maintaining of working memory. (Ray & Cole, 1985, Klimesch, 1996) More recently, the role of oscillations has been predicted to play a role in top-down processing in executive functioning. According to the active-processing hypothesis, the phase dynamics could reflect the neural coordination of task-relevant cortical areas. (Palva & Palva, 2011) Correlated suppression of amplitudes and phase-synchronization have been linked to implementation of visuospatial attention in frontal, parietal, and visual cortexes. (Lobier, et al., 2018) Alternative hypothesis is that increased reflects the pulsed inhibition of task-irrelevant areas (Jensen & Mazaheri, 2010). Thus, the suppression of unnecessary sensory information during complex cognitive processes might also serve as a role for functioning of oscillations has been linked to inhibition of distracting information in working memory (Bonnefond & Jensen, 2013).

Referred as event-related desynchronization (ERD) (i.e., the decreasing of oscillatory activity), the suppression of beta (β) band has been linked to the motor planning activity at various brain areas in motor network. Furthermore, Tzagarakis et al. (2010) have proposed that the ERD of the β band may also be linked to the response uncertainty in motor planning. Schmidt et al., (2019) hypothesize that the clearing out of WM could have a “counterpart in the post movement clear-out of the motor plan in sensorimotor cortex”. Persevering cognitive state as well as top-down processing, and long-range communication has also been linked to β band. Spitzer and Haegens (2017) have proposed that the β band could reflect decision-making process in reactivating task relevant information. Enhanced β has also been linked to impaired cognitive flexibility and control. (Engel & Fries, 2010)

Gamma (γ) oscillations are often seen during active processing of different stimuli. The γ band activation may reflect attentional selection and memory processes. γ could be a fundamental computational mechanism that allow and support fast brain processing (Fries et al., 2007). In impaired learning and memory, the low γ oscillations are reduced. (Mably & LeeColgin, 2018) γ band

oscillations have also been found to support the maintenance of feature-specific information and might take part to binding feature characteristics during the formation of memory representations (Honkanen, et al., 2015).

1.6. Aberrant brain structure and function in ADHD

1.6.1. Structural abnormalities in ADHD

Sometimes, EF abnormalities in brain have been simply referred as a frontal dysfunction. This understanding has been formed from early studies where lesions in frontal areas were found to cause executive dysfunctions. More recently, the frontal dysfunction theories have been revisited to include a diverse connectivity from the frontal areas to other brain regions. (Miyake, et al., 2000, Godefroy, et al., 1999) Miller and Cohen (2001) have been proposing a prefrontal model of executive functions where cognitive control is temporally organized.

Structural changes have been found in grey and white matter volumes (Francx et al., 2016, Batty et al., 2010). Anatomical structure studies have found reduced white matter volume from the right frontal and posterior regions of the brain, as well as caudate asymmetry differences in ADHD children. As the posterior brain areas are related to information access from previous situations and the frontal part in applying this information to the present moment, the reduced white matter volume might result in communication problems between these brain regions. In a 33-year follow up study of adults with ADHD, grey matter was decreased in right caudate, right thalamus, and bilateral cerebellar hemispheres. (Proal et al., 2011) The cerebral cortex in various sites was also found thinner in these individuals. Reduced frontoparietal structures have been reported in children with ADHD measured with diffusion tensor imaging (Nagel, 2011). These findings could predict problems in executive functions that demand the efficient functioning of fronto-parietal regions.

1.6.2. Functional abnormalities in ADHD

Task related contextual information is sent from sensory areas to the prefrontal cortex. Frontal lobe is seen as the fundamental area in executive functions where information from various posterior brain areas is integrated. Aberrant communication between brain's hemispheres and dysfunction in neuronal oscillation patterns has been found in ADHD. The individuals with ADHD could have problems in accessing previously learned information and/or applying the knowledge in new situations. These findings support the proposition that sustained attention could be impaired in

children with ADHD and could point to the direction of impaired self-regulation and executive functioning.

A yet to be defined theory of primary visual cortex and its relation to attentional dysfunction in ADHD has been proposed. Visual network asymmetry and default mode function has been found in and fMRI study on children with ADHD (Hale, et al., 2014). In executive tasks that need inhibition, working memory and attentional regulation, hyper activation in occipital areas have been demonstrated in adults with ADHD in several fMRI studies. (Castellanos & Proal, 2012)

The frontal striatal circuits are often related to the interplay of prefrontal cortex and subcortical areas like striatum and thalamus in these kinds of behaviours. In functional neuroimaging studies the frontal striatal network abnormalities have been linked to ADHD (for a review see Bush et al., 2011). Dorsal attentional network (DAN) has been found to be impaired in ADHD. In previous human and animal studies, FEF and IPS has been related to the top-down mechanisms of attention, memory, and eye movements (Corbetta et al, 2002). ADHD has been linked to dysfunctions in the default mode network, and frontoparietal subsystem.

2. Purpose of the study

The main objectives of this thesis were to study the neural underpinnings of planning period in group of adults with ADHD and healthy control group using Wisconsin card sorting test in ADHD and a control group. Only few previous studies have been conducted in the planning time period of the WCST, but the cognitive processes investigated have most often been referred as preparatory processes. Clinical questionnaires are used to assess the symptoms and types of ADHD.

1. The first objective was to reveal whether behavioural measures would differ in the control and ADHD groups.
2. The second objective was to investigate local oscillation amplitude dynamics associated with planning period in WCST.
3. The third objective was to find out the aberrant local oscillation amplitude dynamics associated with planning period in WCSR un adult ADHD patients and whether this differed from the control group.

The hypothesis is that the local neural activity would be different specifically in the frontal and parietal cortex.

3. Methods

3.1. Participant demographics and recruitment

The volunteer participant groups consisted of a group of 21 adults diagnosed with ADHD (age distribution 37.6±10 years, 10 males) and age-matched 27 controls (age distribution 33±10 years, 11 females) with normal or corrected-to-normal vision. The control participants had to be free of any neurological or psychiatric conditions and free of medications affecting central nervous system. Criteria for both participant groups were that they are not pregnant or have any metal in their bodies. The criterion for the ADHD group participants was an adult ADHD diagnosis from a medical doctor. Whether the participant had medication, was reported only for 14/21 participants in the ADHD group. Five participants out of the 14 participants were reported to have medication. No information regarding taken medications in the measurement day was collected.

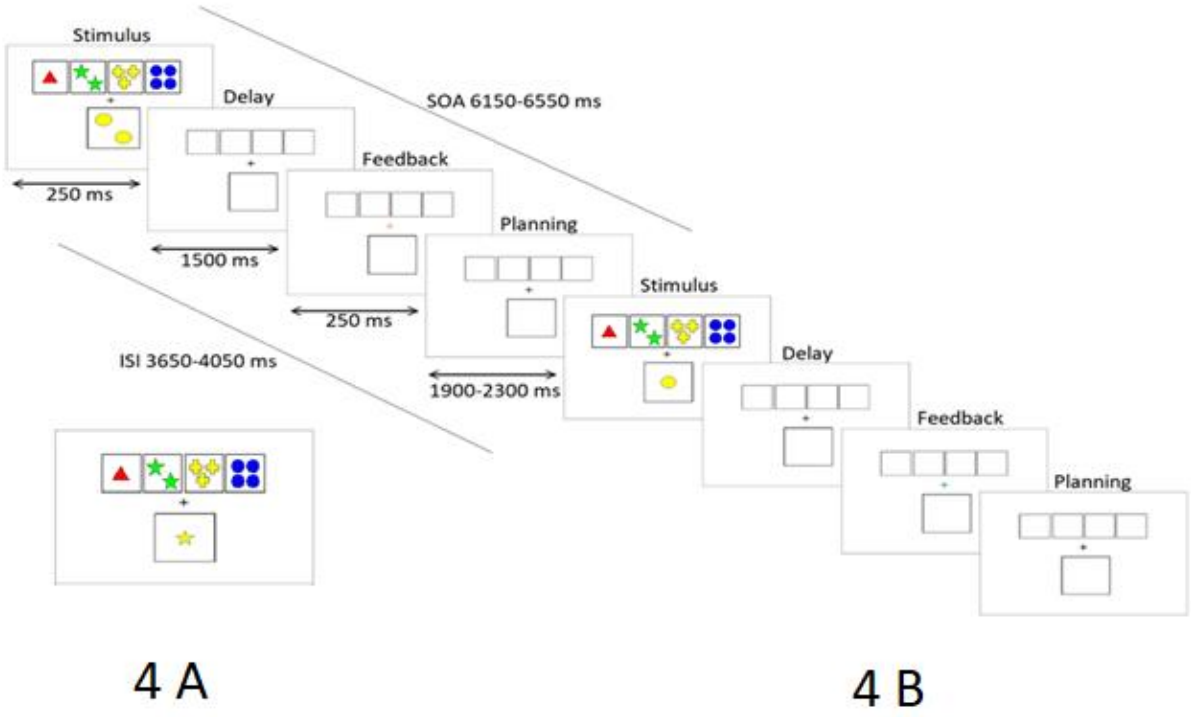
3.2. Recordings

Magnetoencephalography (MEG) was used to measure brain activity during the Wisconsin card sorting test performance. The MEG measurements were conducted with a 306-channel MEG device (Elekta Neuromag Ltd, Helsinki) in the Meilahti hospital premises in Helsinki, Finland. The MEG data were filtered with 0.03–330 Hz band bass with a sampling rate of 1000 Hz. During the MEG recordings, each participant's blinks, and vertical eye movements as well as horizontal eye movements were measured with electro oculography (EOG). Head position changes were measured with head position coils attached to anatomical landmarks. Responses were measured with fibre optic response device that is used to respond by lifting a finger and held in one hand.

In addition, whole head magnetic resonance images (MRIs) were taken for anatomical reconstruction of MED data using Siemens Verio 3T MRI Scanner with resolution of one cubic millimetre.

3.3. Stimuli and experimental paradigms

In Wisconsin card sorting test, the task is to sort a defined number of cards by different rules to certain target cards. In the current version the participants were not able to predict the start of a new rule since each sorting rule was repeated between four and six trials. Barcelo et al., (2002) and Periáñez et al., (2006) have demonstrated that the reaction times or physiological measures did not change after fourth trial inside a rule-series. The sorting rules had three categories: shape, colour, or the number of shapes. The different shapes are circle, star, cross, triangle, colours are blue, yellow, red, green and there can be 1-4 shapes in one card. In the example picture below (Figure 4. A.), the possible sorting rule could be colour yellow, shape star or number one. The participants received a feedback after every response with a cross located between the card rows. Red cross indicated incorrect and green cross indicated correct response. During the rest of the task, the feedback cross stayed white. The rules were unambiguous, which means that only one possible sorting category would be considered correct. The experiment consisted of 450 trials divided to three blocks. One block consisted of 150 trials. The stimuli were run in Presentation environment. Video settings in Presentation were a refresh rate of 60 Hz and image resolution of 600 x 800. The test was shown on a screen in front of the participants. The screen was 1,5 meters away from the participants. The image measures were width: 58 cm and height: 44. 3 cm. Screen brightness was 16 Hz.



4 A 4 B

Figure 4. Example of what the participant sees in one trial (4. A). Task timeline (4. B) with two trials, starting from stimulus.

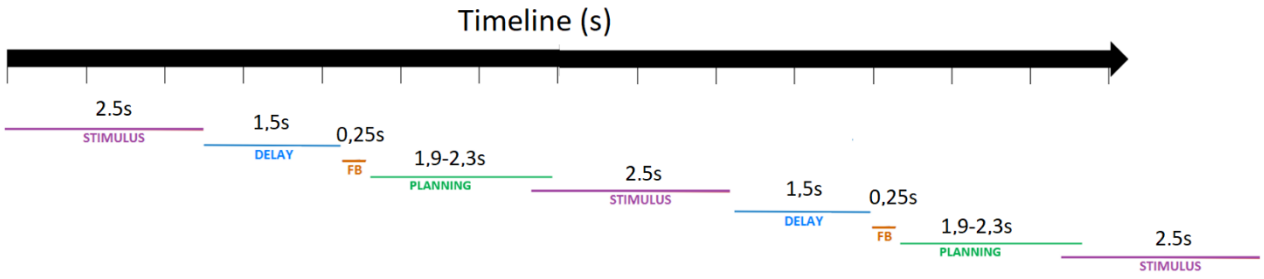


Figure 5. WCST timeline where triggers are visualized in their real timescales.

The task timeline is demonstrated in figure 4. B and 5. The stimulus onset asynchrony (SOA) were between 6150-6650 milliseconds. Inter-stimulus interval was 3650-4050 milliseconds. One trial consisted of stimulus (2500 ms), delay (1500 ms), feedback (150 ms) and planning (1900-2300 ms). The participant was allowed to respond during stimulus or the delay. Baseline was the last 500 ms of the delay. The experiment lasted approximately 45 minutes with three 15-minute blocks.

3.4. Procedure

Both groups were asked to fill a consent form of voluntary participation. The research was approved by the Helsinki university hospital ethical committee and was carried out according to the Declaration of Helsinki. Neuropsychological testing was done on a separate occasion from the brain imaging session, at Neuroscience centre, in Viikki Helsinki. Two clinical questionnaires, the Barratt Impulsiveness Scale (BIS) and Adult ADHD Self-Report-Scale (ASRS-v1.1) were completed. ASRS is a tool for helping the symptom assessment for adult ADHD diagnosis following the DSM-IV criteria. BIS is a measurement tool for assessing impulsiveness traits. The traits are “attentional (impulsive decision making), motor (propensity to engage in spontaneous behaviour) and non-planning (lack of concern for the consequences of one's future actions)” (Patton, Stanford, Barratt, 1995). BIS test results were missing from three controls and four ADHD participants, ASRS results were missing from one ADHD participant and three controls. In addition, the ADHD group completed the Brown Attention Deficit Disorder Scales (BADDS) that measures activation, attention, effort, affect and memory. The BADDS results were missing from one participant.

The brain measurements were carried out in the Meilahti hospital premises. To avoid disturbances in the MEG measurements, the participants were instructed to remove all metal they are wearing for example belts and jewellery. After this, the task was shortly rehearsed. Next, the participants were then seated for the digitization of head coordinates with a 3D measurement device. During the head coordinates measurement, participants were instructed not to move. Then, the head position and grounding coils were attached on the participant according to the landmarks in left forehead, left mastoid, right mastoid, right forehead, and middle forehead.

The participant was ready to be directed to the shielded MEG measurement room. Participant was seated under the MEG device and the seat was adjusted in the correct position so that participant was close to the MEG helmet. The position of the participants was adjusted between the blocks if necessary. This was done to ensure as good measurement results as possible since people tend to change their position farther away from the MEG device during the measurements. The response device was handed to the participant, and they were allowed to decide the response hand. They responded with four fingers: thumb, index finger and middle finger and could choose between pinkie or ring finger. Participants were given further instructions about the task, and they were told that each series would start with one-minute resting state when the participant should just relax. They were also told they could discontinue the task at any point by saying they wish to stop. Participants were given a chance to rest and stretch out between the blocks. Participants were instructed to blink as little as possible and to stay as still as possible. Participants were informed that they could communicate with the researcher though a microphone attached near them and that the lights would be dimmed so that the stimulus screen would be seen better. The measurement was ready to start, and the stimulus screen was brought in front of the participant.

4. Analysis

4.1. Behavioural analysis

For behavioural analysis scripts, Python programming environment was used with MNE package for handling event files that included reaction times and information about correct and incorrect responses. Performance on the behavioural level was examined with reaction times (RT) and hit rates (HR). Reaction time means the time between stimulus onset and the response. Reaction times were calculated for each trial and the mean RT for each participant. The mean RTs for each

participant were then visualized in Python with Seaborn package. Mean reaction times for each group were then examined and a two tailed t-test for two samples was used to see if there was a significant difference between the ADHD and control group. The mean group RTs were then plotted in violin plots with Seaborn. The reaction times were also scatter plotted with the clinical questionnaire scores for the ADHD group. Hit rate means the percent of correct responses for each participant out of all trials they completed. Hit rates were then visualized on individual level with Seaborn. The mean hit rates between the two groups were compared with two tailed t-test for two samples assuming unequal variance. Then, the mean hit rates were plotted with violin plot for visualization.

4.2. MEG and MRI data analysis

For the local neuronal dynamics, a pipeline of data analysis was used to find out the contrast of trials in the planning stage with previous feedback being correct divided from the trials of planning stage with previous feedback being incorrect both within and between the groups. In practice it meant the trials where the rule was maintained were subtracted from the trials where the rule was switched by the participant. The MEG and MRI data analyses were done on Labview environment with the Palva lab member's self-customized tools, Excel, Matlab, Python programming environments. Open-source softwares, Linux based MNE (Gramford, et al., 2014) and Freesurfer (Fischl, 2012) packages. Before starting the analyses, the consistency of raw data and possible bad channels were inspected by eye. Five participants had to be excluded due to missing MRI scans (1), excessive noise in the data (3) or missing measurement sets (1). Maxfiltering and temporal signal space separation (tSSS) was done on the MEG data in MNE Python package. Maxfiltering and tSSS aim to erase the extracranial (outside the head) noise from the data, to fix head position changes during the measurements, and to automatically detect bad channels from the data. (Taulu & Kajola, 2005. Taulu & Simola, 2006) One bad channel, 1013, was marked and interpolated. Head position changes over 10 mm were excluded from the raw data. In Labview and Matlab environments the data was filtered further. Independent component analysis (ICA) was used to erase detected vertical and horizontal eye movements as well as cardiac originating noise. Bad components such as flat-power spectrum, correlation coefficient with EOG channels, and cardiac-like events were looked for and deleted from the data. Next, the raw event analysis parameters were set. This created raw event files including information about measurement signal, eye movements, responses, trigger events

and channels in the data. Then, event files were created, and each trial was given multiple describing tags that included reaction times, responses, feedback information about the current and previous trials and about the timing of blinks related to feedback triggers. The event files are needed for relating the events to the certain time points in the data-analysis.

MRI scan data was analysed alongside with the MEG data. The magnetic resonance images scanned from each participant were analysed for source modelling and anatomical reconstruction. Source modelling is the process of estimating the brain's most probable activity sites. Then, an anatomical model can be reconstructed with the information from both, MEG and MRI measurements. Freesurfer (Fischl, 2012) was used for anatomical reconstruction of the MRIs to create brain's surface files for each participant. Python package MNE was then used with Freesurfer to provide the files for source modelling. Volumetric segmentation, cortical surface reconstruction, flattening, cortical parcellation and labelling were done by utilizing the Freesurfer Destrieux atlas (Destrieux, Fischl, Dale & Halgren, 2010). The MRI-MEG signal spaces distributed in the cortex, were co-registered. Using minimum norm estimates, single-layer boundary element conductivity models for the inner surface of the skull and source models for source recreation, were computed.

Next, forward operators were computed with MNE. Noise covariance matrix (NCM) was made in Freesurfer. The purpose of NCM is to give estimates of errors in the measurement channels and from noise originating outside of the skull. One-minute resting state from the beginning of all three measurement blocks were used for NCM. To solve the inverse problem of neuronal activity, an inverse model was then created for each filter by combining NCM and the forward model using minimum norm estimates. Trials data was formed, and cortex was flattened so that they could be combined by source collapsing. Morlet wavelet filtering (m =5) was used to bring out time related changes in the cut time windows of the activation sources and vertices. Trials data represent filtered and optionally inverse modelled single trials that are cut according to the defined events. The time window for these events was 1.4 seconds before and 4 seconds after the target event commence.

Amplitudes were computed from time window -1.4-4 seconds from the target event onset. These time windows and frequency windows ranging from 3.31-143 Hz were collapsed into 400 parcels. One patch responding approximately 40-200 m^2 activated synaptic cortical areas. To enhance source reconstruction in the individual level, fidelity optimized sparse weighed collapse operators were used (Korhonen et al, 2014). For each participant the mean oscillation amplitude information consisted of 400 parcels, 105 time windows, 38 frequencies in two task conditions.

Then, statistical analyses were conducted within and between groups. Two-tailed non-parametric group statistics with Wilcoxon signed rank test were calculated in Labview for both groups separately. The data was morphed from 400 parcel patches into 200 parcel patches. Between groups comparison for correct-incorrect was calculated with Welch's t-test with 400 parcel patch. The mean signal of the baseline period was subtracted from the data. This was done to extract the information in the data that was not the target of interest here. False-discovery rate (FDR) predictions for each time and frequency window were removed in the level of = 0.05.

For the analysis window (Figure 6.), which was the planning period of WCST, a contrast was calculated between previous trial's feedback being correct and incorrect for all time-frequency windows. This was done to investigate the amplitudes that are left in the planning period when previous trial's feedback was correct and is subtracted from the planning periods when the previous trial's feedback was incorrect.

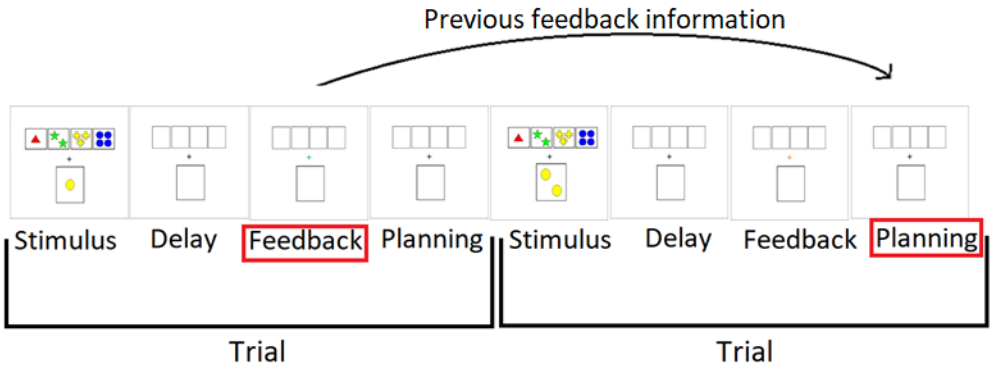


Figure 6. Analysis window of the planning stage related to previous feedback's correct or incorrect information.

Q-value (0.065) was estimated and only values above this threshold were visualized. Then, the contrasts were visualized as time-frequency representations (TFR). The fraction of parcels in the selected time-frequency periods that show positively significant proportions compared with all parcels, was visualized with TFR's. Then, visualization of the brain's flattened surface and further the brain's 3-D model, was done in Labview. For the ADHD group the latencies and frequencies in 3D model were limited to 0.25-1.25 seconds and 9.8-37.8 Hz since this time-frequency window had been found to have the positive proportion of the activation we were interested to inspect. For the control group the range was from 0.3-1.02 seconds and frequencies between 8.14-42.5 Hz. For

between groups comparison the TFR was visualized in time-frequency window of 0.4-1.7 seconds and 3-10 Hz.

5. Results

5.1. Behavioural results

Two tailed t-test for two samples assuming equal variances (F=.89) was used to compare the group values of reaction times between ADHD (*M* = 1.21, *SD* = 0.20) and control (*M* = 1.14, *SD* = 0.21) group. No significant difference (*t* (46) = 1.13, *p* = 0.26) was found for RTs between the ADHD and control group (Table 1., Figure 8). For the hit rates two tailed t-test for two samples assuming unequal variances (*F* = .57) was used to compare the group values of reaction times between ADHD (*M* = 0.57, *SD* = 0.07) and control (*M* = 0.59, *SD* = 0.09) group. No significant difference (*t* (46) = -0.78, *p* = 0.44) was found for the hit rates between the groups (Table 1., Figure 9). The clinical score scatter plots did not reveal a grouping of the observations that would point to the direction of a relationship between reaction times and the clinical scores within ADHD group (Figure 10).

	Controls			ADHD	
	Mean reaction time (s)	Hit rate (%)		Mean reaction time (s)	Hit rate (%)
S0001	1,6	67	**P0001**	1,4	59
S0003	1,4	67	**P0002**	1,4	58
S0005	0,9	66	**P0003**	1,3	63
S0006	1,3	45	**P0004**	1,3	54
S0008	0,9	63	**P0005**	1,4	41
S0036	1,3	53	**P0006**	1,4	53
S0038	1	61	**P0007**	1	58
S0039	1	59	**P0008**	1,3	62
S0049	1,2	59	**P0009**	1,3	58
S0113	1,3	57	**P0011**	1,1	51
S0115	0,9	68	**P0012**	1,5	47
S0116	1,1	39	**P0015**	1,1	59
S0117	0,8	69	**P0016**	1,1	58
S0118	0,9	72	**P0018**	1,4	50
S0119	1	67	**P0019**	1	62
S0120	1,3	51	**P0020**	1,5	48
S0121	1	59	**P0021**	1,1	59
S0123	1,6	43	**P0022**	1	65
S0124	1	67	**P0024**	1	63
S0126	1,3	49	**P0025**	0,8	70
S0127	1,2	59	**P0028**	1	61
S0128	0,9	65			
S0129	1,2	64			
S0130	1,3	51			

Table 1. Mean reaction times (s) and hit rates (%), presented for controls (S before participant number) and ADHD (P before participant number).

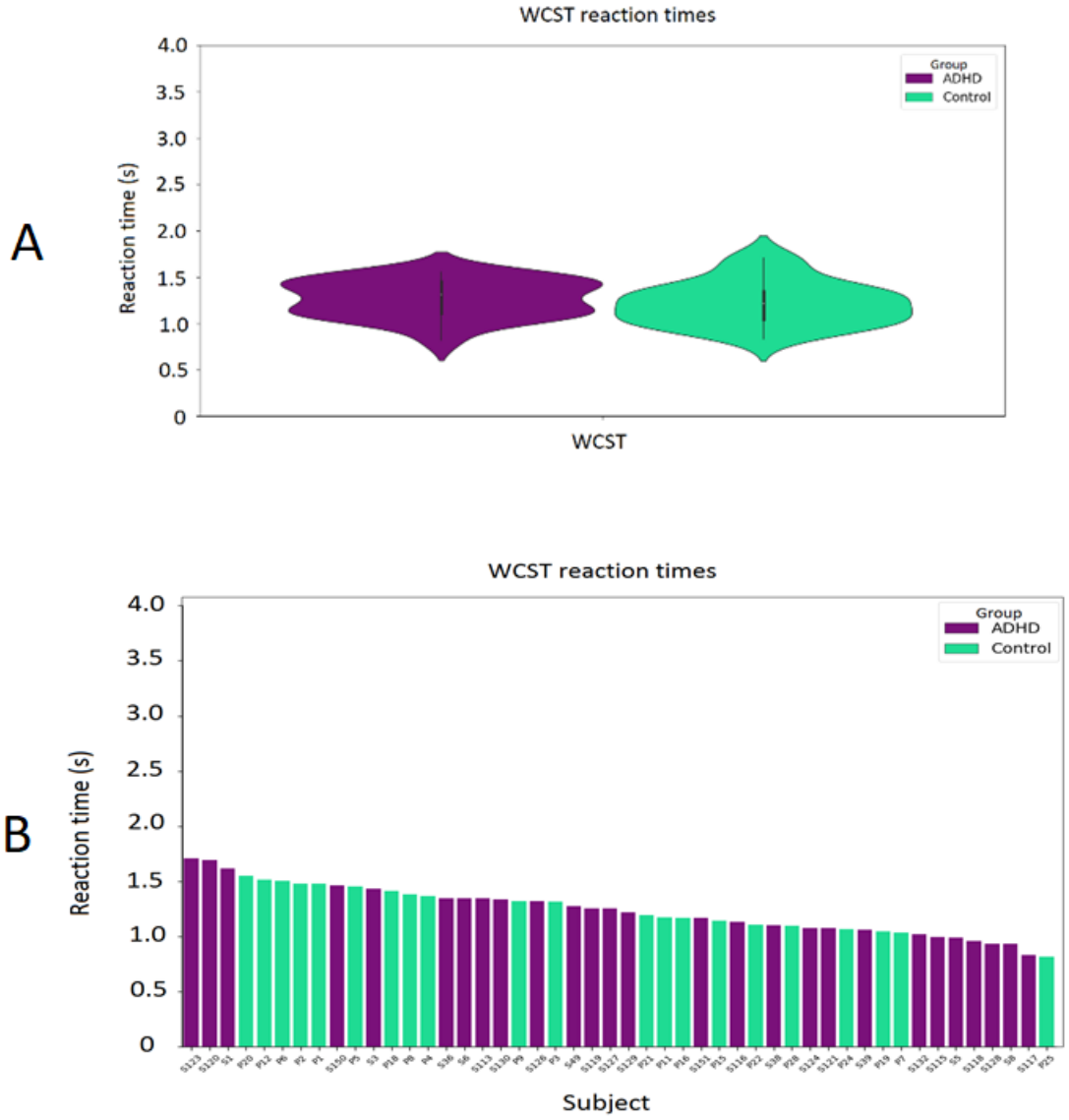


Figure 7. A. Reaction time violin plot for ADHD and control groups. B. Reaction time (s) bar plot for every participant.

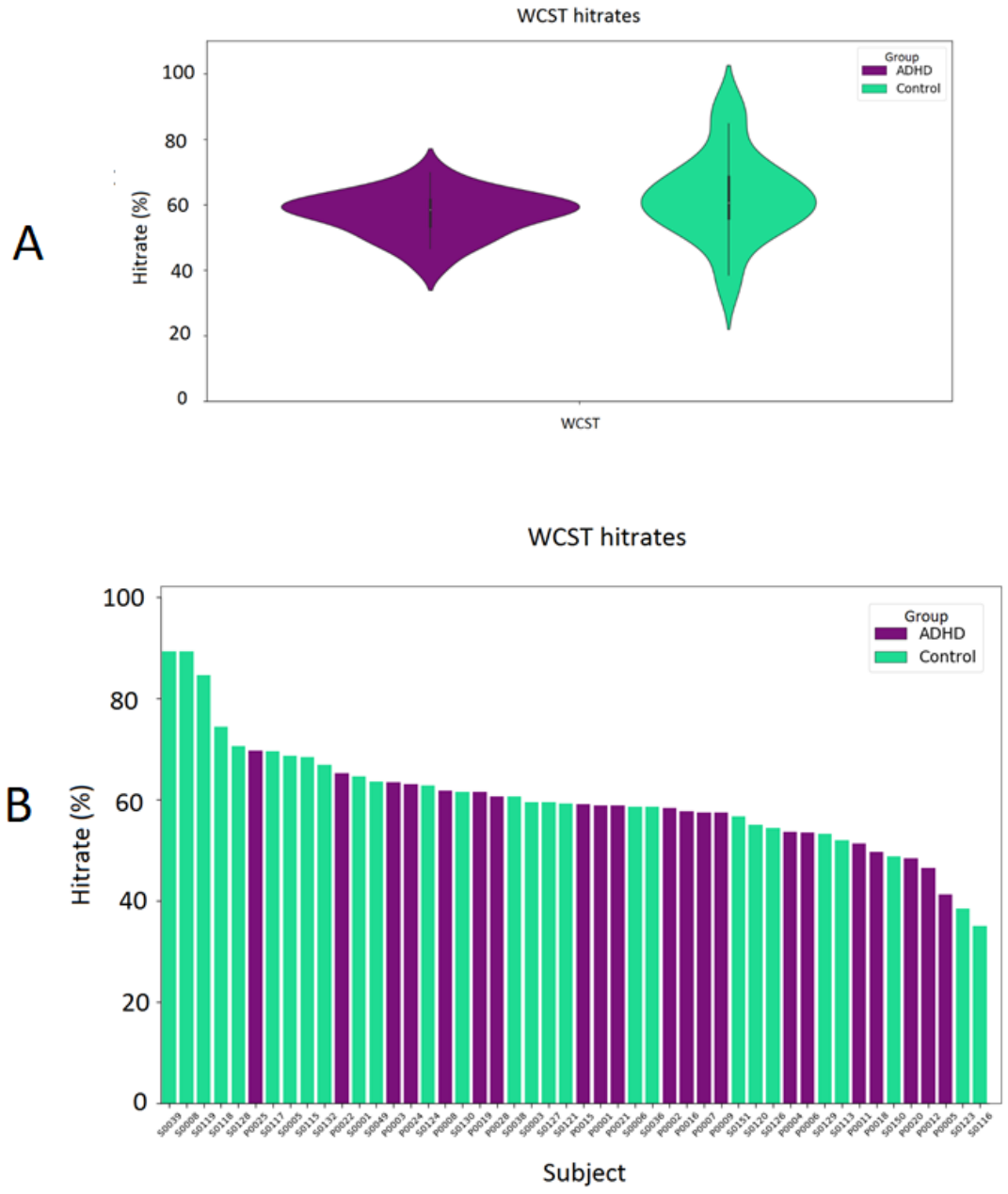


Figure 8.A. Comparison of hit rates in violin plot for ADHD and control groups. B. Hit rate (%) bar plot for each participant.

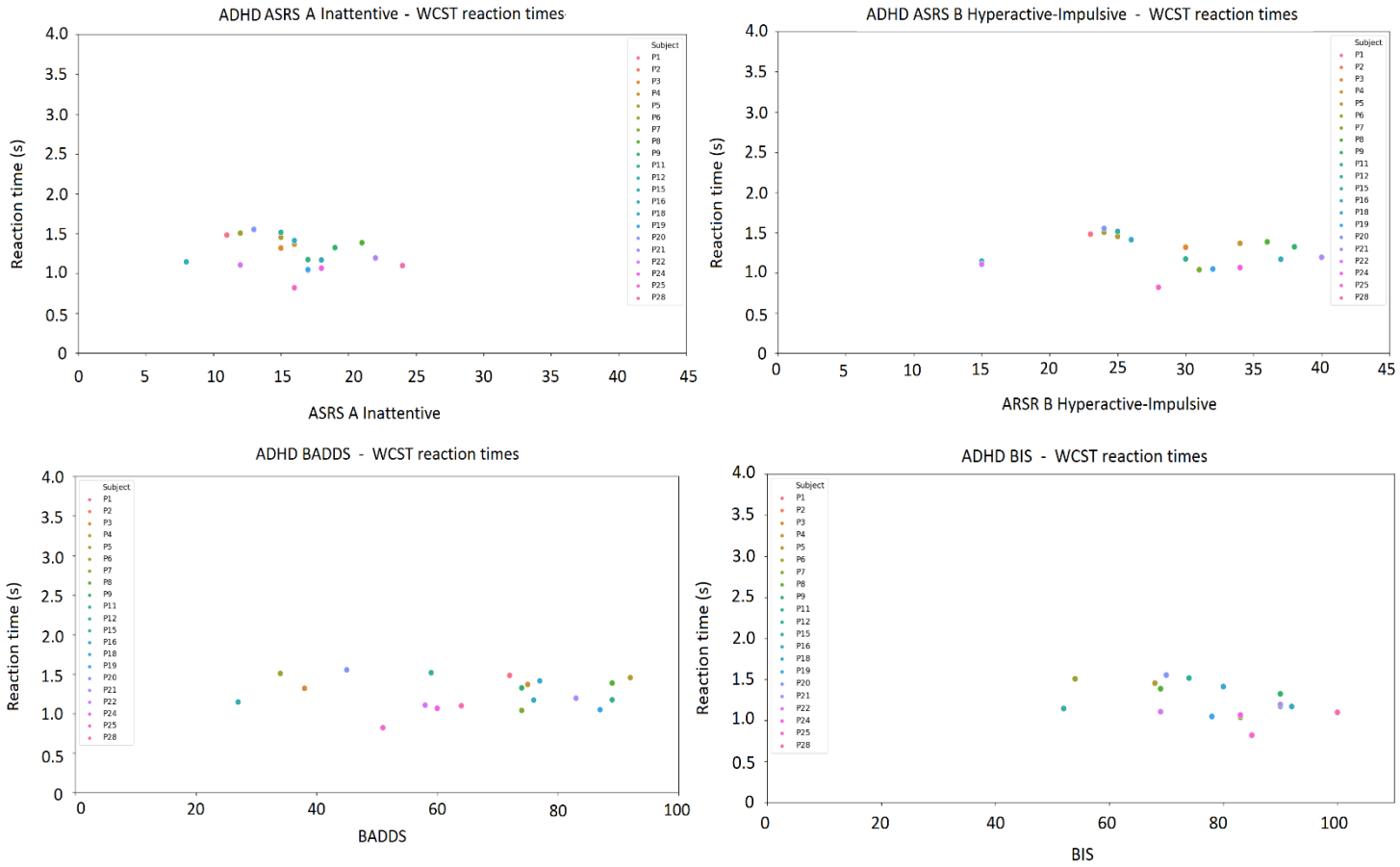


Figure 9. Scatter plots for BIS-RT, BADDS-RT, ASRS (A- Inattentive)-RT, ASRS(B-Hyperactive-Impulsive)-RT among the ADHD group.

5.2. Oscillation amplitude results

To investigate how local oscillation amplitudes were modulated in planning stage during task-rule maintaining we compared stay trials with switch trials in previous feedback information (see Fig. 6) for all analysed frequencies (3-140 Hz). We found out that oscillation amplitudes were greater for control group in α and β bands than the ADHD group. The between groups comparison revealed greater suppression in delta, theta, and alpha band amplitude for the ADHD group. In figure 10, the panels A-C are time-frequency representations (TFR) of the analysis time-window in all analysed frequencies. Panels D and E are the source-reconstructed models on inflated brain showing the positive fraction and panel F, the negative fraction of the significant parcel proportions. The time-frequency window used in visualizations for panels D-E is shown in dashed boxes in panels A-C.

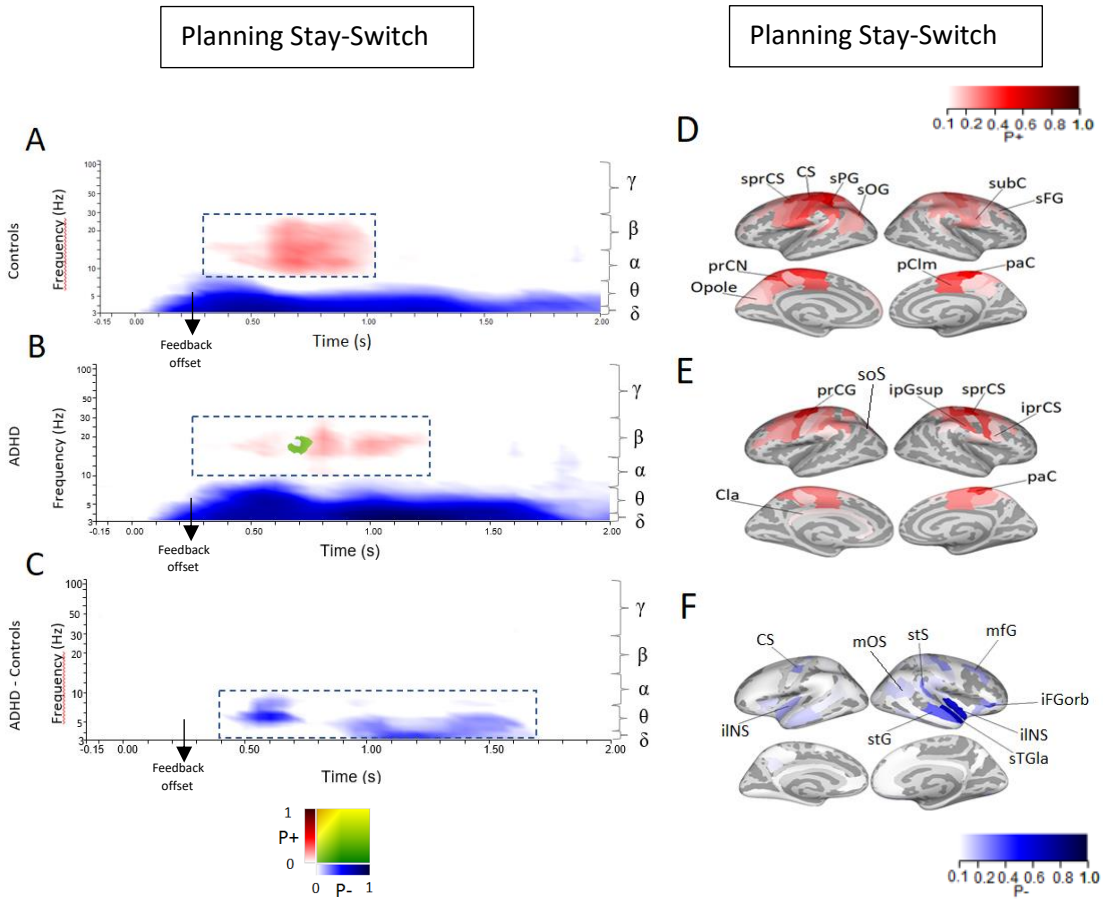


Figure 10. All three TFRs (panels A, B, C) include amplitudes of all analysed frequencies (3.12-140 Hz) in the time window from -0.15 seconds to 2 seconds before and after the planning stage. In the TFRs brackets, oscillations from δ (1-3 Hz), θ (3-5 Hz), (8-15 Hz), β (15-30 Hz) and γ frequencies (30 - 120 Hz) are seen and marked. Offset of the feedback is marked to see when the feedback cross turned white. All panels are contrasts in the planning stage's two conditions of stay-switch in the full time-frequency window (A-C) and limited time-frequency window (D-F). Panels D, E, and F are the modelled visualization of brain's inflated surface in planning period with previous trial's stay-switch. In the A-F panels are time-frequency windows of significant positive fraction (P+) and negative fraction (P-) of activation out of all analysed parcels. Each panel D-F present the left and right hemispheres from lateral and medial view. The colours in the colour scales of the red and blue mean the value of the fraction of positive and negative significant proportion of parcels from all parcels. The dashed box in each TFR in panel A-C are visualized in their neighbouring panels D-F. **A:** The control group TFR. P+ is seen from α to β band activity and P- of sustained δ and θ oscillations to low α band oscillations. **B:** The ADHD group TFR. The green area is an overlap of significant positive and negative fractions. The ADHD group shows P+ in the β band as well as P- of sustained activity in the δ and θ bands. **C:** The TFR of between groups comparison of ADHD-Controls show P- in the δ, θ, and α frequencies. **D**: The control group modelled inflated brain surface. Brain visualization for positive proportion of parcels out of all parcels in time-frequency window of 8-40 Hz and 0.3-1.02 s for. Lateral and medial activity is seen in both hemispheres, with the greatest fraction values centered to the prefrontal and parietal areas. Significant proportions of positive parcels are also seen in the occipital and temporal lobes. **E**: The ADHD group modelled inflated brain surface. P+ in 10-35 Hz, 0.25-1.25 s. The positive proportion of parcels (p+) compared to all parcels with darkest red representing the strongest activation. Oscillations in β band P- from 11-3 Hz, 0.4-1.7 s. Oscillations seen in δ, θ and α. Parcels (P-) are linked to somatomotor, ventral and dorsal, default mode and frontotemporal systems. **F**: The between group modelled inflated brain surface. Difference for the planning stage contrasts from 3-10 Hz in 0.4-1.7 seconds in the lateral view. The greater activity in the significant negative fraction (P-) of parcels is seen in the right hemisphere's temporal lobe and inferior frontal lobe. P- is also seen in the occipital, frontal, and parietal areas.

5.2.1. Increased α and β and suppressed δ, θ bands in frontal, regions during WCST planning in control group

In Figure 10. panel A, a sustained suppressed P- in delta (δ) and theta (θ) can be seen from the commence of the feedback at 0 seconds and throughout the planning period. Significant positive fractions of parcels out of all parcels in alpha (α) and beta (β) oscillation amplitudes in frontal, parietal, temporal, occipital cortex were seen in the control group (Figure 10 D) with a duration of 0.7 seconds. The P+ in the control group were in the parietal areas in right and left paC (paracentral lobule and sulcus), left poCS (posterior central sulcus), poCG (posterior central gyrus) and CS (central sulcus). All these sites have been related to the somatomotor network. The areas related to the default mode network had significant positively activated parcels in left sFG (superior frontal sulcus) in frontal cortex and prCN (precuneus) in parietal cortex. The areas previously related to the dorsal attentional network was represented by P+ activations in left sprCS (precentral supplemental sulcus) in frontal cortex and sPG (parietal supplemental gyrus) in parietal cortex. In left occipital cortex had P+ activity in sOG (supplemental occipital gyrus) related to visual network. Activity in left and right lobes were also seen in areas related the frontal/parietal and ventral attention networks. The parcels with greatest P+ amplitudes were mostly in the lateral left hemisphere and left and right medial areas.

5.2.2. Increased frontal and parietal β oscillations during WCST planning in ADHD group

In Figure 10. panel B, a sustained suppressed P- in δ and θ can be seen after the commence of the feedback at 0 seconds and throughout the planning period. The sustained δ and θ activity is slightly greater than in the control group throughout the analysis time window. The significant positive fractions of parcels in the ADHD group were seen in the β band in frontal and parietal cortex for one second. The significant positive fractions in the frontal lobe related to somatomotor network were seen in the in right prCG (precentral gyrus), CS and right lateral CS and prCG. The parietal lobe areas related to somatomotor network had P+ activations in right paC, dorsolateral and ventromedial poCG. The activity in region related to the dorsal attentional network had P+ activation in left sprCS (precentral supplemental sulcus). P+ activity in the left Cla (anterior cingulate gyrus and sulcus) was observed. This area does not have an assigned brain network in the Destrieux parcellation that was used. ADHD group also had activations in the default mode network in left and right sFS (frontal supplemental sulcus) and prCN. Areas in left and right lobes related to

frontal/parietal and ventral attention networks had positive significant activity as well. Activity was distributed to lateral and medial left and right lobes.

5.2.3. Δ, θ, and α suppression in frontal, parietal, and temporal areas greater in ADHD compared to controls

The between groups comparison of ADHD-controls in stay-switch trials revealed significant differences. The significant negative proportion of parcels out of all parcels when baseline was subtracted are seen in frontal and posterior areas. Significant negative fraction of parcels in right sTG (temporal supplemental gyrus), iFGorb (frontal inferior orbital gyrus), sTS (temporal supplemental sulcus), laShz (temporal middle gyrus), mFG (medial frontal gyrus) and acolS (collateral anterior transverse sulcus). Significant negative fraction of parcels in the left hemisphere's iINS (circular inferior insular sulcus) and CS were seen. A significant negative fraction related to visual network in the right hemisphere's mOS (occipital middle sulcus) was observed.

6. Discussion

Measuring brain with MEG has many advantages and challenges. The non-invasive MEG is a cost-effective brain recording method with excellent temporal and good spatial resolution. Compared with fMRI where the slowness of the hemodynamic activity causes an overlap on the "cue and target period" (Brass & von Cramon, 2004) MEG is more suitable for measuring fast cognitive processes. In MEG the recorded magnetic fields are not interfered by skull's structures which makes the analysis more straightforward than EEG analyses. As in any research, many details must be considered from the initiation of the task design until the interpretation and conclusions of the results. Challenges in MEG research arise for example in measurements, modelling of the brain structure, and analysing the data. To analyse the neuronal data measured with a device susceptible to detecting macroscopic currents of the brain, it is important to filter the data during the measurements and in several stages of the analysis. Filtering during the measurement is done to cut out noise from the data and to increase the signal to noise ratio. Careful source modelling is needed as well as using justifiable statistical analyses. To understand executive functions in structural and functional network levels, brain activity measured with MEG has been found to be a suitable method.

6.1. No significant differences in reaction times, hit rates or clinical questionnaire scores found between ADHD and control group

The previous studies show individual and group differences in the behavioural measures of WCST. Individuals with neurocognitive disorders have been reported to make more errors in the test. The participants might perseverate to incorrect strategies or be unable to switch to previously incorrect category. Some previous studies have shown significant differences in the hit rates in both adults and children with ADHD compared with control groups.

Periáñez et al. (2006) reported that the children with ADHD were not slower in their responses but made more mistakes in the test. In some WCST studies of children with ADHD the reaction times have been showing contrasting results compared to control group reaction times. In the present thesis behavioural measurements did not show significant differences between adults with ADHD and the control group. The reaction times were not correlated with clinical questionnaire scores. No significant differences was observed in hit rates or reaction times between the ADHD and control groups. In this thesis the anticipatory responses were counted as correct. Whether the anticipatory responses are correct or incorrect, is unclear since the participant might have guessed the new correct sorting rule. However, some participants were seen to learn the correct rule based on anticipated response. It remains unstudied, if the learning of rule from the anticipatory response differed between the ADHD and control group. Anticipatory responses have been found to arise in the randomized series length studies since the participant does not know what the next correct rule will be. In the fixed rule series the next correct category could be also guessed by comparing to the previous correct rule categories. It remains unclear what causes the differences in the significance of behavioural measures in WCST for participants with normal and abnormal brain structure and function.

6.2. Less activated sites in prefrontal, parietal and occipital areas in the ADHD group than the control group during planning in WCST

The positive fraction of parcels of ADHD and control groups in the contrast of planning with previously correct and planning with previously incorrect feedback. The top-down neural control and supervisory signalling, that are necessity for executive functions, has been demonstrated in humans and in non-human primates. The supervision from the prefrontal cortex over sub circuitries

i.e., various cortical and sub-cortical areas, during goal-driven behaviours has been reported. FMRI studies using WCST to investigate set-shifting and cognitive flexibility have found activations in antero-dorsal PFC (Nagahama et al., 2001), dorsolateral PFC, temporal, and parietal cortices (Berman et al., 1995), left posterior frontal area and inferior cingulate cortex (Catafau et al., 1998), posterior-ventral PFC (Nagahama et al., 2001). PET study of Lombardi et al., (1999) found activation in right dorsolateral frontal–subcortical circuit. Different areas previously related to brain's functional networks contributing to executive functions are seen in the results. Both groups showed activations in brain areas related the dorsal attentional network. Activation of right and left supplemental precentral sulcus, also known as frontal eye fields, had stronger activation in the ADHD than control group. This may point to the direction that ADHD group has compensatory processing in the dorsal attentional system. It remains to be found for the future studies, which of the brain's functional networks are contributing to the planning period of this study.

Precuneus has been found to have an important contribution to the default mode network's functioning. (Utevsky, et al., 2014). A memory-based "autopilot role" has been suggested for the default mode system during automated decision making. (Vatansever, et al., 2017) The default mode network has also been linked to encode task-relevant information. In the current study the ADHD group do not show as strong activation in the areas related to the DMN as the control group. The lack of activity in ADHD group in left precuneus and other default mode areas, could point to a direction of impairment in autopilot memory process as well as encoding task-relevant information. An imbalance between DMN and task-positive networks has been observed in ADHD (Sonuga-Barke and Castellanos, 2007) and could mean that this mechanism might explain the less activated DMN areas than in the control group.

In previous studies, brain's prefrontal cortex and sensory areas have been linked to the executive functions. Left somatomotor cortex hyperactivation has been viewed in schizophrenia during proactive response inhibition. (Wertz, 2019) In the present study, the activity related to the somatomotor network was centered in the right hemisphere for ADHD group and slightly more to left hemisphere for the control group. This may point to a direction that the ADHD group process information differently than controls and that the processing is right-hemisphere centric. This study revealed many brain sites related to inhibitory processes in both ADHD and the control group. The results pointed to the direction that there might be an inhibitory mechanism underlying the planning stage in the Wisconsin card sorting test. Both groups showed activations in areas related

to the motor inhibitory control and other inhibitory processes. It could be that the participants were preparing for the inhibition of prepotent responding or that these detected areas would serve also for cognitive inhibition and not motor inhibition only. However, interpreting the role of different brain areas related to functional networks in this study should remain in the hypothetical level since the current analysis type of oscillation amplitudes is not suitable for interpreting the connections of the brain's oscillatory activity.

There are several previous studies about planning during the Tower of London/Hanoi, Porteus Mazes and Rey–Osterreith Complex Figure Test of ADHD groups. However, these tests do not demand decision making and planning processes in fast-paced manner. Nevertheless, results of fMRI and PET studies of the London Tower show prefrontal and parietal (lateral prefrontal cortex, premotor cortex, cuneus, caudate nucleus, cingulate cortex, supramarginal gyrus) activity during planning is unified with the current study. (Owen et al., 1995, Dagher et al., 1999, Morris et al., 1993). It must be remembered that these tests or brain measurement methods are great at giving a direction of activated sites but cannot be interpreted to represent fully same phenomena. This is due to the fMRI's slowness in the hemodynamic activation and the unsuitable cognitive tests for measuring fast planning.

In WCST, accessing information of previously learned rules is necessary for an effective performance. Posterior brain areas have been linked to accessing previous information. Frontal areas apply the information conveyed from posterior areas to form a cohesive picture of the current task situation. The clear difference in the activated frontal, parietal and occipital sites between the ADHD and control group could point to impaired cognitive processing in the ADHD group. The ADHD group had the strongest activity in the frontal brain areas and the control group had the strongest activation in the posterior areas. Perhaps the information of previous information is conveyed from the parietal parts to the frontal regions in ADHD group, but for some reason this process is unable to reach the occipital areas.

Ability to shift attention from one demand to another during WCST is closely related to decision making and planning processes. Set shifting has often been investigated during stimulus presentation. In the Buchsbaum et al. (2005), meta-analysis, on the WCST stimulus presentation, activity was seen in lateral prefrontal cortex, anterior cingulate cortex, and inferior parietal lobule. Less robust activities were reported in the opercular region of the ventral prefrontal cortex, bilaterally. Interestingly, Barcelo et al. (2003) have proposed that, the set-shifting would take place

in the feedback period and after feedback, rather than in the stimulus presentation stage. In the stimulus presentation stage, the rules would be rehearsed but after the feedback period, the rule would be planned and decided on. There are few studies using the Wisconsin card sorting test and assessing its preparatory dimension. In a study by Barcelo et al. (2004), preparatory set-shifting was investigated in healthy young adults. The scope of interest was to look at the "task set reconfiguration processes during the task preparation stage of WCST performance". In practice this stage is after the participants have responded and they are presented with feedback. They reported significant differences between shift (incorrect) and non-shift (correct) feedback in three frontal-parietal network areas, in the anterior portion of the inferior frontal gyrus, the anterior cingulate cortex, and the supramarginal gyrus. In Periáñez, et al. (2004) study on preparatory set-shifting with healthy individuals, the MEG activation was found stronger in shifting than in the non-shifting trials.

It has remained unknown what the dynamical neuronal processes underlying the set maintenance i.e., non-shift trials are in WCST. The current results seem to be in line with previous fMRI studies about set-maintenance where it was located to the medial superior frontal gyrus (Wilk, Ezekiel & Morton, 2012) and in the dual-network model of Dosenbach et al., (2008), to anterior, cingulate, and insular cortices. Some studies however propose that task-set adjustment is related to the above mentioned parts of the brain. (Botvinick et al., 2001; Ridderinkhof et al., 2004; Seeley et al., 2007, Menon and Uddin, 2010; Seeley et al., 2007)

6.3. Differing θ, δ, α and β oscillations during WCST planning period between ADHD and control groups

Oscillations in prefrontal cortex (PFC) and posterior brain areas differ in ADHD and control groups during WCST in planning period in previously correct compared to planning with previously incorrect feedback. Aberrant modulation of oscillations has been linked to ADHD throughout the individual's development. The control group's results show oscillation activations for shorter period of time (0.7 s) in more varied oscillation bands (8-40 Hz) than the ADHD group (1 s, 10-35 Hz). This faster modulation of the neuronal activity could point toward a more efficient planning process in the control group. Therefore, it may that inefficient processing could be proposed for the longer activation in the ADHD oscillations. However, interpreting oscillations and their underlying roles, is usually not so straightforward and future studies and analyses should be conveyed to look at the roles of oscillations more closely for example in the network levels.

In their study on set-shifting measured before feedback onset, González-Hernández et al., (2002) have reported the selectively distributed δ, θ, α, β -2, and gamma oscillations to reflect communication of networks through variable populations of neurons, with functional relations to the working memory and the information processing that subserve the WCST performance. They suggests that the maintenance of set would be related to the trials where set-shifting has occurred. By inspection of previous literature, it remains unclear whether the cognitive processes during WCST can be assigned to a strict timeline. For careful task design, more indicators could be found.

In the between groups comparison in this thesis, suppression in δ, θ and α oscillations were found to be significant. δ and θ oscillations have previously been linked to inhibition. θ band has additionally been connected to cognitive control processes and working memory. In the current thesis the α oscillations showed a decrease for a brief time after the feedback offset. However, it remains unclear whether the whole planning period or some part of it could relate also to the processing of feedback information since the two events occur one after the other. Abnormal lateralization of the α band has been reported in some ADHD studies. In the current study this is not yet revealed and remains unclear if the oscillatory activity in the lateral parietal and temporal cortex is related solely to the α band or also θ and δ oscillations.

The α band's role has two differentiating hypotheses: one for the suppression of irrelevant information during task engagement and one for the active role in processing of task-relevant information. A has been linked to selection and suppression of attention and to working memory maintaining. Klimesch et al., (1996) reported that the strengthening of α activity may relate to working memory processes. In their review, Jensen et al., (2017) reported a decrease in the α band oscillatory activity during visual selective attention in ADHD from many previous studies. In the present work the ADHD group had suppressed α activity in the comparison between groups. The control group had activity in the α band for the whole processing time. The greater activity in the increased α band in the control group could point towards more effective processing in the above-mentioned cognitive processes than the ADHD group.

β has been related to maintaining the current information and/or to prevent interference from distraction in a working memory (WM) task delay period. The ADHD group showed activation mainly in the β band. The β frequency was greater in low β band in the control group. Within group contrasts of stay-switch showed longer activation of β oscillations in ADHD. This could point to active inhibition and getting rid of old task information of the ADHD group. β band has also been

related to maintaining the current information, clearing out previous information, and motor planning. Increased relative β band in prefrontal cortex at the end of a task-trial "when working memory information needs to be erased" has been seen in children with ADHD. Thus, in the present thesis the ADHD group could be concentrating on the clearing out of old information related to the task. Spitzer and Haegens (2017) have proposed that β band could reflect decision-making process in reactivating task relevant information. Activating items in working memory with currently unattended memory has been related to the β. (Rose et al., 2016) In the WCST planning stage, recalling the features of the response cards might be present in the trials where staying with the rule or switching the rule. Increase in θ band power has long been thought as an indicator of aberrant ADHD oscillatory activity. Until recently a measure called the θ-β ratio was thought to serve as a biomarker in ADHD but replicating studies found issues. It was concluded that although some ADHD patients have increased θ-β ratio compared to control groups it did not reach a valid position as a biomarker. (See for a review, Jensen, et al., 2017) Recently, specifically the decline in β band power has been linked to ADHD.

6.4. Limitations

The missing information of medications in ADHD group is one limitation in this study. The education background of the participants in control group was fairly heterogenous which should be controlled in the future studies. Relatively small sample size makes room for the need of further investigations. The results should be further analysed, and the testing replicated in different samples.

7. Conclusions

ADHD affects many people through all age groups, but the subjective diagnostic measures do not strike as enough comprehensive. There are several controversies in the diagnostics and the predictive markers of ADHD. Inattentive symptoms in ADHD have been reported to be most persistent to adulthood whereas hyperactive-impulsive symptoms are sometimes eased coming into adulthood (Swanson et al., 1998, Kessler, et al., 2010). However, attentional, cognitive, and motor impulsivity has been found to characterize adult ADHD (Malloy-Diniz, et al., 2007). The studies of children have found a characterization of ADHD in an inability to sustain attention. It is of importance, to do additional research on different age groups of ADHD and compare their results.

It would also be extremely important to establish a cohesive and more objective diagnostic tradition for ADHD. The future development of the diagnostics should take cognitive dysfunctions into account due to their restricting influences in these individuals' lives. Understanding the brain's functioning could help closer to these goals. ADHD is linked to impairments in different domains of executive functions including planning and decision making. Dysfunctions in planning as well as the inhibition of preparatory processes has been found in ADHD. Medication of ADHD group should be controlled and record in the future studies. It has been found in many studies that some people with ADHD use self-medication in the form of different substances that may boost dopamine levels. Substance use disorder has been linked to ADHD. (Wilens, 2004, Levin et al., 1999) As substance abuse is often correlated with other comorbidities it would be important to consider if this factor should also be controlled in the future studies.

Further scoring of the WCST could be conveyed to see whether behavioural markers such as preservation would show differences between the groups as it has in the previous studies. Scoring should be considered carefully since the randomized series length brings more unexpected situations than in the fixed series length designs. For example, scoring only the 4 first responses could be considered since all series have at least this number of trials. The anticipation trials should also be excluded in future studies. Although there are only a few anticipation trials for for each participant, they are not truly correct since they are always in the first trial of a rule series. In the first trial the participant does not know what the correct rule is so they have gotten the response correct by luck.

Shifting rule categories following an error and maintaining the current rule after correct feedback demand planning and decision making for efficient performance. Brain's many areas are activated during these cognitive processes included in executive functions. Inhibition, shifting, and controlling are needed in maintaining and updating information in the WCST. Periáñez et al. (2006) suggested that the deficits in the task for the ADHD group in the preparatory period, would be related to the impairment of ability to inhibit previous rule and their "capacity to consolidate the attentional 'set'". These executive functions should be further investigated in similar and different fast planning tasks.

Several frequency bands have been thought to maintain the communication between different brain regions. The oscillation activations in planning that might be reflecting the maintaining of the current rule showed a place for possible future studies in ADHD. The findings in oscillatory activities may point to the direction that ADHD group tried to suppress the previous information during the

planning in WCST or they could be preparing for response inhibiting. The control group showed more varied oscillatory activations during planning and seemingly more efficient processing. The between groups comparisons will probably shed more light in the WCST planning about the significant differences in neuronal activations in these oscillations. Weaker α oscillations in the ADHD group could tell of impairments in maintaining task-relevant information and working memory processes. Directions towards possible impairment in automated memory processes can also be drawn from the ADHD group's dysfunctioning default mode system. The aberrant modulation of neuronal oscillations is also seen from the current study in the weak beta band and suppressed alpha band, but their actual roles remain unknown.

Finding out the activity in different stages of WCST as well as the dynamic changes can be achieved with further MEG data analyses. The current results in planning period for control group showed more activations in than the ADHD group. This could point to a direction that the ADHD group is concentrating on maintaining the information in working memory that is related to PFC activation rather than preparing for the next stimulus presentation that has been related to the areas posterior from the prefrontal cortex. The previously found communication problems due to structural differences in frontal and posterior brain areas, could be an explanation for some of the differences found in this study for the ADHD group. In the future it would be important to see how the dynamics of activations emerge throughout brain networks. This knowledge could be used to tell which frontal areas the aberrant neuronal mechanisms of the planning processing are using WCST in people with ADHD.

In WCST relevant information must be accessed, and information used in selective and flexible manner during planning and decision making. WCST seems to be a suitable tool to assess fast-paced planning and decision making. The current study's results bring new information of the oscillations during WCST planning stage. The current results show similarities in activated brain areas as in previous studies on brain activity measurements with fMRI, EEG and MEG. The findings of the present thesis are promising and hopefully can aid further investigations. Further study on this data could provide more interesting details of the brain's functional connectivity that could be found out in studying the long-range synchronization of oscillations.

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