UNIVERSITY OF SOUTHAMPTON

FACULTY OF SOCIAL AND HUMAN SCIENCES

Psychology

The electrophysiological correlates of spontaneous brain activity during resting, waiting, and prospective cognition:
Exploring putative neural markers for ADHD

by

Chia-Fen Hsu

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ABSTRACT

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THE ELECTROPHYSIOLOGICAL CORRELATES OF SPONTANEOUS BRAIN ACTIVITY DURING RESTING, WAITING AND PERSPECTIVE COGNITION: EXPLORING PUTATIVE NEURAL MARKERS FOR ADHD

Chia-Fen Hsu

The default mode network (DMN) is characterised by coherent very low frequency (VLF) neural oscillations in the resting brain. The VLF neural oscillations within this network are attenuated following the transition from rest to performance of a broad range of cognitive goal-directed tasks. Whether the resting state VLF oscillations are attenuated during non-cognitive goal-directed tasks such as waiting for rewarding outcomes is not known. Individuals with attention-deficit/hyperactivity disorder (ADHD) display excess VLF neural oscillations both when working on attention tasks and difficulties waiting for delayed rewards. This thesis examined the resting and waiting brain VLF EEG signatures and the associations with the impulsive choice of ADHD.

Direct current EEG (DC-EEG) data were collected under four conditions: i.e. resting, an attention demanding task and two types of goal-directed waiting conditions in two samples. First was a sample of adults who self-reported either high- or low-ADHD scores, and second was a clinic referred sample of children and adolescents with ADHD and age- and gender-matched controls. The results showed significant cognitive task-induced attenuation of VLF EEG both in normal adults and youths. Individuals with ADHD displayed cognitive task induced-attenuation to a reduced level, and they failed to attenuate VLF EEG when waiting. Excess waiting VLF EEG in the youth sample was associated with parents' ratings of delay discounting and delay aversion. These findings implicate the influence of goal-directed nature on the attenuation of resting state VLF EEG because waiting and resting are not identical but share many elements. The results also highlight the potential role of waiting-related neural activity in the pathophysiology of impulsive decision making of ADHD.

Next, this thesis extended the investigation to spontaneous neural oscillations during prospective cognition. Quantitative EEG measures were collected from a third sample (healthy adults) during episodes of prospection. Compared to the resting and waiting states, episodic prospection induced significantly reduced activity in the medial prefrontal cortex (MPFC) and increased activity in bilateral medial temporal gyrus (MTG) across selected frequency bands. Also prospection was associated with an increase of MPFC-MTG phase coherence in delta band compared to resting and waiting states. The findings highlight the heterogeneous nature of DMN in self-referential cognition as well as the engagement of a medial fronto-temporal axis during episodic prospection.

Thesis overview

The thesis contains seven chapters. **Chapter 1 - 3** provide a review of the literature about the default mode network (DMN), Attention Deficit/Hyperactivity Disorder (ADHD) and waiting difficulties of ADHD. **Chapter 4 - 6** are reports of empirical findings. **Chapter 4** reports the modulation of very low frequency electrophysiology (VLF EEG) power from resting to waiting states in healthy adults. **Chapter 5** reports the rest-to-wait modulation of VLF EEG in children and adolescents with ADHD and age- and gender- matched controls. **Chapter 6** compares the EEG correlates within the DMN regions during prospective cognition to those collected from resting and waiting states. **Chapter 7** provides a general discussion for thesis findings.

Chapter 1: The first chapter reviews the literature associated with the default mode network (DMN). It describes the methodologies used in the investigation of the DMN, particularly functional magnetic resonance imaging and EEG. It delineates the discovery of the DMN, the modulation of DMN during cognitive task performance, interactions between DMN and other resting brain networks, as well as the functions that DMN may implicate. It then describes the abnormalities of DMN in individuals with ADHD. The review concludes by a discussion of current methodological challenges and unresolved problems.

Chapter 2: The second chapter provides the general knowledge to the background of ADHD. It outlines the diagnostic features of ADHD, the epidemiology, persistence, prognosis, comorbidity, risk factors, the structural and functional brain alterations and treatment of ADHD.

Chapter 3: The third chapter has special foci on the waiting difficulties of ADHD. It describes the common behavioural manifestations of ADHD cases while they are waiting. It then provides causal models of ADHD and describes how these putative causal mechanisms may contribute to the waiting difficulties of ADHD. Particular emphasis is placed on one theory, the default-mode interference (DMI) hypothesis. This chapter attempts to explain how atypical neural oscillations within the DMN may cause the waiting difficulties of ADHD based on the DMI hypothesis.

Chapter 4: The fourth chapter investigates VLF EEG at rest and during performance of a goal-directed task and two types of waiting conditions. This chapter replicates the cognitive task-induced attenuation of VLF EEG demonstrated by previous research (Helps et al., 2010). Moreover, it provides the first evidence of rest-to-wait attenuation of VLF EEG even though waiting does not involve external information processing and in many ways shares characteristics with rest.

Chapter 5: The fifth chapter applies the methods and analyses of Chapter 4 in a clinic referred sample of children and adolescents with ADHD. This chapter replicates many of the findings from previous chapter. Importantly, individuals with ADHD exhibited cognitive task-induced attenuation to a reduced level, and they did not effectively attenuate the VLF EEG during waiting. Moreover, the rest-to-wait attenuation of VLF EEG negatively correlated with parents' ratings of delay discounting and delay aversion, suggesting the less rest-to-wait attenuation the higher levels of delay aversion and delay discounting.

Chapter 6: The sixth chapter investigates EEG correlates sourced to the DMN regions during episodic prospection, resting and waiting conditions in a sample of healthy adults. It shows that prospective cognition is involved in a fronto-temporal axis compared to resting and waiting states.

Chapter 7: The final chapter provides a summary of the thesis findings and then addresses implications that arise from the thesis. It also describes the limitations of the thesis and suggests future directions for research.

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DECLARATION OF AUTHORSHIP

I, Chia-Fen Hsu declare that the thesis entitled ‘The electrophysiological correlates of spontaneous brain activity during resting, waiting and prospective cognition: Exploring putative neural markers for ADHD’ and the work presented in the thesis are both my own, and have been generated by me as the result of my own original research. I confirm that:

- this work was done wholly or mainly while in candidature for a research degree at this University;
- where any part of this thesis has previously been submitted for a degree or any other qualification at this University or any other institution, this has been clearly stated;
- where I have consulted the published work of others, this is always clearly attributed;
- where I have quoted from the work of others, the source is always given. With the exception of such quotations, this thesis is entirely my own work;
- I have acknowledged all main sources of help;
- where the thesis is based on work done by myself jointly with others, I have made clear exactly what was done by others and what I have contributed myself;
- parts of this work have been published as:

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Definitions and Abbreviations

Abbreviation/Symbol	Definition
2CRT	Two-choice reaction time task
3D	Three-dimensional
ADHD	Attention-deficit hyperactivity disorder
ANOVA	Analysis of variance
BOLD	Blood oxygen level dependent
CBRS	Conner’s Comprehensive Behaviour Rating Scale
CEM	cognitive-energetic model
CNV	Copy number variants
CSS	Current Symptoms Scale
C-WAIT	Choose-to-wait
dACC	Dorsal anterior cingulate cortex
DC	Direct current
DMI	Default mode network interference
DMN	Default-mode network
dmPFC	Dorsal medial prefrontal cortex
EEG	Electroencephalography
EOG	Electro-oculogram
fcMRI	Functional connectivity magnetic resonance imaging
FFT	Fast Fourier transformation

fMRI	Functional magnetic resonance imaging
F-WAIT	Force-to-wait
GWAS	Genome-wide association studies
HF+	Hippocampus formation
ICA	Independent component analysis
IPL	Inferior parietal lobule
LL	Larger later rewards
LMTG	Left medial temporal gyrus
MEG	Magnetoencephalography
MPFC	Medial prefrontal cortex
MTG	Medial temporal gyrus
MTL	Medial temporal lobe
NAcc	Nucleus accumbens
pC	Precuneus
PCC	Posterior cingulate cortex
PET	Positron emission tomography
PLV	Phase locking value
QDQ	Quick Delay Questionnaire
RMTG	Right medial temporal gyrus
ROI	Region of interest
RSN	Resting state networks

SHARe	South Hampshire ADHD Register
sLORETA	Standardised low-resolution electromagnetic tomography
SNP	Single-nucleotide polymorphisms
SS	Smaller sooner rewards
TNN	Task-negative network
TPJ	Temporoparietal junction
TPN	Task-positive network
vACC	Ventral anterior cingulated cortex
VLF	Very low frequency
vmPFC	Ventral medial prefrontal cortex
WISC	Wechsler Intelligence Scale for Children
α	Alpha
β	Beta
Δ	Delta

Chapter 1 The default mode network

1.1 Purpose

This chapter provides a review of the literature relating to the default-mode network (DMN). DMN is a set of brain regions active at rest but attenuated during a wide range of goal-directed tasks. This chapter illustrates the functional significance of the DMN and its implications in the psychopathology of Attention-Deficit/Hyperactivity Disorder (ADHD). DMN has been principally investigated using positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) and recently using electroencephalography (EEG). Thus, this chapter starts with empirical findings using PET and fMRI. It delineates the discovery of the DMN, the modulation during tasks, the interactions between the DMN and task-positive networks, other resting brain networks, as well as the functions that DMN may implicate. The second section reviews EEG literature following a similar structure. The third section illustrates empirical studies with special foci on the DMN abnormalities in ADHD. The review then concludes by a discussion of methodological challenges and unresolved problems.

1.2 Growing importance of the resting brain and default mode network

1.2.1 The discovery of the DMN (PET & fMRI)

Traditional functional imaging studies have investigated task-specific alterations of regional brain activity. The concept of the DMN, first introduced by Raichle et al. (2001), came from observations made during PET and fMRI studies. The authors observed a set of brain regions consistently exhibited reduced activity during the performance of cognitive tasks, compared to a resting condition (Raichle et al., 2001; Shulman, Fiez, et al., 1997). Given that such suppression of activity was strikingly independent of task content and a substantial amount of brain metabolic energy was consumed at rest, Raichle et al., (2001) termed this resting brain network as the DMN, denoting a default state of brain function. The activities within the DMN are characterised by spontaneous oscillations of very low frequency (VLF, normally less than 0.1 Hz, i.e. cycles of 10 second or longer). The DMN activity during wakeful rest appears to reflect resources devoted to general information gathering and evaluation, which is attenuated when externally oriented attention is required (Raichle et al., 2001).

1.2.2 The functional neuro-anatomy and connectivity of the DMN

A meta-analysis of task-related attenuation using activation likelihood estimation across 1711 neuroimaging publications demonstrates that DMN regions comprise the posterior cingulate cortex (PCC), precuneus (Pc), medial prefrontal cortex (MPFC), ventral anterior cingulated cortex (vACC), middle frontal gyrus, bilateral inferior parietal lobules (IPLs) and bilateral medial temporal lobe (MTLs) (Laird et al., 2009).

Notably, the DMN is a large-scale interacting brain system. Functional connectivity combined hierarchical clustering analysis of the DMN regions reveals two subsystems that converge on a midline core (Figure 1.1, Andrews-Hanna, Reidler, Sepulcre, Poulin, & Buckner, 2010). The DMN core consists of an anterior hub (MPFC) and a posterior hub (PCC). Both hubs, in particular the PCC, have strong connections to all other regions comprising the DMN. The medial temporal lobe (MTL) subsystem includes the ventral MPFC (vMPFC), bilateral inferior parietal lobules (IPL), retrosplenial cortex (Rsp), parahippocampal cortex (PHC) and hippocampal formation (HF^+). It becomes activated during the construction of a mental scene based on memory, such as remembering the personal past or imagining the future (Schacter et al., 2012). The involvement of memory processes in MTL subsystem is supported by underlying structural connectivity (Greicius, Supekar, Menon, & Dougherty, 2009). In contrast, the dorsal medial prefrontal cortex (dMPFC) subsystem, including dMPFC, temporoparietal junction (TPJ), lateral temporal cortex (LTC) and temporal pole (Temp), is engaged when individuals consider their present situation or infer other person’s thoughts (Frith & Frith, 2006). The core hubs share functional properties with both subsystems, which are active during spontaneous self-referential thoughts and evoked emotion regardless of temporal context (Andrews-Hanna, Reidler, Sepulcre, et al., 2010).

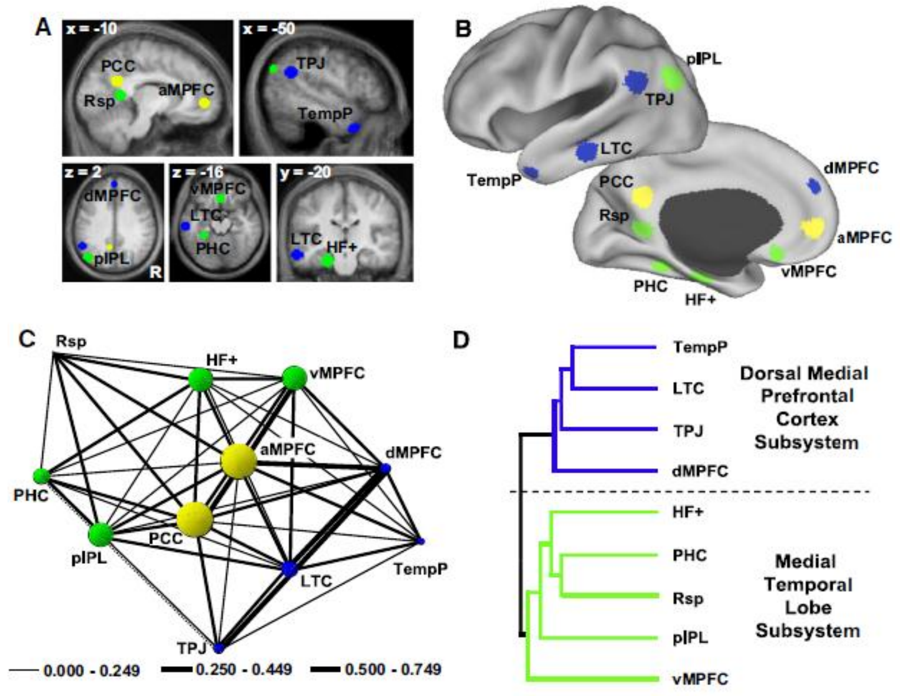


Figure 1.1 The DMN Comprises a midline core and two subsystems.

(A) The DMN regions on transverse slices; (B) The DMN regions on a surface template; (C) Functional pathways between two DMN regions. The line thickness reflects the strength of functional connectivity; (D) The DMN includes two subsystems. The medial temporal lobe subsystem (MTL, marked in green) includes the ventral MPFC (vMPFC), bilateral inferior parietal lobules (IPL), retrosplenial cortex (Rsp), parahippocampal cortex (PHC) and hippocampal formation (HF^+). The dorsal medial prefrontal cortex subsystem (dMPFC, marked in blue) includes dMPFC, temporoparietal junction (TPJ), lateral temporal cortex (LTC) and temporal pole (Temp).

Note. Picture was adopted from Andrews-Hanna et al., (2010).

1.2.3 The development of the DMN

Investigation into the maturing architecture of the DMN has yielded inconsistent results. Some studies identified a DMN-like network in children and adolescents (7-13 years) with a substantial correlation between the anterior and posterior DMN hubs (Supekar et al., 2010; Thomason et al., 2008). Other studies reported a weaker level of functional connectivity across the DMN in young cohorts, especially between PCC and MPFC (Fair et al., 2008; Kelly et al., 2009). These studies suggested that the DMN regions were sparsely connected in childhood and only became integrated into a more cohesive network in adulthood - a developmental trajectory of the DMN. However, there was also evidence demonstrating that the DMN regions were integrated differently in children compared with adults, rather than being immature pieces of an adult network (Fair et al., 2009; Power, Fair, Schlaggar, & Petersen, 2010). Such inconsistent findings possibly originate from methodological issues such as the selection of seed region, considering the DMN in isolation or including other functional networks, or the criteria for significance employed (Power et al., 2010). At present it is not clear whether the DMN is organised in a similar manner in childhood and adulthood. A comprehensive investigation for the age effect on the DMN is required.

1.2.4 The modulation of the DMN

1.2.4.1 Attenuation in the transition from resting to working

While active during wakeful rest, the DMN activity is attenuated but not extinguished following the transition from rest to engagement in goal-directed tasks, such as response inhibition (Liddle et al., 2011), working memory (Fassbender et al., 2009; Fransson, 2006) and visuospatial tasks (Gilbert, Bird, Frith, & Burgess, 2012). Significant DMN attenuation following the onset of goal-directed tasks appears to be necessary for effective switching of brain states from resting to working (Fox et al., 2005; Greicius, Krasnow, Reiss, & Menon, 2003; Raichle & Snyder, 2007). Failure of suppression has been proposed as a major source of momentary lapses in attention which constrains cognitive performance (Sonuga-Barke & Castellanos, 2007).

A notable exception to this general pattern of DMN attenuation relates to tasks involving self-referential processing during which the DMN regions are generally active and only specific DMN regions are attenuated. For instance, the vMPFC has been shown to be attenuated during tasks involving both self-referential and non-self-relevant judgments, whereas the activity in the dMPFC increased during the self-referential judgment task (Gusnard, Akbudak, Shulman, & Raichle, 2001).

1.2.4.2 The role of task difficulty and effort

DMN activity may persist during passive visual processing or well-practiced tasks when cognitive requirements are not sufficiently challenging (Greicius et al., 2003; Greicius & Menon, 2004). Although task-induced attenuation of DMN activity is independent of task content, it is associated with cognitive load. The more demanding the task is the stronger the attenuation of DMN would be (Fassbender et al., 2009; Gilbert et al., 2012; Singh & Fawcett, 2008).

1.2.5 Relationships between the DMN and other networks

1.2.5.1 The task positive network

The resting brain incorporates both task-negative and task-positive components. The DMN is referred as a ‘task-negative network (TNN)’ because it is more active at rest than during task performance. Importantly, the DMN activity negatively correlates with a second network, i.e., the ‘task-positive network (TPN)’, consisting of regions typically activating during goal-directed, externally oriented attention tasks (see Figure 1.1; Fox et al., 2005). TPN includes the dorsolateral prefrontal cortex (DLPFC), intraparietal sulcus, the frontal eye field, supplemental motor area and insula. The temporal linkage between the DMN and TPN reflects that an internally oriented, self-referential process and an externally oriented, attention-demanding state may interact in order to meet environmental requirements. The competitive relationship between the DMN and TPN ensures that individuals can keep alert and attentive to unexpected or novel events (Fox et al., 2005; Fox, Snyder, Zacks, & Raichle, 2006; Fransson, 2005, 2006; Sidlauskaite et al., 2014). This antagonistic relationship between DMN and TPN instigated the default mode interference hypothesis (DMI), which proposes that the trade-off balance of neural activity between the two networks is responsible for optimal cognitive performance. The DMN activity which persists during cognitive tasks may cause disrupted responses and periodic attentional lapses (Sonuga-Barke & Castellanos, 2007). Furthermore, DMI hypothesis suggests that the DMN and TPN are likely to be two distinct components of one single brain system. The functional coupling between the two networks may actually play a more import role on cognitive processes than is the DMN activity alone (Broyd et al., 2009; Sonuga-Barke & Castellanos, 2007).

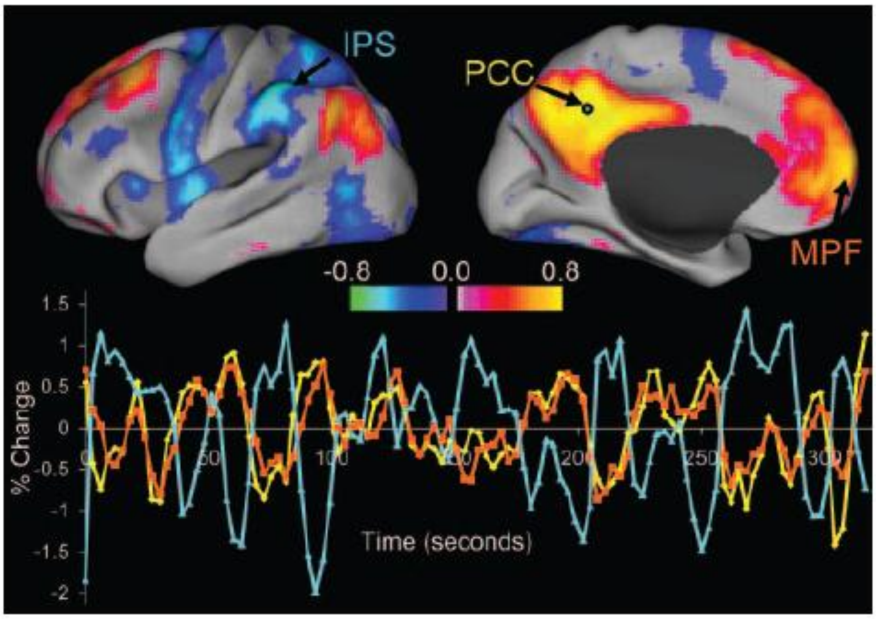


Figure 1.2 Correlations between the default note network and task positive network.

Series of BOLD signals from regions of the DMN (yellow: PCC, orange: MPFC) and from TPN (blue: IPS) in time domain. In this example the PCC is set as the seed region. This displays positive correlations with the MPFC, the anterior hub of DMN. Simultaneously, the activity of the PCC is negatively correlated with the IPS, one of the regions which show greater activation during task performance.

Note: BOLD: blood oxygen level dependent; DMN: default mode network; IPS: intra-parietal sulcus; MPFC: medial prefrontal cortex; PCC: posterior cingulate cortex. The figure was adapted from Fox et al. (2005).

1.2.5.2 Other resting state networks

Spontaneous fluctuations are coherent in low frequency, which are synchronised to several functional organised resting state networks (RSNs). Figure 1.2 provides a comparison of RSNs identified across fMRI studies.

Using a data-driven, probabilistic independent component analysis, Damoiseaux et al. (2006) examined the connectivity of spontaneous BOLD signals. The authors identified ten RSNs, including the DMN, primary sensory and motor processing networks, visual and auditory cortices, and two networks involving memory and executive function (Damoiseaux et al., 2006). About the same time, De Luca and colleagues applied a similar experimental approach and demonstrated five RSNs, including the DMN, distinct sensory, motor and cognitive brain systems (De Luca, Beckmann, De Stefano, Matthews, & Smith, 2006). Notably, Yeo et al., (2011) derived a reliable set of RSNs from a large number of normal adults (i.e. 1000 participants, who were divided evenly into a discovery set and a replication set). The RSNs, including the frontoparietal, dorsal attention, ventral attention, sensorimotor, primary visual cortex, limbic, and the DMN, to a substantial extent replicated previous findings (Yeo et al., 2011). Although the network map of Yeo et al. is not the only way to segregate functional connectivity of the resting brain, it has become an influential reference for later studies because of the large- sample size and stringent data processing methodology employed (Cortese et al., 2012).

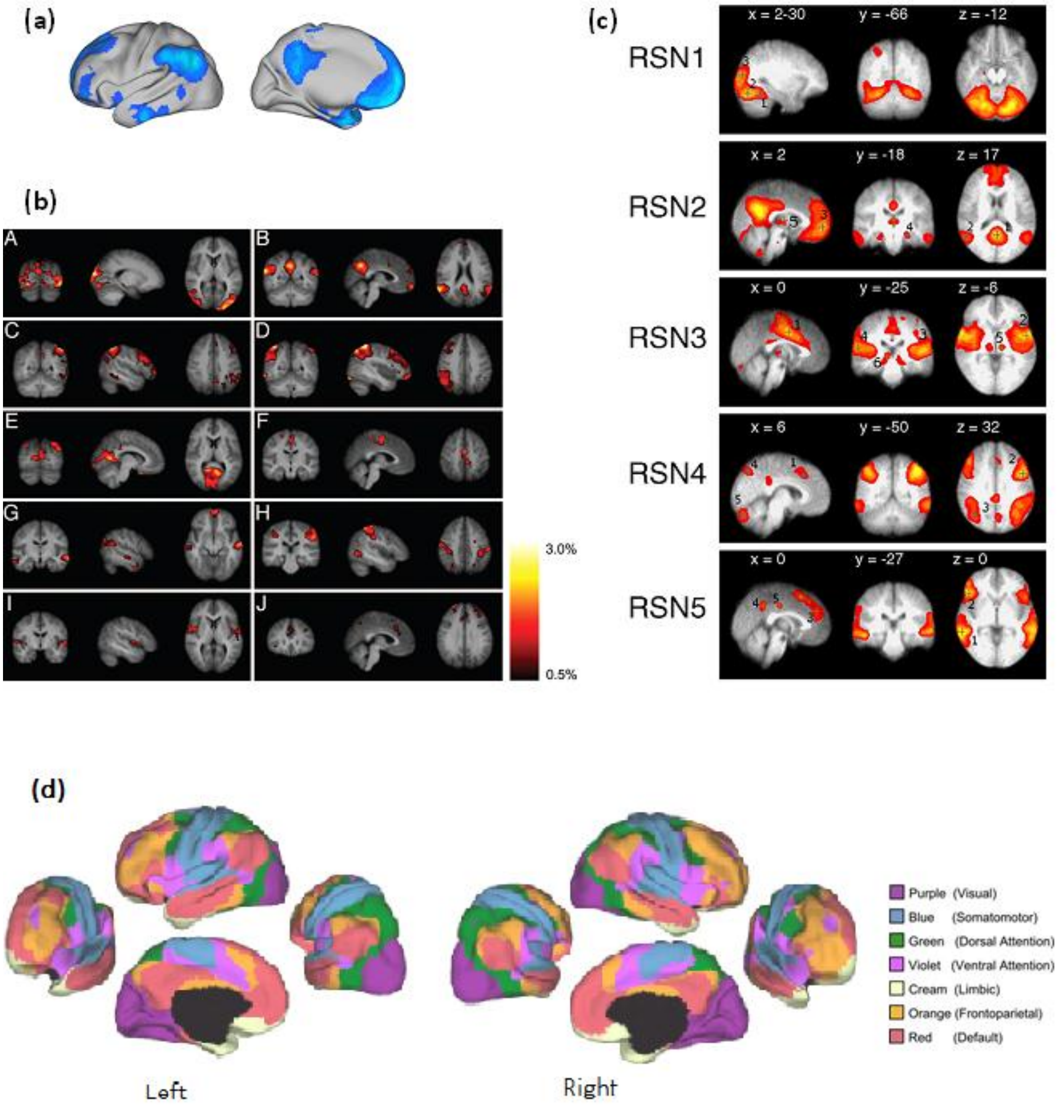


Figure 1.3 Resting state networks across studies.

(a) Default mode network (blue); (b) ten resting state networks identified by Damoiseaux et al. (2006); (c) five resting state networks identified by De Luca et al. (2005); and (d) seven resting state networks identified by Yeo et al. (2011).

Note. Picture (a) was adapted from Bucker et al. (2008); (b) was copied from Damoiseaux et al. (2006); (c) was copied from De Luca et al. (2005) and (d) was adapted from Yeo et al. (2011).

1.2.6 The functions of the DMN – is the brain really ever at rest?

Exploring the functions of the DMN is challenging because the resting state is an open condition and not constrained by specific stimuli. Nevertheless, two sources of data currently provide information about the DMN functions: i) monitoring external environment and ii) spontaneous self-referential cognition (Buckner, Andrews-Hanna, & Schacter, 2008).

1.2.6.1 Monitoring the environment: The sentinel hypothesis

First, the DMN is associated with monitoring the external environment, like a “sentinel” (Gilbert, Dumontheil, Simons, Frith, & Burgess, 2007; Gusnard & Raichle, 2001; Hahn, Ross, & Stein, 2007). Resting state is typically a condition of readiness during which individuals spontaneously generate a general level of watchfulness (Gilbert et al., 2007; Shulman, Fiez, et al., 1997). The DMN is likely to support low level of attention in an unfocused manner when an individual is not engaging in a specific cognitive task.

Several lines of evidence have supported the “sentinel” hypothesis. For example, attenuation in the DMN regions was more pronounced in processing foveal stimuli compared to peripheral stimuli (Shulman, Fiez, et al., 1997). Hahn et al. (2007) observed that some regions of the DMN were more active when performing a target-detection task with unpredictable stimulus (Hahn et al., 2007). Gilbert et al. (2007) found increased activity in the MPFC associated with trials with faster reaction time (Gilbert et al., 2007). There was also indirect evidence showing that brain injuries in precuneus, the posterior hub of DMN, elicited Balint’s syndrome, a disability of tunnel vision and failure of perceiving simultaneous objects (Rizzo & Vecera, 2002). Furthermore, a recent study showed that DMN activity was attenuated at an early stage when individuals anticipated state-switching from resting to working (Sidlauskaite et al., 2014). These studies highlight that the DMN regions are not simply active at rest but also play a role in stimulus oriented processes. This allows an individual to remain alert to unexpected environmental events (Buckner et al., 2008; Mantini & Vanduffel, 2013).

1.2.6.2 Spontaneous Cognition: The internal mentation hypothesis

Second, the DMN is engaged during spontaneous cognition, including a diverse forms of self-referential, internally oriented cognitive states, such as mind wandering (Christoff, Gordon, Smallwood, Smith, & Schooler, 2009; Mason et al., 2007), episodic prospection (Spreng & Grady, 2010), autobiographical memory (Addis, Wong, & Schacter, 2007; Spreng, Mar, & Kim, 2009) and moral decision making (Reniers et al., 2012). These mental processes, although distinct from task content, all require individuals to imagine a scenario or perspective other than the present context.

The anatomic findings provided convincing support for the involvement of the DMN in spontaneous, self-referential processes. The DMN includes a MTL subsystem. The bilateral medial temporal lobes and their connections to hippocampus formation are associated with planning and episodic memory, i.e., the ability to encode and retrieve past personal experiences and information (Dickerson & Eichenbaum, 2010). On the other hand, increases of activity in the ventral MPFC have been demonstrated during self-referential processing (D'Argembeau et al., 2007; Gusnard et al., 2001; Mitchell, Macrae, & Banaji, 2006). Taken together, it seems that the MTL subsystem is involved in memory retrieval, which provides the foundation for internal mentation (Tulving, 2002), while the ventral MPFC mediates the process of self-related simulation (Kim, 2012; Szpunar, Watson, & McDermott, 2007) and complex perspective-taking (Frith & Frith, 2006; Van Hoeck et al., 2013).

In summary, the DMN appears to play a reciprocal role in monitoring the external environment and mediating internal mentation. The dynamic nature of DMN activity enables an individual to adapt behavioural responses when needed, provides integrated representations of the environment and the self, and facilitates other cognitive processes, such as making perspective decisions and behavioural control (Mantini & Vanduffel, 2013; Raichle & Snyder, 2007). Exploring the functional significance of DMN is crucial and will ultimately better our understanding of the human brain.

1.3 Electrophysiological studies of the resting brain

1.3.1 The potential significance of studying neural oscillations using EEG

EEG is the recording of electrical activity along the scalp which measures changes in voltage between two large groups of neurons (Banaschewski & Brandeis, 2007). For some time EEG studies have reported spontaneous brain activity at rest (Berger, 1969a, 1969b), but it is only recently that EEG is used to investigate DMN-related activity in very low frequency. Compared to other neural imagining techniques such as PET and fMRI, EEG provides a direct measure of brain oscillations and has excellent temporal resolution, in the order of milliseconds. A drawback of EEG is that it has a low spatial resolution. However, discrete and distributed source-modelling algorithms are now available to localise EEG activity effectively (Michel et al., 2004). Moreover, high-density electrode recording, co–registration with structural MRI data and simultaneous EEG-fMRI recording have been successful. Compared to other neural imaging techniques (e.g. MRI), EEG procedures are non-invasive and friendly to vulnerable subjects such as children or individuals with ADHD. Hence, EEG is a great vehicle to explore different states (e.g. rest and waiting) and the time course of cognitive processes in normal and clinical populations.

Resting state EEG research has traditionally investigated frequency bands higher than those of DMN fluctuations (e.g. > 1.5 Hz). Recently it has been extended to the very low frequency band corresponding to the DMN activity. The following paragraphs will introduce studies of traditional EEG frequency bands and then illustrate the EEG findings in ultraslow frequency related to the DMN (EEG-DMN).

1.3.2 Resting state EEG in different frequency bands and their functions

EEG signals are often categorised into discrete frequency bands, i.e. delta: 1.5-4 Hz, theta: 4-7 Hz, alpha: 8-12 Hz, Beta: 12-30 Hz, and Gamma: 30-100 Hz. The band width differs slightly from study to study. Different EEG frequency bands are associated with distinct cognitive aspects and brain states. Delta has been typically found in adults during sleep, suggesting sensory disengagement (Anderson & Horne, 2003). Theta has been thought of as a marker of sleep propensity (Vyazovskiy & Tobler, 2005). Increases of theta power are associated with subjective reports of sleepiness (Aeschbach et al., 1997) and sleep deprivation (Babiloni et al., 2014). Alpha has been considered as an indicator of ‘cognitive idling’ and restfulness (Bazanova & Vernon, 2013). Enhanced alpha activity, especially in the frontal area, has been associated with self-referential thoughts (Knyazev, 2013b). Attenuation of alpha activity, often combined with increases of theta activity, is related to increases in cognitive load (Meltzer, Negishi, Mayes, & Constable, 2007). Beta is an index of cortical arousal, reflecting active cognitive processing and concentration (Rangaswamy et al., 2002). Gamma involves in both primary and cross-model sensory processing (Kanayama, Sato, & Ohira, 2007; Miller, 2007). It is modulated by cognitive processes such as attention and memory (O. Jensen, Kaiser, & Lachaux, 2007). Decreased gamma activity is associated with cognitive decline in individuals with Alzheimer’s disease, whereas increase gamma activity is found in individuals with ADHD (Herrmann & Demiralp, 2005).

1.3.2.1 EEG-DMN: Traditional frequency bands

Chen and colleagues (2008) investigated the spatial distribution of the resting state EEG power spectrum using high-density EEG recordings in 15 healthy adults. The EEG data were collected from an eyes-closed and an eyes-open resting condition, each lasting for three minutes. The topographical maps are shown in Figure 1.3. In both resting sessions, delta was located mainly in the prefrontal area. Theta was distributed over the frontal-central area. Alpha was dispersed across posterior regions. Beta was widely distributed across frontal and posterior regions and gamma is sourced to prefrontal region. Spatial distributions across frequency bands were fairly consistent between eyes-open and eyes-closed conditions. Chen et al., (2008) suggested that these stable and frequency-specific EEG maps should become known as the EEG-DMN despite the fact that the frequency of oscillations was higher than those implicated in the DMN.

Later, Knyazev et al. (2011) investigated the spatial pattern of resting EEG spectrum and reported that only the alpha map displayed a significant overlap with the DMN. Moreover, the alpha activity in the posterior DMN hub was associated with self-referential thoughts generated during rest, and was attenuated during the processing of external stimuli (Knyazev, Slobodskoj-Plusnin, Bocharov, & Pylkova, 2011). Following this work, Knyazev and colleagues replicated the relationships between self-referential thoughts and increases in resting alpha activity within the DMN regions (Knyazev, 2013a; Knyazev, Savostyanov, Volf, Liou, & Bocharov, 2012).

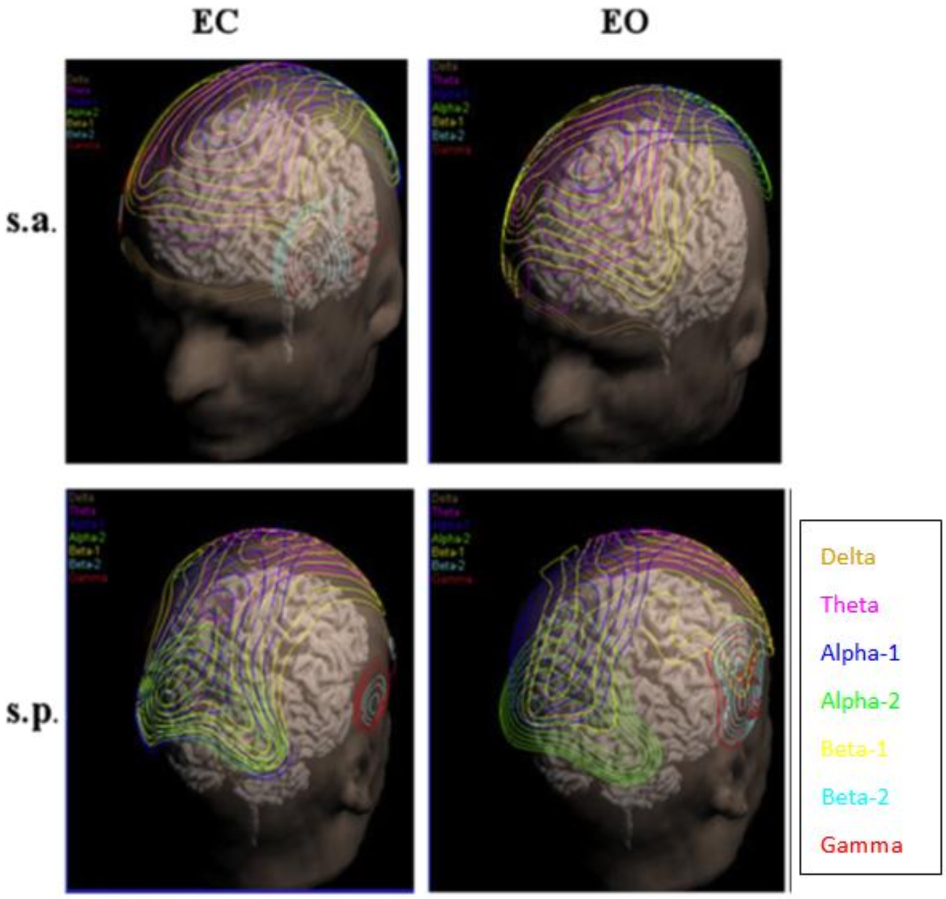


Figure 1.4 Spatial distribution of traditional EEG frequency bands.

Distribution of traditional EEG frequency bands during eyes closed (EC, left column) and eyes open (EO, right column) conditions, presented in superior-anterior (s.a., top panel) and superior posterior (s.p., bottom panel) perspectives.

Note. Picture was adapted from Chen et al., (2008).

1.3.2.2 EEG-DMN: Ultra-slow frequencies

Using direct current (DC) coupled recording of EEG, brain oscillations in the VLF band were observed in adults during sleep (Vanhatalo et al., 2004), as well as when performing a somatosensory stimulus detecting task (Monto, Palva, Voipio, & Palva, 2008). However, these studies did not attempt to explore the spatial pattern of VLF EEG. By contrast, Helps et al. (2008) demonstrated a reliable and stable resting state VLF EEG network in healthy young adults. Notably, the VLF EEG power within the network was attenuated from resting to performing an attention task, just as that has been observed in the DMN (Helps, Broyd, James, Karl, & Sonuga-Barke, 2009). Individuals who were rated high on ADHD symptoms exhibited reduced resting VLF EEG power compared to the low ADHD scorers within this VLF EEG network (Helps, James, Debener, Karl, & Sonuga-Barke, 2008). Further work from this group demonstrated that the intracranial sources of rest-to-task attenuation was localised to MPFC, PCC, pC and temporal regions, with a significant overlap with the DMN (Broyd, Helps, & Sonuga-Barke, 2011).

Although VLF EEG was considered by some to be physical noise or methodological artefact, accumulating evidence from many species indicates that it reflects real neural activity (Palva & Palva, 2012). In addition, there is evidence showing that spontaneous VLF EEG between spatially remote brain regions are synchronising as a larger scale neural network, which couples with the more constrained local networks formed by higher frequency neural activity (Demanuele, Broyd, Sonuga-Barke, & James, 2013; Vanhatalo, Voipio, & Kaila, 2005). However, the functional significance of VLF EEG has yet to be determined. Since DC-EEG and fMRI BOLD signals measure different aspects of neural activity, further research using simultaneous EEG-fMRI is required to directly explore the relation between VLF EEG and DMN activity.

1.3.3 Coherence

EEG coherence measures the synchrony of neural oscillations generated by two spatially separate populations of neurons. High coherence reflects functional assemblies while low coherence indicates substantial variation (Nunez et al., 1997).

The maturation of human resting EEG coherence from infancy to adulthood has been demonstrated by Thatcher and colleagues (Thatcher, Walker, & Giudice, 1987), who reported that EEG coherence between short distance electrode pairs increased as a function of age, whereas the EEG coupling between long distance electrode pairs declined. The most pronounced change occurred from 6 months to 4 years (Thatcher, North, & Biver, 2008). Abnormalities of resting EEG coherence have been implicated in mental disorders such as bipolar disorder and schizophrenia (Kam, Bolbecker, O'Donnell, Hetrick, & Brenner, 2013), autism (Murias, Webb, Greenson, & Dawson, 2007) and ADHD (Clarke, Barry, McCarthy, Selikowitz, & Brown, 2002). For instance, children with ADHD showed elevated resting EEG coherence in delta and theta bands between shorter distance electrode pairs and reduced coherence in alpha band between longer distance electrode pairs at rest, suggesting impaired cortical differentiation and specialisation (Barry, Clarke, McCarthy, & Selikowitz, 2002). Studies of resting EEG coherence on DMN-related activities are relatively rare. Travis and colleagues identified increases of frontal and parietal inter-hemispheric EEG coherence during meditation compared to an eye-closed rest condition, showing some sources overlapping with the midline structures of the DMN (Travis et al., 2010).

Although EEG coherence seems to be a promising technique for exploration of EEG-DMN the results need to be explained with caution. At present most studies have computed oscillatory coherence between two surface electrodes. Because neural activity generates a widespread EEG pattern, it is possible that more than one electrode picks up the activity of an underlying source - a phenomenon termed field spread. Thus, computing the synchronisation between pair of sensors or electrodes may be problematic. Consequently, examining neural interactions on the level of reconstructed localised, intracranial sources has been suggested (Schoffelen & Gross, 2009).

1.3.4 The Modulation of the EEG-DMN

Significant attenuation of VLF EEG power within the VLF network following the transition from resting to performance of an attention demanding task has been demonstrated in adults (Broyd et al., 2011; Helps et al., 2009), as well as in children and adolescents (Helps et al., 2010). In healthy adults, the level of rest-to-task attenuation differentiated self-ratings on the inattentive symptoms of ADHD (Helps et al., 2009).

However, previous VLF EEG studies differed in their strategy for operationalising the VLF EEG network. For instance, Help et al. (2008) selected the electrodes which showed higher *resting* VLF EEG power than the average as components of the network, whereas Broyd et al. (2011) considered that the top one third of electrodes that exhibited the highest *rest-to-task attenuation* of VLF EEG power comprised the VLF network. Although both studies adopted a data driven approach, the strategies used to identify VLF EEG networks were distinct. The methodological difference makes comparisons and interpretations of the VLF EEG networks across studies difficult. Hence developing an *a priori* strategy for network establishment seems essential for future studies.

1.3.5 The relationship between EEG frequency bands and fMRI/PET DMN

A number of studies demonstrate a direct link between spontaneous VLF fluctuations in BOLD signals and EEG in both traditional (Laufs, Kleinschmidt, et al., 2003; Mantini, Perrucci, Gratta, Romani, & Corbetta, 2007) and ultra-slow (Hiltunen et al., 2014) frequency domains.

1.3.5.1 Traditional frequencies

Using simultaneous EEG-fMRI recording, several RSNs have been identified, which corresponded to a range of previously described RSNs, and each was characterised by a specific pattern of EEG power (Laufs, Kleinschmidt, et al., 2003; Mantini et al., 2007; Yuan, Zotev, Phillips, Drevets, & Bodurka, 2012). Hlinka and colleagues (2010) demonstrated that EEG spectral power (1-30 Hz) explained a substantial degree of the DMN activity (70%), with significant partial correlation of DMN functional connectivity to delta (r = -.73) and beta (r = .53) bands (Hlinka, Alexakis, Diukova, Liddle, & Auer, 2010). Visual alpha power has been found to correlate positively with

DMN BOLD signals during eyes open resting conditions but not during eyes closed conditions (Mo, Liu, Huang, & Ding, 2013).

Studies using simultaneous EEG-fMRI also demonstrated an association between task-induced DMN attenuation and the change of EEG activity. Increases in theta power in DMN areas, especially within the anterior and poster DMN hubs, were associated with task-induced attenuation of DMN BOLD signals (Meltzer et al., 2007; Scheeringa et al., 2009). Reduced gamma power (60-140 Hz) was associated with task-induced attenuation of DMN activity, reflecting the increase in task difficulty and behavioural performance (Ossandon et al., 2011).

1.3.5.2 Ultra-slow frequencies

Hiltunen et al. (2014) extended the investigation of resting EEG oscillations in the VLF band (0.01-0.1 Hz) and examined the association of VLF EEG with spontaneous BOLD fluctuations. The authors separated the resting VLF EEG scalp potential into independent components and demonstrated significant correlations between VLF EEG components and spontaneous VLF BOLD signals. Notably, the relationships between VLF EEG and BOLD time series signals were tightly mapped to previously identified RSNs networks, including the DMN (Hiltunen et al., 2014). Hiltunen et al. (2014) provided a direct evidence that spontaneous fluctuations in BOLD signals and slow cortical potential in the VLF band are indeed temporally correlated at rest, supporting that resting VLF EEG potential and spontaneous BOLD fluctuations underpin the same (at least partially) neural mechanism. However, it is not yet clear if the amplitude and power of spontaneous VLF EEG also mirror the resting BOLD fluctuations. Moreover, the relationship between VLF EEG and DMN

BOLD signals in the transition from resting to task performance requires further investigation.

1.4 Resting network dysfunctions in ADHD

1.4.1 Default mode dysregulation in mental disorder

Atypical DMN activities have been observed in a wide range of mental disorders, such as Alzheimer disease (Greicius, Srivastava, Reiss, & Menon, 2004), schizophrenia (Garrity et al., 2007), bipolar disorder (Ongur et al., 2010) and ADHD (Castellanos et al., 2008). For a detailed review see Broyd et al. (2011). Aberrant patterns of DMN may present in a number of ways, each reflecting different aspects of psychopathology, including altered connectivity between regions within the DMN, dysfunctional anti-correlation between the DMN and TPN, as well as altered level of DMN activity during rest and task performance (Broyd et al., 2011). In the following section I review these altered patterns of DMN abnormalities in ADHD. Table 1 provides a summary for the empirical studies of the DMN including a clinical sample of ADHD.

1.4.2 Default mode dysregulation in ADHD

1.4.2.1 Altered functional connectivity within the DMN

Functional connectivity within the DMN reflects network integrity. Reduced functional connectivity of the PCC with the MPFC and the other DMN regions was demonstrated in ADHD children (Fair et al., 2010; Tomasi & Volkow, 2012) and adults (Castellanos et al., 2008). Within the control group the PCC was positively correlated with the MPFC while within the ADHD group the correlation was reduced (Castellanos et al., 2008). Uddin et al. (2008) examined the same data set of Castellanos et al. (2008) using a network homogeneity measure. The authors reported that on a global level the two groups did not differ in DMN homogeneity; however, the ADHD group showed a significantly reduced level of network homogeneity in the posterior hub of the DMN, particularly the precuneus (Uddin et al., 2008). Cao et al., (2006) examined the regional homogeneity of fronto-striatal cerebellar circuits between ADHD and control groups. The authors reported reduced regional homogeneity within the ADHD group, specifically in bilateral inferior frontal gyrus, right inferior ACC, left caudate, bilateral pyramis and left precuneus, which suggesting that altered patterns of DMN functional connectivity may involve other brain networks (Q. Cao et al., 2006). However, a recent study showed the opposite effect – i.e. increased functional connectivity within the DMN in adults with ADHD (McCarthy et al., 2013).

Using magnetoencephalography (MEG), Frazon identified a reduced level of oscillatory coupling of PCC with MPFC and right IPL, combined with an increased level of synchrony between bilateral IPLs in adults with ADHD, compared with controls. Notably, this aberrant pattern of functional coupling in ADHD was normalised with treatment of methylphenidate.

1.4.2.2 Altered antagonism between the DMN and task positive network

There has been evidence indicating altered patterns of antagonism between the DMN and TPN in ADHD. Tian et al., (2006) were the first to investigate the resting state functional connectivity in ADHD. The authors reported increased functional connectivity of the dorsal anterior cingulate cortex (dACC) with bilateral dACC, bilateral thalamus, bilateral cerebellum, bilateral insula and brain stem in children with ADHD, compared with healthy controls. Tian et al. (2008) reported similar results in a subsequent study re-analysing the same data set using a method which the authors described as a resting-state activity index. In contrast, Castellanos et al., (2008) observed a different pattern, specifically a decreased level of resting state functional connectivity of dACC with other DMN regions in adults with ADHD. Later studies have demonstrated a more consistent trend toward reduced anti-correlation between the DMN and TPN in ADHD over the developmental course (X. Cao et al., 2009; Sun et al., 2012). Recently, Sripada and colleagues (2014) found reduced connectivity within the DMN using a large sample of children and adolescents with ADHD (N=757). Moreover, the results showed diminished anti-correlation between the DMN and the ventral attention network, specifically increased coupling between the PCC and right anterior insula and supplementary motor area. These network connection abnormalities exhibited right lateralisation even after Bonferroni correction for multiple comparisons (Sripada et al., 2014).

1.4.2.3 Altered DMN activity from resting to working

Atypical DMN activity is characterised by dysfunction of introspective mental processes. Persisting DMN activity during an externally oriented, attention demanding task has been proposed as a major source of attention lapses which constrain cognitive performance (Castellanos et al., 2008). Individuals with ADHD showed a reduced resting state activity within the DMN, particular in the anterior hub (Cannon, Kerson, & Hampshire, 2011; Wilson et al., 2013). Compared to controls, individuals with ADHD also show a reduced level of DMN attenuation when engaged in cognitive tasks, which paralleled poor task performance such as elevated number of errors, longer reaction time and increased response variability (Fassbender et al., 2009; Peterson et al., 2009). Consistent with this, Cortese and colleagues (2012) examined 55 task-based fMRI studies in ADHD. The authors reported that children with ADHD displayed hyperactivation in the default mode, somatomotor and ventral attention networks, accompanied with hypoactivation in the frontoparietal and the ventral attention network across cognitive tasks. In adults, ADHD-related hyperactivation is shown in the visual, dorsal attention and default network, while hypoactivation is predominant in the frontoparietal network.

Treatment with methylphenidate improved the DMN attenuation in the MPFC and PCC on a Stroop task in 16 children with ADHD (Peterson et al., 2009). Moreover, motivational factor seems to play a role in DMN suppression. Liddle et al. (2011) reported that individuals with ADHD failed to suppress DMN activity in a low incentive condition of a go/no go task and this was normalised during the high incentive condition and when on stimulant medication. By contrast, the control group attenuated the DMN activity during all conditions (Liddle et al., 2011).

Using DC-EEG, Help et al., (2010) demonstrated reduced resting VLF EEG power and reduced task-induced attenuation in children and adolescents with ADHD (Helps et al., 2010). Broyd, Helps, and Sonuga-Barke (2011) observed that the sources of

VLF EEG attenuation differentiated individuals with high ratings of ADHD symptoms from controls. Within the control group, attenuation was localised to medial prefrontal regions while for the high ADHD group the attenuation was predominantly located on the temporal lobes (Broyd, Helps, & Sonuga-Barke, 2011).

In sum, ADHD is associated with a general pattern of hypoconnectivity at resting state within the DMN, specifically between the anterior and posterior hubs, although increased connectivity was observed in other functional pathways. Atypical connections between the DMN and TPN, as well as failure of DMN attenuation in the transition from resting to cognitive task performance, likely reflect the deficits of interaction between endogenous and exogenous information processing in ADHD.

Table 1.1 A summary of empirical studies of default mode network activity in individuals with ADHD.

	Measure	Subject	Task	DMN connectivity		DMN activity	
				DMN	DMN-TPN	Rest	Attenuation
Tian et al. (2006)	fMRI-ROI	Youths	RS	-	↑ ref. dACC	-	-
Cao et al. (2009)	fMRI-ROI	Youths	RS	↓ ref. putamen	-	-	-
Castellanos et al., (2008)	fMRI-ROI	Adults	RS	↓ ref. pC/PCC	↓ ref. dACC	-	-
Uddin et al., (2008)	fMRI-NeHo	Adults	RS	↓	-	-	-
Fassbender et al., (2009)	fMRI-WB	Youths	WM task	-	-	-	↓
Peterson et al., (2009)	fMRI-WB	Youths	Stroop task	-	-	-	↓*^{s}
Helps et al, (2010)	DC-qEEG	Youths	RS & RT task	-	-	↓	↓
Fair et al., (2010)	fMRI-ROI	Youths	RS	↓	-	-	-
Liddle et al., (2011)	fMRI-ROI	Youths	Go/no go task	-	-	-	↓*$^{s,\dagger m}$
Cannon et al., (2011)	fMRI-WB & qEEG	Adults	RS & Stroop task	-	-	↓	-
Sun et al., (2012)	fMRI-ROI	Youths	RS	-	↓ref. dACC	-	-
Tomasi et al., (2012)	fMRI-fc density	Youths	RS	↓	-	-	-
Frazon et al., (2013)	MEG-ROI	Adults	RS	↓*^{s} PCC-MPFC & RIPL;↑LIPL-RIPL	-	-	-
Wilson et al., (2013)	MEG-ROI	Adults	RS	-	-	↓*^{s}	-
McCarthy et al., (2013)	fMRI-ROI	Adults	RS	↓	-	-	-
Sripada et al., (2014)	fMRI-ROI	Youths	RS	↓	↑	-	-

Note. dACC: dorsal anterior cingulate cortex; EEG: electroencephalogram; fc: functional connectiveity; fMRI: functional magnetic resonance imaging; LIPL: left inferior parietal lobule; MEG: magnetoencephalography; MPFC: medial prefrontal cortex, NeHo: network homogeneity; PCC: posterior cingulate cortex; RIPL: right inferior parietal lobule; ROI: region of interest; RS: resting state; RT: reaction time; WB: whole brain voxel-wise analysis; WM: working memory; *[s] improved by stimulants; [†m] enhanced by motivation.

1.5 Methodological challenges

Various neuroimaging techniques and data processing strategies have been applied to resting brain research. This section will briefly introduce the techniques and analytical strategies commonly used in the exploration of resting brain.

1.5.1 Different neuroimaging techniques

The DMN has been principally investigated using fMRI and PET although investigations with EEG and MEG are developing. Functional magnetic resonance imaging (fMRI) measures the hemodynamic responses using blood-oxygen level dependent (BOLD) signals which reflect the level of oxygen released from blood to brain neurons. It measures brain activity through associated changes in blood flow based on the fact that this will increase to a brain region that is in use. PET is a nuclear medical imaging technique which produces three-dimensional images of functional processes. It detects gamma radiation emitted by the radioactive isotope introduced into the blood supply system before the recording. PET was used to delineate brain regions which show task-induced attenuation in early DMN research (Raichle et al., 2001). EEG measures the post-synaptic potential difference from large populations of neurons (Banaschewski & Brandeis, 2007) while MEG maps the brain activity from magnetic fields produced by electrical currents. Because these neural imaging techniques measure different aspects of brain activity, further studies examining the relationship among resting state activity recorded from different techniques are required.

1.5.2 DC-EEG recordings

Investigating EEG in VLF bands raises a number of methodological issues which need to be addressed. Conventional EEG studies adopt alternating current (AC) recording, which imposes a high-pass filter and automatically removes low frequency signals. By contrast, DC-EEG coupled recording does not impose any filter so that all VLF components are preserved. However, DC-EEG recording signals are vulnerable to slow drift artefacts, i.e. signals shifting over time, which violate the stationary assumption of signal processing. Fortunately, drift artefacts can be removed with careful computation during data pre-processing. Moreover, drift rate can be stabilised by using sintered silver/silver chloride electrodes and high chloride gel. Thus, DC-EEG coupled recording can to be used effectively to record VLF neural oscillations through careful pre-processing.

1.5.3 Approaches of data processing

Two data processing approaches are commonly used in the resting brain research, which are i) regions-of-interest (ROI) and ii) independent component analysis (ICA). In contrast to the whole brain analysis, ROI analysis narrows down the inspection to ‘selected’ brain regions, voxels or electrodes based on *a priori* knowledge. Compared to the whole brain analysis, ROI analysis usually has higher statistical power because it constrains the number of multiple comparisons. However, it may exclude possible findings from unselected regions. In contrast, ICA is a completely data-driven method which decomposes data into separate temporally- or spatially-independent components. In comparison with ROI, ICA is a model-free approach which does not need an *a priori* hypothesis. However, the determination of extracted components is by its nature subjective and requires researchers to decide which components reflect true brain activity and which components are physical artefacts. There are pros and cons for both methods, nevertheless, the two methods appear to produce comparable results in the exploration of the resting brain (Greicius et al., 2004).

1.6 Current controversies and unresolved issues related to the DMN

1.6.1 Does the brain have a baseline?

Despite all the progress in exploring the DMN, it has been argued that spontaneous VLF oscillations might be a consequence of physical artefacts, such as cardiac or respiratory cycles rather than a direct response of neural activity (Cordes et al., 2000; Lowe, Mock, & Sorenson, 1998; Morcom & Fletcher, 2007). However, supporting evidence has showed that spontaneous oscillations can be differentiated from other physiological activities (De Luca et al., 2006). Moreover, RSNs can be reliably identified either at individual subject or at group level, suggesting they are not random artefacts (Damoiseaux et al., 2006; De Luca et al., 2006; Hiltunen et al., 2014).

1.6.2 Functional heterogeneity in the DMN

The DMN is a heterogeneous brain system which exhibits distinct patterns of activity during different tasks requiring extrinsic and intrinsic attention. Task-induced suppression during externally-oriented tasks has been robustly identified in the anterior and posterior midline DMN hubs such as MPFC and pC. On the other hand, task-related increases have been demonstrated during introspective processes in a set of DMN regions including bilateral MTGs and MPFC. A meta-analysis of functional connectivity within the DMN confirmed that the DMN comprises different subsystems, with each appearing to serve specific functions (Laird et al., 2009). However, there is also negative evidence with weak functional connectivity seen between the MPFC and MTG (Buckner et al., 2008). Future research mapping the regional coherence or connectivity across distinct cognitive functions would facilitate the understanding of the DMN processes.

1.6.3 The resting and waiting brain

The original formulation of the DMN proposed by Raichle (2001) highlighted the goal-directed nature of activity rather than its cognitive character causing the attenuation of DMN activity. This leads to the prediction that the transition from rest to other types of goal-directed activity with little or no cognitive load should also provoke attenuation of VLF oscillations in the DMN. A simple task such as waiting for a delayed outcome is an example of goal-directed activity which involves little or no information processing demands, but nonetheless requires an outcome-related focus and the application of effort to persist until the goal is achieved. However, there have not been studies directly comparing the DMN activities between resting and waiting. It is not clear if DMN activity would be attenuated from resting to waiting, similar to what has been demonstrated from resting to working on cognitive attention demanding tasks.

1.7 Summary and the next steps in the thesis

DMN is a set of widely distributed, but functionally connected brain regions which are active during wakeful rest and differentially implicated in a range of introspective self-referential cognitive states, such as episodic prospection. During goal-directed tasks the DMN is attenuated, while the task specific networks are activated. DMN attenuation seems to be independent of task content but is associative with task difficulty. Atypical reduced connectivity within the DMN and altered antagonistic relationships between the DMN and task positive networks have implicated in a number of mental disorders, especially for ADHD.

ADHD is a pervasive neurodevelopmental disorder with core symptoms of inattention, hyperactivity and impulsivity. Individuals with ADHD are often restless, impulsive and have waiting difficulties. Although this disorder is commonly seen among children and adolescents, the underpinning neural deficits are not well understood. Exploring spontaneous neural oscillations during resting and waiting may help to understand the cause of ADHD. The next chapters will review the current literature on ADHD and provide a background review for this disorder.

Chapter 2 Background to ADHD

2.1 Purposes

ADHD is a common and impairing mental health condition that affects individuals across the lifespan. The educational and emotional impairments it raises impose enormous burden on the family and society (Schubiner & Katragadda, 2008). Although ADHD is one of the most widely researched psychiatric disorders, its pathophysiology has not been not well understood. This chapter will outline the clinical features, aetiology, psychopathology and treatment of ADHD. It aims to introduce the background of ADHD and lay a foundation for the subsequent chapter focusing on the waiting difficulties of this clinical group.

2.2 Clinical features of ADHD

2.2.1 Diagnosis

ADHD is characterised by inattention, hyperactivity and impulsivity with associated patterns of functional impairment (American Psychiatric Association [APA], 2013). Over the past century the terminology of ADHD has varied. The terms applied to ADHD include ‘minimal brain damage’, ‘minimal brain dysfunction’, attention-deficit disorder (ADD) and hyperkinetic disorder. Currently the diagnostic criteria for ADHD (Table 1) are based on the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* published by the APA (*DSM-5*; APA, 2013).

ADHD is defined as a set of developmentally inappropriate behaviours in either or both the inattention and the hyperactivity/impulsivity domains. Inattention often presents as an inability to sustain attention and disorganisation. Hyperactivity refers to excessive motor activity. Impulsivity presents as acting rashly before thinking of the consequences, interrupting others and having trouble waiting. The disturbance must result in deficits in educational, occupational or social functioning in multiple settings (e.g., school and home). Children must present at least six symptoms from either or both symptom domains, whereas adolescents or adults over 17 years must display at least five symptoms in either or both domains.

Table 2.1 Diagnostic Criteria for Attention-Deficit/Hyperactivity Disorder.

A. Either (1) or (2)

(1) Inattention:

Six (or more) of the following symptoms of inattention for children up to age 16, or five (or more) for adolescents 17 or older; symptoms have persisted for at least 6 months to a degree that is maladaptive for developmental level.

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

(2) Hyperactivity and impulsivity:

Six (or more) of the following symptoms of hyperactivity-impulsivity for children up to age 16, or five (or more) for adolescents 17 or older; symptoms have persisted for at least 6 months to a degree that is maladaptive for developmental level.

Hyperactivity

(a) Often fidgets with taps hands or feet, or squirms in seat.
(b) Often leaves seat in situations when remaining seated is expected.
(c) Often runs about or climbs in situations where it is inappropriate (adolescents or adults may be limited to feeling restless).
(d) Often unable to play or engage in leisure activities quietly.
(e) Is often ‘on the go’ acting as if ‘driven by a motor’.
(f) Often talks excessively.

Impulsivity

(g) Often blurts out answers before questions have been completed.
(h) Often has trouble waiting his/her turn.
(i) Often interrupts or intrudes on others (e.g. butts into conversations or games).

B. Several inattentive or hyperactive–impulsive or symptoms were first present before age 12 years.
C. Some symptoms are present in two or more settings (e.g. at home, school or work; with friends or relatives).
D. There is clear evidence that the symptoms interfere with, or reduce the quality of, social, school, or work functioning.
E. The symptoms do not happen only during the course of schizophrenia or another psychotic disorder. The symptoms are not better explained by another mental disorder (e.g. Mood Disorder, Anxiety Disorder, Dissociative Disorder, or a Personality Disorder).

Note: Individuals with ADHD must meet the conditions A to E. Table was adapted from DSM-5 (APA, 2013).

2.2.2 Presentations

ADHD is a heterogeneous condition. Individuals with ADHD do not exhibit identical clinical characteristics nor the same neuropsychological impairments (Banaschewski et al., 2005). DSM-5 describes three presentations of ADHD: (1) ADHD predominantly inattentive type (IT), applied when individuals meet the clinical cut-off for the attention domain but not the hyperactivity/impulsivity domain; (2) predominantly hyperactive-impulsive type (HT), a relatively rare condition for those meeting the criteria for the hyperactivity/impulsivity only; and (3) combined type (CT), the most common form for those meeting the cut-off for both domains. There is evidence suggesting that different presentations of ADHD are associated with distinct pathophysiological mechanisms (Clarke, Barry, McCarthy, & Selikowitz, 2001). However, the clinical validity of ADHD presentations has been controversial because it may change over the course (Woo & Rey, 2005). Lahey and colleagues (2005) followed up 118 children over eight years. The authors reported that the majority of individuals shifted their presentations of ADHD at least once (IT: 66.7%, HT: 91.4%, CT: 68.7%). This finding suggests that the current categorisation based on behavioural manifestation may not be ideal. Identifying reliable and objective measures such as electrophysiological markers would help better delineation of pathophysiological mechanisms underpinning ADHD. The neural markers may also be used for the determination of aetiologically or pathophysiologically homogenous sub-groups (Clarke et al., 2002).

2.2.3 Prevalence

ADHD symptoms are pervasive across nationalities. The condition is believed to affect 5.29 - 7.1% of children and adolescents worldwide (Polanczyk, de Lima, Horta, Biederman, & Rohde, 2007; Willcutt, 2012). Children who are suspected of having ADHD account for 30-50% of referrals to mental health services (Stefanatos & Baron, 2007). Western countries, especially the US, have a higher incidence rate, possibly due to the increased awareness of the disorder (Faraone, Sergeant, Gillberg, & Biederman, 2003). According to a recent large scale meta-analysis, the number of ADHD population has remained stable over the past three decades although there is a significant variation in estimated prevalence (Polanczyk, Willcutt, Salum, Kieling, & Rohde, 2014). These differences have been argued to reflect methodological differences (e.g. methods of diagnosis and diagnostic criteria) instead of geographical location.

2.2.4 Gender difference

Boys are more likely to be diagnosed as having ADHD than girls, but the sex difference seems to disappear by adulthood (Rucklidge, 2008). In children, the boy-to-girl ratios range from 3:1 to 9:1 in clinical samples (Szatmari, 1992) whereas the ratios vary from 1:1 to 3:1 in community samples (Willcutt & Pennington, 2000). Boys are more likely to display the combined presentation while girls are more likely to meet criteria of the inattentive presentation (Willcutt & Carlson, 2005). Moreover, boys with ADHD are more likely to be referred for externalising problems such as hyperactivity, aggression, oppositional or conduct behaviours (Rucklidge, 2008). In contrast, girls with ADHD have more internalising problems such as inattention, anxiety, social withdrawal, depression and intellectual impairment (Gaub & Carlson, 1997; Gershon, 2002; Rucklidge & Tannock, 2001). The gender difference may relate to referral bias, gender-related expectation and socio-environmental influences (Rucklidge, 2008).

2.2.5 Persistence: ADHD as a life-span disorder

Converging evidence show that a substantial number of individuals with ADHD continue to experience symptoms across the lifespan, despite some improvement occurring with the increase of age (Asherson, Chen, Craddock, & Taylor, 2007; Barkley, Fischer, Smallish, & Fletcher, 2002; Davidson, 2008; Faraone et al., 2000). Adults with

ADHD often develop coping skills to compensate for their symptoms (Faraone, Biederman, & Mick, 2006). Hyperactivity may be replaced by internal restlessness, difficulty relaxing and fidgetiness; inattention is manifested as the problem relating detail; and impulsivity may be expressed as impatience and waiting difficulties (Asherson et al., 2007). A meta-analysis of longitudinal studies of ADHD demonstrated that around 15% of individuals with ADHD continued to meet full criteria at age 25, and approximately 65% of individuals met the definition for partial remission of ADHD (Faraone et al., 2006). The estimated prevalence of adults with ADHD falls between 4% and 5% (Davidson, 2008; Kessler et al., 2006). Although there is a growing awareness of the impact of ADHD on adults, many ADHD cases remain undiagnosed until their own children are evaluated for the disorder.

2.2.6 Prognosis

The estimated number of children with ADHD who continue to have problems in adulthood varies widely from study to study. While Mannuzza and Klein (2000) reported that most children they followed into adulthood were gainfully employed and educated (Mannuzza & Klein, 2000), other studies reported that there is a high rate (up to 80%) of ADHD cases who continue to experience problems during adolescence (Biederman, Mick, & Faraone, 1998). Subsequent studies demonstrated that adolescents and young adults with ADHD are at risk for school failure, emotional difficulties, interpersonal relationship problems, frequent job changing, risk-driving, multiple marriages and trouble with the law (Barkley, 2004; Murphy & Barkley, 1996; Spencer, Biederman, & Mick, 2007). The outcome of the Multimodal Treatment Study for Children with ADHD – a multisite, longitudinal study designed to evaluate treatments of ADHD - suggests that while medication treatment was initially effective for core ADHD symptoms, combining psychological treatments yielded additional improvement in psychosocial difficulties (P. S. Jensen et al., 2007). However, by the 8 year follow up children with a combined presentation of ADHD still had significant behavioural difficulties no matter what treatments they received (Molina et al., 2009). Although many individuals with ADHD never fully remit their ADHD symptoms, a thorough treatment programme that is tailored to personal needs can help individuals cope with their symptoms and lead to a more productive and successful life.

2.2.7 Comorbidity

A large number of individuals with ADHD (over 60%) present with co-existing psychiatric disorders (Sobanski, 2006). ADHD is commonly comorbid with Oppositional Defiant Disorder (ODD, 54-67%) and Conduct Disorder (CD, 20-50%) (Barkley, 2006; Gillberg et al., 2004; P. S. Jensen, Martin, & Cantwell, 1997). Other mental problems, such as anxiety (15-47%), mood disorders (16-38 %), impulse control disorders (19.6%) and substance use (15.2%) are also concurrent conditions with ADHD (Biederman, 2005; Kessler et al., 2006). Learning difficulties, Tourette's syndrome and personality disorders may combine with ADHD (Gillberg et al., 2004). Adults with ADHD are more likely to have a diagnosis of anxiety disorders, substance use and personality disorder than children (Biederman et al., 1993; Sobanski, 2006). Comorbid conditions may mask ADHD symptoms and implicate different types of pathology. Careful history taking is required when making differential diagnoses.

2.2.8 Is ADHD a dimensional or categorical disorder?

ADHD is conceptualised as a categorical disorder in the current diagnostic system. People are assigned to a particular category – they either have the disorder or they do not. Implementing a category-based approach has a number of advantages. First, it is easy to use because it sets clear distinctions between health and illness. Second, it facilitates the communication between professionals and the standardisation of treatment plans. Third, it meets the political and economic considerations. For example, in the UK, since the National Health Service and private insurance companies have limited resources, a categorical approach allows individuals to justify their needs and claim for reimbursements. However, there has been debate about the dichotomous classification for ADHD (Coghill & Sonuga-Barke, 2012; Marcus & Barry, 2011). According to the current diagnostic criteria, individuals who display less than the threshold of symptom criteria are not given a diagnosis of ADHD although those symptoms may also cause significant impairments in everyday life.

In contrast, a dimensional approach treats ADHD as a continuous trait. One of the advantages of dimensional approach is that it provides a quantitative profile by evaluating the degree of symptomatic manifestations. The evidence-based measures for effect sizes can be used in both clinical and research settings (Hudziak, Achenbach, Althoff, & Pine, 2007). Importantly, dimensional model can be combined with the categorical approach into a diagnostic system, which may better capture experiences of ADHD and benefit individuals with ADHD in the long term.

2.3 Aetiology

ADHD is aetiologically heterogeneous. Existing data shows that no single aetiological pathway can fully explain the causal pathways of ADHD. Instead, genetic and environmental factors and their interaction all play an important role in ADHD.

2.3.1 Genetic influence

Evidence from family, twin and adoption research suggests that ADHD is a highly heritable condition (estimated heritability: 76%; Faraone et al., 2005). Research has identified a number of ADHD-related candidate genes. Notably, many of these are catecholaminergic genes, such as the dopamine receptor D4 and D5 (DRD4, DRD5) and dopamine transporter gene (DAT1; Banaschewski, Becker, Scherag, Franke, & Coghill, 2010). This is consistent with the fact that stimulant medication decreases ADHD symptoms by blocking the dopamine transporter. Other genetic components, such as receptors and transporters of noradrenergic and serotonin system are also related to ADHD (see Faraone et al., 2005; Gizer, Ficks, & Waldman, 2009 for a review).

Candidate gene-based studies only explain a small effect of the genetic contribution to ADHD. In the last decade a new approach termed genome-wide association studies (GWAS) has been developed. GWAS is a data-driven approach identifying disorder-related genes using common single-nucleotide polymorphisms (SNP) and the rare copy number variants (CNV). Researchers have identified an increased burden of risk SNPs and CNVs at genome-wide level (Stergiakouli et al., 2012), but have failed to demonstrate genome-wide significance of these (Ashmore & Cheng, 2013). This has several implications. First, it suggests that ADHD presents as a heterogeneous disorder. Lack of homogeneity in study populations has led to the conclusion that a single unitary cause is unlikely. Second, the disorder appears to involve multifactorial pathways which are caused by some genetic variants with small effect sizes. Alternatively, the multiple ADHD subtypes might have different genetic mechanisms or multiple phenotypes, suggesting genetic heterogeneity of ADHD. Another implication is that the environmental factors may amplify genetic effects. The influence of environments is discussed below.

2.3.2 Environmental influence

A number of environmental factors that interfere with brain development during pregnancy and early childhood increase an individual's susceptibility to ADHD. The risk factors include maternal smoking (Linnet et al., 2003), alcohol consumption (Mick, Biederman, Faraone, Sayer, & Kleinman, 2002), extremely low birth weight (Botting, Powls, Cooke, & Marlow, 1997; Lahat, Van Lieshout, Saigal, Boyle, & Schmidt, 2014) and exposure to toxins (Banerjee, Middleton, & Faraone, 2007). ADHD is associated with lower socio-economic status (Russell, Ford, Rosenberg, & Kelly, 2014), large family size and discordant family relationships (Deault, 2010). Early social deprivation (e.g., institution-reared children) increases the risk of manifesting ADHD-like symptoms (Kreppner, O'Connor, & Rutter, 2001), but the underlying mechanism appears to differ from typical ADHD (Sonuga-Barke & Rubia, 2008). Interpreting environmental effects is complicated by the presence of correlations between environmental exposures and genetic factors shared between children with ADHD and their family (Biederman, 2005). Where these are controlled the environmental effects are often reduced (Knopik et al., 2006).

2.3.3 Gene by environment interaction

The influence of environmental effects on ADHD may interact with genetic factors. For instance, maternal smoking during pregnancy has been identified as an independent predictor of hyperactive/impulsive symptoms (Langley, Holmans, van den Bree, & Thapar, 2007). However, the association between maternal smoking during pregnancy and the hyperactive/impulsive symptom is stronger with children who have a DAT genotype (Kahn, Khoury, Nichols, & Lanphear, 2003). This finding highlights the importance of environmental and genetic interaction. It suggests that ADHD is more heritable in a risky environment (Pennington et al., 2009; Rosenberg, Pennington, Willcutt, & Olson, 2012). Therefore, simple genetic and environmental association seems insufficient to explain the spectrum of ADHD. In contrast, gene by environment interactions, as the basis of epigenetic may modify the manifestations of the disorder (Archer, Oscar-Berman, & Blum, 2011).

2.4 Pathophysiology

ADHD is viewed as a neurodevelopmental disorder in DSM-5. The rapid growth of neuroimaging research in ADHD means it is not possible in this section to cover in great depth of this literature. Instead, it briefly reviews abnormalities in brain structure and function, the alterations in white matter integrity and functional connectivity, as well as neurotransmitters associated with ADHD.

2.4.1 Aberrant brain structure

Brain structural alterations relating to ADHD can be organised in two domains: volume reduction and decreased cortical thickness. Individuals with ADHD show a pattern of general volume reduction in the whole brain, but especially in the prefrontal cortex, striatum (Castellanos et al., 1996; Castellanos et al., 2002; Hill et al., 2003; Mostofsky, Cooper, Kates, Denckla, & Kaufmann, 2002), and cerebellum (Seidman, Valera, & Makris, 2005; Valera, Faraone, Murray, & Seidman, 2007). However, there is evidence suggesting increased cortical thickness in the primary sensorimotor cortex in adults with ADHD (Duerden, Tannock, & Dockstader, 2012). Longitudinal evidence shows a global reduction in cortical thickness in ADHD with a maturational lag for a mean of three years (Shaw et al., 2007; Shaw et al., 2006).

2.4.2 Abnormal brain function

Neuroimaging studies have examined the neural correlates of ADHD across a wide range of cognitive tasks examining executive function, temporal processing and reward processing domains. A meta-analysis for 16 fMRI studies regarding executive function demonstrated a general pattern of hypoactivity in the frontal cortex (Dickstein, Bannon, Castellanos, & Milham, 2006). Specifically, individuals with ADHD showed reduced activity in the dorsolateral and inferior prefrontal cortex, anterior cingulate cortex, orbitofrontal cortices, bilateral parietal lobe, basal ganglia and thalamus. This was accompanied by increased activity in the left frontal lobe, middle frontal gyrus, insular and right paracentral lobule. Given the existence of a sufficient number of studies using tasks evaluating response inhibition, the authors narrowed the analysis to response inhibition alone and reported a more limited set of brain regions where showing the group effects. The ADHD group displayed reduced activity in the inferior PFC, cingulate cortex, left parietal lobe and right caudate, as well as increased activity in the middle frontal gyrus and right paracentral lobule (Dickstein et al., 2006). Subsequent studies replicated ADHD-related reduced activity in the fronto-striatal circuits during tasks involving executive control (K. Konrad, Neufang, Hanisch, Fink, & Herpertz-Dahlmann, 2006; Rubia, Smith, Brammer, & Taylor, 2007).

Research examining temporal processes have noted ADHD-related hypoactivity in ventral and dorsal prefrontal cortex, cingulate and cerebellar regions in children with ADHD during tasks involving motor timing, temporal discrimination and temporal unpredictability (Durston et al., 2007; Rubia, Halari, Christakou, & Taylor, 2009; Smith, Taylor, Brammer, Halari, & Rubia, 2008).

In terms of reward processing, a recent meta-analysis demonstrated a medium effect size in ventral-striatal hyporesponsiveness in ADHD (Cohen' d = 0.48; Plichta & Scheres, 2014). Reduced activity in the ventral striatum during reward anticipation has been observed in adolescents (Scheres, Milham, Knutson, & Castellanos, 2007), and adults with ADHD (Carmona et al., 2012; Strohle et al., 2008) although there is one negative finding (Paloyelis, Mehta, Faraone, Asherson, & Kuntsi, 2012). Consistently, adults with ADHD display reduced activity in ventral striatum during the presentations of both immediate and delayed monetary rewards. Moreover, the clinical group shows increased activity in the dorsal striatum and amygdala compared to controls during the processing of delayed rewards only (Plichta et al., 2009).

2.4.3 Structural and functional connectivity

Traditionally ADHD has been conceptualised as showing dysfunction of frontal-striatal circuit. However, emerging evidence has highlighted the involvement of other circuits and their interconnections in the pathophysiology of ADHD. Studies on structural connectivity using diffusion tensor imaging have indicated abnormalities in the left frontotemporal, frontoparietal, frontocerebellar, as well as parieto-occipital white matter tracts in ADHD across different age groups (Ashtari et al., 2005; Davenport, Karatekin, White, & Lim, 2010; A. Konrad et al., 2010; Silk, Vance, Rinehart, Bradshaw, & Cunnington, 2009).

Moreover, individuals with ADHD display altered functional connectivity during tasks involving working memory (Wolf et al., 2009), response inhibition (Cubillo et al., 2010; Rubia, Halari, Cubillo, et al., 2009), interference control and time discrimination (K. Konrad & Eickhoff, 2010; Vloet et al., 2010). The research suggests that ADHD not only have localised abnormalities in discrete brain regions, but also display distributed disturbances in large-scale brain networks and the brain synchronisation (Castellanos & Proal, 2012; K. Konrad & Eickhoff, 2010; Sripada et al., 2014). Interestingly, stimulant medication not only improves regional activation but also normalises the dysfunctional connectivity of ADHD (Rubia, Halari, Cubillo, et al., 2009).

2.4.4 Neurotransmitters

Neurotransmitter imbalance and dysfunction appears to play an important role in ADHD, in particular with regard to dopamine. Dopamine cell bodies lie in mid-brain structures including ventral tegmental area and substantia nigra. Dopaminergic projections from the midbrain to basal ganglia, nucleus accumbens and limibic system are involving in reward processing. Low levels of dopamine are thought to cause symptoms of ADHD (Tripp & Wickens, 2009). Methylphenidate, one of the most common stimulant medications for ADHD, blocks dopamine transporters and increases the concentration of dopamine in the synaptic cleft to enhance the efficiency of chemical metabolism. Dopaminergic system appears to modulate other neurotransmitters, especially norepinephrine (Del Campo, Chamberlain, Sahakian, & Robbins, 2011) and serotonin (Oades, 2008). Medications targeting these neurotransmitters are also commonly used in the treatment of ADHD.

2.5 Treatments

2.5.1 Medication

ADHD can be treated using medication, either alone or combined with psychological therapy. While treatment may alleviate symptoms, it is not able to cure ADHD. At present, stimulants (especially methylphenidate and dexamfetamine) are the primary pharmaceutical treatment of choice. Non-stimulant medications, such as atomoxetine (Strattera, a selective norepinephrine reuptake inhibitor), tricyclic antidepressants and their successors (selective serotonin reuptake inhibitors, SSRIs) can also be used as alternatives. The effectiveness of stimulants in the treatment of ADHD has been well documented in clinical trials since the 1950s (Gibson, Bettinger, Patel, & Crismon, 2006). However, medications for ADHD can cause side-effects such as growth retardation and an increased propensity for drug use. These can usually be managed through dose modification. Implementing breaks from medication and regular monitoring for height and weight are often recommended for those on long term treatment (Howland, 2009).

2.5.2 Psychosocial intervention

A number of psychosocial treatments are available to help individuals with ADHD coping with their symptoms. Cognitive training (normally selectively focus on a specific cognitive domain such as attention or working memory) involves repeated practice on exercises that become more challenging with the improvement of performance (Klingberg et al., 2005; Rutledge, van den Bos, McClure, & Schweitzer, 2012). Behavioural therapy motivates ADHD cases to modify unfavourable behaviours through operant learning. Good behaviours are encouraged with praise or rewards (Toplak, Connors, Shuster, Knezevic, & Parks, 2008). Parent training educates parenting skills and techniques to deal with children’s challenging behaviours (Anastopoulos, Shelton, DuPaul, & Guevremont, 1993). Social skills training helps individuals with

ADHD in their social interactions and interpersonal relationships (Chang, Tsou, Shen, Wong, & Chao, 2004). Neurofeedback attempts to stimulate individuals to maintain cortical arousal through visible physiological indices (Loo & Barkley, 2005; Strehl et al., 2006).

Psychosocial interventions are often combined with medication or used alone as an alternative, particularly when concerns about medication are raised. However, the effectiveness of nonpharmacological interventions has not yet been fully established (Sonuga-Barke et al., 2013).

2.6 Chapter summary

ADHD is a common psychiatric disorder which causes significant functional impairments across the lifespan. A number of risk factors, both environmental and genetic and their interaction increase the susceptibility to ADHD. Individuals with ADHD display brain structural and functional abnormalities across multiple brain networks which regulate cognitive, motivational and emotional operations. Medication and psychosocial treatments appears to alleviate symptoms but not fully cure ADHD.

Waiting plays an important role in symptoms of ADHD, in particular impulsivity and hyperactivity. The next chapter will focus on waiting difficulties of ADHD. It provides the current theoretical models to explain possible causal pathways for the waiting problems of this clinical group.

Chapter 3 Waiting difficulties in ADHD

3.1 Purpose

Waiting is common in daily life, for instance, waiting for the bus or queuing at check-outs. In many cases it pays off to wait for a consequence of a choice or a delayed commencement of an activity. However, individuals with ADHD, in particular children, often engage in it reluctantly as if waiting is a mission impossible. Waiting is a somewhat abstract and vague state. Difficulties of waiting can express in a number of ways and have various causes, such as dislike of waiting or the inability to wait.

This chapter illustrates the common waiting difficulties seen in ADHD. It reviews a number of causal models in relation to ADHD and develops testable predictions of possible waiting difficulties involved in this clinical group. It also provides the current evidence for each of the causal models. Firstly, this chapter illustrates the cognitive energetic model (CEM), delay discounting models and delay aversion hypothesis. Subsequently, particular emphasis will be placed on the default mode interference (DMI) hypothesis of ADHD (Sonuga-Barke & Castellanos, 2007). The original formulation of DMI hypothesis proposed by Sonuga-Barke and Castellanos suggests that excess resting neural oscillations during goal-directed tasks may cause periodic attention lapses. In this chapter the DMI hypothesis is applied to explain the waiting difficulties of ADHD. It is suggested that excessing resting neural oscillations may not only interfere cognitive task performance but also affect waiting tolerance. Individuals with ADHD may experience difficulty of waiting because they fail to effectively attenuate the DMN activity when waiting. Finally, this chapter will conclude with the neuro-economic model of ADHD (Sonuga-Barke & Fairchild, 2012), a mixed model that integrates several causal models of ADHD decision making processes into a neurocognitive system.

3.2 Multi-faceted nature of waiting difficulties

Waiting difficulties have a number of manifestations, including impulsive decision making and increased degree of task-unrelated activity. Individuals with ADHD show a propensity for an immediate over a delayed reward even when this will lead to less profit in the long term (Luman, Oosterlaan, & Sergeant, 2005). The preference toward reward immediacy over reward magnitude is considered as a key element of impulsivity (Scheres, Tontsch, & Thoeny, 2013), whereas the choice for larger rewards reflects self-control (Rachlin, 1995).

Waiting difficulties in ADHD also express as increased levels of off-task activities during periods of delay. For instance, Antrop and colleagues (2005) analysed the behaviours of children with ADHD and controls while they were in waiting situations in the classroom. Children with ADHD expressed elevated level of motor activity, off-task behaviours, stimulation-seeking, noise making and negative emotion compared to the controls. These maladaptive behaviours were improved with the presence of non-temporal stimulation (i.e. reading the children a story; Antrop, Buysse, Roeyers, & Van Oost, 2005).

Both impulsive decision making and increased level of task-unrelated activity may be regarded as coping strategies undertaken in different contexts to meet environmental requirements. Although waiting deficits of ADHD have been widely acknowledged, particularly in clinical settings, previous literature seems to place greater emphasis on the ability to wait (e.g. impulsive choices), but relatively less attention to affective components of waiting (e.g. dislike of waiting). From a scientific point of view the affective factor of waiting is important because it seems to be associative with the motivational style of ADHD, either innate or acquired, to escape and/or avoid delay (Bitsakou, Psychogiou, Thompson, & Sonuga-Barke, 2009). Thus, it is imperative to explore the influence of emotional factors on the basis of behavioural manifestations of waiting capacity.

3.3 Theories of waiting difficulties in ADHD

A number of theoretical models of ADHD have been proposed in recent years which can be used to guide systematic investigations of waiting difficulties in ADHD. These models include state dysregulation (Sergeant, 2005), delay discounting (Scheres, Sumiya, & Thoeny, 2010), delay aversion (Sonuga-Barke, 2003, 2005), and intrusion of resting brain activity (Sonuga-Barke & Castellanos, 2007), as well as an integrated model adopting a neuroeconomic perspective (Sonuga-Barke & Fairchild, 2012). Each model makes different predictions as to the manifestations of waiting difficulties in ADHD. Supporting evidence for each hypothesis is provided accordingly.

3.3.1 The cognitive energetic model (CEM) of ADHD

3.3.1.1 Model description

The cognitive-energetic model (CEM) suggests that information processing can be accounted by interactions among attention mechanisms, energetic states and executive management systems (Figure 3.1; Sergeant, 2000, 2005). The CEM contains three levels. The bottom level comprises computational components of attention, including information encoding, central processing and response output. The middle level contains three distinct energetic pools, i.e., arousal, effort, and activation. The relationships between these energetic pools are of particular importance in ADHD. Arousal denotes phasic responses that are time-locked to stimulus processing and affected by signal intensity and novelty. The arousal pool is thought to be associated with mesencephalic reticular formation and amygdala. Activation is associated with tonic physiological readiness to respond. It is affected by task variables such as preparation, alertness, time-of-day and time on task. The activation pool is associated with basal ganglia and striatum. Effort is the energy required to meet task demands, which is affected by factors such as cognitive loads and motivation. The effort pool is associated with hippocampus. It plays an important role in exciting and inhibiting the other two energetic pools. On the top of energetic pools is a management system, comparable to the concept of executive function. It is associated with planning, monitoring, detection for errors and error correction. The executive system can be localised to the prefrontal cortex. The three levels of CEM have been suggested to interact through both top-down and bottom-up routes (Sergeant, 2005).

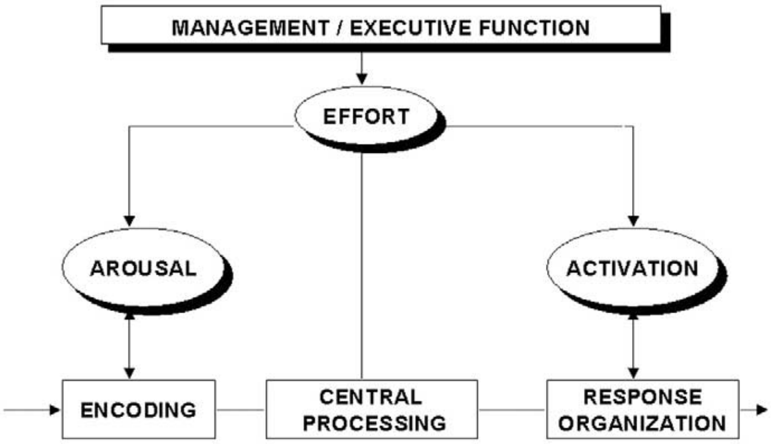


Figure 3.1 The Cognitive-Energetic Model (CEM).

The CEM includes three level of information processing. The first level is the executive control system. The second level contains three energetic states, including arousal, effort, and activation. The third level includes the encoding stage, a central stage for memory and a motor stage.

Note. The figure was adapted from Sergeant (2005).

3.3.1.2 Prediction of the manifestations of waiting difficulties in ADHD according to CEM

The CEM suggests that ADHD is related to defects at all three levels, in particular the energetic states. Individuals with ADHD have difficulty adjusting their effort, arousal or activation pools to meet environmental demands. According to the CEM model, waiting difficulties may arise because of dysregulation of the physiological states to meet requirements. During waiting, individuals with ADHD may exhibit altered level of arousal and activation compared to control subjects, in particular when a period of delay is imposed. Moreover, individuals with ADHD would exhibit insufficient effort and motivation to complete waiting tasks.

3.3.1.3 Evidence for energetic dysfunction in ADHD

Previous findings of elevated levels of behavioural activity in ADHD provide preliminary evidence for their altered energetic states. Compared to controls, individuals with ADHD generally exhibit higher level of motor activity even when sleeping (Konofal, Lecendreux, Bouvard, & Mouren-Simeoni, 2001; Macneil et al., 2011; Silvestri et al., 2009). Also they make more impulsive responses in both reward and punishment conditions in go/no go tasks (Gomez, 2003). Furthermore, deficits of response inhibition in a low incentive condition were normalised in conditions with higher incentives (Liddle et al., 2011; Slusarek, Velling, Bunk, & Eggers, 2001), suggesting that impulsive responses in ADHD were modulated by a generalised effort/motivation effect.

The CEM predicts that patients with ADHD will experience difficulties in any situation that requires them to adjust energetic states, especially those tasks with extremely slow and fast event rate. However, empirical studies have inconsistent findings. Scheres, Oosterlaan and Sergeant (2001) found that individuals with ADHD performed more poorly (i.e. slower in response time and greater in response variability) than controls on the task with slow event rate only. However, Metin and colleagues systematically reviewed the effects of event rate on go/no go tasks in ADHD. The authors demonstrated significant group differences in both tasks with fast and slow event rates. Moreover, fast and slow event rates have differential effects on the performance of ADHD: the ADHD group responded slowly in tasks with slow event rates and made more commission errors on tasks with fast event rates. But there was no group difference in terms of response variability (Metin, Roeyers, Wiersema, van der Meere, & Sonuga-Barke, 2012). The CEM model cannot readily explain the lack of event rate effect on reaction time variability for this meta-analysis study.

3.3.2 ADHD as a disorder of delay discounting

3.3.2.1 Model description

Delay discounting models denote that the subjective value of a delayed reward declines as a function of the delay preceding its delivery. Evaluation of delay discounting usually includes two choices - a smaller but immediate reward (SS) and a larger but delayed or later reward (LL). Opting for the SS has been defined as an impulsive choice because it will result in less profit in the future, whereas choosing LL has been referred to as self-control (Winstanley, Eagle, & Robbins, 2006). Behavioural studies consistently demonstrated a hyperbolic relationship between the subjective value of a reward and the delay to its delivery (Ainslie, 1975; Broos et al., 2012; Ho, Mobini, Chiang, Bradshaw, & Szabadi, 1999). The hyperbolic function (e.g. Figure 3.2) can derive subjective-specific discounting parameters which can be used to evaluate how individuals discount the value of a delayed reward (Mazur & Biondi, 2009; Peters & Büchel, 2010). The LL is normally preferred over the SS when the delay of LL is short. However, this tendency of LL reduces with the increase of the delay to its delivery. When the delay of LL increases to some degree it would be judged as considerably longer than the delay of SS. By this time individual may shift their preference from LL to SS. Importantly, Individuals with ADHD discount the value of a delayed reward much quickly than controls (Scheres, Tontsch, Thoeny, & Kaczkurkin, 2010).

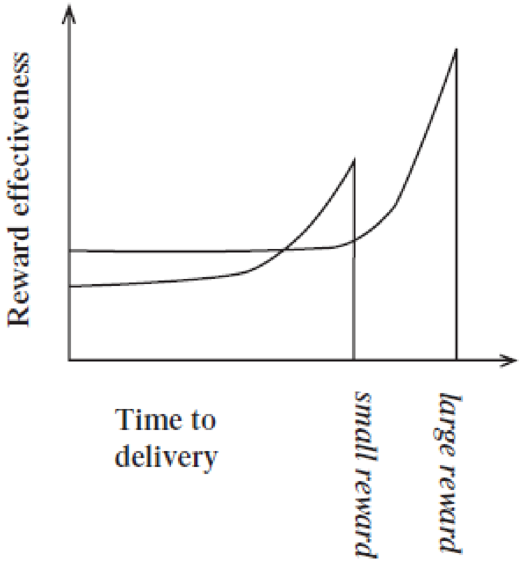


Figure 3.2 An example of delay discounting models for choice preference.

Reward preference predicted by hyperbolic discounting function. The larger (LL) reward is preferred over the smaller (SS) reward when the delay to its delivery is short (towards the left of the graph). This tendency to choose LL will switch as by the time when the delay of SS is judged as considerably shorter than the delay of LL.

Note. The figure was adapted from Ainslie, 1975.

3.3.2.2 Prediction of waiting difficulty in ADHD with delay discounting paradigm

Delay discounting paradigms focus on the decision making processes between rewards magnitude and delay duration. It is predicted that individuals with ADHD will show preference of SS over LL compared to controls as a consequence of impulsive choice because choosing SS will cause less profit in the long term. The model does not make specific predictions to the behaviours or emotions expressed during waiting in this clinical group.

3.3.2.3 Evidence for delay discounting in ADHD

Delay discounting can be assessed using single-choice paradigms (i.e., reward magnitudes and delay durations are fixed across trials) and more sophisticated paradigms (i.e., reward magnitudes and delay durations vary across trials in order to derive the function between subjective value of rewards and the pre-reward delays). Several research lines have consistently demonstrated a greater preference for SS over LL in ADHD in both real and hypothetical delay tasks (Barkley, Edwards, Laneri, Fletcher, & Metevia, 2001; Bitsakou et al., 2009; Marco et al., 2009; Scheres et al., 2013; Scheres, Tontsch, et al., 2010), despite the negative results (Scheres et al., 2006). The tendency to forego LL in favour of SS has been specifically associated with ADHD combined and hyperactive/impulsive presentations but not inattentive presentation (Scheres, Lee, & Sumiya, 2008; Scheres, Tontsch, et al., 2010).

3.3.3 The delay aversion model of ADHD

3.3.3.1 Model description

The delay aversion model proposes that ADHD reflects an altered motivational style that drives individuals to escape or avoid delay rather than executive dysfunction (Sonuga-Barke, Taylor, Sembi, & Smith, 1992). It agrees with the delay discounting model that individuals with ADHD experience alterations in brain dopaminergic reward system and deficits in signalling delayed outcomes which cause them to discount delayed rewards to a greater extent than normal. Moreover, the delay aversion model suggests that individuals with ADHD may experience negative emotional reaction during a period of delay because of failures to effectively engage in delay-rich environments. Over time a generalised feeling of aversion towards a period of delay develops, which in term leads to maladaptive behaviours (Sonuga-Barke, 2002). When there is a chance to reduce the delay, individuals with ADHD would take a non- or less delayed option. By contrast, when the delayed period is imposed and fixed that escape or avoidance of waiting is not possible, they would express elevated level of activity, possibly for the purpose of decreasing subjective feeling of waiting (Bitsakou et al., 2009; Sonuga-Barke, 1994). This is illustrated in Figure 3.3.

Later, Sonuga-Barke extended the delay aversion hypothesis to a dual pathway model built on the fact that delay aversion and poor inhibitory control are independent characteristics in ADHD (Sonuga-Barke, 2002).

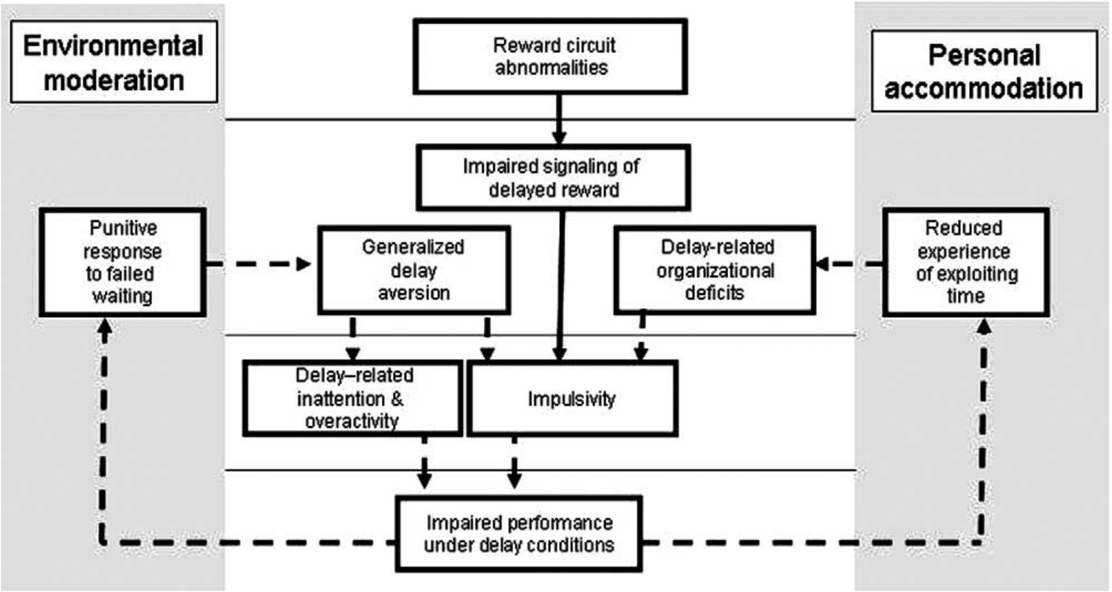


Figure 3.3 Model of the development of ADHD from delay aversion.

Note. The figure is copied from Sonuga-Barke (2005).

3.3.3.2 Prediction of waiting difficulty in ADHD with delay aversion model

Delay aversion hypothesis suggests that patients with ADHD would find waiting for a delayed outcome particularly difficult (Sonuga-Barke, 1994). They will avoid waiting if possible. If they are forced to wait or imposed a period of delay, they may become frustrated, display inattentive behaviours or increase levels of motor activity so that they may feel time is passing more quickly.

3.3.3.3 Evidence for delay aversion hypothesis in ADHD

Many individuals with ADHD act on a momentary basis without taking a long-term perspective. This behavioural pattern has been consistently demonstrated in tasks with delay discounting paradigms. Individuals with ADHD are more likely to choose immediate rewards even if they are aware the choices may not be rational. Notably, the preference for immediate rewards emerges only when reducing overall delay is possible. If the selection of an immediate reward does not reduce the total time engaged in the experimental task, individuals with ADHD are able to wait for longer rewards (Marco et al., 2009; Sonuga-Barke, Williams, Hall, & Saxton, 1996). This suggests that individuals with ADHD are not unable to wait but only try to avoid the delay of an outcome. Furthermore, delay aversion, temporal processing and inhibition deficits have been demonstrated to be independent components co-existing in ADHD (Solanto et al., 2001; Sonuga-Barke, Bitsakou, & Thompson, 2010), supporting the hypothesis of dual pathway model.

Neuroimaging findings suggest that ADHD is associated with altered ventral striatal dopaminergic regulation during reward processing (Sagvolden, Johansen, Aase, & Russell, 2005; Tripp & Wickens, 2008, 2009). Adults with ADHD showed reduced function in the brain reward pathway (midbrain and nucleus accumbens), with dopamine correlates closely related to the self-ratings of motivational traits (Volkow et al., 2011). In addition, research has demonstrated ADHD-related alterations in the emotional brain centre (Dalgleish, 2004) towards delayed rewards. The delays of reward appeared to evoke greater activity in dorsal caudate nucleus, amygdala and insula in adults with ADHD compared to controls (Lemiere et al., 2012; Plichta et al., 2009). Consistently, Wilbertz et al., (2013) found a positive correlation between the neural activity in inferior temporal cortex and right amygdala and the length of delay within the ADHD group. These studies support the delayed period as a state that induces negative affect in ADHD.

3.3.4 The default mode interference (DMI) hypothesis of ADHD

3.3.4.1 Model description

The DMI hypothesise suggests that the intrusion of DMN activity during a goal-directed task is the major source of attentional lapses in ADHD (Sonuga-Barke & Castellanos, 2007). Specifically, DMN activity will be initially attenuated in the transition from resting to the onset of goal-directed task but re-emerge over time (as discussed in the preceding chapter). If DMN activity goes above a hypothetical threshold it will compete with the task-specific neural activity and cause periodic attention lapses. See Figure 3.4.

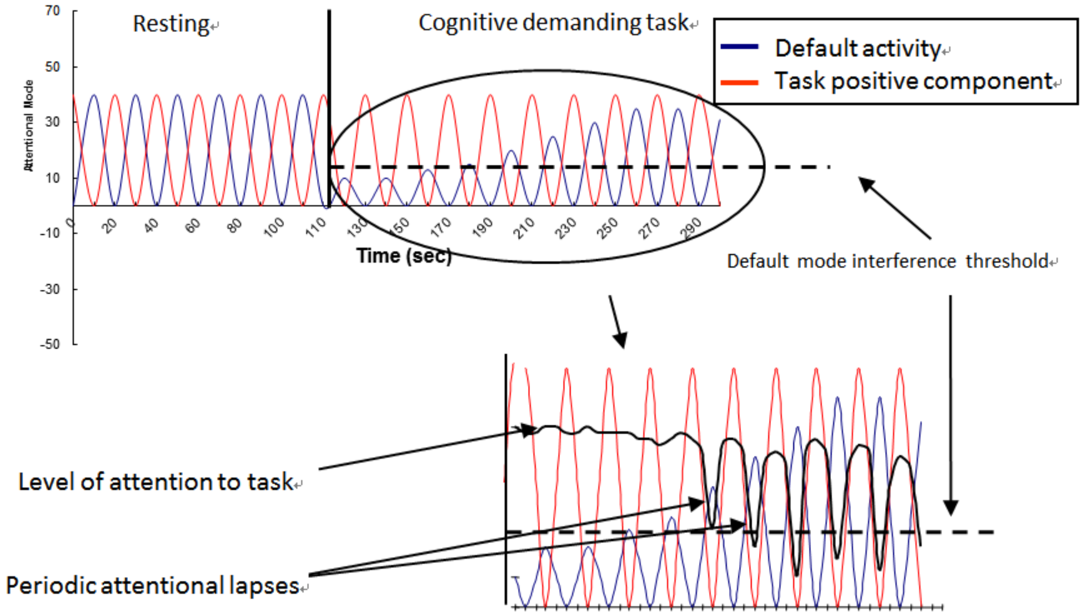


Figure 3.4 Default mode activity intrusions in ADHD.

The default-mode interference hypothesis proposes that the default activity is initially attenuated during a cognitive demanding task (above right) compared to rest (above left). This activity re-emerges over time. If it exceeds a hypothetical threshold during task performance, lapses in attention would occur.

Note. The picture is modified from Sonuga-Barke & Castellanos (2007).

3.3.4.2 Prediction of manifestations of waiting difficulty in ADHD with DMI model

The DMI model itself leads to several testable predictions: first, in normal circumstance there will be cognitive task-induced attenuation in the transition from rest to task performance. Second, the task induced attenuation of DMN would occur regardless of the task content, as long as the general requirements such as engagement of sustained attention and cognitive loads are fulfilled. Third, a posited threshold may exist. When DMN activity is over this threshold, interferences of task performance will occur, while below which there will be no apparent impairment. Fourth, the degree of task-induced attenuation will be influenced by both individual differences and state- or task-related factors such as fatigue, boredom or motivation. Fifth, when the default activity exceeds the posited threshold, individuals would experience intrusions of spontaneous thoughts and increased response variability. Finally, thought intrusions or attention lapses would occur at a slow pace, around .01 to .1 Hz, which synchronises with DMN activity.

It is not clear yet how individuals modulate DMN activity during waiting. Although both resting and waiting involve a period of idle time with little cognitive demands, waiting has a particular goal. The goal-directed nature may differentiate the waiting brain from the resting brain and thus generating attenuation of DMN activity. During waiting individuals with ADHD may fail to attenuate DMN activity effectively. In addition, the intrusions of DMN activity during waiting may involve increased task-independent or introspective thoughts because DMN activity is associated with self-referential thoughts and mind wandering.

3.3.4.3 Evidence for default mode interference hypothesis in ADHD

Transient but frequent lapses of attention, as well as moment-to-moment variability and inconsistency of performance, are all common characteristics of ADHD. Researches regarding to DMN abnormalities in ADHD have been discussed in Chapter 1 (see *1.4 Resting brain network dysfunctions in ADHD*). Briefly individuals with ADHD exhibited altered resting functional connectivity between DMN and task positive networks (Castellanos et al., 2008; McCarthy et al., 2013; Uddin et al., 2008). In addition, they failed to attenuate DMN activity effectively during the engagement of cognitive goal-directed tasks (Fair et al., 2010; Fassbender et al., 2009; Liddle et al., 2011). Helps and colleagues (2010) testified the DMI in children with ADHD using DC-EEG. The authors demonstrated that individuals with ADHD expressed less attenuation compared to healthy controls from resting to performance of an attention task. Importantly, the reduced task-induced attenuation of VLF EEG was correlated with elevated levels of response errors and response variability (Helps, et al., 2010). The result was in consisent with previous finding in healthy adults by the same research group (Helps et al., 2009), as well as a fMRI study demonstrating reduced attenuation in vmPFC during a working memory task and its correlation to increased response variability in ADHD (Fassbender et al., 2009). Moreover, task-induced attenuation of VLF EEG showed a significant correlation with inattentive symptoms of ADHD (Helps et al., 2010). There has been promising evidence supporting the DMI hypothesis. However, researchers have not explored the relationship between the modulation of DMN activity and waiting difficulties in ADHD.

3.3.5 ADHD as a disorder of decision making – a neuro-economic perspective

3.3.5.1 Model description

Sonuga-Barke and Fairchild (2012) proposed a mixed model to explain the causal pathways of ADHD from a behavioural economic perspective. This model integrates previous biological and neuropsychological findings regarding ADHD. The model focuses on three brain networks, including the DMN, dorsal and ventral fronto-striatal circuits. Each of these networks provides specific hypotheses about the decision making processes in ADHD. First, the altered functional connectivity between the core hubs of the DMN (MPFC-PCC) affects introspective processes, such as prospection. This produces disrupted sense about imagining future states, planning and goal-setting. Second, deficits in the dorsal fronto-striatal network lead to executive dysfunction and impair the ability to correctly evaluate choice options. Third, damages of the ventral fronto-striatal loop that involving dopaminergic regulation and reward processing cause disruptions to signal future rewards and stimulus-response learning. This is illustrated in Figure 3.5.

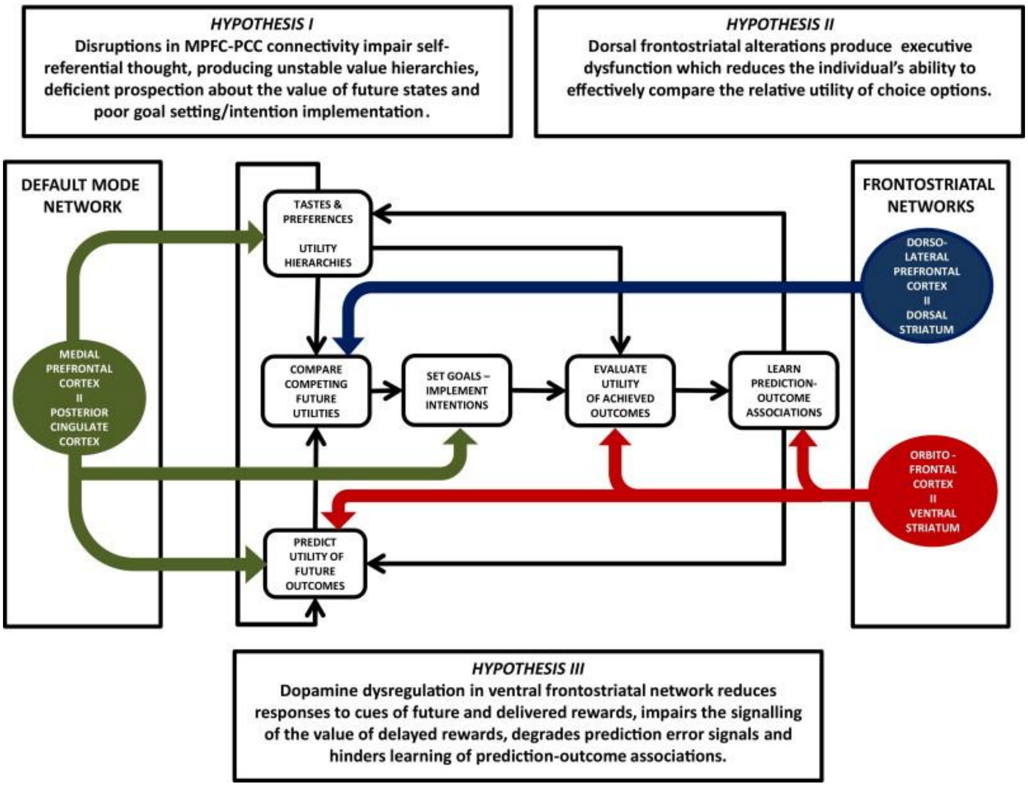


Figure 3.5 The neuroeconomic decision-making processes in ADHD.

Note. The picture was adapted from Sonuga-Barke & Fairchild (2012).

3.3.5.2 Prediction of manifestations of waiting difficulty in ADHD with the neuroeconomic model

Waiting difficulties of ADHD can be caused by deficits in each of the DMN, dorsal and ventral fronto-striatal netwoks and their interactions. Waiting difficulties may be caused by false evaluation and prediction for a future event based on individuals's past experience and current information. Deficits in farsighted decision making may also be driven by unrational or impulsive choices. When waiting individuals with ADHD may generate task-unrelated thoughts or spontaneously engaging in self-referential thinking.

3.3.5.3 Evidence supporting the neuroeconomic model of ADHD

Different lines of researches have demonstrated abnormal resting functional connectivity within the DMN in ADHD (Castellanos et al., 2008; Uddin et al., 2008), as well as the involvement of DMN in episodic prospection (Addis et al., 2007; Buckner & Carroll, 2007). However, researchers have not directly investigated the DMN dysfunction in ADHD and its relation with waiting and self-referential thoughts, in particular prospective cognition.

There is convergent evidence from neuroimaging studies and neuropsychological studies showing ADHD-related abnormalities in dorsolateral fronto-striatal circuits during tasks involving sustained attention, working memory and executive function (Ongur et al., 2010; Wolf et al., 2009), as well as reduced ventral-striatal activity during reward processing (Durston, Belle, & Zeeuw, 2011; Plichta et al., 2009). Importantly, some of these deficits can be improved by stimulant medication (Rubia et al., 2014; Rubia, Halari, Cubillo, et al., 2009).

The neuroeconomic model encompasses systems regulating intrinsic thoughts, external inputs and motivation and the interplay among these processes. It provides a comprehensive and integrative framework that can be applied on the search of psychopathophysiology pathways of ADHD (Banaschewski et al., 2005).

3.3.6 A summary of theoretic models of waiting difficulties in ADHD

Although not all models attempt to describe the waiting difficulties in ADHD, this chapter attempt to formulate predictions of the behavioural manifestations of waiting difficulties in ADHD. See Table 3.1 for a summary.

Table 3.1 Characteristics of waiting responses from different models of ADHD.

Models	**Theory Overview**	**Predictions of waiting difficulties**
ADHD as state dysregulation.	ADHD results from a context-dependent failure to regulate the level of effort, activation or arousal states to meet environmental requirements.	When waiting individuals with ADHD may exhibit altered levels of arousal, as well as insufficient effort and motivation to complete waiting tasks.
ADHD as delay discounting.	ADHD devalues the delayed reward more quickly than the controls.	Individuals with ADHD would prefer reward immediacy over reward magnitude and show a tendency towards non-waiting options.
ADHD as delay aversion.	ADHD results from a motivational desire to escape or avoid a period of delay and the negative affection caused by a delayed outcome.	Individuals with ADHD develop negative affective responses to waiting. They would avoid or escape a period of delay, or display task independent behaviours to reduce the negative feeling if a delay is unavoidable.
ADHD as default-mode interference.	ADHD results from the intrusion of low-frequency spontaneous oscillations into active state.	Waiting difficulties occur when failing to attenuate the resting brain activity to an appropriate degree during delay.
ADHD as an uneconomic decision-making process.	ADHD was an expression of compromised integration among default-mode function, executive function and stimulus-response learning.	Individuals with ADHD may fail to attenuate the DMN activity during waiting, misjudge the goal of waiting and display increased self-referential thoughts.

3.4 Chapter summary

Difficulty waiting is one of the most significant behavioural characteristics of ADHD. The causal pathways of waiting problems and behavioural manifestations can vary across different situations. This chapter reviews existing theoretical models of ADHD, formulate waiting difficulties in ADHD and develop testable predictions. Difficulty waiting can be caused by state dysregulation, delayed reward discounting, delay aversion, persisting resting brain activity and suboptimal decision making for future outcomes.

The DMI model suggests that persisting DMN activity during a goal-directed task constrains cognitive task performance. It is not clear if the DMN activity is also attenuated during waiting, and whether this rest-to-wait attenuation relates to the waiting difficulties in ADHD. To address this question it is essential to examine the DMN activity during waiting, and to compare the waiting DMN activity with other states, such as resting and working on a cognitive task.

3.5 The aims of the thesis

The main purpose of the thesis is to explore how people modulate their resting brain activity during waiting using DC-EEG. Furthermore, it aims to investigate whether individuals with ADHD display atypical brain activity while waiting and whether such atypical brain activity is associated with their waiting difficulties. To achieve these aims, three independent DC-EEG studies were performed. The first two studies explored the rest-to-wait modulation of VLF EEG in healthy adults (**Chapter 4**) and in children and adolescents with ADHD and their age-matched controls (**Chapter 5**). The predictions included the following:

i) Previous findings of rest-to-work attenuation would be replicated (Helps et al., 2010; Helps et al., 2009; Helps et al., 2008).
ii) VLF EEG would be attenuated from resting to waiting in healthy participants.
iii) Compared to controls, individuals with ADHD would display less attenuation when working on a cognitive task and during waiting.
iv) The rest-to-wait attenuation of VLF EEG would be localised to regions within the DMN.
v) The waiting VLF EEG would be associated with traits of delay aversion and delay discounting.

Furthermore, DMN involves self-referential processes such as prospection. Episodic future thinking appears to reduce delay reward discounting through an enhancement of prefrontal-temporal interactions (Peters & Büchel, 2010). Thus, the third empirical study extended the investigation to explore EEG correlates of prospective cognition within core DMN regions and their associations with impulsive choices (**Chapter 6**). It was predicted that thinking about future would induce attenuation of EEG activity in medial prefrontal region because of its goal-directed nature and increases in medial temporal areas because the engagement of memory loads. Moreover, prospective cognition would increase EEG coherence between the prefrontal and temporal areas comparing to resting and waiting states. Finally, **Chapter 7** provided a summary of findings and a general discussion for study implications.

Chapter 4 Very low frequency neural oscillations during resting, waiting and working states

4.1 Introduction

As reviewed in **Chapter 1**, the default mode network (DMN) is one of the resting brain networks, characterised by spontaneous neural oscillations in very low frequency (VLF) of around 0.1 Hz or less. The VLF neural oscillations within the DMN attenuates during the transition from a resting state to the performance of a number of cognitive, goal-directed tasks (Raichle et al., 2001), with the exception of those involving self-referential processing (Addis et al., 2007; Buckner & Carroll, 2007). Given the fact that dominant neuropsychological and neuroimaging studies have focused on cognitive processes provoked by incoming sensory information (Shulman, Corbetta, et al., 1997), goal-directed tasks have typically been paralleled to effortful laboratory based paradigms which require individuals to focus on and process externally oriented, attention demanding stimuli. However, other types of goal-directed activity with little or no cognitive input involved, such as waiting for a delayed outcome may also involve cognitive information processing. Nevertheless, it is unclear whether the transition from resting to waiting state would provoke the attenuation of the DMN.

Exploring how the DMN functions during waiting is important because waiting and resting states share many common features but they are not identical processes. On one hand, both waiting and resting involve a period of idle time with little or no cognitive stimuli involved. On the other hands, waiting seems to differ from resting in certain perspectives. In daily life we often wait for a result or reward (the goal or outcome), but rest following exerted effort and the completion of a goal-directed task. In this sense, “waiting time” can be seen as reframed “resting time” and vice versa - the same event experienced in a different way by their antecedents and consequences. It is possible that reframing this idle time from a passive and recuperative (i.e. resting) to a more active and motivated goal-directed perspective (i.e. waiting), induces the change of activity within the DMN. Moreover, in everyday life there are occasions when an individual is presented with the choice to wait for a future goal or reward, or alternatively, to forgo that delayed reward and to continue with the original activities. In other occasions waiting may be imposed on an individual, during which time an individual is forced to wait so that he/she has to endure the delay. It is unclear whether different types of waiting circumstances induce different level of attenuation in terms of VLF neural oscillations within the DMN.

This study investigated these issues by comparing the level of rest-to-wait attenuation of VLF EEG to that seen in the transition from resting to working on a cognitive task. Previous research by Help and colleagues identified a robust resting state VLF EEG network with high spatial stability and temporal reliability (Helps et al., 2008). The slow neural oscillations within the VLF EEG network significantly attenuated following the transition from resting to cognitive task performance (Broyd et al., 2011; Helps et al., 2010; Helps et al., 2009), which has also been demonstrated in DMN blood oxygen level dependent (BOLD) signals measured using functional magnetic resonance imaging (fMRI) (Fassbender et al., 2009). Moreover, the intra-cranial sources of VLF EEG network showed a significant similarity with the regions of the DMN identified using fMRI (Broyd et al., 2011). This study built on previous VLF EEG studies and used direct current coupled electroencephalography (DC-EEG) as a vehicle to explore the spontaneous neural oscillations during resting, waiting and working states. Compared to fMRI, EEG has excellent temporal resolution and offers a more direct measure of neural activity than BOLD signals (Demanuele et al., 2013), which make it a great platform for the investigation.

Given the fact that individuals with Attention-Deficit/Hyperactivity Disorder (ADHD) display reduced attenuation of DMN BOLD signals and VLF EEG during task performance (Fassbender et al., 2009; Helps et al., 2010; Liddle et al., 2011), and they often find goal-directed tasks involving waiting for delayed rewards difficult, this study also examined the potential impact of ADHD symptoms on the goal-directed activity-induced attenuation of VLF EEG during periods of waiting.

4.1.1 Study aims

This study had three specific aims. First, it attempted to replicate the previous findings that VLF EEG would attenuate following the transition from rest to performance on a cognitive goal-directed task (Broyd et al., 2011; Helps et al., 2010; Helps et al., 2009). Second, it examined whether goal-directed waiting induces attenuation of resting state VLF EEG in a similar manner to the cognitive goal-directed task. For the purpose of exploring the influence of self-determination and motivation in waiting, participants were presented with two different types of waiting conditions: a “forced-to-wait (F-WAIT)” condition – where participants were imposed to a period of delay and a “choose-to-wait (C-WAIT)” condition – where participants were given a choice to wait for a reward (see *4.2.3 Procedure* section for details). Third, it aimed to examine the influence of ADHD symptoms on these effects.

4.1.2 Predictions

It was predicted that: (i) VLF EEG power would attenuate during the transition from resting to a cognitive goal-directed task in consistent with previous studies; (ii) resting state VLF EEG power would attenuate during waiting tasks in a similar way to that seen in the cognitive task (especially when the waiting event is incentivised and freely chosen); (iii) the C-WAIT condition would induce higher level of attenuation compared to the F-WAIT condition because it is more goal-oriented when participants decide for themselves whether or not to wait compared to passively waiting; and (iv) participants with high self-ratings of ADHD symptoms would show reduced attenuation from resting to both cognitive and non-cognitive waiting conditions (F-WAIT and C-WAIT) in comparison to participants with low self-ratings of ADHD symptoms.

4.2 Methods

This study was approved by the School of Psychology Ethics Committee, University of Southampton.

4.2.1 Participants

287 undergraduate students from the University of Southampton were screened on the basis of their self-ratings of ADHD symptoms using the *Current Symptoms Scale* (CSS, Barkley & Murphy, 1998). Students who scored above the top 20th percentile (i.e. high ADHD symptom group, reporting six or more ADHD symptoms) and those below the bottom 20th percentile (i.e. low ADHD symptom group, reporting zero or one symptom) were invited to take part in this study. Participants who reported a diagnosis of neurological disorders, a history of brain injury, use of any psychotropic substance more than twice in the last six months, or problems of substance abuse or dependence were excluded from the study. Participants were asked to refrain from consuming caffeine or nicotine for at least two hours prior to testing. One participant refused to complete the C-WAIT condition and was excluded from further analysis. 21 participants with high self-ratings of ADHD symptoms and 19 participants with low self-ratings of ADHD symptoms (aged 18 to 43 years) completed all EEG sessions. Previous EEG research has identified significantly reduced attenuation of VLF EEG from resting to cognitive task performance in ADHD cases compared to the control group, with a sample size of 16 in each group (Help et al., 2010; effect size: 0.84, estimated sample size ≧ 19, power = 0.80, one-tailed test and alpha = 0.05). Therefore the sample size of this study was thought to be adequate to detect group difference in waiting induced attenuation of VLF EEG. However, eight participants were further excluded because of excessive EEG artefacts even after artefact removal techniques had been applied (five from the

high ADHD symptom group and three from the low ADHD symptom group). The final comparisons were conducted with data of the remaining 32 participants (16 per group).

4.2.2 Design

This study had a within group repeated-measures design. Participants completed a single testing session. All participants were asked to complete four EEG sessions which were presented with a pseudo-randomised sequence.

4.2.3 Procedure

Participants were familiarised with the electrophysiology laboratory and EEG recording procedure before the informed consent was taken. Then they were seated in a comfortable chair in the testing room and fitted with an electrode cap. The halogen light in the testing booth was dimmed for the duration of the experiment.

The experimental sessions included one working, two resting and two types of waiting conditions. During the working conidtion (WORK) participants were requested to complete a two-choice reaction time task (2CRT). The 2CRT was separated into two blocks (T1, T2). It required participants to indicate the direction of arrows presented on the computer screen by pressing a button on a response box. Left pointing arrows required left handed button presses and right pointing arrows required right handed button presses. The presentation time of the arrow was 400ms, with an inter-stimulus interval (ISI) of 600 ms. Each block had 600 trials and the duration of the whole block was 10 minutes. Participants were instructed to focus their attention and respond as quickly and accurately as possible. The short ISI was adapted in this study to ensure that the task was simple but attentionally demanding (in this study the correct response rate was 92.88%).

In the resting condition (REST), participants were instructed to relax and focus on the fixation cross presented on the monitor for five minutes. The first resting condition (R1) occurred at the start of the experiment, while the second condition (R2) was presented after the completion of a block of 2CRT. The waiting conditions included two types of waiting circumstances. In the "force-to-wait" (F-WAIT) condition participants were instructed to wait for five minutes before the next experimental session commenced. In the "choose-to-wait" (C-WAIT) condition participants were given a choice to decide if they wanted to wait five minutes for a monetary incentive (a lottery ticket for £20 prize) or to opt out and terminate the waiting period. The order of the different conditions was counterbalanced across participants in order to ensure as far as possible within the constraints dictated by the different waiting and resting conditions that potential order effect was controlled. Each participant was randomly assigned to one of the following four sequences: i) R1; C-WAIT; T1; R2; T2; F-WAIT, ii) R1; C-WAIT; T1; F-WAIT; T2; R2, iii) R1; T1; R2; T2; F-WAIT; C-WAIT, and iv) R1; T1; F-WAIT; T2; R2; C-WAIT. DC-EEG was continuously recorded throughout all conditions. The experiment, including EEG set up, lasted approximately 120 minutes.

4.2.4 ADHD symptom screen

The *Current Symptoms Scale (CSS)* was used to screen the level of ADHD symptoms. *CSS* contains 18 items formulated in accordance with *DSM-IV* criteria. It has two subscales: inattention and hyperactivity/impulsivity. It is scored using a four-point Likert scale (never, occasionally, often, and very often). Its psychometric properties have been validated: construct validity .35-.85; 4 week test-retest reliability .78 - .86 (Collett, Ohan, & Myers, 2003). To reduce the potential self-report bias, two sets of *CSS* data were collected. The first set was from the participants themselves and the second was collected using an adapted version from a significant other, i.e. spouse, friends or relatives (Barkley & Murphy, 1998). For example, "I talk excessively" in the former became "He/she talks excessively" in the latter. The second version was completed for all but four participants.

4.2.5 Electrophysiological Acquisition

The continuous scalp electroencephalogram was recorded using a Neuroscan Synamps^2 70 channel EEG system at 500 Hz via 24 bit A/D converter with DC procedure, combined with a 70 Hz low-pass filter. Participants were fitted with an electrode cap with 66 equidistant electrodes with a nose reference (Easycap; Hersching, Germany). The electro-oculogram (EOG) was recorded using Ag/AgCl electrodes above and below the left and right eye. Impedance was kept below 5 kΩ for all electrodes.

4.2.6 EEG data processing

EEG signals from the first 55 electrodes were used for analysis. EEG data were processed with MATLAB (version R2010a) and re-referenced to an average reference. The linear trend caused by drift was removed using the ‘detrend’ command in MATLAB. Independent component analysis (ICA) was used to remove artefacts and ocular movements from the data. The EEG signals were then reconstructed by back-projection of all artefact-free components. Data were subjected to fast Fourier transformation (FFT). One minute Hamming windows with 20 second overlap were used. The EEG power of the VLF band (0.02–0.20 Hz) was calculated for each condition and each participant (Helps et al., 2010; Helps et al., 2008; Penttonen & Buzsáki, 2003). The spatial location of the VLF EEG network was established using only the data of the low ADHD symptom group because it was hypothesised that participants in the high ADHD symptom group may show atypical patterns of VLF EEG activity. The group mean (N=16) of rest-to-task power attenuation (calculated by subtracting the VLF EEG power of the task condition from the power of the rest condition) for each electrode was calculated. The first 18 electrodes exhibiting the most prominent rest-to-work attenuation, i.e. the first third of the 55 electrodes with the highest attenuation of VLF EEG power from resting to the performance of the 2CRT task were considered for the purpose of this study as being within the VLF EEG network, while all the others were considered to fall outside the VLF EEG network. Subsequently, the average of VLF EEG power across the electrodes within the VLF EEG network was calculated for each participant and for each condition respectively. Similarly, the mean power across electrodes outside the network was calculated. The value of EEG power was then natural log transformed for further analysis because it was not normally distributed (Gasser, Bächer, & Möcks, 1982).

4.2.7 Data analysis

Given the similarity of the instructions and strength of VLF EEG power, data from T1 and T2, and R1 and R2 were averaged to increase the reliability of the measurement and to further reduce the impact of potential order effects. Data from the F-WAIT and C-WAIT conditions were analysed separately given their different characteristics. This produced four levels of the Condition factor: REST: (R1+R2)/2; WORK: (T1+T2)/2; F-WAIT and C-WAIT. First we examined the spatial localisation of resting state VLF EEG power, as well as the spatial distribution of goal-directed activity-induced attenuation of VLF EEG power (the level of attenuation was calculated by subtracting the VLF EEG power in the WORK, F-WAIT, and C-WAIT conditions from the REST condition). In order to address questions relating to the size of the attenuation for the whole sample, two-way repeated measures ANOVAs were run with the VLF EEG power as the dependent variable, Network (within or outside) and Condition (REST versus WORK, REST versus F-WAIT, REST versus C-WAIT respectively) as the within-subject factors. The difference in VLF EEG power between resting state and goal-directed activities for within and outside the network was calculated using Cohen's d. Finally, Group (high and low ADHD symptom group) was added into the ANOVA model as an independent variable in order to examine the influence of ADHD symptoms on spontaneous VLF EEG.

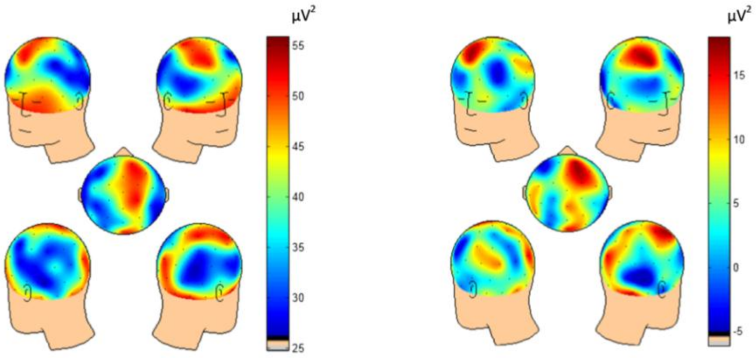
4.3 Results

4.3.1 Spatial distribution of VLF EEG power at rest and cognitive task-induced attenuation

Figure 4.1 (a) shows the spatial localisation of VLF EEG power at resting state. Visual inspection for the resting VLF EEG power found maximal activity in the frontal pole region extending to the centroparietal area. Figure 4.1 (b) shows the spatial distribution of the rest-to-work attenuation – i.e. the VLF EEG power difference from resting to 2CRT task performance. The rest-to-work attenuation of VLF EEG was most evident in the midline regions, stretching from the frontocentral area to the parietal and temporal regions.

4.3.2 Does ‘goal-directed waiting’ attenuate resting state VLF EEG power?

The scalp distributions of rest-to-wait attenuation of VLF EEG power are shown in Figure 4.2. The C-WAIT-induced attenuation of VLF EEG power had a similar spatial profile to the rest-to-work attenuation, while the F-WAIT-induced attenuation was more centralised and displayed maximal power in the frontocentral and centroparietal regions.

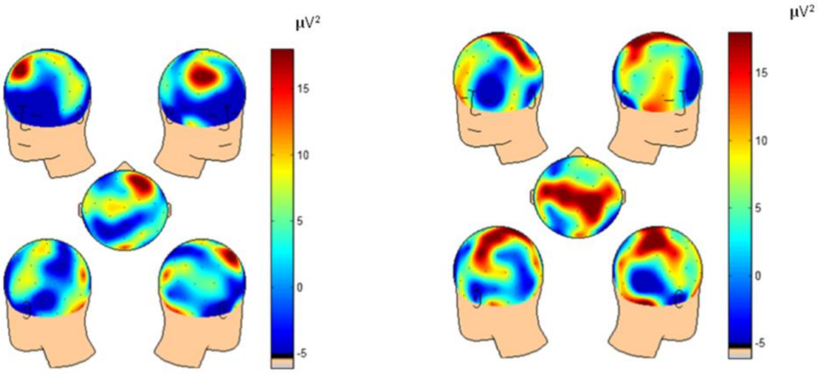


(a) Resting state

(b) WORK induced attenaution

Figure 4.1 Scalp distributions of very low frequency EEG (a) at rest and (b) rest-to-work attenuation.

The attenuation was calculated by subtracting the VLF EEG power during the two-choice reaction time task from resting state. Red represents higher level of attenuation from resting to task performance.



(a) F-WAIT induced attenuation

(b) C-WAIT induced attenaution

Figure 4.2 Scalp distributions of rest-to-wait attenuation of very low frequency EEG.

(a) Rest-to-F-WAIT attenuation and (b) Rest-to-C-WAIT attenuation. The value of attenuation in very low frequency EEG power was calculated by subtracting the power of waiting conditions from the resting condition. Red represents higher level of attenuation from resting to task performance.

Table 4.1 presents the VLF EEG power at rest and during each of the three goal-directed conditions for the whole sample. Two-way repeated measure ANOVAs showed significant main effects of Network and interactions between Condition and Network across the comparisons of resting and the three goal-directed activities (p <.01). In each case there was substantial attenuation of VLF EEG power. The goal-directed activity-induced attenuation was greater *within* the VLF EEG network compared to the one that fell *outside* the network across all conditions. Within the VLF EEG network, the cognitive task induced the greatest attenuation of resting VLF EEG power, closely followed by the C-WAIT. The difference between REST and F-WAIT did not reach statistical significance.

Table 4.1 Differences in low frequency EEG power (μV^2) between resting and goal-directed activities.

Within network Mean (SD)			Outside network Mean (SD)			Main effect (*Condition*)		Main effect (*Network*)		*C* x *N*	
						F	*p*	*F*	*P*	*F*	*p*
REST	**WORK**	**Cohen's *d***	**REST**	**WORK**	**Cohen's *d***						
3.74 (0.35)	3.47 (0.31)	0.82	3.57 (0.30)	3.52 (0.28)	0.17	8.96	.005	8.94	.005	30.62	<.001
	C-WAIT	**Cohen's *d***		**C-WAIT**	**Cohen's *d***						
	3.41 (0.56)	0.72		3.39 (0.48)	0.44	11.51	.002	12.15	.001	15.44	<.001
	F-WAIT	**Cohen's *d***		**F-WAIT**	**Cohen's *d***						
	3.60 (0.49)	0.34		3.56 (0.42)	0.02	1.01	.323	13.59	.001	8.45	.007

Notes: WORK: the two-choice reaction time task; C-WAIT: choose-to-wait task; F-WAIT: forced-to-wait task; C x N: Condition and Network interaction. Two-way repeated measures ANOVAs with Condition and Network as the within-subject factors were performed for REST versus WORK, REST versus C-WAIT, and REST versus F-WAIT respectively. Power value was natural log-transformed.

4.3.3 Are ADHD symptoms related to goal-directed activity-induced attenuation of VLF EEG?

Table 4.2 provides the demographic information, questionnaire ratings of participants' ADHD symptoms and performance on the 2CRT. The two groups were comparable in terms of age and gender. The high ADHD group made more errors on the 2CRT ($t(30) = 2.70$, $p = .01$) compared to the low ADHD group. There was no group difference in reaction time and response variability ($t(30) < 1.69$, $p > .05$). As expected, the high ADHD symptom group reported significantly higher scores in terms of inattention and hyperactivity/impulsivity than the low ADHD symptom group. The ratings from close friends/relatives of participants confirmed a significant group difference in the inattentive subscale and total scores. Ratings of hyperactivity and impulsivity symptoms for the high ADHD symptom group showed a non-significant trend. Moderate correlations were found between self and friend/relative reports in total scores and inattentive symptoms. A three-way repeated measure ANOVA showed significant differences in Condition ($F(3, 28) = 6.49$, $p = .002$) and Network ($F(1, 30) = 4.24$, $p = .048$), but no effect of ADHD group status. There was not Group interactions with the other factors (all $p > .1$).

Table 4.2 Group characteristics and ratings of ADHD symptoms.

	High ADHD group *N*= 16 Mean (SD)	Low ADHD group *N*= 16 Mean (SD)
Age (years)	22.75 (3.84)	21.31(6.06)
Number (%) males	4 (25%)	4 (25%)
Current Symptoms Scale (CSS)		
Self-report		
Total score	28.13 (6.26)	7.75 (3.09)**
Inattention	15.63 (3.61)	4.25 (1.92)**
Hyperactivity/ impulsivity	12.50 (3.33)	3.50 (1.83)**
Friend or relative report		
Total score	13.85 (9.42)	8.27 (6.91)*
Inattention	7.31 (5.45)	3.73 (3.69)*
Hyperactivity/ impulsivity	6.54 (5.03)	4.53 (4.19)
Two choice reaction time task (2CRT)		
Total Errors	52.63 (26.84)	32.88 (11.78)*
Mean RT (ms)	325.11 (34.79)	307.97 (21.07)
SD of RT	71.93 (22.13)	61.08 (14.29)

Notes: *p<.05, **p<.001; High ADHD symptom group: Adult participants scored six or more self-rated inattentive or hyperactive/impulsive symptoms. Low ADHD symptom group: adult participants scored just one or zero self-rated symptoms.

4.4 Discussion

Previous studies have demonstrated that resting VLF oscillations attenuate during the transition from resting to goal-directed cognitive task performance, e.g. with fMRI (Fassbender et al., 2009) and DC-EEG (Helps et al., 2009). This study explored whether goal-directed waiting conditions (where the processing of externally oriented, attention demanding stimuli is absent) provoke the attenuation of resting VLF EEG power in a similar way as the cognitive tasks do. There were four findings of particular note. First, consistent with previous studies using DC-EEG (Broyd et al., 2011; Helps et al., 2009), the finding of rest-to-work attenuation of VLF EEG power was replicated. Second, significant C-WAIT-induced attenuation of resting VLF EEG power was observed, with a spatial distribution similar to the attenuation found when performing the 2CRT task. Third, the attenuation of resting VLF EEG power differed as a function on waiting condition type: the attenuation was greater when waiting was freely chosen and incentivised (i.e. the C-WAIT) compared to when participants were forced to wait (i.e. the F-WAIT). Fourth, contrary to the prediction, the high and low ADHD symptom groups did not differ in terms of goal-directed activity-induced attenuation of resting VLF EEG power.

4.4.1 The impact of cognitive reframing from resting to waiting

This study provided the first evidence of significant attenuation of VLF EEG in the transition from resting to a free-chosen waiting event. This raises some important questions regarding the nature of resting and waiting and their impact on VLF neural oscillations. Since the participants were idle and not working on external information processing during both the resting and waiting conditions, why then were the neural signatures for the REST and the C-WAIT condition so different given the prima facie similarity of these states? It appeared that the instruction to wait reframed the experience of resting, changed the purpose of this period of idle time, and altered the pattern of VLF oscillations in a similar way to a cognitive goal-directed task did. In line with this argument, the fMRI study conducted by Benjamin et al. (2010) demonstrated the influence of cognitive reframing on the DMN activity. They showed that in comparison with relaxed resting state, giving participants specific instructions during resting – i.e. to attend or ignore the scanner background noise – increased neural activity in the dorsal medial prefrontal cortex, a core component of the DMN, even with the absence of increase in cognitive load (Benjamin et al., 2010). In addition, the VLF oscillations within the DMN have shown different activation patterns in various stimulus-free conditions when the contents of thoughts were manipulated. For instance, the DMN is more active during prospective planning than alphabet- or text-recitation (Preminger, Harmelech, & Malach, 2011). Taking into account the results of the current study it appears that cognitive reframing of the resting period has the power to alter brain processes and change the engagement to task-related processes.

4.4.2 Potential factors which influence the attenuation of very low frequency EEG

The attenuation induced during the C-WAIT condition was similar to the one induced during the cognitive task (WORK). This raises fundamental questions about the necessary task characteristics which are sufficient to induce the attenuation of resting VLF oscillations. Clearly the requirement for information processing of external stimuli, of the sort used in the cognitive task in this study, is not a necessary component since the C-WAIT had little or no cognitive load but still produced substantial attenuation. If the attenuation of VLF EEG is not caused just by increased cognitive load, what is the necessary condition for the attenuation? Considering the characteristics shared by the cognitive goal-directed task and the C-WAIT condition in the current study, there are a number of possibilities: i) goal-directedness, ii) a motivated state, and ii) effortful attention to external stimuli or incentives.

4.4.2.1 The impact of goal-directedness

The goal-directed nature of tasks may be crucial for the attenuation of resting VLF EEG power. In the early theoretical formulations relating to the DMN, it was postulated that attenuation of resting neural activity occurred during goal-directed behaviours without reference to the cognitive character of the tasks (Raichle et al., 2001). Goal-directedness refers to an intrinsic drive to achieve a specific objective or desired result (Solway & Botvinick, 2012). In this sense, both the 2CRT and waiting tasks could be considered goal-directed even if external stimulation and information processing demands were minimal as was the case in the waiting tasks. In this regard, it was also interesting that significant attenuation of VLF EEG power was observed during the C-WAIT condition but not during the F-WAIT condition. One possible explanation for this result could be that the F-WAIT condition was perceived by the participants as an intermediate session in-between the other conditions, and as a result it was less goal-directed and only produced a trend towards suppression of resting VLF EEG power. However, the idea that the attenuation depends just on goal-directedness of a task cannot explain the fact that DMN activity increases during tasks involving self-referential processes, such as autobiographical memory and prospective planning, because these tasks are also goal-directed (Preminger, Harmelech, & Malach, 2011; Spreng et al., 2009).

4.4.2.2 The impact of motivational factors

The C-WAIT-induced attenuation may be accounted for by differences in motivational state. Intrinsic motivation refers to the motivation originating from “inside” the individual because of the enjoyment or interest elicited by a task itself, while extrinsic motivation relates to the presence of extrinsic positive (or negative) consequences contingent on task performance (Ryan & Deci, 2000). Our study manipulated extrinsic motivation between waiting conditions by motivating participants to choose to wait for the incentive in the C-WAIT condition, while forcing them to passively wait during the F-WAIT condition. Therefore the difference in attenuation of resting VLF EEG power between the two waiting conditions may potentially be due to the degree of extrinsic motivation in each task. However, intrinsic motivation may also contribute to the attenuation of resting VLF EEG power, as during cognitive task performance participants were asked to perform the best they could, but were not rewarded. The importance of motivational factors in DMN attenuation has been highlighted by Liddle et al. (2011), who demonstrated a significant motivational effect on the resting fMRI BOLD signals in individuals with ADHD. The authors observed a significant attenuation of DMN activity in a high incentive condition but not in a low incentive condition when participants with ADHD were off medication. In contrast, the control group showed a similar level of attenuation in both incentive conditions. It is possible that individuals with ADHD require higher levels of incentive to modulate the resting brain effectively or that modulation occurs as a function of intrinsic as opposed to extrinsic motivation. There may also be a threshold for motivation in order resting VLF oscillations to be effectively attenuated. Future studies are needed to investigate the resting VLF EEG during conditions with varying levels of incentives to clarify this issue.

4.4.2.3 The impact of anticipatory attention

Another possible explanation for the rest-to-wait attenuation is that it requires effortful attention to external stimuli. Indeed the degree of attenuation of VLF oscillations in the DMN has been suggested to reflect the amount of mental effort or sustained attention required by a given task (Fassbender et al., 2009). Empirical evidence suggests that task-related attenuation of VLF oscillations is more prominent during challenging tasks, whereas it is reduced during well-practiced or low attention demanding tasks (Fassbender et al., 2009; Jolles, Grol, Van Buchem, Rombouts, & Crone, 2010; Singh & Fawcett, 2008). While resting, individuals often “tune out” their attention from external stimuli and become more internally focused. This is reflected by increased activity in regions of the DMN, which is often accompanied by task irrelevant thoughts (Christoff et al., 2009). During waiting, attention is possibly directed, if not to the waiting task itself, to the reward available in the future (the anticipated outcome). We describe this voluntary, endogenous driven as “anticipatory attention” rather than sustained attention – the maintenance of a state of readiness in anticipation of the outcome as soon as the waiting period is over. Anticipatory attention is a mental state in preparation for imminent external events. It involves mental effort and therefore results in attenuation of VLF EEG. It can be argued that anticipatory attention is closely related to the concept of “prospection” which involves the introspective ability to project oneself into the future (Addis et al., 2007). However, prospection and anticipatory attention may involve different mental processes. For example, envisaging a future event has been associated with increased rather than decreased activity in the DMN regions (Spreng et al., 2009). In this study the opposite pattern was observed - resting VLF EEG power decreased rather than increased during periods of anticipatory attention, suggesting that anticipatory attention involves different neural mechanisms than prospection. Furthermore, Sonuga-Barke & Fairchild (2012) have argued that it is the functional connectivity within regions of the DMN rather than the regional VLF neural activity alone that influences the ability to form and focus on future goals. While the investigation of EEG coherence during task performance was beyond the scope of this study, other studies examine neural oscillations during waiting and prospective tasks, as well as the coherence of neural oscillations between the DMN and the other brain networks are required.

To summarise, it is suggested that the attenuation of resting VLF EEG power may be caused by the goal-directed nature of activities, the motivated nature of the task, and the involvement of effortful attention. The possibility that these components interact with each other cannot be ruled out. Therefore their contribution to the attenuation of resting VLF EEG power may be difficult to differentiate. Moreover, this study cannot exclude other possibilities which may also contribute to the rest-to-wait attenuation of VLF EEG. For example, suppression of goal-irrelevant thoughts and preparation of attention may also influence the activity of VLF oscillations.

4.4.3 Associations with symptoms of ADHD

In this study, the high and low ADHD symptom groups did not differ in terms of the size of attenuation of resting VLF EEG power. This finding is consistent with one previous study (Broyd et al., 2011), but contradicts the findings of another (Helps et al., 2009). This inconsistency may be due to that those participants with higher ADHD symptoms did not have a clinical diagnosis of ADHD. Their inclusion in the high symptom group was based on their self-report of having six or more ADHD symptoms. Although they were selected carefully according to ADHD symptom scores, both from self-reports and the ratings of one of their close friends or relatives, they may not show altered resting brain activity to the same degree as individuals with a clinical diagnosis of ADHD. Despite this result, the potential connection between waiting difficulty and disruptions of DMN could not be ruled out as both deficits have been repeatedly found in individuals with ADHD (Castellanos et al., 2008; Luman et al., 2005). Furthermore, prospective planning, underpinned by

DMN activity, appears to play a role in waiting abilities. Prospecting about a future event could possibly reduce the delay discounting of a farsighted decision, and consequently increase the subject’s ability to wait (Benoit, Gilbert, & Burgess, 2011). Exploring the functionality and mechanism of spontaneous neural oscillations and its relation to ADHD will help to further our understanding of ADHD psychopathology.

4.4.4 Limitations

This study is the first to demonstrate rest-to-wait attenuation of VLF EEG. There are a number of limitations that need to be taken into account. First, the findings of this study were based on non-clinical ADHD groups thus the results may not be able to generalise to a clinical population. Second, the resting conditions that were employed in this study were not fully randomised. Although data from the first and the second resting conditions were averaged, the influence of order effect through fatigue cannot be completely ruled-out. Third, the sample size was small which may reduce the chances to show significant attenuation of VLF EEG power during the F-WAIT condition. Fourth, the F-WAIT condition was designed as a compulsory session while the C-WAIT condition was a voluntary condition. There was a risk of losing data of the C-WAIT condition from those with a low motivation to wait. Finally, given the fact that VLF EEG studies are rare, the VLF EEG network in this study was identified used a data-driven approach. Future studies should attempt to localise the intracranial sources of VLF EEG or co-register the EEG signals with fMRI.

4.5 Conclusions

This study identified significant attenuation of VLF EEG power following the transition from resting to waiting when participants actively chose to wait, but not when the waiting was imposed. The degree of rest-to-wait attenuation of VLF EEG was similar to rest-to-work attenuation during cognitive task performance, even though the waiting condition did not involve cognitive information processing and in many ways shared common characteristics with the resting state. A comparison between the results across the resting, waiting and working conditions indicates that goal-directedness, rather than cognitive load, and the motivated state, as well as the involvement of effortful attention are the crucial characteristics for attenuation of VLF EEG.

4.6 Directions for the next study in this thesis

This study provided the first evidence that resting VLF EEG attenuated during goal-directed waiting tasks in healthy young adults. However, in contrast to the original prediction, the rest-to-wait attenuation between high- and low ADHD symptom groups were not significantly different. As mentioned above, a possible reason for this result may be that the participants in this study were all university students without a clinical diagnosis of ADHD. A second study which applied a similar protocol to a group of children and adolescents with a clinical diagnosis of ADHD and a group of age and gender-matched typically developing controls was conducted and reported in **Chapter 5**. The protocol was revised so that each of the four conditions

(REST, WORK, C-WAIT and F-WAIT) was presented once, with each condition lasting for five minutes. The four conditions were fully randomised. In order to evaluate the relationship between rest-to-wait attenuation and waiting impulsivity, the second study also collected parents' ratings in terms of delay discounting and delay aversion. Moreover, it examined the intracranial sources of rest-to-work/wait attenuation of VLF EEG using distributed source modelling.

Chapter 5 Very low frequency neural oscillations during resting, waiting and working states in ADHD

5.1 Introduction

Attention-deficit/hyperactivity disorder (ADHD) is a heterogeneous disorder implicating multiple brain networks which regulate active engagement during cognitive, motivational and emotional operations (Cortese & Castellanos, 2012). Individuals with ADHD display atypical patterns of spontaneous brain activity, reflected in very low frequency (VLF: <0.1Hz) blood-oxygen-level dependent (BOLD) signals within the default mode network (DMN) during wakeful rest when no specific task is being undertaken (Castellanos et al., 2008; Sripada et al., 2014; Tian et al., 2008). When engaging in cognitive tasks, they fail to effectively supress the DMN BOLD signals (Fassbender et al., 2009; Peterson et al., 2009), which may explain patterns of periodic attentional lapses and intra-individual reaction time variability (Helps, Broyd, Bitsakou, & Sonuga-Barke, 2011).

Recent studies using direct current coupled electroencephalography (DC-EEG) also identified a temporally and spatially stable resting VLF EEG network in healthy young adults with maximal power distributed across midline frontal and posterior scalp regions (Helps et al., 2008). The intra-cranial sources of this scalp activity have been localised to several DMN brain regions (Broyd et al., 2011). Moreover, children and adolescents with ADHD display reduced attenuation when working on attention demanding tasks with this attenuation correlated with their attentional performance (Helps et al., 2010).

Individuals with ADHD display difficulty waiting for future outcomes and prefer to choose smaller sooner (SS) over larger later rewards (LL) even when this leads to less reward overall (Marco et al., 2009). The investigations for this “impulsive choice” in ADHD have focused on: (i) a reduced ability to resist temptation linked to executive dysfunction (Barkley et al., 2001), reflecting alteration in the dorsal fronto-striatal network (Dickstein et al., 2006); (ii) increased discounting of the value of future rewards (Scheres, Tontsch, et al., 2010), reflecting hypo-activation of the reward brain centre (e.g., ventral striatum; Costa Dias et al., 2013); and (iii) negative affection generated by the experience of delay (i.e. delay aversion; Sonuga-Barke, 2002) mediated by hyper-activation within the brain’s emotion centre (e.g. insula and amygdala; Lemiere et al., 2012; Plichta et al., 2009; Wilbertz et al., 2013). The default-mode interference (DMI) hypothesis proposed by Sonuga-Barke & Castellanos (2007) suggests that persisting DMN activity constrains cognitive task performance. From the DMI perspective, excess DMN activity may induce difficulty of waiting. However, the potential role of intrinsic brain activity during waiting in individuals with ADHD and its relation to the impulsive choice of ADHD has not been investigated.

The study presented in **Chapter 4** drew a parallel between waiting and resting brain states – highlighting some similarities and also some important differences. Interestingly, it revealed that in typically developing adults the VLF EEG signature for waiting, especially when this was freely chosen and rewarded, was more similar to that displayed while working (on a simple cognitive task) than during resting – with VLF EEG power attenuation seen in anterior and posterior medial scalp regions in both states (Hsu, Broyd, Helps, Benikos, & Sonuga-Barke, 2013). However, it is unclear if individuals with ADHD display altered pattern of spontaneous VLF EEG during waiting.

5.1.1 Study aims

This study examined the VLF EEG and the intracranial sources in a sample of children and adolescents with ADHD and their age and gender-matched healthy controls. The aims of this study were to : (i) replicate the findings of the previous chapter that the typically developing controls would display significant rest-to-wait attenuation of VLF EEG; (ii) examine whether individuals with ADHD, compared to controls, fail to attenuate spontaneous VLF EEG during the switch from resting to both working and waiting states*; (iii) investigate the source localisation of VLF EEG attenuation between ADHD and control groups* and (iv) investigate whether this excessive waiting VLF EEG would be associated with higher levels of delay aversion and delay discounting.

5.1.2 Predictions

It was predicted that: (i) the control group would display significant rest-to-work and rest-to-wait attenuation of VLF EEG with the attenuations localised to DMN-related regions; (ii) ADHD individuals, in contrast to the controls, would fail to attenuate the resting VLF EEG power during cognitive task performance and waiting conditions; (iii) within the control group rest-to-work and rest-to-wait attenuation would be localised to midline structures which overlap with the DMN. Within the ADHD there might be some attenuation shown in midline structures but it might fail to reach statistical significance; and (iv) there would be a negative correlation between the rest-to-wait attenuation and the levels of delay aversion and delay discounting.

5.2 Methods

The study was approved by the University of Southampton Psychology Ethics Committee and the Southampton and South West Hampshire Research Ethics Committee A. All parents and participants gave written informed consent and children gave assent.

5.2.1 Participants

Twenty-one children aged between 9 and 15 years with both a clinical and a research diagnosis of ADHD and 21 typical developing controls participated in this study. Individuals with ADHD were recruited from local clinics through the South Hampshire ADHD Register (SHARe, http://www.southampton.ac.uk/share). They all completed the standard SHARe assessment battery, including Wechsler Intelligence Scale for Children, fourth edition (WISC-IV), a semi-structured psychiatric diagnostic interview (NIMH DISC-IV; Shaffer, Fisher, Lucas, Dulcan, & Schwab-Stone, 2000), as well as parent and teacher versions of the Conner’s Comprehensive Behaviour Rating

Scale (CBRS; Conners, 2008). Exclusion criteria were: a) the presence of other developmental or psychiatric disorders (except oppositional defiant disorder and conduct disorder) as diagnosed by clinicians; b) IQ less than 70, and c) medication use (except short acting stimulants). The average time between the time when ADHD cases completed SHARe assessment and the experimental testing is 238 days. Medicated patients refrained from medication for at least 24 hours prior to testing. The controls were recruited from local schools and clubs. They completed the short form of WISC-IV (Vocabulary and Block Design) and their parents completed the CBRS. Controls were excluded if they had an estimated IQ less than 70 or if they met clinical cut-offs on any ADHD subscale. The two groups did not differ in terms of age and sex (Table 5.1). Individuals with ADHD had lower estimated IQ compared to controls.

5.2.2 Design

The study had a mixed-model repeated-measure design. Both the ADHD and control participants completed a single testing session. EEG were recorded during four experimental conditions (See section *5.2.3 Procedure*). The order of these assessments was counterbalanced. The testing took two hours. Each family was reimbursed £30 for their time and travel expenses.

5.2.3 Procedure

This study modified the protocol of the study presented in **Chapter 4** (please see detailed information in *4.2.3 Procedure*). Participants were asked to complete a resting and two types of waiting conditions, as well as a cognitive task during EEG recording. Each condition lasted five minutes. In the resting condition (REST), participants were instructed to relax and focus on the fixation cross on the monitor. In the working condition, participants completed a 300 trial two-choice reaction time task (2CRT). Each trial lasted 1s, which included stimulus presentation time for 400ms and inter-stimulus interval for 600ms. Participants were required to indicate the direction of an on-screen arrow by pressing the “left” or “right” button on a response box. They were asked to focus their attention and respond as quickly and accurately as possible (correct rate: control: 89%; ADHD: 81%). In the forced-to-wait (F-WAIT) condition participants were instructed to wait for five minutes before they could start the next experimental session. In the choose-to-wait (C-WAIT) condition they were given a choice to wait for five minutes to win a ticket of a £20 lottery draw, or to immediately terminate the waiting period (one ADHD case declined this invitation but completed the other EEG sessions which were included in the analysis). Condition order was counterbalanced using a Latin square table (Bailey, 2008). Each participant was randomly assigned to one of the following sequences: i) REST; 2CRT; C-WAIT; F-WAIT: ii) 2CRT; F-WAIT; REST; C-WAIT; iii) F-WAIT; C-WAIT; 2CRT; REST; iv) C-WAIT; REST; F-WAIT; 2CRT.

After completion of each condition, participants were prompted to answer three questions about their emotion and experience (see Appendix 1). The first question asked “How do you feel during the session” and provided a face scale (5 faces, Face 1 is a happy face and Face 5 is definitely frowning). The second question asked “How hard did you find the session” (5 drawings, Drawing 1 pictures someone carring a very light backpack and Drawing 5 shows someone carring an extremely heavy bag). The third question asked “How much time during the session would you say your mind wandered?” and provided a visual analog scale (from 0% not at all to 100% all the time).

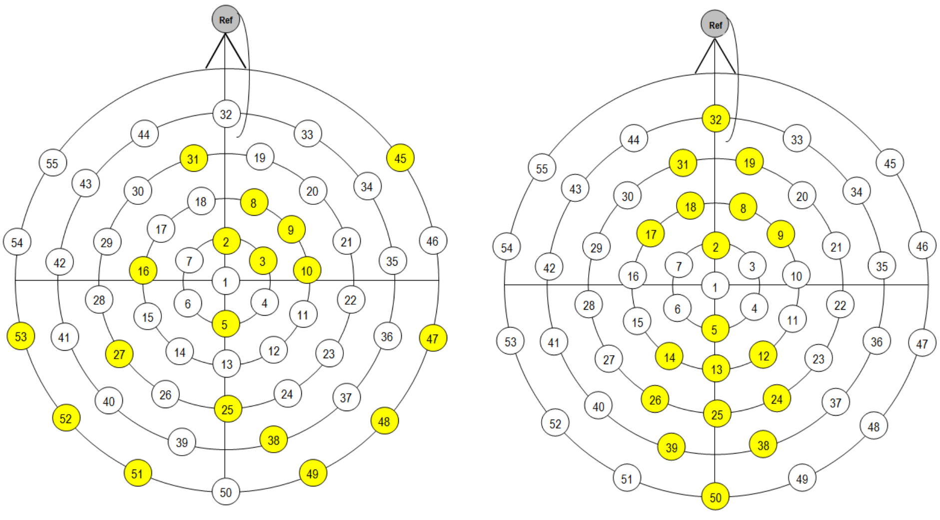
All participants’ parents completed the previously validated Quick Delay Questionnaire (QDQ; Clare, Helps, & Sonuga-Barke, 2010) for the assessment of participants’ delay-related problems. QDQ is a Likert type scale measuring delay discounting (5 items) and delay aversion (5 items).

5.2.4 Electrophysiological Acquisition

EEG was recorded using a Neuroscan Synamps^2 70 channel system via 24 bit A/D converter and a direct current (DC) procedure, combined with a 70 Hz low-pass filter and 500 Hz sampling rate. Participants were fitted with an electrode cap with 66 equidistant electrodes, with a nose reference (Easycap; Hersching, Germany). Electro-oculogram (EOG) was measured using Ag/AgCl electrodes placed below the left and right eyes. Impedance was kept below 5 kΩ.

5.2.5 EEG data processing

Data was initially referenced to the nose electrode. The first 55 of 66 electrodes were selected for further processing and re-referenced to an average reference using MATLAB (version R2010a). The linear trend caused by DC drift was removed using the ‘detrend’ command in MATLAB. Independent component analysis (ICA) was used to remove all artefacts and ocular movements with fast ICA algorithm (Hyvärinen, 1999). EEG signals were reconstructed by back-projection of all artefact-free components and subjected to fast Fourier transformation (FFT). One minute Hamming windows overlapped by 20-sec were applied. The VLF EEG power within the very low frequency band (0.02-0.2 Hz) was calculated (Penttonen & Buzsáki, 2003). Based on previous VLF EEG studies (Broyd et al., 2011; Helps et al., 2010; Hsu et al., 2013), we a priori identified a VLF EEG network consisting of two groups of midline electrodes (anterior and posterior clusters, see Figure 5.1). The power from the selected electrodes was averaged and natural log-transformed to correct for non-normality (Gasser et al., 1982). Two participants (one with ADHD) were excluded because of poor data quality which continued to obscure the EEG even after ICA was performed. The final comparisons were conducted on two groups of twenty.



(a) (b)

Figure 5.1 Electrodes selected for the VLF EEG network.

The selected electrodes are shown in yellow in (a) the previous study, defined by the top 18 electrodes showed highest rest-to-work attenuation in the control group (see Chapter 4); and (b) in the present study, identified a priori based on previous DMN research.

5.2.6 Source localisation

Standardised low-resolution electromagnetic tomography software (sLORETA; Pascual-Marqui, 2002) was used for source localisation. Artefact-free EEG was down-sampled from 500 Hz to 25 Hz using the 'decimate' command in MATLAB in order to meet the computational constraints of sLORETA. The down-sampled EEG data in time series were then exported in ASCII format from MATLAB to sLORETA. Using sLORETA package we computed the cross-spectra and corresponding electric generators which contained the information of cortical three-dimensional (3D) distribution. The computed sLORETA images represented the amplitude of current source density in 6239 voxels, with a spatial resolution of 5 mm.

5.2.7 Data analysis

The group difference in the QDQ subscales was tested using independent t-tests. Subjective experience ratings and VLF EEG power differences were assessed separately using two-way repeated measures ANOVAs with Condition (REST, WORK, C-WAIT and F-WAIT) as the within-subject factor and Group (Control vs. ADHD) as the between-subjects factor. Analyses were run with and without IQ as a covariate. Effect sizes were calculated using Cohen's *d*. Correlations between REST-to-WORK/WAIT power differences and delay-related questionnaire measures were calculated using Pearson's *r*. With regard to source localisation, the within subject differences between sLORETA images for REST and each of the non-REST conditions (WORK, F- and C-WAIT) were computed for the control and ADHD groups separately using sLORETA statistics package. Follow-up testing computed the between group difference (ADHD and controls) for each of these condition contrasts. The sLORETA images were compared using non-parametric permutation tests based on the estimation of empirical probability distribution for the maximum of a *t*-statistic via 5000 randomisation with a conservative significance threshold, correcting for multiple comparisons of all 55 electrodes and 6239 voxels (Nichols & Holmes, 2002).

5.3 Results

5.3.1 Behavioural and questionnaire measures

Individuals with ADHD displayed more inattentive and hyperactive/impulsive symptoms compared to the controls. They had significantly higher delay aversion and delay discounting scores on the QDQ. Moreover, the ADHD group made more errors during the performance of 2CRT task. Their response variability was also significantly higher than the control group (Table 1).

Table 5.1 Demographic and clinical characteristics.

	Control (N=21) Mean (SD)	ADHD (N=21) Mean (SD)	*t*/χ^2	*p*
Age	11.47 (1.69)	11.00 (1.95)	0.85	.40
Gender (male/female)	17/4	20/1	2.04	.34
Estimated IQ *(WISC-IV)*†	105.48 (13.16)	97.29 (12.43)	2.07	.05*
Conners Comprehensive Behaviour Rating Scale (CBRS)				
***Parent report* (T score)**				
Inattentive type	54.62 (10.83)	86.43 (5.61)	-11.95	< .001***
Hyperactive-Impulsive type	54.05 (11.54)	86.05 (6.93)	-10.89	< .001***
Quick Delay Questionnaire (QDQ)				
Parent report				
Total score	21.62 (6.48)	41.24 (6.68)	-9.66	<.001***
Delay aversion	11.14 (3.48)	21.48 (3.76)	-9.24	<.001***
Delay discounting	10.48 (3.39)	19.76 (3.51)	-8.73	<.001***
Two choice reaction time task (2CRT)				
Total Errors	32.62 (20.50)	55.81 (38.00)	-2.46	.02*
Mean RT (ms)	474.82 (64.85)	484.19 (51.91)	- 0.52	.61
SD of RT	105.41 (37.52)	138.07 (35.09)	-2.91	<.01**

Note. †WISC-IV: Wechsler Intelligence Scales for children. **p* < .05; ***p* < .01; ****p* <.001

5.3.2 Subjective experience ratings

There were significant group effects on emotion (*F* = 4.90; *p* = .03) and mental effort (*F* = 18.46; *p* < .01), suggesting that children with ADHD were more frustrated and spent more effort across conditions. The group difference on mind wandering was not significant (*F* = 1.53; *p* =.22). The main effect of Condition was significant for mental effort and mind wandering (*F* > 4.08; *p* ≤ .01) and marginally significant on emotion (*F*: 2.43; *p* = .07). Follow-up analysis showed that Condition effect on mental effort was mainly driven by C-WAIT, i.e. Participants found that C-WAIT was significantly easier than other conditions. Participants also reported a lower degree of mind wandering during WORK condition compared to other conditions, as well as less mind wandering during C-WAIT compared to REST. The interaction between Group and Condition was not significant.

5.3.3 VLF EEG power

The levels of mean VLF EEG power within the network of each condition are shown in Figure 5.2. There was a significant main effect of Group (*F* (1, 37) = 16.92, *p* < .001) and Condition (*F* (3, 111) = 21.22, *p* < .001), as well as a significant Group by Condition interaction (*F* (3, 111) = 9.02, *p* < .001). Controls displayed significantly and substantially lower levels of VLF EEG power in the WORK, F-WAIT and C-WAIT conditions compared to the REST condition (Control: Cohen's $d^{\text{WORK}} = 1.41$; $d^{\text{C-WAIT}} = 1.17$; $d^{\text{F-WAIT}} = 1.21$). In the ADHD group the VLF EEG power was reduced in the WORK condition compared to the REST condition, but not in the C-WAIT or F-WAIT condition (ADHD: Cohen's $d^{\text{WORK}} = 0.82$; $d^{\text{C-WAIT}} = -0.16$; $d^{\text{F-WAIT}} = -0.34$). Moreover, the effect of REST-to-WORK attenuation in ADHD was significantly smaller than seen in controls ($t\ (38) = 2.30$; $p < .03$). Adding IQ as a covariate reduced the Condition effect ($F < 1.50$; $p > .20$), but other effects remained significant ($F^{\text{Group}} > 4.84$, $p < .05$; $F^{\text{Group by Condition}} > 4.94$, $p < .05$).

REST-to-WAIT but not REST-to-WORK difference in scalp VLF EEG power was negatively correlated with parents' combined QDQ ratings (F-WAIT $r = -.53$, $p < .01$; C-WAIT $r = -.42$; $p < .01$; WORK $r = -.19$, $p = .23$). This suggests the less REST-to-WAIT attenuation the higher levels of delay aversion and delay discounting.

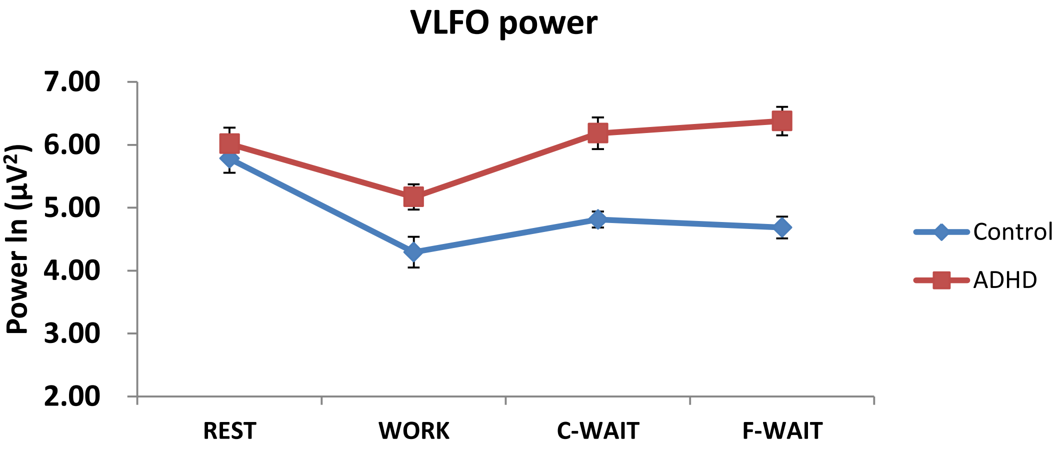


Figure 5.2 VLF EEG power during *resting*, *working* and *waiting* conditions.

Note. 2CRT: two-choice reaction time task; C-WAIT: condition when participants chose to wait; F-WAIT: condition when participants were forced to wait. Power value was natural log-transformed.

5.3.4 Spatial distribution of VLF EEG

Figure 5.3 shows the whole scalp distribution of VLF EEG power. At REST both groups showed maximal power along the frontal pole and midline regions. During WORK the VLF EEG power was lower for both groups although it remained greatest in the frontal pole and centro-parietal areas. Within the ADHD group the C-WAIT and F-WAIT VLF EEG signatures were more similar to REST than WORK despite some evidence of focal reductions in frontal areas and temporo-parietal junction and a degree of exacerbation in temporal and centroparietal locations. In contrast, the VLF EEG signatures of control group during C- and F-WAIT were similar to that during WORK with suppression of EEG power across the whole scalp.

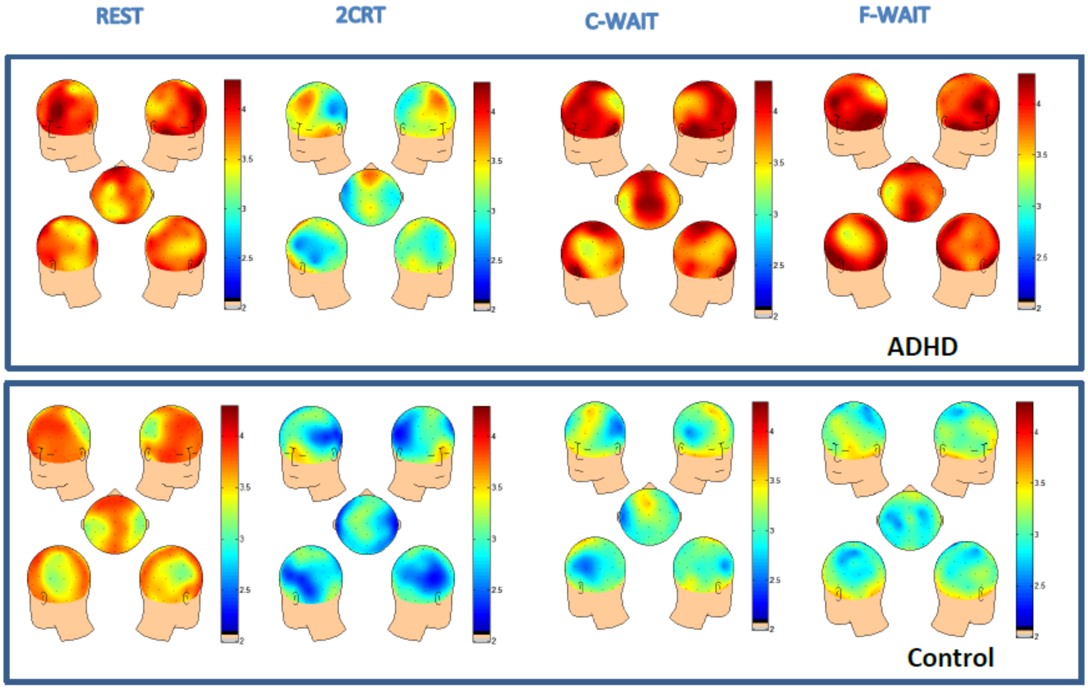


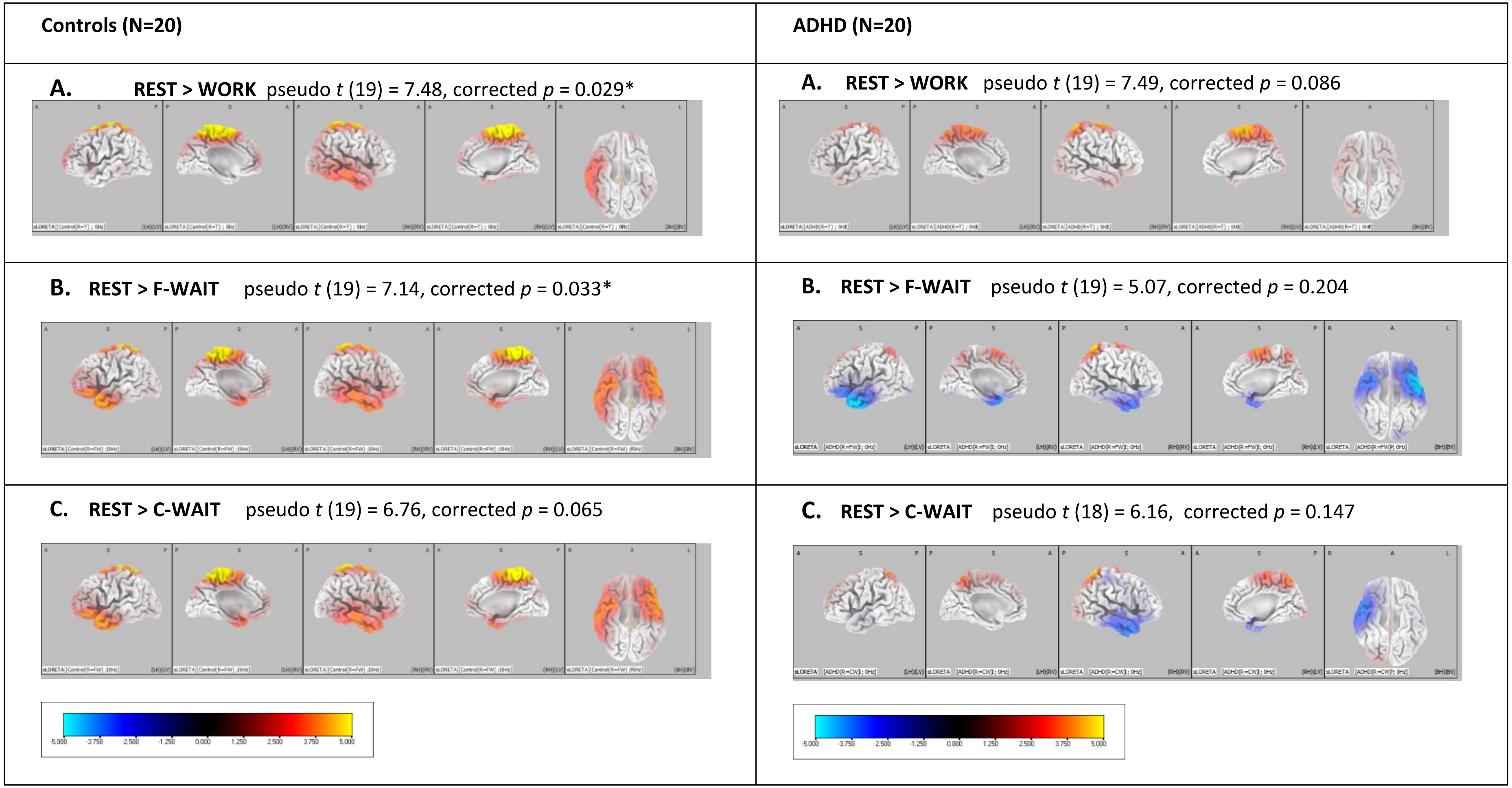
Figure 5.3 Spatial distributions of very low frequency EEG across resting, cognitive task and waiting conditions.

Data are collected from the 55 electrode sites across the scalp. Top row: ADHD group; bottom row: typically developing controls.

Note. 2CRT: two choice reaction time task; C-WAIT: condition when participants chose to wait; F-WAIT: condition when participants were forced to wait. Power value was natural log-transformed.

5.3.5 Source localisation for the attenuation of VLF EEG

As predicted, sLORETA localised the resting VLF EEG for both groups to midline structures, including key DMN regions such as the medial frontal gyrus (BA 6 & 8) and precuneus (BA 31) (see *Appendix 2*). Figure 5.4 shows the intracranial sources for the contrast between REST and non-REST conditions. In line with the scalp distribution, sLORETA identified significant WORK and F-WAIT induced attenuations within the control group in the medial frontal gyrus (BA 6), precentral and postcentral gyrus (BA 4), as well as the paracentral lobule (BA 6) (REST vs. WORK: pseudo $t = 7.48$, corrected $p = 0.03$; REST vs. F-WAIT, pseudo $t = 7.14$, corrected $p = 0.03$). For controls the contrast between REST and C-WAIT conditions failed to reach significance after stringent control for multiple testing (pseudo $t = 6.76$, corrected $p = 0.07$), albeit the attenuations were localised to similar regions. The ADHD group displayed REST-to-WORK attenuation in similar regions but the effects were smaller and failed to reach significance (pseudo $t = 7.49$, corrected $p = 0.09$). Nominally significant REST to C- and F-WAIT reductions occurred in DMN-related regions, including the precuneus, superior parietal lobule, postcentral gyrus and medial frontal gyrus (F-WAIT: pseudo $t = 5.07$, corrected $p = 0.20$; C-WAIT: pseudo $t = 6.16$, corrected $p = 0.15$), but these were not significant when p values were adjusted for multiple testing. Within the ADHD group there were increases of VLF EEG activity in the temporal areas near limbic lobe and insula (blue regions on Figure 5.4) during the F-WAIT and C-WAIT conditions compared to the REST condition. In terms of group comparison, for the REST-to-F-WAIT contrast there was a significant group difference in the insula (BA 13) and inferior frontal gyrus (pseudo $t = 3.65$, corrected *p* = 0.04). For the REST-to-C-WAIT contrast a significant group difference was identified in the insula, middle and superior temporal gyrus (BA 13, 21, 22, 41; pseudo *t* = 3.67, corrected *p* = 0.01). There was no group difference in terms of the REST-to-WORK transition (*p* = .42).



Controls (N=20)

A. **REST > WORK** pseudo t (19) = 7.48, corrected p = 0.029*

B. **REST > F-WAIT** pseudo t (19) = 7.14, corrected p = 0.033*

C. **REST > C-WAIT** pseudo t (19) = 6.76, corrected p = 0.065

ADHD (N=20)

A. **REST > WORK** pseudo t (19) = 7.49, corrected p = 0.086

B. **REST > F-WAIT** pseudo t (19) = 5.07, corrected p = 0.204

C. **REST > C-WAIT** pseudo t (18) = 6.16, corrected p = 0.147

Figure 5.4 The intracranial sources of the differences between resting and the cognitive task or waiting conditions.

5.3.6 Correlation between VLF EEG in temporal area and QDQ

To explore these unpredicted temporal lobe/insula effects further, we then correlated activity within these regions during waiting using sLORETA generators with the delay aversion and discounting scores on the QDQ. There were highly significant positive correlations between QDQ scores and F-WAIT activity in the insula (MNI[x/y/z] = -35/20/5; $r^{\text{delay aversion}} = .57$; $p < 0.001$; $r^{\text{delay discounting}} = .57$; $p < .001$) and inferior frontal gyrus (MNI [x/y/z] = -35/25/0; $r^{\text{delay aversion}} = .51$; $p = 0.001$; $r^{\text{delay discounting}} = .53$; $p < .001$); and C-WAIT activity in the superior temporal gyrus (MNI [x/y/z] = 50/-20/5; $r^{\text{delay aversion}} = .46$; $p <0.01$; $r^{\text{delay discounting}} = .42$; $p <.01$), middle temporal gyrus (MNI [x/y/z] = 60/-30/-5; $r^{\text{delay aversion}} = .41$; $p <0.01$; $r^{\text{delay discounting}} = .37$; p <.05) and insula (MNI [x/y/z] = 45/-15/5; $r^{\text{delay aversion}} = .53$; $p =0.001$; $r^{\text{delay discounting}} = .50$; $p =.001$). F-WAIT activity in the insula positively correlated with response variability on the 2CRT task ($r = .40$, $p = .01$). However, there was no correlation between the other regional EEG power during F-WAIT or C-WAIT and performance indices (including total error, RT and SD of RT) on the 2CRT task (all $r < .30$; $p > .05$).

5.4 Discussion

Despite considerable recent interest in the resting brain this study is the first to examine the spontaneous VLF EEG during waiting status in ADHD. We set out to test three hypotheses. First, healthy participants would demonstrate significant rest-to-wait attenuation of VLF EEG. Second, individuals with ADHD, compared to controls would display excess spontaneous VLF EEG power during waiting, similar to that observed in the past when they are working on goal-directed tasks. Third, that this excess activity would be related to measures of impulsive choice. There were a number of findings of note.

5.4.1 Rest-to-work attenuation of VLF EEG was replicated in healthy youths

This study replicated prior evidence of suppression of VLF EEG power during episodes of waiting and working relative to resting in healthy children and adolescents (Hsu et al., 2013). This study supports the view that in terms of spontaneous brain activity, waiting, despite some characteristics in common with resting, is similar to other goal-directed activities such as performing information processing tasks. There have been debates about the functional status of VLF EEG as a measure of real neuronal activity, and the extent to which it is functionally similar to the BOLD oscillations (Demanuele et al., 2013; Vanhatalo et al., 2005). The localisation of sources to midline structures in this study raises new questions about the relationship of VLF EEG network and the DMN. Indeed recent studies using simultaneous EEG-fMRI recordings have identified a direct association between spontaneous BOLD signals and EEG in both infra-slow (Hiltunen et al., 2014) and higher frequency domains (Laufs, Kleinschmidt, et al., 2003; Mantini et al., 2007). There is also evidence indicating an association between the change of theta power and rest-to-work attenuation of BOLD signals in DMN regions during cognitive task performance, particularly in the anterior MPFC (Meltzer et al., 2007; Scheeringa et al., 2009). Further work should investigate the BOLD signals during waiting, as well as the functional significance of VLF EEG and its relationship with traditional EEG frequency bands.

5.4.2 Individuals with ADHD displayed reduced rest-to-work attenuation

Individuals with ADHD, compared to controls, showed excess VLF EEG power within the VLF EEG network when working relative to resting along the midline structures such as frontal pole and stretching to centroparietal areas. They also displayed a significantly higher error rate when working on the attention task. This is consistent with previous EEG (Helps et al., 2010) and fMRI literature (Fair et al., 2010; Fassbender et al., 2009; Liddle et al., 2011). Moreover, this findings is in line with the prediction of default mode interference (DMI) hypothesis, which suggests the persisting DMN activity during a task is a major source of periodic attentional lapses (Sonuga-Barke & Castellanos, 2007).

5.4.3 Altered VLF EEG during waiting in ADHD

Third, this study demonstrated that individuals with ADHD displayed excess VLF EEG activity during waiting conditions – in fact the apparent lack of suppression when judged across the scalp was even more marked for waiting than it was for working, despite isolated and non-significant effects in a number of specific DMN regions. There are a number of possible explanations for this finding. First, and most straight-forwardly, individuals with ADHD may simply fail to supress the VLF EEG power when transitioning from resting to waiting, as is suggested by the DMI hypothesis. This could be the result of failures in executive control (Willcutt, Doyle, Nigg, Faraone, & Pennington, 2005) or to problems engaging brain mechanisms recently implicated in state-to-state switching (i.e., salience network; Menon & Uddin, 2010). An alternative hypothesis is that, rather than a failure to suppress resting brain activity, excess VLF EEG power during waiting represents a positive decision to engage in introspective and self-referential mental activity, such as mind wandering, typically associated with VLF EEG activity in the core DMN regions (Buckner & Carroll, 2007).In this sense excessive VLF EEG activity in DMN-related regions might represent a cognitive coping strategy to deal with the aversiveness during waiting (Marco et al., 2009; Sonuga-Barke et al., 1992). It can therefore be an internalised manifestation of the common finding that children with ADHD display more distracted and hyperactive behaviour when waiting in situations with low levels of stimulation. Opposite to our expectation, children with ADHD did not report higher extent of mind wandering across all conditions. It may reflect that VLF EEG and mind wandering are not associated. However, the confounding from internal and external contextual factors on self-reports such as social expectation could not be ruled out.

5.4.4 Correlations between rest-to-wait attenuation and delay aversion

Fourth, as predicted the attenuation in VLF EEG from resting to waiting was found to be related to delay aversion and heightened delay discounting as rated by parents. It is at present unclear what is cause and what is effect here. On one hand, failure to supress VLF EEG during waiting might impair the individual's ability to focus on, and achieve, the goal of waiting. On the other hand, as suggested above, it may be that the more delay averse and impulsive an individual is the more they engage in self-referential processing during waiting, for the purpose of reducing negative affections arising from the period of delay (Sonuga-Barke, 2002). In some ways the latter view seems more likely, as the former appears to contradict the literature relating to the role of the DMN in setting a personally desired goal for a future event (Sonuga-Barke & Fairchild, 2012).

5.4.5 Correlations between waiting temporal activity and QDQ

Finally, an unpredicted increase in VLF EEG activity in the insula and specific temporal regions was observed in ADHD cases during the waiting periods and this was positively correlated with the level of delay aversion and delay discounting. In hindsight these effects could have been predicted on the basis of previous fMRI studies supporting the idea that delay during waiting is aversive to individuals with ADHD. Specifically, research has identified elevated activation in the emotional brain centre (Dalgleish, 2004) for this clinical group during their responsiveness to a period of delay. For example, Plichta and colleagues (2009) identified increased activity in amygdala in adults with ADHD compared to healthy controls during the choices of delayed rewards (Plichta et al., 2009). Lemiere et al. (2012) found increased insula and amygdala activity during the anticipation of an inescapable delay (Lemiere et al., 2012). Wilbertz and colleagues (2013) reported a positive association between the activity in the inferior temporal cortex and right amygdala and the length of delayed period in the ADHD but not in the control group (Wilbertz et al., 2013). The current results therefore provide some of the first evidence linking the EEG power in the temporal regions to delay aversion (Broyd et al., 2012), although we admit the difficulty to examine deep cortical structures using scalp recording EEG signals.

5.4.6 Limitations

The study had a number of limitations. First, ADHD group had lower IQ than controls; however, analyses were run with and without IQ as a covariate and this did not change the results. Second, there was a delay between the time when ADHD cases were diagnosed and when they took part in the study (average 238 days). ADHD symptom remission may reduce the group effect. However, the group difference in VLF EEG attenuation was still significant in this study despite of the time lag. Third, the use of sLORETA may constrain the interpretation as the images produced by sLORETA lack for precise spatial resolution. Focal activities may be over- or under-estimated. Despite this, recent evidence demonstrates that deep sources can be reliably estimated from scalp-recorded EEG data (Lucka, Pursiainen, Burger, & Wolters, 2012; Michel et al., 2004), with significant correspondence to hemodynamic procedures used in the same tasks (Mulert et al., 2004). The localisation of VLF EEG to DMN-related regions found in the current study is plausible. Fourth, the characterisation of impulsive choice was assessed by one measure. Future research should include a broader battery of measures.

5.5 Conclusions

Chapter 4 demonstrated that the VLF EEG power attenuation seen from resting to waiting for a reward in healthy adults is similar to that previously observed during the transition from resting to working on an information processing task. This study replicated the rest-to-wait attenuation in healthy children and adolescents and provides the evidence that the rest-to-wait attenuation of VLF EEG was localised to some regions of the DMN. Importantly, individuals with ADHD displayed excessive DMN-related VLF EEG activity during waiting, which was associated with parents' ratings of delay-related problems. This study is the first to explore waiting VLF EEG and its relation to the waiting difficulty of ADHD. Further study should explore the underlying neural mechanism of internalised, self-referential activity (e.g. prospection) and the association with impulsive decision making.

5.6 Directions for the next study in this thesis

The studies presented in Chapter 4 – 5 demonstrated the spontaneous neural oscillations changes from resting to waiting states, even though the waiting condition shared many characteristics with the resting condition. At rest individuals often engage into self-referential processing such as mind wandering and future prospection (Christoff, 2012). In order to explore the association of neural mechanism and functionality between waiting and prospection, a third study was designed and is presented in **Chapter 6**. It compared the quantitative EEG measures sourced to the DMN regions in young adults during episodes of prospection with that seen during resting and while waiting for rewards. The results showed that episodic prospection implicated a medial fronto-temporal axis which differentiated prospection from resting and waiting states.

Chapter 6 Spontaneous activity during episodic prospection: electrophysiological evidence implicating a medial fronto-temporal axis

6.1 Introduction

The default mode network (DMN) is implicated in a range of introspective self-referential cognitive states, such as episodic prospection (Spreng & Grady, 2010), autobiographical memory (Addis et al., 2007; Spreng et al., 2009), mind wandering (Christoff et al., 2009) and moral decision making (Reniers et al., 2012). These mental processes, although differing in terms of task content, share common features, i.e. they all involve shifting one's perspective from the present context to an alternative, past or future context. DMN plays an important role in the integration of autobiographical information to drive decisions relating to the desired future goal (Sonuga-Barke & Fairchild, 2012). Central to this is episodic prospection - the ability to mentally envisage possible future event and states (Boyer, 2008; Lin & Epstein, 2014). Functional magnetic resonance imaging (fMRI) studies have implicated a medial fronto-temporal axis as a putative neural mechanism underpinning prospection (Andrews-Hanna, Reidler, Huang, & Buckner, 2010). The medial prefrontal cortex and medial temporal lobe interact to facilitate processes of self-projection into the future (Bar, 2009; Buckner & Carroll, 2007). This is consistent with research showing that the medial temporal lobe is involved in autobiographical memory retrieval and provides the foundation for internal mentation (Tulving, 2002), while the medial prefrontal cortex is implicated in self-related simulations (Kim, 2012; Szpunar et al., 2007) and complex perspective-taking processes (Van Hoeck et al., 2013).

Although the neural correlates of self-referential cognition and the resting brain have been investigated previously using a range of different methods such as electroencephalography (EEG) and fMRI (Christoff, 2012; Helps et al., 2010; Helps et al., 2009; Helps et al., 2008; Knyazev, 2013b; Knyazev et al., 2012; Smallwood, Brown, Baird, & Schooler, 2012; Spreng et al., 2009), studies of the association between prospection and DMN have been limited solely to fMRI. This study extended previous investigations to the EEG correlates within the DMN regions during episodic prospection. Participants were asked to consider the use of money in future scenarios, i.e. to estimate what a monetary amount could buy and also imagine themselves actually spending it (Benoit et al., 2011). Two control conditions were used: i.e. resting and waiting, in order to differentiate the specific EEG correlates of prospection from those seen in similar brain states.

Although episodic prospection and resting activate some common neuroanatomical regions within the DMN they are not identical states. For instance, spontaneous thoughts which are generated during resting are often unconstrained and lack a specific focus, whereas episodic prospection involves definite scenarios and has a clear temporal focus. In this sense prospection has a more goal-directed and effortful nature than resting. It also involves the systematic access and integration of memory about past experiences and future possibilities. Given this it was expected to see greater suppression of core DMN hubs such as medial prefrontal cortex (seen in goal-directed tasks) and increased activation of medial temporal lobe (seen in autobiographical memory tasks) during prospection comparing to the pure resting condition. The brain states occurring when individuals are actually waiting for future events also provides an interesting contrast with the process of prospection about those events. The study presented in **Chapter 4** demonstrated attenuation of very low frequency (VLF) EEG power within the frontal regions when individuals were 'waiting' for rewards compared to when they were resting (Hsu et al., 2013). It is suggested that this suppression may be caused by the goal-directed nature of waiting. However, there was no evidence of increased activation of medial temporal lobe suggesting that once the decision to wait had been taken there was limited prospective thinking.

6.1.1 Study aims

This study aimed to extend the current literature by comparing young adults' quantitative EEG measures (i.e. amplitude and phase coherence) within the DMN regions during episodes of prospection with that seen during resting and while waiting for rewards.

6.1.2 Predictions

It was predicted that: (i) compared to resting, prospection would be associated with decreased activity in the medial prefrontal region (given its more goal-directed nature); and (ii) compared to both resting and waiting conditions prospection would be associated with increased medial temporal lobe activity and the phase coherence between medial temporal lobe and medial prefrontal area (given its likely use of autobiographical and self-referential elements).

6.2 Methods

The study was approved by the School of Psychology Ethics Committee, University of Southampton.

6.2.1 Participants

Twenty-two students (18-35 years) recruited from University of Southampton completed the study. The exclusion criteria were: (i) a history of brain injury; (ii) a diagnosis of neuropsychiatric disorder; (iii) use of any psychotropic substance more than twice in the last six months; and (iv) a history of substance abuse or dependence.

All participants refrained from consuming caffeine or nicotine at least two hours prior to the testing.

6.2.2 Design

This study had a within group repeated-measures design. Participants completed a single testing session. All participants completed identical assessments. The order of these was counterbalanced.

6.2.3 Procedure

Participants were familiarised with the electrophysiology laboratory and EEG recording procedures before informed consent was taken. They completed EEG recording during three conditions including episodic prospection, resting and waiting. The experiment took approximately 120 minutes.

The PROSPECTION task was adapted from the protocol developed by Benoit et al (Benoit et al., 2011). Participants were asked to both estimate what a monetary amount could purchase and then imagine themselves spending that money in those situations. Each scenario included an “estimate” condition and an “imagine” condition. For example, for the lunch scenario they were asked to elaborate as much detail as possible about where they would be and what might happen if in 30-day time they were given £20 to spend for a lunch event. Each condition lasted for 30 seconds. Prior to commencement participants were asked to rate 24 everyday scenarios in terms expected level of enjoyment (e.g. lunch, pub, cinema, city break). The twenty events with the highest ratings were selected for the main task. The four scenarios not chosen were employed as practice. Each scenario was then randomly assigned one of the combinations of five reward magnitude (£10, 12, 15, 18, 20) and four delays (30, 60, 90, 120 days). The resulting 40 trials were split into two blocks with a short break in the middle of testing, presented in a random order.

The REST condition asked participants to relax for five minutes and focus on the fixation cross on the monitor. In the waiting condition (C-WAIT) participants were given a choice to wait for five minutes to win a ticket for a £20 lottery draw, or to immediately terminate the waiting period.

6.2.4 Electrophysiological Acquisition

EEG was recorded using a Neuroscan Synamps2 70 channel system via 24 bit A/D converter with direct current (DC) procedure, combined with a 70 Hz low-pass filter, sampling at 500 Hz. Participants were fitted with an electrode cap with 66 equidistant Ag/AgCl electrodes and a nose reference (Easycap; Hersching, Germany). EEG data from the first 55 electrodes were used for analysis. Impedance was kept below 5 kΩ. Electro-oculogram (EOG) was record using Ag/AgCl electrodes placed below the left and right eyes to measure vertical movements.

6.2.5 EEG data processing

EEG data processing was performed using Brain Electrical Source Analysis (BESA research 6.0) programme. The entire EEG signals in time series were transformed into a 29-node regional source montage (Figure 6.1, Franzen et al., 2013; Wilson et al., 2013) via inverse spatial filtering. Each regional source node had three orthogonal orientations. After transforming into source space, the time series signals were divided into epochs of 1600ms and screened for artefact. Artefact rejection was performed based on a fixed threshold method supplemented with careful visual inspection. For each condition and participant, the artefact-free epoch were transformed into time-frequency space using complex demodulation (Hoechstetter et al., 2004). The following analysis sampled frequency between 1 and 50 Hz in steps of 0.5Hz and steps of 100ms at the epochs.

To increase the power and sensitivity, a hypothesis driven, region of interests (ROI) strategy which focused on the signals sourced to the core DMN hubs was employed. The seed regions of ROI analysis included the midline anterior and posterior hubs of the DMN, i.e. medial prefrontal gyrus (MPFC) and precuneus (pC), as well as areas related to episode memory, i.e. left and right middle temporal gyrus (LMTG & RMTG). LMTG and RMTG were examined separately in order to determine brain localisations of prospection. Also it allowed us to evaluate the coherence of MTG between two hemispheres. The absolute amplitude spectrum within each seed region was extracted and nature log transformed to normalise the distribution (Gasser et al., 1982). Phase coherence was computed using phase-locking value (PLV) through the method described by Lachaux and colleagues (Lachaux, Rodriguez, Martinerie, & Varela, 1999). For each participant the PLVs were calculated over epochs for each region pair, each frequency band and each condition respectively. The PLV calculates the correlation between two normalised spectral density functions. It reflects the integration between two spatially apart signals and separates the effect of amplitude. The values of PLVs range from 0 to 1. Value close to 1 indicates the phases between two signals at a given frequency are well synchronised, whereas value close to 0 indicates substantial phase variation.

This study focused on three bands sampled from across the full range of EEG frequencies (delta (Δ): 1-4 Hz, alpha (α): 8-12Hz and beta (β): 12-34Hz). Delta is the lowest conventional EEG frequency band and is suggested to reflect sensory disengagement (Anderson & Horne, 2003). Alpha activity, which often shows a negative correlation with the theta activity, is associated with restfulness and self-referential thoughts (Knyazev et al., 2012). Beta has been considered as an index of cortical arousal, reflecting active cognitive processing and concentration (Rangaswamy et al., 2002).

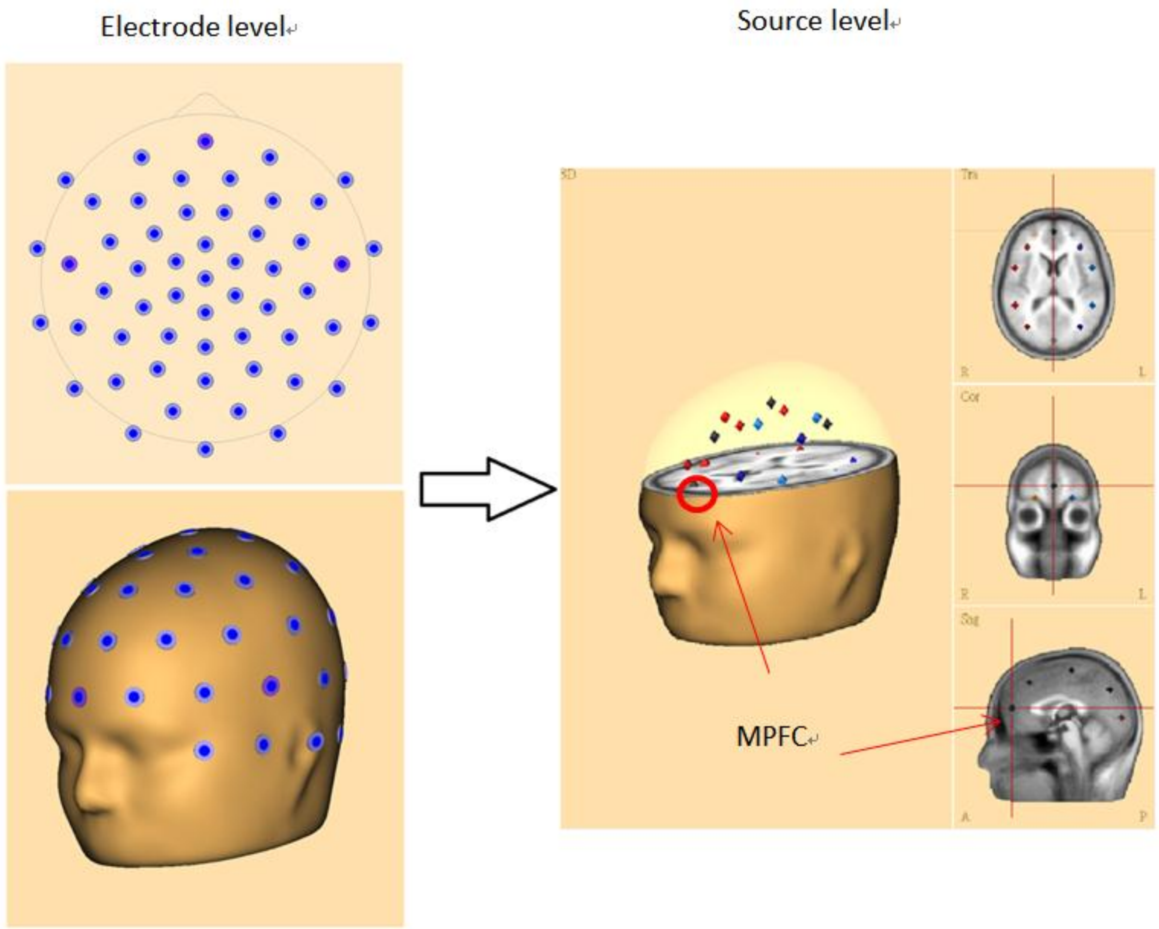


Figure 6.1 The regional source model.

Scalp recorded EEG signals from 55 electrodes (left) were fitted to a 29-regional source model (right) adopted from Wilson et al. (2013). Each node of the model was spaced equidistant apart (> 1 cm^3). The brain oscillations across the whole scalp were sourced to the nearest node. Therefore the source represents activity over an extended brain region rather than the amount of activation at a specific neuroanatomical coordinate. For example, the arrow points to the MPFC seed region, which covers the medial and superior frontal gyrus areas.

6.2.6 Data analysis

Two participants were excluded from the analysis. One participant did not complete the waiting condition because of a technical problem. The other participant's EEG data quality was poor, probably due to her afro. The condition differences were tested using two-way repeated measures ANOVAs with Condition (PROSPECTION versus REST and PROSPECTION versus C-WAIT) and Region (LMTG, MPFC, pC, RMTG) as the within subject variables and EEG amplitude as the dependent variable. Similarly, the differences of PLVs were tested using two-way repeated measure ANOVAs with Condition (as above) and Pathway (MPFC-LMTG, MPFC-pC, MPFC-RMTG, LMTG-pC, LMTG-RMTG and pC-RMTG, six in total) as the within subject factors. Post hoc tests with Bonferroni correction were applied to clarify significant interaction effects.

6.3 Results

6.3.1 Amplitude

There was no difference between the "estimate" and the "imagine" components on the PROSPECTION task (see *Appendix 3*), thus these were combined for the main analysis. Table 6.1 provides a summary of statistical effects. Figure 6.2 shows the EEG amplitude for regional seeds for each condition by frequency band. The ANOVAs for amplitudes showed a significant main effect of Region and a Condition x Region interaction in all frequency bands. The effects of Condition were significant in the alpha and beta bands. Compared to the REST condition, the PROSPECTION task induced significantly lower activity in the MPFC in all frequency bands. A similar pattern was seen for the pC region in the alpha band. In addition, there was an increase of LMTG activity in the delta and alpha bands, as well as an increase of RMTG activity in the delta band. For the ANOVAs comparing the PROSPECTION task and C-WAIT conditions there were significant main effects of Region and Condition, as well as Condition x Region interactions in all frequency bands. Compared to the C-WAIT condition, the PROSPECTION task was associated with reduced MPFC activity in the alpha band. Moreover, the PROSPECTION task induced a bilateral increase of MTG activity across all frequency bands, as well as increased pC activity in the delta band.

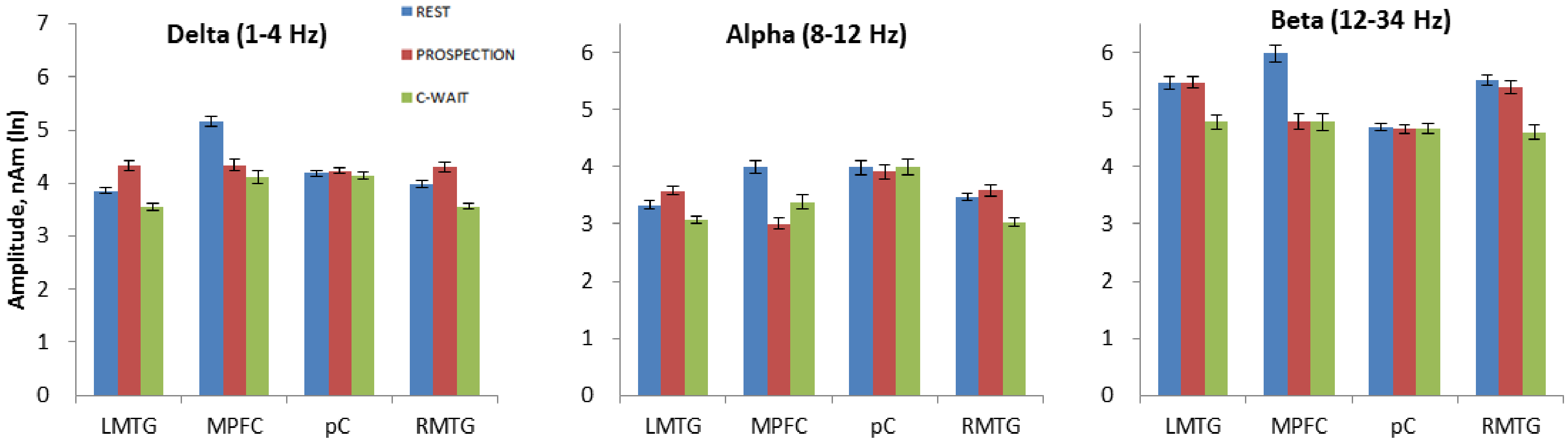


Figure 6.2 EEG amplitudes within the seed sources in the resting, prospection and waiting conditions by frequency bands.

Note. MPFC: medial prefrontal gyrus; pC: precuneus; LMTG: left middle temporal gyrus: RMTG: right middle temporal gyrus. Bars represent standard errors.

Table 6.1 Summary of ANOVAs for EEG amplitude comparing prospection with resting and waiting states.

Amplitude (ln)	**Condition**	**Region**	**Interaction**	**Post hoc results** **PR > R or PR > W** **(*p* <.05)**	**Post hoc results** **PR < R or PR < W** **(*p* <.05)**
PROSPECTION (PR) vs. REST (R)					
Delta	*F*=.01	*F*=38.37***	*F*=52.97***	PR>R: LMTG & RMTG	PR<R: MPFC
Alpha	*F*=9.02**	*F*=10.64***	*F*=39.77***	PR>R: LMTG	PR<R: MPFC & pC
Beta	*F*=22.39***	*F*=30.91***	*F*=26.71***	N/A	PR<R: MPFC
PROSPECTION (PR) vs. C-WAIT (W)					
Delta	*F*=.49.90***	*F*=6.27**	*F*=18.46***	PR>W: pC, LMTG & RMTG	N/A
Alpha	*F*=11.17**	*F*=18.08***	*F*=25.45***	PR>W: LMTG & RMTG	PR<W: MPFC
Beta	*F*=42.52***	*F*=8.16***	*F*=17.98***	PR>W: LMTG & RMTG	N/A

Note. ***p* < .01, ****p* < .001; Post hoc analysis used Bonferroni correction. MPFC: medial prefrontal gyrus; pC: precuneus; LMTG: left middle temporal gyrus: RMTG: right middle temporal gyrus.

6.3.2 Phase coherence

Figure 6.3 shows the PLVs of each pathway pairs across conditions per frequency band. Table 6.2 provides the statistical information. Figure 6.4 marks the significant results of PLVs in the delta band implicating the PROSPECTION task. Compared to the REST condition, there were significant main effects of Pathway across all frequency bands. The Condition effect was significant in both the delta and alpha bands. Moreover, there was a significant Condition x Pathway interaction in the delta band, which was driven by significantly greater phase coupling in the links between MPFC and pC, MPFC and RMTG, as well as LMTG and RMTG during the PROSPECTION task. While compared to the C-WAIT condition, the main effect of pathway was significant across all frequency bands. The significant main effect of condition and the interaction were only seen in the delta band. Compared to the C-WAIT condition, the PROSPECTION task showed higher phase coupling in the link between the MPFC and RMTG, as well as between LMTG and RMTG.

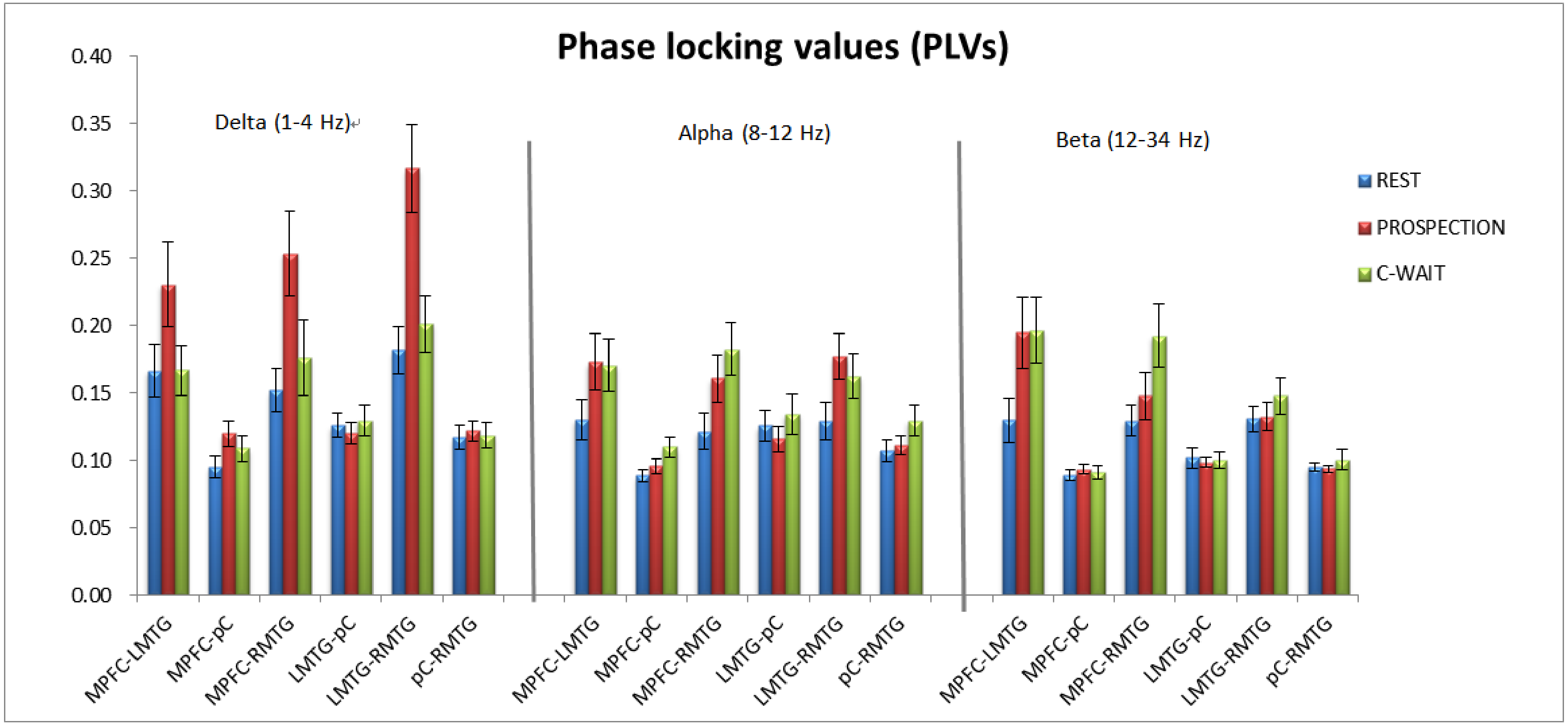


Figure 6.3 EEG phase coherences in the resting, prospection and waiting conditions by frequency bands.

Note. MPFC: medial prefrontal gyrus; pC: precuneus; LMTG: left medial temporal gyrus; RMTG: right medial temporal gyrus (RMTG). Bars represent standard errors.

Table 6.2 Summary of ANOVAs for phase coherence comparing prospection with resting and waiting states.

Phase coherence (PLVs)	Condition	Region	Interaction	Post hoc results PR > R or PR > W	Post hoc results PR < R or PR < W
PROSPECTION (PR) vs. REST (R)					
Delta	F=14.11***	F=30.03***	F=6.86***	MPFC – pC* MPFC – RMTG*** LMTG – RMTG***	N/A
Alpha	F=8.21**	F=8.10***	F=2.24	N/A	N/A
Beta	F=2.96	F=14.88***	F=2.42	N/A	N/A
PROSPECTION (PR) vs. C-WAIT (W)					
Delta	F=8.94**	F=27.87**	F=4.77**	MPFC – RMTG* LMTG - RMTG **	N/A
Alpha	F=.91	F=8.59***	F=.73	N/A	N/A
Beta	F=1.51	F=21.10***	F=.67	N/A	N/A

Note. **p* < .05, ***p* < .01, ****p* < .001; Post hoc analysis used Bonferroni correction. MPFC: medial prefrontal gyrus; pC: precuneus; LMTG: left middle temporal gyrus: RMTG: right middle temporal gyrus.

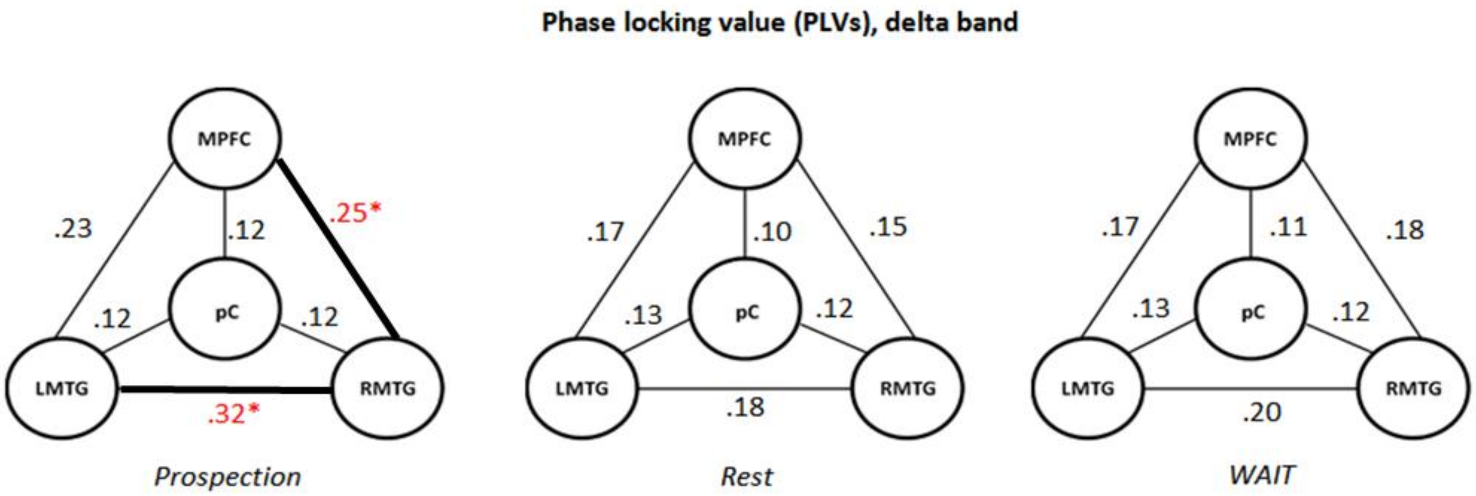


Figure 6.4 Differential patterns of phase coherences in the delta band.

The values in red showed the pathways with significantly greater coherence during the PROSPECTION task compared to both REST and WAIT conditions. PROSPECITON > Rest: MPFC-pC, *p* = .011; MPFC-RMTG, *p* = .001; LMTG-RMTG, *p* = .001. PROSPECITON > C-WAIT: MPFC-RMTG, *p* = .05; LMTG-RMTG, *p* = .003. Post hoc analysis used Bonferroni correction.

Note. MPFC: medial prefrontal gyrus; pC: precuneus; LMTG: left medial temporal gyrus; RMTG: right medial temporal gyrus (RMTG).

6.4 Discussion

Previous research using fMRI has implicated a medial fronto-temporal axis within the DMN nodes in episodic prospection. Here we compared the EEG amplitude and phase coherence of these nodes during the PROSPECTION task and two control conditions, i.e. REST and C-WAIT. There were a number of findings of note.

6.4.1 Activity in the medial prefrontal region was attenuated during prospection compared to resting and waiting.

First, the PROSPECTION task was associated with significant amplitude reductions in the MPFC region, which in line with the study prediction and the goal-directed nature of the task. This effect was most marked for the comparison with the REST condition where it was seen across the three frequency bands examined. It was also accompanied by a significant reduction of the pC alpha activity. Results in the past regarding the roles of MPFC in self-referential processing have been inconsistent – with some studies showing elevated and some reduced MPFC activity during episodic prospection. For instance, increased activity in the MPFC during prospective thinking (Addis et al., 2007; Benoit, Gilbert, Frith, & Burgess, 2012; Lavallee & Persinger, 2010) but reduced activity in the MPFC was seen during an internally oriented but attention-demanding task (Gilbert et al., 2012). Furthermore, the dorsal MPFC activity was increased during a self-referential judgment task while the ventral MPFC was attenuated, suggesting the multifaceted contribution of the MPFC to internal oriented cognition (Gusnard et al., 2001). The inconsistency in a way reflects the fact that prospection is self-referential and also goal-directed and effortful. On the one hand, the attenuation of activity in the MPFC during episodic prospection compared to the resting state might suggest an actual reduced engagement of self-referential processes (Knyazev, 2013b) – which is unlikely to be the case in this study. More likely in the current case is that compared to the resting state, episodic prospection requires mental effort. Some of the inconsistency between studies with regard to the MPFC therefore can be explained by the choice of different control conditions. For instance, Benoit et al. (2011) compared the "imagining" condition with the "estimate" condition (both goal-directed and effortful tasks) and found reduced MPFC activity in the later, whereas in this study we contrasted a general prospection condition with pure resting. By including the REST condition as a comparison in the current experiment we were to some extent able to isolate the neural correlates of the goal-directed nature of prospective thinking process.

6.4.2 Activity in the medial temporal areas was increased during prospection compared to resting and waiting.

Second, the PROSPECTION task was associated with increased MTG activity. The effects were strongest for the comparison with the C-WAIT condition where they were present bilaterally for all frequency examined bands while for the comparison with the REST condition they were only seen bilaterally in the delta band and in the left MTG in the alpha band. This finding is significant for a number of reasons. First, it confirms fMRI studies that have previously implicated DMN temporal regions during prospective thinking – suggesting that envisioning the future involves the integration of function subserved by this region (i.e., autographical memory). Second, the different direction of activity changes vis-a-vis the MPFC during prospection (increase rather than decrease) highlights the differentiated nature of the DMN and its functional heterogeneity (Laird et al., 2009). Third, the fact that the contrast was greatest between the PROSPECTION task and C-WAIT condition suggests that in the latter condition, once the decision to wait is made, there is little active envisioning of the future. In fact there is evidence to suggest that focusing on future outcomes while waiting makes the task more frustrating and difficult (Broyd et al., 2012). In contrast, during resting it is quite possible that there was some element of day dreaming occurring which may activate brain regions involving in both retrospective and prospective cognition.

6.4.3 Increased phase coherence

Third, the PROSPECTION task was associated with increased synchrony within the DMN regions particularly implicating temporal regions – although the synchrony of MPFC – pC was also enhanced compared to the REST condition. This finding highlights the importance of taking a systems neuroscience view of the role of the DMN in self-referential cognitive processes (Cortese et al., 2012). Research on functional connectivity is in its infancy and has been principally investigated using fMRI. Travis and colleagues recently uncovered evidence of frontal inter-hemispheric EEG coherence during meditation compared to resting, with sources overlapping the DMN (Travis et al., 2010). The work of Travis et al. provided promising evidence for using EEG coherence as a measure of spontaneous cognition. However, their study computed the synchrony of EEG signals between electrode pairs on the scalp level. To our knowledge, this study is the first to apply measures of EEG coherence between intracranial sources corresponding to the DMN. Further work is required to replicate and validate the current findings.

The way that the MPFC and MTG interact to provide the neural foundations for prospection has not been not well understood. The MTG is a crucial brain region subserving episodic memory and is active when consciously recollecting personal experience (Dickerson & Eichenbaum, 2010). It has been proposed to coordinate associative processing of memory systems and provide a basis for imagination (Bar, Aminoff, Mason, & Fenske, 2007). It interacts with the MPFC, the area associating with self-projection and decision making, to mediate more complex processes such as perspective taking (Van Hoeck et al., 2013) and mentalising (Frith & Frith, 2006). Fink and colleagues (2009) investigated the EEG activity among tasks requiring creative thinking and a habitual task between professional and novice dancers (Fink, Graif, & Neubauer, 2009). The authors reported a significant task effect where creative tasks enhanced alpha activity in the frontal, frontocentral and centrotemporal brain regions. Although both creative and prospective thinking processes involve seeking associative information from episodic memory, creative thinking lays a great stress on generating novel ideas, which possibly enhances the activity in frontal area. By contrast, prospective thinking focuses on anticipating similar events and elaborating their detail, which may rely mainly on associative information and therefore activate the temporal lobe memory circuits.

6.4.4 Limitations

This study had several limitations that need to be considered when interpreting the results. First, the EEG regional sources reflected a collection of neural activity within an extended area instead of at a specific neuroanatomic coordinate. The activity of a seed region may involve signals from neighbouring structures. Further work using a whole brain analysis and/or co-registration of structural imaging data is recommended. Second, EEG coherence measure may be contaminated by volume conduction of the current through separating sources. However, the interference of volume conduction has been demonstrated to be most dominant in high frequencies (e.g. 40-50 Hz) but has less effect on lower frequency bands (Srinivasan, Winter, Ding, & Nunez, 2007). Moreover, the influence of volume conduction decreases with the increase of the distance between two sources. In this study the nodes of each source pathway were remote from each other. Besides, our results showed that prospection implicated greater delta EEG synchrony among MPFG and MTGs compared to resting state. Our findings therefore seem to reflect genuine source coherence. Third, although PLV was used as an index of coherence to separate it from the contribution of amplitude, the confounding with amplitude effects cannot be entirely ruled out. Fourth, this study focused on EEG signatures in traditional frequency bands instead of infra-slow brain waves. The main purpose of this study was to differentiate EEG correlates during prospection from resting and waiting. Thus the prospection task required participants to make short imaginations (30s per trial) for various scenarios in case participants finished their imagination early they may became bored or mind wandering. Applying the examination of VLF EEG in current study design is not ideal because it requires a continuous recording longer enough to contain a few slow brain waves (e.g. 5 min). Further research could amend the prospection task and extend the exploration into infra-slow frequency bands. Fifth, this study did not compare the EEG during prospection with other cognitive tasks. With the reference to an adequate task condition would be useful to control the effect of cognitive load. Fourth, this study did not compare the EEG during prospection and other cognitive tasks. However, an adequate task condition would be a useful control condition along with resting and waiting states because it would control the influence of cognitive load. Finally, the findings of this study were based on a modest size of sample and non-clinical participants. It is important for the future work to examine EEG signatures during episodic prospection with a larger population including a group of clinical subjects.

6.5 Conclusions

Here we extended the study of the neural mechanisms underpinning episodic prospection from fMRI to EEG. Compared to pure resting and waiting states, episodic prospection was associated with significantly reduced MPFC activity and increased MTGs activity across frequency bands and an increase of MPFC-MTG phase synchrony in the delta band. These results highlight the differentiated nature of the DMN in self-referential cognition and the importance of a medial fronto-temporal axis in prospective cognition.

Chapter 7 General discussion

7.1 Introduction

Previous research has demonstrated that individuals with ADHD failed to attenuate spontaneous neural oscillations within the default mode network (DMN) in the transition from resting to engaging in cognitive tasks (Fassbender et al., 2009; Helps et al., 2010; Liddle et al., 2011). The default mode interference (DMI) hypothesis proposes that the reduced attenuation may be a major source of the disruption of task performance (Sonuga-Barke & Castellanos, 2007). This thesis extends the DMI hypothesis and predicts that the interference of DMN activity may not only affect cognitive task performance when processing external cognitive stimuli, but may also influence internal oriented processes such as waiting for a delayed reward. This thesis investigated spontaneous neural oscillations between resting and waiting states using direct current coupled electroencephalography (DC-EEG), as well as ADHD-related dysregulation of the resting brain activity when waiting. Moreover, it explored if waiting played a role in prospective thinking - as both of the two processes seemed to involve anticipation to the future. To these ends three independent studies were performed. The first two studies investigated very low frequency (VLF) EEG during resting, waiting and working on a cognitive task in healthy adults (**Chapter 4**), and in children and adolescents with ADHD (**Chapter 5**), respectively. The last study explored the EEG correlates within DMN regions during episodic prospection compared to resting and waiting states (**Chapter 6**). This final chapter provides a general discussion for the findings across studies and their implications. The limitations of the studies and some directions for future research are discussed.

7.2 Summary of findings

7.2.1 VLF EEG between resting and waiting

Spontaneous VLF EEG at rest and during two different types of waiting conditions (C-WAIT – choosing to wait for five minutes for a lottery ticket, and F-WAIT – be forced to wait for five minutes), and during cognitive task performance (a simple reaction time task) was assessed in a sample of university students with either high- or low-ADHD self-rating scores in **Chapter 4**, and in a sample of clinic-referred children and adolescents (aged 9 to 15) with ADHD and age and gender-matched healthy controls in **Chapter 5**. Table 7.1 provides a summary of the main findings from both chapters.

Table 7.1 A summary of main findings from Chapter 4 and Chapter 5.

	Chapter 4	Chapter 5
1. Participants have a clinical diagnosis of ADHD	×a	✓
2. A VLF EEG network was identified along the frontal midline and central posterior cortex.	✓b	✓
3. At rest the VLF EEG was more active within the network than outside of the network.	✓	✓
4. Significant rest-to-work attenuation of VLF EEG within the network was identified in healthy participants.	✓	✓
5. Significant rest-to-wait attenuation of VLF EEG within the network was identified in healthy participants.	✓	✓
6. The rest-to-work/wait attenuation of VLF EEG located at midline structures overlapping with the DMN.	✓	✓
7. Incentive induced greater rest-to-wait attenuation.	✓	×
8. ADHD is associated with reduced rest-to-wait attenuation of VLF EEG.	×	✓
9. Waiting increased VLF EEG in temporal areas in ADHD.	×	✓
10. Rest-to-wait attenuation was related to delay aversion and delay discounting.	×	✓

Note. a) The high-ADHD group in **Chapter 4** comprised individuals who were rated as having six or more ADHD symptoms. But none of them had a clinical diagnosis of ADHD; b) in **Chapter 4** the VLF EEG network was defined using a data-driven approach with the 18 electrodes showing highest rest-to-task attenuation, whereas in **Chapter 5** the VLF network was defined *a priori* using 18 electrodes along the anterior and posterior scalp midline.

It is clear from Table 7.1 that the two studies gave a number of consistent findings except the group effect of ADHD was significant in **Chapter 5** only. One possible reason was that the adult samples in **Chapter 4** were high functioning university adult students without a clinical diagnosis of ADHD. Moreover, in both chapters the control groups exhibited significant rest-to-wait attenuation of VLF EEG to a similar level as the degree of rest-to-work attenuation seen in that study. The waiting conditions with and without a monetary reward induced different effects on the rest-to-wait attenuation in the two age samples. While adults exhibited greater attenuation of VLF EEG when waiting for a reward (C-WAIT) compared to the condition when they were forced to wait (F-WAIT) in **Chapter 4**, the children and adolescents showed similar levels of attenuation during the two types of waiting condition tasks in **Chapter 5**. Furthermore, individuals with ADHD exhibited reduced attenuation of VLF EEG during cognitive task performance. Notably, during waiting they did not effectively attenuate the resting VLF EEG. Instead, they displayed increased VLF EEG activity in the temporal regions including insula and amydgala although this effect was not significant after correcting for multiple comparisons. Moreover, within the whole sample the rest-to-wait attenuation of VLF EEG was correlated with delay aversion and delay discounting scores rated by participants' parents, suggesting an association between the dysregulation of spontaneous VLF EEG and waiting difficulties.

7.2.2 Episodic prospection implicates a medial frontal-temporal axis compared to resting and waiting states.

The exploration of spontaneous neural oscillations was extended from waiting conditions to occasions of episodic prospection in **Chapter 6**. Functional magnetic resonance imaging (fMRI) studies have implicated a medial fronto-temporal axis within the DMN during episodic prospection. **Chapter 6** provides the first quantitative EEG evidence of similar effects - sourced to the regions of the DMN during episodic prospection. Specifically episodic prospection is associated with significantly reduced activity in the medial prefrontal area (MPFC) and increased activity in the bilateral medial temporal gyrus (MTGs) across delta, alpha and beta frequency bands, and an increase of MPFC-MTG phase coherence in delta band compared to resting and waiting states. This study highlights the importance of a medial fronto-temporal axis in prospective cognition and the heterogeneous nature of the DMN in spontaneous, self-referential cognition.

7.3 Implications of thesis findings

The thesis is the first to extend the investigation of VLF EEG to waiting state and its association with the waiting difficulties of ADHD. It is also the first to differentiate the EEG correlates sourced to the DMN regions from episodic prospection to resting and waiting states. There are a number of promising findings. The implications of these results are discussed below.

7.3.1 Rest-to-wait attenuation of VLF EEG

7.3.1.1 What causes the attenuation of the spontaneous VLF EEG?

Chapter 4 – 5 present the first examination of VLF EEG during the transition from rest to waiting tasks. Crucially the studies demonstrated that resting VLF EEG not only attenuated during cognitive task performance – a very important character of the DMN activity, but also attenuated during low cognitive demanding waiting tasks in healthy adults and youths.

The demonstration of rest-to-wait attenuation of VLF EEG is of particular interest because it sheds light on active top-down control required for the modulation of the resting brain activity. In contrast to the dominant neuroimaging literature which focuses on attenuation induced by active ‘working’ states, it is clear from this thesis that cognitive information processing is not the only cause of VLF EEG attenuation. As suggested in **Chapter 4**, a number of internal and external characteristics, including the goal-directedness of the task, mental effort and motivational factors and their interplay may affect the extent of VLF EEG attenuation.

7.3.1.2 The role of the goal-directed nature of tasks in the modulation of VLF EEG

Both resting and waiting involve a period of idle time in the absence of external oriented attention demanding stimuli. However, compared to resting, waiting has a particular goal and ends with a specific outcome being secured. In this regard waiting is like a subjective reframed state of resting, with a goal-directed nature which generates an intrinsic drive toward the desired result. It is suggested that the intrinsic drive for success may significantly change the neural resources allocation and cause attenuation of resting VLF EEG. As demonstrated in **Chapter 5,** the working and waiting induced attenuation of VLF EEG was most pronounced along frontal midline structures (e.g. medial frontal gyrus, BA 6). Consistently, as described in **Chapter 6**, episodic prospection was also produced attenuation in the MPFC area but not in other DMN regions across traditional frequency bands compared to resting. Taken together, the goal-directed nature may be crucial for the attenuation of resting brain activity, at least in frontal areas.

7.3.1.3 The influence of motivation on rest-to-wait attenuation

As mentioned **in Chapter 4**, motivation may enhance the attenuation of VLF EEG as the adult participants exhibited greater suppression of VLF EEG during the C-WAIT condition – when they chose to wait for an incentive, rather than in the F-WAIT condition – when they were forced to wait. However, the influence of this incentivisation was not significant in the sample of children and adolescents described in **Chapter 5**. One possible explanation is that the motivational effect is more significant in adults than in children and adolescents because research has showed that people become more selective in spending their resources with the increase of age (Carstensen, 1995). The other possible explanation is that the influence of motivation may be mediated by other factors, such as task difficulty. Emerging evidence has suggested that the level of attenuation is not only affected by incentives (Liddle et al., 2011) but also by the level of cognitive load (McKiernan, Kaufman, Kucera-Thompson, & Binder, 2003). It is possible that the waiting tasks are more effortful to children and adolescents than to the adults therefore the youths exhibited significant rest-to-wait attenuation during both waiting tasks. In some way the latter explanation seems to be more plausible because the monetary reward for waiting in this thesis (a ticket for a £20 lottery draw) is supposed to be more valuable and motivating to youths than adults, which is not consistent with the former explanation. However, the relationship between motivation and task difficulty and their interaction on the modulation of VLF EEG requires further investigation.

7.3.1.4 Developmental trajectories of the DMN

In this thesis the first study observed that healthy adults attenuated resting VLF EEG significantly when they chose to wait, but they attenuated VLF EEG to a less extent when they were imposed to a period of delay. However, the second study showed that in typically developing children the level of attenuations of VLF EEG were similar between the two waiting conditions. As reviewed in Chapter 1, studies regarding to the development of the DMN have incongruent findings. It is not clear whether the divergent finding between the two studies in this thesis reflects age difference. A future study with longitudinal design and a larger sample size is required before a sound conclusion can be made. Moreover, children with ADHD have shown abnormal development trajectories in brain volume (Castellanos et al., 2002). Exploring abnormalities in the developmental course of the DMN in ADHD cases across the life span would be particularly useful for the understanding of psychophysical pathology of ADHD.

7.3.1.5 Could VLF EEG mirror DMN BOLD activity?

Similar to DMN BOLD fluctuations, the VLF EEG power was active at rest and attenuated during the performance of an attention demanding task. The rest-to-work attenuation of VLF EEG was sourced to midline structures overlapping with the regions of the DMN. This raises the question of whether the VLF EEG mirrors the DMN BOLD activity in this respect. As mentioned in **Chapter 1,** the scalp EEG recordings and fMRI BOLD signals are different measurements of neural activity. The relationship between fMRI and EEG signals is complicated and not well understood (Laufs, Krakow, et al., 2003). Although simultaneous EEG-fMRI studies have identified a relationship between very low frequency fluctuations in scalp recorded EEG and BOLD signals at rest (Hiltunen et al., 2014), the literature has not investigated the relationship between the attenuation of VLF EEG power and the suppression of DMN BOLD signals during working and waiting. Direct comparison for the attenuation of VLF EEG and DMN BOLD signals is beyond the scope of this thesis. But this relationship can be tested by co-registering the EEG signals with structural imagines attained from MRI or using simultaneous fMRI-EEG recordings in the future work.

7.3.1.6 Reduced rest-to-work attenuation of VLF EEG in ADHD

As mentioned in **Chapter 3**, the DMI hypothesis suggests that persisting DMN activity during cognitive task performance produces a pattern of occasional attentional lapses, a problem commonly observed in ADHD (Sonuga-Barke & Castellanos, 2007). As predicted from the DMI hypothesis, individuals with ADHD showed less rest-to-work attenuation of VLF EEG than controls (**Chapter 5)**. This was accompanied with increased performance errors and elevated response variability. These findings were in line with previous literature using DC-EEG (Helps et al., 2010) and fMRI (Fassbender et al., 2009), although the investigation of the periodic nature of response errors was not the focus of this thesis (Helps et al., 2011),

7.3.1.7 Altered waiting VLF EEG in ADHD

While the healthy controls displayed rest-to-wait attenuation of VLF EEG, individuals with ADHD exhibited excess VLF EEG activity during both waiting tasks in term of VLF EEG power judged across the scalp network, despite the existence of isolated and non-significant attenuations in a number of DMN regions (**Chapter 5**).

Chapter 3 describes five theories of ADHD and the possible explanations and predictions for the waiting difficuties found with individuals with this disorder. The cognitive-engergetic model (CEM) suggests that information processing is determined by the interplay of attention, state factors (i.e. arousal, activation and motivation) and executive function. Individuals with ADHD are hypothesised to have deficits at all three levels, in particular the state factors. Waiting difficulties of ADHD may be explained as state dysregulation, i.e. they may be due to a lack of motivation to wait, or individuals with ADHD may not make sufficient effort or arousal when waiting. Although the thesis did not evaluate the subjective value of effort and objective measures of arousal, it included two types of waiting conditions with and without incentives for waiting to explore to influence of self-determination and motivation in rest-to-wait attenuation of VLF EEG. However, the incentive of C-WAIT condition did not improve the level of attenuation of VLF EEG in children and adolescents with ADHD (**Chapter 5**) although it caused more prominent attenuation in the adult sample compared to the waiting condition without incentives (**Chapter 4**). As discussed above the influence of motivation may be mediated by task difficulty, subject age and medication (see *7.3.1.3 The influence of motivation on rest-to-wait attnuation*). This thesis therefore cannot find direct evidence supporting the CEM.

The delay discounting and delay aversion hypothesis predict that participants with ADHD would prefer non-waiting over waiting options (Scheres, Tontsch, et al., 2010; Sonuga-Barke, 2003). If waiting is inescapable they would become frustrated, display excess behaviours for the purpose of self-stimulation or distraction so that the aversive feeling of waiting could be reduced. In this sense the excess VLF EEG activity during waiting may reflect a positive coping strategy, e.g. engaging in introspective and self-referential mental activity, such as mind wandering (Christoff et al., 2009). The results in **Chapter 5** tend to support the delay aversion hypothesis rather than the delay discounting of ADHD because the majority of participants with ADHD (20 out of 21) completed the C-WAIT task and waited for five minutes even though they were offered a chance to quit the delay. According to the subjective experience ratings, children with ADHD appeared to be more frustrated and spent more effort to complete the experiment. But when there was an incentive for waiting they found waiting was easier despite their self-report of mind wandering did not differ from the control group. Moreover, during waiting individuals with ADHD displayed increased VLF EEG in areas around the brain's emotional centre, i.e. insula and amygdala, suggesting that waiting induced negative affection in ADHD. This finding was in line with previous fMRI studies which demonstrated an altered level of increased activity in the striatum and amygdala during delayed reward processing in ADHD (Plichta et al., 2009; Wilbertz et al., 2013).

The original fomulation of the DMI hypothsis suggests that the the instruction of DMN activity during cognitive tasks would produce periodic disruptions of performance (Sonuga-Barke & Castellanos, 2007). From this point of view waiting difficulties of ADHD may be caused by persisting VLF EEG during waiting tasks. This argument was supported as individuals with ADHD failed to supress the VLF EEG activity when transitioning from resting to waiting tasks. Based on the DMI hypothesis, the disruptions of performance would emerge in very low frequency. The waiting difficulties seen in individuals with ADHD, such as displaying higher levels of activity, fidgeting or squirming in their seat or becoming more and more frustrated may be coupled with periodic instruction of DMN activity. Studying temporal synchrony between behavioural manifestations of waiting difficulties and excessive waiting VLF EEG was beyond the scope of this thesis, but future studies could examine the periodicity of waiting difficulties by collecting subjective and objective measures, e.g. taking video recording during waiting and coding participants' responses or using self-report questionnaires to quantify spontaneous thoughts and emotions during waiting.

The integrative neuroeconomic model of ADHD proposed by Sonuga-Barke and Fairchild (2012) suggests that DMN plays an important role in the integration of past and future-related autobiographical information to drive decisions relating to a desired goal. Importantly altered VLF neural oscillations might influence individual's ability to focus on, and achieve, the goal of waiting (Sonuga-Barke & Fairchild, 2012). This thesis showed that participants with ADHD were able to complete the waiting tasks but showed abnormalities in rest-to-wait attenuation of VLF EEG. It appears that the participants with ADHD were able to make a decision with long term pay-off but failed for it to be delivered. Future studies on decision making processes in ADHD and their connection with waiting VLF EEG are therefore recommended.

7.3.1.8 Association between disruption of waiting VLF EEG and waiting difficulties

The level of VLF EEG attenuation from resting to waiting was negatively correlated with the scores of delay aversion and delay discounting as rated by participants' parents (**Chapter 5**). This suggested the less rest-to-wait attenuation the heightened delay aversiveness and delay discounting. It is difficult to address the relation of causality between the attenuation of spontaneous VLF EEG and waiting difficulties. On one hand, the disruption of rest-to-wait attenuation of VLF EEG may impair an individuals' ability to focus on the goal of waiting and to tolerate a period of delay. On the other hand, as suggested by the delay aversion hypothesis if individuals are more averse to a period of delay and/or more impulsive then they are more likely to engage in self-referential thinking during waiting so that the negative feeling arising from delay may be reduced (Sonuga-Barke, 2002, 2005). As suggested above the former possibility should be verified by examining whether there is any periodicity in the timing of waiting difficulties and temporal coupling with the VLF EEG. The latter view have been tested by collect the participants' subjective reports of minding wandering after completing the waiting condition in **Chapter 5**, but there was no significant group difference.

7.3.2 Spontaneous neural oscillations during episodic prospections

7.3.2.1 The heterogeneous nature of the DMN in self-referential cognition

Attenuation of the DMN activity has been observed across a number of goal-directed tasks, with the exception of tasks involving self-referential processing, during which the DMN activity is increased (Andrews-Hanna, Reidler, Huang, et al., 2010). As the level of attenuation is suggested to reflect relative sources that need to be allocated to goal-directed task performance (McKiernan et al., 2003), it remains unclear why it is particularly during introspective processing that the DMN is not attenuated - these processes also have a goal-directed nature.

As demonstrated in **Chapter 6,** during episodic prospection, participants suppressed EEG amplitude in the MPFC and increased activity in the bilateral MTGs compared to that seen in resting and waiting states, suggesting functional heterogeneity in the DMN (Laird et al., 2009). While the increases in the MTGs were in line with the literature, the decreases in the MPFC appeared to contradict the idea that DMN regions were recruited during introspection and self-projection (Addis et al., 2007; Andrews-Hanna, Reidler, Huang, et al., 2010; Benoit et al., 2011). Although this inconsistency can partly be accounted by methodological issues (e.g. the selection of baseline condition), the current findings highlighted the possibility that the goal-directed nature of self-referential processes may cause attenuation in specific DMN regions. The MTG is the hub of one DMN subsystem which is recruited during memory retrieval, an essential ability when imagining about the future (Schacter et al., 2012). MPFC is one of the DMN regions which attenuate during goal-directed task performance (Fox et al., 2005; Raichle et al., 2001). MPFC is also associated with self-related simulations (Kim, 2012; Szpunar et al., 2007) and complex perspective-taking processes (Van Hoeck et al., 2013). Taken together, the role of MPFC in a self-referential but also goal-directed and effortful information process is complex. In addition, it is unclear if the current finding of attenuation in the MPFC region between episodic prospection and resting and waiting states is a distinct pattern only occurs in EEG correlates. Further work is required to study the functional significance of distinct DMN regions using different neuroimaging techniques.

7.3.2.2 Functional connectivity during episodic prospection

Episodic prospection induced greater delta phase coherence between the MPFC and MTGs compared to resting and waiting. Moreover, the synchrony between MPFC and precuneus was enhanced during episodic prospection compared to the resting state (**Chapter 6**). This finding highlights the importance of investigating large scale neural systems in spontaneous cognition (Castellanos & Proal, 2012; Cortese et al., 2012). It also supports the argument of Sonuga-Barke and Fairchild that the neural connectivity between regions of the DMN plays a more important role in the introspective processes than the regional activity alone (Sonuga-Barke & Fairchild, 2012). However, **Chapter 6** focused on the functional connectivity between DMN regions only. It is unclear whether the phase synchrony emerged only within the DMN, or if there is a wide spread pattern across the scalp. Future work in this area should examine EEG phase synchrony between other brain networks.

7.3.2.3 The impact of prospection on waiting

While some neuroimaging studies have demonstrated that envisioning about the future reduced discounting of delayed rewards implicating medial fronto-temporal interactions (Benoit et al., 2011; Lin & Epstein, 2014; Peters & Büchel, 2010), other research suggested that focusing on future outcomes while waiting made the task more frustrating and difficult (Broyd et al., 2012). The study reported in **Chapter 6** did not support the impact of episodic prospection on waiting. The contrast of EEG correlates between episodic prospection and waiting produced significant differences in the MPFC and MTGs areas, suggesting that while the decision to wait was made there was little envisioning involved . However, it remains uncertain if prospection affects the decision making process about whether to wait for a future reward. It is quite possible that prospective thinking, planning or anticipation have a significant influence on the decision making process of waiting.

7.4 Limitations

Several limitations have to be taken into account in interpreting the results of the studies described in this thesis.

First, the sample sizes employed among the studies were quite small. The first sample contained 21 high-ADHD scorers and 19 controls, the second sample contained 21 youths with ADHD and 21 controls, and the third sample contained 22 young adults. These sample sizes were sufficient to detect significant statistical differences between groups and conditions predicted but not for others, especially when the correction of multiple comparisons was made. Moreover, the limited sample size did not give sufficient power to determine the differences of EEG correlates between different ADHD presentations.

Second, in this thesis only one study was performed in a clinical sample with ADHD. As an alternative approach, the other studies assessed the ADHD effect from rating scores of symptoms of ADHD from healthy volunteers. As mentioned in **Chapter 2,** ADHD may be a continuous trait rather and a diagnostic category. Integrating dimensional and categorical approaches across all studies will better the investigation of psychophysiology in ADHD.

Third, the C-WAIT task in this thesis was designed as a voluntary condition that participants were free to decide whether they would like to complete it or simply quit it. Those who completed this waiting task may not have serious problem about waiting. For future research it is recommended to use a different task design that combines a fixed period of waiting topped up with varied delayed period to test the limit of participants' waiting tolerance.

Fourth, waiting difficulties have distinct manifestations. The studies reported within this thesis collected EEG recordings during waiting, but participants' real-time behavioural responses during waiting conditions were missed. Without behavioural data it is difficult to evaluate how participants reacted to waiting conditions. However, the rating scores about delay discounting and delay aversion provide general information to participants' responses to waiting in everyday life.

Fifth, given the limited spatial resolution of EEG signals, it is essential to apply the current paradigm in multi-model imaging studies as allowing simultaneous EEG-fMRI or magnetoenchphalography (MEG) recordings.

Finally, this thesis focused on neural oscillations within the VLF EEG network and the DMN regions. It is important to extend the investigation to other resting state networks and the task positive network (TPN) in the future. Since the DMN has an anti-correlated relationship with the TPN, it would be important to examine if there is also an anti-correlated component between different VLF EEG networks.

7.5 Future directions

The emerging literature on the resting brain inspired this thesis to evaluate the spontaneous neural oscillations between resting and waiting states and the association with waiting difficulties in ADHD. The results showed that while healthy controls attenuated VLF EEG from resting to waiting, individuals with ADHD did not suppress VLF EEG when waiting. Moreover, the lack of rest-to-wait attenuation was associated with impulsive decision making and delay aversion. Extending from the investigation, this thesis also explored the neural oscillations during episodic prospection and demonstrated that EEG correlates within the DMN differentiated episodic prospection from resting and waiting states. These results should be replicated in larger samples before sound conclusions can be made. Nevertheless, a number of implications can be developed from the current findings of this thesis. These can potentially make a significant impact in the psychopathology and treatment of ADHD. The applications and future directions in clinical, theoretical and research perspectives are discussed below.

7.5.1 Clinical perspectives

This thesis found that altered rest-to-wait attenuation of VLF EEG in a sample of ADHD group (**Chapter 5**). As ADHD is a heterogeneous disorder, it will be very important to assess whether altered waiting VLF EEG is associated with a specific ADHD presentation or a general pattern among children with ADHD. Based on the current literature, children with ADHD combined presentation have a stronger propensity to forego larger delayed benefits for immediate rewards compared to individuals with inattentive presentation and controls (Scheres et al., 2013; Scheres, Tontsch, et al., 2010). Hence future studies could include a group of ADHD combined presentation, a group of ADHD inattentive presentation and a group of matched typically developing controls to test if altered rest-to-wait attenuation of VLF EEG occurs in ADHD combined presentation group only. On the other hand, it may be possible to visualise the degree of rest-to-wait attenuation in VLF EEG and applied it on the neurofeedback treatment for ADHD. The degree of rest-to-wait attenuation can be used as a physiological index when developing training programme for the tolerance of waiting. Furthermore, this field of research can be extended to other psychiatric disorders characterised by impulsivity, such as substance use, conduct disorder, bipolar disorder and pathological gambling (Bickel, Jarmolowicz, Mueller, Koffarnus, & Gatchalian, 2012; Reynolds, 2006).

7.5.2 Research perspectives

The fact that spontaneous VLF EEG is attenuated during a period of delay highlights the goal-directed and effortful nature of waiting. The DMI hypothesis suggests that the intrusion of spontaneous VLF neural oscillations create periodic disruptions of task performance. This thesis extended the original DMI hypothesis and demonstrated that persisting spontaneous VLF EEG during waiting is associated with questionnaire ratings of delay aversion and delay discounting. It is important to record and analysis behavioural manifestations of waiting difficulties in the future work so that it is possible to assess the temporal characters between the excess waiting VLF EEG and occurrences of waiting difficulties in ADHD.

With regard to episodic prospection, the current thesis demonstrated that when envisioning future events specific DMN regions are implicated compared to resting and waiting states. Notably, episodic prospection may reduce delay discounting

(Benoit et al., 2011; Lin & Epstein, 2014; Peters & Büchel, 2010), possibly because that thinking about future promotes the consideration of delayed outcomes. However, current literature rarely explored the affective components of prospection (Lavallee & Persinger, 2010; Lin & Epstein, 2014). In a recent study Lin and Epstein (2014) demonstrated that the effect of episodic prospection on delay discounting was most prominent among participants with greater working memory, indicating the individuals with higher cognitive resources may be more capable for delay gratification because they have less difficulties visualising future outcomes. With regard to the emotional valence of prospection, 'neutral' future thinking reduced a greater extent of delay discounting compared to 'positive' future thinking among participants who displayed higher working memory capacity and those showed higher inhibition control on a go/no go task. Hence the authors suggested that positive affect may attenuate the protective effects of working memory on delay discounting. In this sense it appears that episodic prospection, emotional valence and working memory simultaneously modulate reward delay discounting. Follow-up research can extend the findings of this thesis and explore the effects of emotional valence and cognitive capacity on prospective thinking and their relations to waiting difficulties of ADHD.

7.5.3 Theoretical perspectives

The neuroeconomic model of ADHD proposed by Sonuga-Barke and Fairchild (2012) provides an integrative view for the different stages of economic decision-making processes and their links with the DMN, dorsal and ventral frontostriatal brain networks. The dynamic interactions among these brain networks/circuits are predicted to affect the efficacy of information processing in ADHD. As individuals with ADHD may have different degrees of alterations in each network, this theoretical model provides an integrative and inclusive framework for the analysis of different aspects of ADHD-related neuropsychological deficits. This thesis demonstrated supporting evidence for the model as there was a connection between excess waiting VLF EEG activity (corresponding to the DMN) and two components of impulsive choice – i.e. delay discounting and delay aversion. However, this thesis did not include comprehensive neuropsychological assessment to evaluate the effect of executive function underpinning the dorsal frontostriatal circuit. It is important for future work to systematically examine the alterations of each of these three networks and the effects of their interplays during a wider range of internal and external economic cognitive processes in individuals with ADHD. For instance, it is imperative to examine the influence of prospective thinking on delay discounting in ADHD, as well as whether this effect is affected by their working memory capacity and response inhibition.

7.6 Concluding remark

The aims of this thesis were to explore spontaneous neural oscillations during resting and waiting and to investigate the possible roles of these EEG correlates in waiting difficulties of ADHD. This thesis provided the first evidence that waiting induced attenuation of the resting state VLF EEG occurs even in the absence of external cognitive stimuli. Individuals with ADHD, however, failed to attenuate VLF

EEG during waiting. Moreover, they displayed increased activity in temporal brain regions when waiting perhaps reflecting to their delay aversiveness and delay discounting. These findings improved our current understanding about the dysfunction of VLF EEG modulation in ADHD as well as broader aspects of the pathophysiology of their waiting difficulties.

With regard to episodic prospection, when envisioning the future a number of DMN regions were engaged. Specifically, episodic prospection was associated with significantly reduced activity in MPFC and increased activity in bilateral MTGs across the delta, alpha and beta bands compared to resting and waiting states. Moreover, enhanced phase coherence between MPFC and MTG in the delta band was observed. The findings highlighted the heterogeneous nature of the DMN in self-referential cognition as well as the importance of a medial fronto-temporal axis in prospective cognition.

Appendix

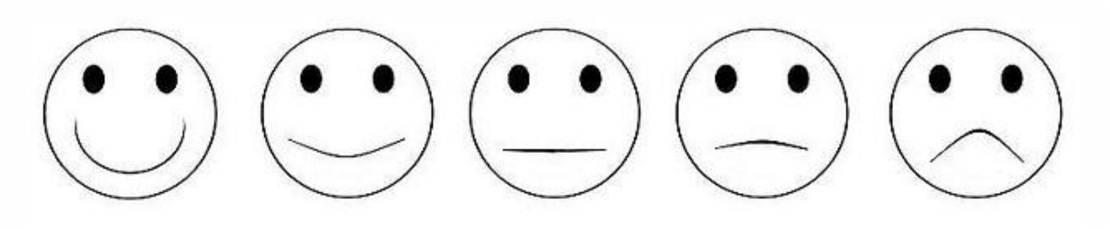
Appendix 1

Session Evaluation

Name/ID: ____________________ Date: ___________ Session: ______________

1. **How did you feel during the session?**

(Please place a mark on the picture to indicate)



2. **How hard did you find the session?**

(Please place a mark on the picture to indicate)

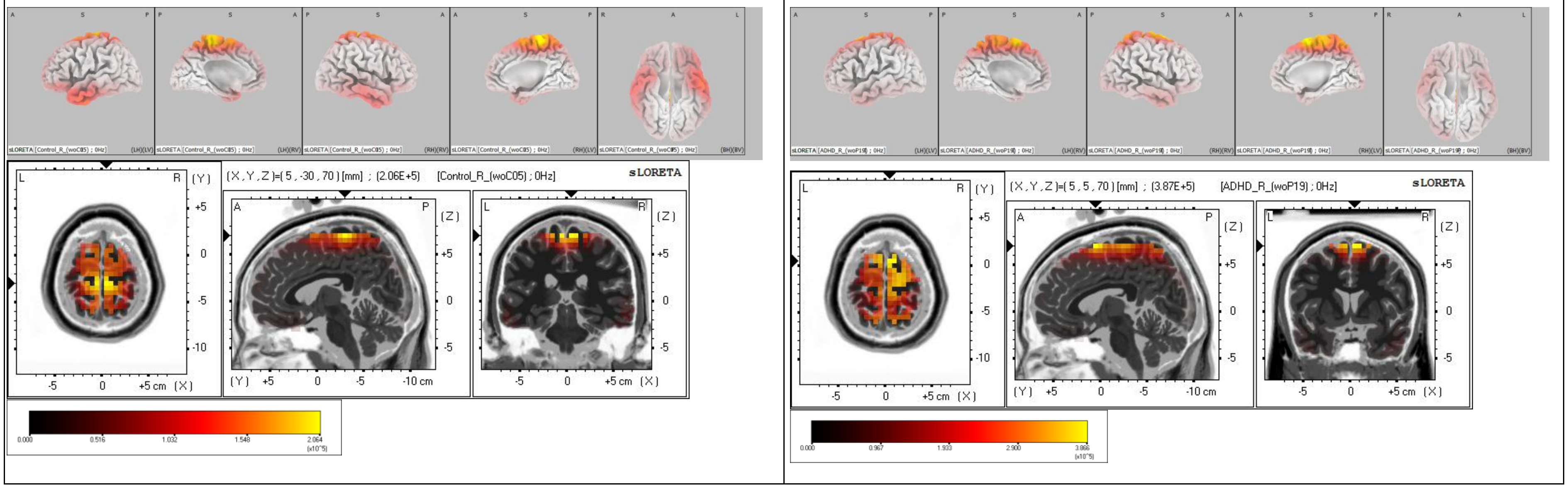
3. **How much time during the session would you say your mind wandered?**

(Please place a vertical mark on the line below to indicate)

0% **100%**

Not at all **All the time**

Appendix 2


(a) Control group

Resting state

(b) ADHD group

Resting state

Figure A. 1. sLORETA images of very low frequency resting EEG. Left panel: typical developing controls; right panel: individuals with ADHD.

Appendix 3

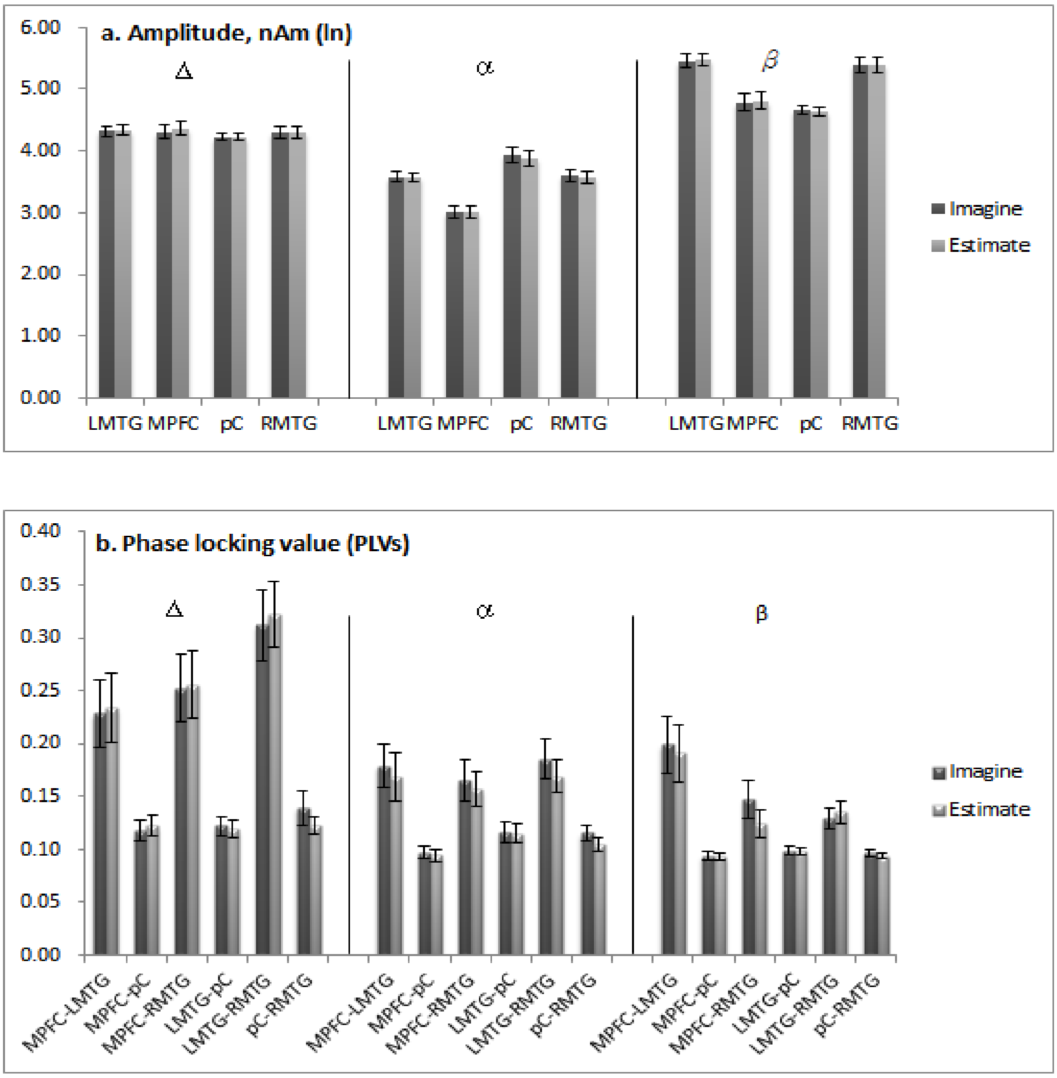


Figure A. 2. The EEG amplitude and coherence between Imagine and Estimate condition by frequency bands.

Two-way ANOVAs with Condition and Region (for amplitude) or Pathway (for coherence) as within subjects were performed for each frequency band respectively. The main effects of Condition and the interaction were not significant (*F*: .04-3.48, all *p* > .05), except the alpha coherence was elevated in the Imagine condition compared to the Estimate condition across all pathways (*F*: 4.28, *p* = .052).

Note. Δ: delta < 4 Hz; α: alpha 8-12 Hz andβ: beta 12-34 Hz.

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