UNIVERSITY OF SOUTHAMPTON

FACULTY OF MEDICINE, HEALTH & LIFE SCIENCES

School of Psychology

Response Variability in ADHD: Exploring the Possible Role of Spontaneous Brain Activity

by

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ABSTRACT

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RESPONSE VARIABILITY IN ADHD: EXPLORING THE POSSIBLE ROLE OF SPONTANEOUS BRAIN ACTIVITY

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Attention-Deficit/Hyperactivity Disorder (ADHD) is the most common psychiatric disorder of childhood and manifests as symptoms of developmentally inappropriate inattention, impulsivity and hyperactivity. Although numerous deficits have been identified in ADHD, one of the most consistent findings is that patients with ADHD are more variable in the speed of their reaction time (RT) responses on neuropsychological tasks than control children. In 2008, the default-mode interference hypothesis of ADHD was introduced by Sonuga-Barke and Castellanos as a biologically plausible account of this increased within-subject variability in ADHD. This hypothesis suggests that some patients with ADHD might not effectively attenuate low frequency resting brain activity from rest to task and that these low frequency oscillations may then intrude onto task performance and cause periodic attention lapses. These periodic attention lapses would manifest as increased variability in RT data.

The present thesis provided the first test of this hypothesis using DC-EEG. We assessed the power in very low frequency EEG bands (< .1 Hz) during rest and during goal-directed task performance 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 adolescent boys with ADHD and age- and gender-matched controls. We found that in both samples, low frequency EEG was generally attenuated from rest to task, but the degree of this attenuation was lower in ADHD or inattentive participants compared to controls. We also found that periodicity was evident in RT data, and that there was synchrony between low frequency fluctuations in RT data and low frequency EEG. These findings provide some initial support for the default mode interference hypothesis. The findings also highlight the potential involvement of low frequency electrodynamics in attentional processes and in the pathophysiology of ADHD.

Thesis Overview

This thesis contains eight chapters. The first three chapters provide a review of the literature about Attention Deficit/Hyperactivity Disorder (ADHD), response variability in ADHD and the default-mode interference hypothesis.

Chapter One: The first chapter provides the background to ADHD: it outlines the diagnostic features of ADHD, the epidemiology, risk factors, and functional impact of ADHD, and then describes the evidence as to whether ADHD is best described as a dimensional or categorical disorder and whether ADHD is a heterogeneous disorder.

Chapter Two: The second chapter more specifically describes the phenomenon of increased response variability in ADHD. It outlines five key research questions which were proposed by Castellanos et al. (2005) to guide a programme of research into the causal processes of response variability in ADHD. The chapter then offers theories of ADHD and describes how these putative causal mechanisms may contribute to increased response variability in ADHD. Particular emphasis is placed on one theory, the default-mode interference hypothesis of ADHD.

Chapter Three: The third chapter reviews the literature and methodology associated with the default-mode interference hypothesis of ADHD. It describes the methodologies used in investigations of the default-mode of brain activity, particularly functional magnetic resonance imaging and electrophysiology, it then describes the key methodological issues associated with investigating the default-mode interference hypothesis i.e. examining whether periodic patterns exist in behavioural data, and determining whether there is synchrony between fluctuations in low frequency brain activity and declines in performance.

Chapters four through seven report the empirical findings from this thesis. Chapters four and five report the empirical findings from a sample of adults who self-reported either high- or low-ADHD scores, and chapters six and seven replicate these analyses in a sample of clinic referred adolescent boys with ADHD and age- and gender-matched controls.

Chapter Four: The fourth chapter investigates low frequency EEG at rest and during goal-directed task performance. In this chapter we identify a relatively stable network of low frequency oscillations at rest (slow 3, S3, .06 - .2 Hz) and show that power in this network at rest differentiates an inattentive high ADHD subgroup. We also report that during goal-directed task performance, S3 power is generally attenuated and more widely dispersed across the scalp than at rest but inattentive participants do not show the same rest-task attenuation of resting S3 power within the S3 network as other participants.

Chapter Five: The fifth chapter assesses the association between intra-individual variability in task performance and low frequency EEG. In this chapter we report that power in a specific RT frequency band – S3- is able to improve the prediction of group membership (high- or low-ADHD) beyond normal global measures of variability. We also show that there is synchrony between fluctuations in low frequency EEG and low frequency fluctuation in RT data. Furthermore, we show that participants who do not effectively attenuate their resting low-frequency EEG from rest to task exhibit the greatest synchrony between S3 EEG and S3 RT signals.

Chapter Six: The sixth chapter replicates the methods and analyses of Chapter 4 in a clinic referred sample of ADHD cases. In this chapter we replicate many of the findings from Chapter 4. We identify a broadly similar resting network of S3 EEG and show that patients with ADHD exhibit lower power in this network than controls at rest. We also show that patients with ADHD exhibit less attenuation of low frequency EEG from rest to task than controls.

Chapter Seven: Similarly, the seventh chapter replicates the methods and analyses of Chapter 5 in a clinic referred sample of ADHD cases. Again, we were able to replicate many of the findings from Chapter 5, and we show that there is synchrony between fluctuations in low frequency EEG and low frequency fluctuations in RT data, and we also show that participants who exhibit the least rest-task S3 attenuation show the greatest similarity between their S3 EEG and S3 RT signals.

Chapter Eight: The final chapter of the thesis provides a summary of the thesis findings and then addresses the main issues that arise from the thesis by answering a number of key questions. It also describes the limitations of the thesis and suggests future directions for research.

Contents

DECLARATION OF AUTHORSHIP

I, Suzannah Helps declare that the thesis entitled 'Response Variability in ADHD: Exploring the Possible Role of Spontaneous Brain Activity' 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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Signed: ……..

Date:…….

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Definitions and abbreviations

Abbreviation/ Symbol	Definition
AC	Alternating current
ACC	Anterior cingulate cortex
ADHD	Attention-Deficit/Hyperactivity Disorder
ADHD-C	ADHD combined subtype
ADHD-I	ADHD inattentive subtype
ANOVA	Analysis of variance
ASD	Autism spectrum disorder
BOLD	Blood oxygen level dependent signal
CD	Conduct disorder
CEM	Cognitive-energetic model
CPT	Continuous performance task
d	Cohen's measure of effect size
DAT	Dopamine transporter
DC	Direct current
df	Degree of freedom
DMN	Default-mode network
DRD4	Dopamine D4 receptor
DSM-IV	The diagnostic and statistical manual of mental disorders - 4th edition
ECG	Electrocardiogram
EEG	Electroencephalogram
EF	Executive Function
EOG	Electro-oculogram
ERP	Event-related potential
F	Fisher's *F* ratio

FFT	Fast Fourier Transformation
fMRI	Functional magnetic resonance imaging
HFA	High functioning autism
HRV	Heart rate variability
Hz	Hertz, a unit of frequency, defined as the number of cycles per second
ICA	Independent component analysis
IQ	Intelligence quotient
ISI	Inter-stimulus interval
K-S	Kolmogorov-Smimov test of normality
M	Mean (arithmetic average)
MEG	Magnetoencephalography
MPFC	Medial prefrontal cortex
N	Total number in a sample
NAA	A metabolite that is associated with myelin synthesis
ns	Non-significant
ODD	Oppositional Defiant Disorder
p	Probability
PCA	Principal components analysis
PCC	Posterior cingulate cortex
PET	Positron emission tomography
PSD	Power Spectral Density
r	Pearson product-moment correlation
ROI	Region-of-interest
RT	Reaction time
S1	Slow 1 frequency band (.05-1.5 Hz)
S2	Slow 2 frequency band (.2-.5 Hz)

S3	Slow 3 frequency band (.06-.2 Hz)
S4	Slow 4 frequency band (.02-.06 Hz)
SART	Sustained attention to response task
SD	Standard deviation
SDQ	The strengths and difficulties questionnaire
SSRT	Stop-signal reaction time
t	Computed value of t test
T1	Time 1
T2	Time 2
TEP	Transdermal epithelial potential
VLFO	Very low frequency oscillation
WISC-III	Wechsler Intelligence Scales for children
χ^2	Computed value of a chi-square test
σ	Sigma, the standard deviation of the normal distribution
τ	Tau, the mean of the exponential component
μ	Mu, the mean of the normal distribution
μV	Micro-volt, one millionth of a volt
Ω	Ohm, a unit of electrical impedance
2-CR RT task	Two-choice response reaction-time task

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Chapter 1 Background to ADHD

1.1 Diagnostic Features of ADHD

Attention Deficit Hyperactivity Disorder (ADHD) manifests as symptoms of developmentally inappropriate inattention, impulsivity and hyperactivity. For a diagnosis of ADHD in the fourth edition of the diagnostic and statistical manual of mental disorders (DSM-IV), impairment from these symptoms must be present in two or more situations, normally home and school, the symptoms must have arisen prior to the age of seven and must have persisted for six months (American Psychiatric Association, 2000). In ADHD, the effects of inattention are likely to be evident in both school and work settings, manifesting as increased errors due to insufficient attention to instructions or detail. Patients with ADHD may also find it difficult to sustain attention in tasks, leaving tasks incomplete or avoiding tasks that require sustained attention. They are also likely to be easily distracted by irrelevant stimuli, such as background conversation, and to be forgetful in daily activities. Hyperactivity in ADHD is often displayed by fidgeting or difficulties remaining seated even when it is expected, such as during school. Children with ADHD are also likely to run or climb at inappropriate times; however in adults with ADHD this is more likely to manifest as a general feeling of restlessness. Patients with ADHD are also likely to talk excessively and to find it difficult to engage quietly in leisure activities. As patients with ADHD are impulsive, they tend to have difficulties turn-taking in games and may also intrude on others and interrupt inappropriately, blurting out answers to questions before the questions have been completed and butting in to conversations (American Psychiatric Association, 2000).

1.1.1 ADHD Subtypes

The DSM-IV describes 18 symptoms of ADHD, nine symptoms of inattention and nine symptoms of hyperactivity or impulsiveness. Three subtypes of ADHD are described in the DSM-IV: 1) ADHD-combined type, which reaches the clinical cut off (six symptoms) for each of the inattentive and the hyperactive-impulsive symptoms; 2) ADHD-predominantly inattentive type, which meets the clinical cut off for inattentive symptoms but not hyperactive symptoms; and 3) ADHD-predominantly hyperactive type, which conversely meets the clinical cut off for hyperactive-impulsive symptoms but not inattentive symptoms. Several studies have investigated the validity of the two factors proposed by the DSM-IV, inattention and hyperactivity/impulsivity. Factor analyses tend to support this model, two factors emerge and the DSM-IV symptoms load onto their predicted factor (Beiser, Dion, & Gotowiec, 2000; Collett, Crowley, Gimpel, & Greenson, 2000; Hartman et al., 2001). However, the clinical validity of these subtypes remains unclear (e.g. Biederman & Faraone, 2005). Lahey, Pelham, Loney, Lee, & Willcutt (2005) conducted a longitudinal investigation into the stability of the DSM-IV subtypes. They reported that although the diagnosis of ADHD was relatively stable, children diagnosed with ADHD often shifted between ADHD subtypes over the eight year

investigation. This was most pronounced in children diagnosed with ADHD-hyperactive/inattentive subtype, of whom 91% met criteria for a different subtype in at least one of the assessments and who mostly shifted to an ADHD-combined type over time.

1.1.2 Associated Disorders

In the majority of cases (60-100%) patients with ADHD also meet the diagnostic criteria for another DSM-IV disorder (see Gillberg et al., 2004, for a review). Almost half of children with ADHD also have Oppositional Defiant Disorder (ODD) or Conduct Disorder (CD), however further associations exist between ADHD and Learning Disorders, Mood Disorders, Anxiety Disorders, Developmental Co-ordination Disorder and Tourette's Disorder (American Psychiatric Association, 2000).

ODD is a pattern of defiant and disobedient behaviour towards authority figures and CD describes a more severe form of these behaviours which includes the violation of other peoples' basic rights and social norms. ODD and CD have been shown to share similar genetic liability and ODD appears to represent a milder, earlier onset version of CD (e.g. American Psychiatric Association, 2000). These behaviours, characteristic of ODD and CD, are distinct from the hyperactivity and impulsivity exhibited by children with ADHD, as although the behaviours of ADHD can be disruptive they do not violate social norms. Therefore, the DSM-IV recommends that when criteria for both disorders are met, both diagnoses should be given. However, the high incidence of a comorbid diagnosis of ADHD with ODD or CD suggests that the distinction between these disorders may be artifactual, that is, they may be alternative manifestations of the same underlying syndrome. Some evidence suggests that the mechanisms underpinning the two disorders may differ. For example, the developmental trajectories of ODD/CD and ADHD appear to differ, ODD/CD predicts later criminal activity but ADHD predicts poor school achievement (Nadder, Rutter, Silberg, Maes, & Eaves, 2002) and, furthermore, ODD/CD is not as highly heritable as ADHD (Levy, Hay, McStephen, Wood, & Waldman, 1997). However, in a large twin study of over 1,000 twin pairs Nadder et al. (2002) showed that the co-morbidity of ADHD and ODD/CD symptomatology was largely determined by shared genetic factors and not environmental factors independent of ADHD. Environmental factors were important in the development of ODD/CD alone but not to its co-variation with ADHD. The shared genetic factors may include shared genetic-environment interactions, for example the presence of ADHD may bring about an adverse home environment, which may increase the likelihood of ODD/OC symptoms. Shared genetic factors may also indicate shared genetic risk factors, such as a personality trait like sensation seeking which may contribute to the development of either disorder. Thus, it remains unclear whether ADHD and ODD/CD represent different behavioural manifestations of the same underlying syndrome.

1.2 Epidemiology of ADHD

1.2.1 Prevalence of ADHD

ADHD is the most common psychiatric disorder of childhood and although prevalence estimates vary depending on the diagnostic criteria used and the population that is sampled, it is thought to affect 5-10% of children world-wide. Cross-cultural comparison of the incidence of ADHD has proved difficult as diagnostic practices as well as interpretations of behaviour often differ across countries. However although there is an increased reported incidence of ADHD in the West, it is thought that presentation of clinical symptoms is similar across cultures (Elia, Ambrosini, & Rapoport, 1999).

1.3 Risk Factors for ADHD

1.3.1 Gender

Male gender has been identified as a risk factor for ADHD. Males are more likely than females to be diagnosed with ADHD. Clinical samples typically present boy-to-girl ratios of 3:1 to 9:1, however this ratio is often much lower in community samples, and is closer to 2:1. This is likely to indicate a referral bias and may signify that ADHD is less disruptive in females than in males (Elia et al., 1999). However the male to female ratio appears to be lower for the ADHD inattentive subtype than the combined- or hyperactive/impulsive subtypes. Willcutt & Carlson (2005) report that for children with a clinical diagnosis of ADHD (any subtype), males are more likely than females to meet criteria for ADHD-combined type and ADHD-hyperactive subtype, but females are more likely than males to meet the criteria for ADHD-inattentive subtype. That is, 39% of females with ADHD meet the criteria for ADHD-inattentive subtype but only 30% of males meet these criteria. Similar findings were also reported in a meta-analysis of studies using population samples (Willcutt & Carlson, 2005).

1.3.2 Genetic Risk

Both twin and adoption studies have shown ADHD to be a heritable disorder and heritability estimates converge at about .7, which indicates that ADHD has a significant genetic component (e.g. Stevenson, 1992; Faraone et al., 2005). Furthermore, a number of candidate genes that demonstrate replicated association with ADHD have been identified; many of these have been associated with dopamine networks, such as the dopamine transporter gene, DAT1, and the dopamine receptor gene, DRD4. This is unsurprising given that methylphenidate, an effective stimulant medication for ADHD, works by blocking the dopamine transporter and imaging studies of ADHD suggest dysfunction of the dopamine-rich frontalstriatal circuits (e.g. Kuntsi, McLoughlin, & Asherson, 2006). However, non-stimulant medications, such as atomoxetine, have also been shown to be effective in the treatment of ADHD (e.g. Banaschewski, Roessner, Dittmann, Santosh, & Rothenberger, 2004) and other genetic components have also been implicated in ADHD, notably genes involved in the

noradrenergic system (noradrenergic receptors and transporters) and in the serotonergic system (serotonin receptors and transporters) (see Faraone et al., 2005, for a review).

1.3.3 Environmental Risk

Low social class, family dysfunction and maternal mental disorders have all been identified as risk factors for childhood ADHD (Biederman et al., 1995). Furthermore, foetal exposure to maternal alcohol has been shown to increase the risk of ADHD. Both prospective and retrospective studies have shown an association between maternal alcohol consumption during pregnancy and later behavioural problems allied with ADHD (e.g. Brown et al., 1991; Mick, Biederman, Faraone, Sayer, & Kleinman, 2002). Similar associations have been identified between maternal prenatal smoking and ADHD (e.g. Schmitz et al., 2006; Rodriguez & Bohlin, 2005). However Kahn, Khoury, Nichols, & Lanphear (2003) found that childhood hyperactivity and inattention was only associated with maternal smoking behaviour when the child also had a specific DAT genotype (two 480-base-repeat alleles). This study emphasises the importance of considering the interaction between environmental and genetic risk factors in investigations of the causal processes in ADHD.

1.4 Functional impact of ADHD

ADHD is found to have a negative impact on children's development. Children with ADHD typically under-perform at school and do not achieve the grades predicted by their age and IQ (Barry, Lyman, & Klinger, 2002) they are also more likely to experience social dysfunction (Maedgen & Carlson, 2000) and poor self-esteem (Edbom, Lichtenstein, Granlund, & Larsson, 2006). Furthermore, there is a higher risk of both cigarette smoking and substance abuse in ADHD (Wilens & Biederman, 2006). Moreover, ADHD has been found to have a negative impact on family function. Parents of children with ADHD are more likely than parents of control children to report role dissatisfaction or role distress – dissatisfaction with parenting or parenting performance (Podolski & Nigg, 2001).

However functional impairment may differ across the different ADHD subtypes. Lahey et al. (1998) reported that all subtypes of ADHD were associated with functional impairment, even when potential confounds such as the presence of ODD or CD were controlled for and that all subtypes of ADHD were associated with social difficulties. However, other difficulties were specific to individual subtypes. For example, only parents of children diagnosed with ADHD-hyperactive subtype reported significantly more accidental injuries than parents of control children and only inattentive symptoms were associated with teacher reports of shyness, lack of co-operation and poor mathematics scores. Furthermore, academic underachievement in ADHD is often more highly correlated with symptoms of inattention than with symptoms of hyperactivity-impulsivity (e.g. Carroll, Maughan, Goodman, & Meltzer, 2005; Lee & Hinshaw, 2006). Thus, ADHD appears to impair many aspects of functioning within the individual both socially and academically, however these functional impairments may vary with ADHD subtype.

1.5 ADHD as a dimensional or categorical disorder

Controversy exists as to whether ADHD is best described as a distinct category or as an extreme variation along a continuous dimension of behaviour. Diagnostic systems such as the DSM-IV implicitly suggest that ADHD is a categorical disorder; the diagnostic criteria in the DSM-IV state that individuals who score above a certain, meaningful, cut-off are diagnosed with ADHD and thus, are qualitatively different from those below the cut-off. Such a view would suggest that any underlying causal processes will be specific to patients with ADHD and a distinction would exist between them and healthy controls. An alternative view is that ADHD represents an extreme variation of a continuously varying trait; thus patients with ADHD would differ from controls only by degree and causality would be associated with normal variation in the population (Haslam et al., 2006).

Researchers who favour a dimensional approach to ADHD criticise the categorical view for imposing an arbitrary diagnostic cut-off and for categorising normal childhood behaviours as a disorder. Furthermore, this categorical approach has been criticised as constraining research, forcing dichotomous categories that reduce statistical power and create unrealistic assumptions of an endogenous aetiology (Sonuga-Barke, 1998). Empirical evidence also tends to support a dimensional rather than a categorical view of ADHD. Firstly, ADHD symptoms typically form a unimodal distribution; a categorical disorder is likely to demonstrate a bimodal distribution representing two distinct categories, affected and unaffected probands. Secondly, twin-studies (e.g. Levy et al., 1997) have shown that the high heritability that is characteristic of ADHD is robust across definitions of ADHD both as a continuous trait and when cut-offs of increasing severity are used. If a categorical approach were more appropriate for ADHD, when more severe symptom cut-offs were adopted it would be expected that the heritability estimates would change.

However, these factors are not incompatible with a model of ADHD as a categorical disorder. Firstly, Haslam et al. (2006) report that a categorical disorder that consists of high and low symptoms can manifest as a unimodal distribution and furthermore, the statistical techniques that are typically adopted in twin-studies to give a measure of heritability carry an underlying assumption that the variables are continuous, which may unduly bias the outcome of such measures. However recent analyses have adopted taxometric measures to overcome these problems. Taxometric measures compare patterns of covariation between variables to indicate whether the data best fit a categorical or a continuum model without carrying underlying assumptions of either model. Such analyses have typically favoured a continuum model of ADHD (e.g. Haslam et al., 2006; Frazier, Youngstrom, & Naugle, 2007). A model of ADHD as a dimensional disorder would have several implications. Firstly it would suggest that there is not a single underlying dichotomous risk factor for ADHD, the presence of which would determine the presence of ADHD. Therefore, it is likely that either 1) a single factor presents as a continuous trait or 2) that several risk factors combine in ADHD.

1.6 Heterogeneity in ADHD

Existing data supports the second assertion; no single core deficit has, thus far, been identified that is able to differentiate patients with ADHD from controls. Instead it appears likely that a number of risk factors, both environmental and genetic, combine and interact to increase susceptibility to ADHD. Given that different patients meeting the diagnostic criteria for ADHD are likely to be affected by different combinations of risk factors and quite distinct aetiological pathways, it is unsurprising that ADHD presents as a heterogeneous disorder. At a clinical level, patients with ADHD often present with other comorbid disorders (see section 1.1.1.2 Associated disorders). In fact, Kadesjo & Gillberg (2001) report that cases of ADHD without any other comorbid disorder are rare (<15%) and they suggest that such a group would probably be highly atypical of ADHD and should not be used in studies to inform clinical decisions. Furthermore, patients with ADHD do not exhibit consistent neuropsychological impairments. Nigg, Blaskey, Stawicki, & Sachek (2004) demonstrated that on 5 measures which have been shown to be associated with ADHD (stop signal reaction time, reaction time variability, Stroop interference, continuous performance task commission errors and trailmaking) no more than half of the children with ADHD in their sample were identified as impaired on any given measure (using a cut-off of the 90th percentile). Furthermore, the children with ADHD were not simply those who performed poorly on multiple tasks. One fifth (21%) of all of the children with ADHD showed no impairment on any of the tasks whereas nearly 10% of the control children showed impairment on three or more tasks.

Clearly ADHD is not a homogenous disorder, patients with ADHD do not demonstrate identical clinical characteristics nor do they exhibit the same neuropsychological impairments (Banaschewski et al., 2005). Therefore, single cause models of ADHD are likely to be inappropriate; Sonuga-Barke (2005) suggested that it may be more appropriate to consider individual single-cause models of ADHD as complementary approaches to a multi-factorial disorder. Such a multi-factorial model of ADHD is likely to be more complex than a number of independent pathways, with each pathway being mediated by other factors to its own ADHD behavioural phenotype, such as a cognitive deficit pathway and a motivational pathway (Sonuga-Barke, 2005). It is likely that the different pathways will interact with each other. Although it may be possible for a child to develop ADHD as a result of the contribution of a single pathway, it is likely that most patients with ADHD will receive contributions from several pathways and the ADHD phenotype will be expressed only when the additive and interactive effects of these pathways reach a certain threshold (Sonuga-Barke & Castellanos, 2005). Furthermore, Coghill, Nigg, Rothenberger, Sonuga-Barke, & Tannock (2005) suggest that the exact nature of these interactions may influence disease severity and treatment response.

Endopehnotypes, genetic traits that mediate the pathway between genotype and phenotype, will be crucial in identifying these pathways. Endophenotypes assist the identification of more homogenous subgroups of patients with ADHD, which are more likely to share common aetiological pathways. Numerous putative endophenotypes of ADHD have been suggested including, deficits of response inhibition, delay aversion and increased

response variability. In the following section I will describe the evidence for response variability as an endophenotype of ADHD.

Chapter 2 Response Variability in ADHD

2.1 Background to Response Variability in ADHD

One of the most consistent findings across studies in ADHD research is that patients with ADHD are more variable in the speed of their reaction time (RT) responses on neuropsychological tasks than control children (e.g. Kalff et al., 2005;Klein, Wendling, Huettner, Ruder, & Peper, 2006; Scheres, Oosterlaan, & Sergeant, 2001; van Meel, Oosterlaan, Heslenfeld, & Sergeant, 2005). Specifically, patients with ADHD have been found to exhibit greater within-subject variability in their responses during a particular testing session. The finding of increased intra-individual variability in ADHD has been replicated across tasks, laboratories and cultures (Castellanos & Tannock, 2002; Klein et al., 2006). However, until recently, this phenomenon has been disregarded and considered as experimental 'noise'. Little research has attempted to examine the role of response variability in causal models of ADHD and its functional significance – how it relates to the pathophysiology of ADHD - remains unclear. Recently, Castellanos & Tannock (2002) highlighted this problem and suggested that, given the ubiquity of its occurrence in ADHD, increased intra-individual response variability may be an aetiologically important characteristic of ADHD. Furthermore, they claimed that its role within the causal processes of ADHD should be systematically examined. Later Castellanos et al. (2005) proposed a framework that would support such analyses. They identified five key research questions, which would lend towards a programme of research that addresses the deficits in the area. This chapter will address each of these research questions in turn, and then outline a number of causal models of ADHD and describe how these causal mechanisms might contribute to increased response variability in ADHD. Particular emphasis will be placed on one theory –the default mode interference hypothesis of ADHD (Sonuga-Barke & Castellanos, 2007)

2.1.1 How robust is the association between response variability and ADHD?

The first question proposed by Castellanos et.al., (2005) addresses the relationship between ADHD and intra-individual response variability. Typically, ADHD investigations have been primarily concerned with measures of RT speed or response accuracy and measures of variability have been reported only at the group level. This fails to distinguish between intra- and inter-individual variability and describes little about the association between response variability and ADHD (Castellanos et al., 2005). Only recently has interest developed in response variability within ADHD, and investigators have begun to report intra-individual measures of variability - typically SD of RT scores. Thus, group comparisons can be made using individuals' SD of RT as the dependent variable. Using this method of analysis, increased intra-individual response variability has been shown to be more strongly and reliably correlated with ADHD symptoms than many other neuropsychological measures (Epstein et al., 2003; Kuntsi, Oosterlaan, & Stevenson, 2001). Furthermore, intra-individual

response variability has been shown to be a strong predictor of success on a Go/No-Go task (Bellgrove, Hester, & Garavan, 2004). Bellgrove et al.(2004) suggest that previous findings of poor performance in ADHD on inhibition tasks may have been caused by underlying response variability rather than inhibitory control deficits; however it is not possible to determine causality from these findings, so it is also possible that success on a Go/No-Go task may impact on intra-individual response variability. Thus, preliminary evidence is promising, intra-individual variability appears to be associated with ADHD. However it is important to bear in mind that such response variability is not a necessary requirement for ADHD. In a meta-analysis of three data sets, Nigg, Willcutt, Doyle, & Sonuga-Barke (2005) demonstrated that although response variability was strongly associated with ADHD, group differences between patients with ADHD and controls were in the range of d = .77 to d = .75, this effect was not as strong as the group difference on Stop Signal Reaction Time (d = .88 to d = .79). Furthermore, when impairment was considered as performing above the 90th percentile of controls, only half of the patients with ADHD were considered as impaired on RT variability. Thus, although there may be a relationship between response variability and ADHD, only a subset of patients with ADHD are likely to experience a specific deficit in intra-individual measures of variability.

2.1.2 Is response variability in ADHD random noise or a dynamic-periodic phenomenon?

The second question addresses the structure of ADHD-related intra-individual response variability, which may provide meaningful information about the underlying pathophysiology of ADHD. If response variability were found to have a periodic structure, this may yield information about underlying causal biological mechanisms, which tend to contain some element of periodicity themselves. However random variability that does not contain a periodic, temporal structure is more likely to represent global dysregualation of behaviour. The SD of RT statistic is unable to describe temporal fluctuations in variability and thus, other statistical measures will be necessary to elucidate this issue. Leth-Steensen, Elbaz, & Douglas (2000) used an ex-Gaussian model to conduct a more detailed analysis of the RT data from children with ADHD. The ex-Gaussian model (Ratcliff, 1979) assumes that the RT distribution can be represented as the sum of a normal (Gaussian) distribution and an exponential curve and has three parameters, mu (μ) the mean, and sigma (σ) the SD of the normal component, and tau (τ) the mean of the exponential component. This analysis allows the mean RT from slower responses, evident in τ, to be calculated independently from the mean RTs in the normal distribution (see Figure 2.1).

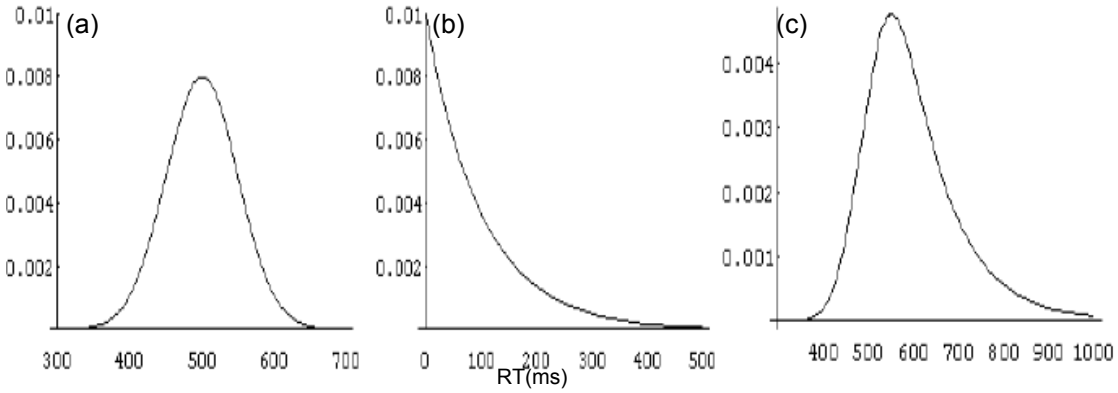

Figure 2.1: Probability density functions for a) a normal distribution, b) an exponential distribution, and c) the resulting ex-Gaussian curve from Heathcote (1996).

Leth-Steensen et al. (2000) demonstrated that when the mean and SD of RT were calculated using standard parametric calculations based on a normal distribution, boys with ADHD were slower and more variable than the age-matched controls and were similar to those of younger boys. However, using an ex-Gaussian analysis of the same data indicated that the children with ADHD were performing qualitatively differently from the younger boys. The boys with ADHD were found to perform similarly to the age-matched controls on measures of μ and σ (the mean and SD of the normal distribution) and both of these groups differed from the younger children (μ and σ were both significantly larger in the younger group). However the ADHD group were similar to the younger boys on measures of τ and both of these groups differed from the age-matched controls (controls had a significantly smaller τ).Thus, it appears that the distributional data from the ADHD boys is qualitatively different from that of the younger boys. Although both of these distributions are characterised by a high positive skew (i.e. a large τ), the younger boys' distributions are also characterised by general slower and more varied responses (i.e. larger values of μ and σ), which is not exhibited by the children with ADHD. In fact, the values of the ADHD boys' μ and σ were comparable to those of the age-matched controls, which indicates that on the majority of responses, the ADHD boys were as fast as boys of their own age. However, the larger value of τ indicates that the boys with ADHD's slow responses were much slower than the age-matched controls. Therefore, the responses of the boys with ADHD were generally similar to those of the age-matched controls but contained an unusually high proportion of very slow responses. These findings have since been replicated using a larger sample and a better validated measure of RT (Hervey, 2004).

This distributional profile is consistent with the assumption that patients with ADHD, although able to respond to stimuli as effectively as age-matched controls, may experience frequent lapses of attention. Lapses in attention would manifest as responses on the slow end of the response distribution, increasing the positive skew and the value of τ. However, the precise nature and frequency of these attention lapses remains unclear from these data. In order to establish whether there is any periodicity to these attention lapses, it is important that this intra-individual variability is reported and analysed in a manner that captures the

temporally dynamic nature of any fluctuations that might exist within the data. Castellanos et al. (2005) employed signal processing techniques on time-series RT data to this end. Signal processing techniques are typically used to analyse periodic activity in biological rhythms, such as heart rate and respiration. Techniques such as Fast Fourier Transformations (FFT) and Power Spectral estimates can be used to ascertain the nature of these signals, providing information about the power and amplitude of specific frequency bands within them. Fast Fourier Transforms decompose a signal into its constituent sine waves and are able to describe the amplitude and phase for each frequency wave. Similarly, Power Spectral estimations are able to describe the power of the different frequency components in the signal and enable power, as the area under the curve, to be calculated for specific frequency bands. Thus, these techniques are able to identify the power and amplitude of specific frequency oscillations within the signal.

Castellanos et al. (2005) applied these techniques to RT data to determine whether the length of RTs (which is likely to indicate lapses in attention) demonstrates any periodicity. They analysed the time-series RT data obtained from both controls' and ADHD patients' performance on an Erikson flanker task and showed that in both groups, RT oscillated at a specific frequency, centred around 0.05 Hz[1] (corresponding to a cycle every 20 seconds), however the power of this oscillation was significantly higher in the ADHD group than in the control group. Furthermore, after the administration of methylphenidate to the ADHD participants, the power of these oscillations was reduced to that of the controls. This finding was replicated by the same group (Di Martino et al., 2008), again using the time series of RTs from an Erikson flanker task, patients with ADHD were shown to exhibit greater power in RT fluctuations at this frequency than controls. Furthermore, they also showed that that power in this frequency band was able to predict the diagnosis of ADHD above and beyond a global measure of variability, SD of RT.

A different group have reported similar findings using a fixed-sequence Sustained Attention to Response task (SART) to obtain time series RT data from children with ADHD and controls (Johnson et al., 2007, Johnson et al., 2008). In this task, participants were shown the digits 1 – 9 in a fixed order and were required to respond by pressing a response button to each digit except the No-Go digit '3'. They used FFT analysis to calculate power in what they described as fast frequencies (those faster than a cycle of the SART: .077-.33Hz) and slow frequencies (those slower than a cycle of the SART: .077-.33Hz) and showed that a group of impaired-ADHD children (defined by the number of commission errors made) were distinguishable from an unimpaired group of children with ADHD and controls by the power they exhibited in this fast frequency band, which is very similar in frequency to the band identified by Castellanos et al. (2005). Thus, although this is fairly preliminary, it appears that there may be some temporal structure to response variability, with RTs oscillating at low

[1] The frequency of oscillations is normally described in hertz (Hz), which is a unit of cycles per second (thus 1 Hz denotes one cycle per second and 50 Hz denotes 50 cycles per second).

frequencies, and a lapse in attention occurring approximately every 20 seconds. As these effects appear to be specific to a particular low frequency band and power in this RT frequency band operates above and beyond that of SD of RT, it will be important to consider this RT frequency band in future measures of variability.

However, FFT analyses have certain assumptions and the behavioural tasks that have so far been used to obtain time series data for these analyses have not necessarily met these assumptions. This issue is discussed in depth in section *3.3.1 Capturing Temporal Patterns in Behavioural Data*, however, briefly, to obtain suitable data, a task should sample frequently (i.e. the inter-stimulus interval [ISI] duration should be as short as possible), the task should be of long enough duration to contain multiple cycles of the target rhythm, it should not entrain particular frequencies, and ideally should not allow missing or incorrect responses. As neither the Erikson flanker task nor the SART task meet all of these requirements, the results obtained from these tasks, although promising, should be viewed with some caution.

2.1.3 Does response variability vary dynamically as a function of context, task and state?

The third question proposed by Castellanos et al. (2005) addresses the dynamic nature of response variability in ADHD. Normal functioning is affected by numerous factors such as task, context and individual state. Therefore, Castellanos et al. (2005) claim that response variability is also likely to be contextually dependent on some of these factors as ADHD is a highly context dependent disorder. Moreover, understanding how response variability is affected by these factors allows the possibility of constraining variability and enhancing performance in ADHD. Therefore it is important that the effects of these factors on response variability are examined. Recently, Klein et al. (2006) reported that intra-individual variability appears to be task-independent. They reviewed different parameters from both control children and children with ADHD on four different neuropsychological tasks (a continuous performance task, a Go/no-Go task, a stop-signal reaction time task and an N-back task). Consistent with previous findings, intra-individual variability emerged as the best discriminator between the children with ADHD and controls, furthermore, controlling for this variability substantially reduced group differences in other measures. Moreover, intra-individual variability appeared to be a single construct within ADHD, that is, children who were highly variable on one task were also likely to be variable on other tasks. Similarly, Johnson et al., (2008) report that measures of intra-individual variability from the SART show a reasonable degree of stability in control children over a six week test-retest period. The global measure of variability SD of RT was most stable (r =.75) but both the fast and the slow SART frequency domain measures also showed reasonable stability (r = .60, r =.64 respectively). This research suggests that intra-subject variability is likely to represent a fundamental feature of the participant and not of the task and to be relatively stable over time. However, in a recent study, Vaurio, Simmonds, & Mostofsky (2009) showed that the periodicity of RT data on a Go/No-Go task varied in ADHD as a function of task demand. They showed that in a

simple Go/No-Go task, ADHD patients were best discriminated from controls in a frequency band from .027 - .074 Hz, but in a complex version of this task, the ADHD patients were best discriminated from controls in a higher frequency band .074 - .202 Hz. Therefore, it is possible that intra-individual variability does vary as a function of task difficulty. However, research into this has been limited and further research and replication is necessary before sound conclusions can be drawn

2.1.4 Is response variability unique to ADHD or shared with other brain pathologies?

The fourth question proposed by Castellanos et al. (2005) addresses the particular nature of response variability in ADHD. Increased intra-individual response variability is not unique to ADHD but is also found in disorders such as schizophrenia (van den Bosch, Rombouts, & van Asma, 1996), dementia (MacDonald, Nyberg, & Backman, 2006), and in traumatic brain injury, specifically lesions of the frontal lobes (Stuss, Murphy, Binns, & Alexander, 2003). Geurts et al. (2008) investigated the specificity of intra-individual variability in ADHD by comparing children with ADHD to children with high functioning autism (HFA), autism spectrum disorders (ASD), Tourette's syndrome and typically developing controls. All children performed a simple 2-choice RT task and variability was assessed in terms of: SD of RT; ex-Gaussian measures of mu, sigma and tau; and frequency domain measures of RT. They report that children with ADHD were *less* variable than children with HFA or ASD and did not differ from controls, regardless of which measure of variability was adopted. These findings are atypical, given that no significant differences in intra-individual variability were identified between children with ADHD and typically developing controls, however Geurts et al. (2008) claim that in their study they stringently tested for comorbid ASD, and excluded any comorbid cases from the ADHD group, they claim that other studies may not be as rigorous in their test for comorbid ASD, and thus comparisons between ADHD and controls may be confounded by comorbid ASD (which in their study was highly associated with increased variability). In future studies of response variability it will be important to stringently assess ASD status in ADHD cases.

Therefore, it is currently unclear whether response variability in ADHD differs from the increased variability found in other disorders. Response variability may represent a generalised characteristic of brain pathology and thus, provide little information about the pathophysiology of ADHD. However response variability in ADHD may differ qualitatively or quantitatively from the variability found in other disorders and, for example, exhibit a different temporal structure of variability or exhibit greater or lesser levels of variability. Identifying the fundamental features of response variability in ADHD may offer insight into how response variability might relate to the causal processes of ADHD. In reality response variability in ADHD is likely to have some similarities to the response variability found in other disorders, which may reflect shared causal processes that overlap the nosologic DSM-IV criteria.

2.1.5 Does response variability reflect processes causally related to ADHD?

The fifth question that Castellanos et al. (2005) propose concerns the cause of response variability in ADHD. Understanding the temporal and contextual nature of response variability may provide clues about the underlying pathphysiology of ADHD, however unless the pathway between behavioural symptoms and underlying pathology is known, the variability may simply represent symptom manifestation. Therefore it is important to understand the physiological mechanisms that underlie response variability in ADHD. In order to identify these mechanisms it will be important to use techniques that are able to probe the elements that mediate this causal pathway. Analyses that focus on different physiological levels such as electroencephalogram (EEG) or heart rate variability recordings may be of particular benefit as these biological systems are also found to exhibit periodic fluctuations. If response variability was found to manifest periodicity at a particular frequency, similar frequency fluctuations in biological systems may indicate a good starting point for further investigation. If these biological systems were found to respond similarly to the periodic fluctuations in variability, this would provide evidence for their role in the causal processes of ADHD.

2.2 Theories of Response Variability in ADHD

Further ideas for the causal role of fluctuations in response variability may be evident in causal models of ADHD. Numerous different causal mechanisms have been proposed in the different theories of ADHD, which offer alternative suggestions as to why response variability may be an important characteristic of ADHD. These include theories of executive dysfunction, delay aversion, state regulation difficulties, astrocyte dysfunction and inertia of the resting-state, each of these theories offers alternative explanations of why response variability may exist in ADHD and correspondingly different predictions as to the way in which response variability may manifest in ADHD. These theories will now be described and a summary which highlights each theory's prediction of response variability in ADHD presentation will be offered.

2.2.1 ADHD as a disorder of Executive Function

2.2.1.1 *Background to Executive Function*

Patients with ADHD often exhibit difficulties in tasks that require 'top-down' cognitive processes such as planning, set-shifting and inhibition. Therefore, researchers have suggested that ADHD might be a disorder of *executive function* (EF). EF has been described as 'the ability to maintain an appropriate problem solving set for attainment of a future goal' (Welsh & Pennington, 1988, pp 201). This set may include; inhibiting or deferring a response, creating a mental representation of the task and strategic planning. Thus, EFs are the primary top-down cognitive processes that are associated with goal-directed behaviour and are allied with five principle, inter-related domains: inhibition, set shifting, working memory, fluency and planning (Sergeant, Geurts, Huijbregts, Scheres, & Oosterlaan, 2003).

2.2.1.2 *Executive Function Theories of ADHD and response variability*

A breakdown of executive control would increase in the randomness of behaviour (Castellanos et al., 2005), thus, any executive dysfunction theory of ADHD would predict that the variability exhibited by patients with ADHD would be random and not display any temporal characteristics, i.e it would not be periodic.

2.2.1.3 *Evidence for Executive Dysfunction in ADHD*

There is substantial evidence that patients with ADHD perform less well than healthy controls on tasks that require EF. For example, patients with ADHD have been shown to perform less well on working memory tasks such as digit span repetition tasks (e.g. Stevens, Quittner, Zuckerman, & Moore, 2002; Perugini, Harvey, Lovejoy, Sandstrom, & Webb, 2000), and to have more difficulties with spatial memory tasks than healthy controls (e.g. Bedard, Martinussen, Ickowicz, & Tannock, 2004). Similarly there is some evidence that patients with ADHD show deficits in planning (e.g. Barkley, Grodzinsky, & Dupaul, 1992), set shifting and verbal fluency (Nigg, Hinshaw, Carte, & Treuting, 1998). In a recent meta-analysis, Willcutt, Doyle, Nigg, Faraone, & Pennington (2005) reported that similar effect sizes were identified between groups of ADHD patients and controls on measures of inhibition, working memory, planning and set-shifting (d = .51to .69). However such studies typically do not control for non-executive abilities and Marks et al. (2005) demonstrated that in pre-school children at risk of ADHD any group differences in EF measures were removed after controlling for non-executive abilities. Therefore, the evidence for a general pattern of EF difficulties in ADHD remains unclear.

2.2.1.4 *ADHD as a Disorder of Response Inhibition*

An alternative model of executive dysfunction in ADHD was proposed by Barkely (1997). Barkley (1997) suggested that ADHD may have a core deficit in response inhibition - the ability to withhold a proponent response- and the general pattern of EF impairment in ADHD would stem from this primary impairment. Barkley (1997) suggests that response inhibition is fundamental to all behaviour regulation and that higher order behaviours such as language, planning and social behaviour depend on successful inhibition of responses. He claims that the impulsive, hyperactive and inattentive behaviours displayed by patients with ADHD occur when inhibition is ineffective.

2.2.1.5 *Evidence for ADHD as a Response Inhibition Disorder*

Evidence for the role of response inhibition deficits in ADHD has largely come from experiments using the stop task paradigm. The stop task requires participants to respond to a given cue, except for when a stop signal is presented (normally an auditory tone), in which case they must inhibit this response. When the stop signal is presented early, the response is likely to be inhibited, but if it is presented later the response is likely to be executed. The time course of inhibitory control is estimated by the stop-signal reaction time (SSRT). The SSRT indicates the length of time prior to the ‘go’ cue that a person must be presented with a stop

signal in order to successfully inhibit a response. Patients with ADHD typically exhibit impaired performance on the stop task, demonstrating longer SSRTs and a higher number of errors than healthy controls (e.g. Nigg et al., 2005). However, akin to the difficulties in other measures of EF, the interpretation of these results is problematic. Firstly, patients with ADHD also perform more poorly on the go component of the task, which does not require inhibition; they are slower and more variable in their speed of responding and make a higher number of omission and commission errors than the control group. This cannot be explained in terms of an inhibition deficit as the go task does not require any inhibition, only reaction to a cue (Kuntsi et al., 2001). Furthermore, this pattern of behaviour negates the underlying assumptions of the Stop task, as patients with ADHD tend to respond more slowly to the go cue, calculation of their SSRT may be inaccurate if this is not accounted for. Furthermore, the Stop signal task also imposes demands on the participant to hold task instructions, to process stimuli and to prepare for stimuli responses and it appears likely that patients with ADHD are impaired in these elements of the task (Castellanos, Sonuga-Barke, Milham, & Tannock, 2006). Stronger evidence for this theory would exist if an inhibitory deficit were found to remain after all non-executive task components were controlled.

2.2.2 The Delay-Aversion Model of ADHD

2.2.2.1 *Hypotheses*

In contrast to models of ADHD as executive dysfunction, the Delay Aversion Model of ADHD (Sonuga-Barke, Taylor, Sembi, & Smith, 1992) proposes that ADHD is caused by alterations in motivational rather than executive processes. The delay aversion model suggests that patients with ADHD experience impairment in the signalling of delayed rewards which is caused by a biologically predetermined shortened reward-gradient and this causes patients with ADHD to discount delayed rewards to a greater extent than normal. This may manifest as impulsivity, as patients with ADHD choose to avoid delay or, in conditions where delay is unavoidable, they may try to avoid the subjective experience of delay by allocating their attention to aspects in the environment so that time appears to pass more quickly and appear hyperactive or inattentive. This is illustrated in Figure 2.2.

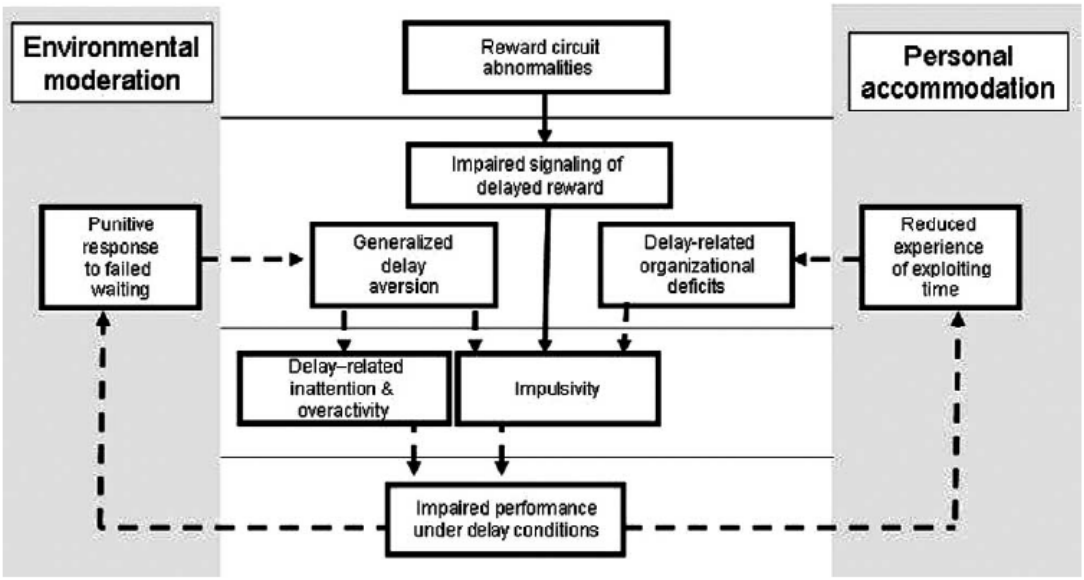

Figure 2.2: Model of the development of ADHD from impaired signalling of delayed rewards (from Sonuga-Barke, 2003).

2.2.2.2 *Delay Aversion and response variability in ADHD*

The Delay Aversion Model predicts that impaired performance will specifically occur during conditions that include delay. Correspondingly, increases in variability should also occur during these conditions.

2.2.2.3 *Evidence for the Delay-Aversion Model of ADHD*

Many patients with ADHD do appear to be delay averse. On tasks that require children to make a choice between a small, immediate reward and a larger, delayed reward, hyperactive children are more likely than controls to choose the small, immediate reward. However this finding only stands when choosing the immediate reward reduces the overall delay, when a post-reward delay is introduced which equalises overall delay between the two responses, hyperactive children show increased preference for the larger, delayed reward (Sonuga-Barke et. al., 1992). This suggests that hyperactive children are not unable to wait but instead choose not to wait in order to avoid delay. Solanto et al. (2001) showed that inhibition deficits and delay aversion appear to be dissociated in ADHD; the two measures are not highly correlated but combined they are able to identify the majority of ADHD cases from a sample. This led Sonuga-Barke (2002) to propose a dual-pathway model of ADHD in which a deficit in inhibition and delay aversion represent separate aetiological pathways to ADHD.

2.2.3 The Cognitive-Energetic Model of ADHD

2.2.3.1 *Hypotheses*

The cognitive-energetic model (CEM), proposed by Sergeant, Oosterlaan, & van der Meere (1999), offers a further motivational model of ADHD. The CEM suggests that information processing is controlled by the interaction of attention, state factors and executive

functions (EF) (see Figure 2.3).

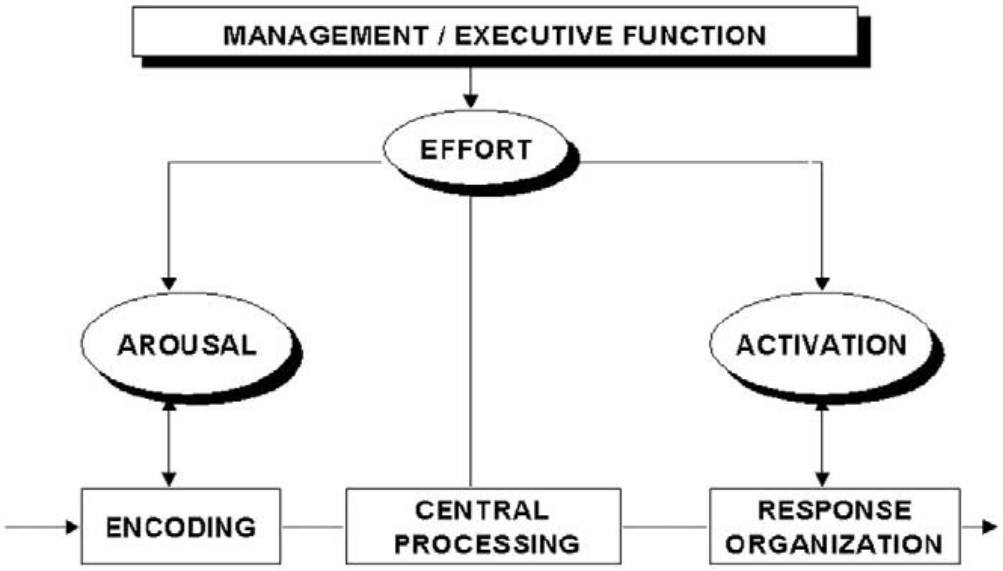

Figure 2.3: The Cognitive-Energetic Model describes three levels of information processing (from Sergeant, 2005).

The three levels shown in the CEM are hypothesised to interact in both top-down and bottom-up routes. The first level of the CEM consists of the computational mechanisms of attention, encoding, search, decision and motor organisation. The second level of the CEM comprises of three energetic pools, *effort*, *activation* and *arousal*. Effort, the energy necessary to meet task demands, is affected by factors such as cognitive load. Activation, tonic physiological activity, is associated with factors such as time-of-day and time on task; and arousal, which is defined as response to a specific stimulus, is affected by factors such as stimulus novelty. The third level of the CEM is a management system, comparable to the concept of EF, which is involved in planning, monitoring and detecting errors and includes control of response inhibition (Sergeant et al., 1999).

2.2.3.2 *The CEM and response variability in ADHD*

Sergeant et al. (1999) suggest that, based on the CEM, the deficits frequently observed in patients with ADHD might be caused by energetic dysfunction. Specifically, Sergeant claims that patients with ADHD may have difficulty in modifying their levels of effort and activation to meet task demands. Thus, patients with ADHD would specifically experience difficulties when performing tasks that require them to adjust their level of effort or activation. This can be tested using tasks that assess energetic state, such as event rate manipulation (the rate at which stimuli are presented). Event rate has been shown to influence performance by altering the energetic state of the participant (Sanders, 1983). A fast event rate may cause over-arousal or over-activation, which is likely to result in rapid but inaccurate responding. Conversely a slow event rate may cause under-arousal or under-activation, which would

similarly result in slow and inaccurate responding (Sergeant, 2005). An energetic dysfunction account of ADHD would predict that patients with ADHD will find it difficult to adjust their arousal and activation levels to meet the demands of very fast or very slow event rates, however they would be likely to perform as well as controls on conditions that present stimuli at normal, intermediate rates (van der Meere & Stemerdink, 1999). According to the CEM, it should be during tasks with very fast or very slow event rates that patients with ADHD will experience the most impairment and thus, will exhibit the most intra-individual variability.

2.2.3.3 *Evidence for energetic dysfunction in ADHD*

The previous findings of a variable response style in patients with ADHD have been used as preliminary evidence of their difficulties in modifying their response style to meet task demands; insufficient effort or activation exhibited by patients with ADHD would result in more task errors and more variable responses. Furthermore investigations that have manipulated event rates have demonstrated partial support for the CEM: patients with ADHD have typically been found to perform more poorly than controls on tasks with a slow event rate and similarly to controls in intermediate event rate conditions. However their performance on tasks with fast event rates has not been found to be impaired compared to controls (e.g. Scheres et al., 2001). The CEM predicts that patients with ADHD will experience difficulties in any condition that requires them to adjust their levels of effort or activation and so would expect patients with ADHD to also perform more poorly on tasks with a fast event rate. Therefore, it appears that patients with ADHD may specifically demonstrate impaired performance on conditions with slow event rates, those which require them to respond to stimuli with long inter-stimulus delays rather than to any conditions that require them to adjust their level of effort. The CEM can not readily explain these findings.

2.2.4 ADHD as a Disorder of Astrocyte Function

A further model of ADHD has been proposed by Russell et al. (2006) who claim that intra-individual variability in ADHD may be caused by deficient astrocyte function. Astrocytes are brain cells that provide support and nutrition to neurons but are not involved in signal conduction and Russell et. al., (2006) hypothesise that in ADHD astrocytes may fail to produce sufficient lactate, which impacts both performance and development. This is based on a theory by Todd & Botteron (2001), *the energy-deficiency model*. Todd & Botteron state that in healthy brains, energy required for brain function is obtained by astrocyte cells that uptake glucose from blood capillaries and convert this to lactate, which can then be stored as glycogen. Astrocytes also play a role in neural signalling as they contain neurotransmitter receptors. Furthermore, amphetamine treatment stimulates glucose uptake in the frontal lobes. Therefore, Todd and Botteron (2001) suggest that in ADHD, reduced catecholaminergic input results in insufficient energy metabolism (by astrocytes) in the frontal lobes. Russell et al. (2006) expand on this theory to further describe how such astrocyte function, in addition to the function of other glial cells, oligodendrocytes, may cause intra-individual variability in ADHD.

2.2.4.1 *Hypotheses - relating atstrocye dysfunction to increased response variability in ADHD*

Russell et al. (2006) describe two ways in which deficient glial cell function may cause increased variability in ADHD.

1) In ADHD, astrocytes are unable to provide sufficient energy to neurons during demanding tasks, which causes inconsistent performance.
2) During development in ADHD oligodendrocytes (cells that form myelin, a substance that improves the speed of signal conduction, around cell axons) are not provided with enough energy (lactate) to enable them to sufficiently myelinate cell axons, which causes signal conduction in these cells to be less efficient.

Thus, increased intra-individual variability will specifically occur during demanding tasks, when the brain's energy requirements are high and the deficient astrocyte function fails to provide sufficient energy to the brain. Some evidence for each of these hypotheses exists.

2.2.4.2 *Possible evidence for impaired energy provision by astrocytes during task performance.*

Zametkin et al. (1990) reported that during task engagement, adults with ADHD utilise approximately 8% less glucose across various brain regions than healthy controls. Furthermore, the greatest differences in glucose utilisation between ADHD patients and controls occurred in the superior frontal, premotor and somatosensory corticies. This appears to support the assertion that in ADHD astrocyte utilisation of glucose is deficient. Russell et. al., (2006) also describe differences in ADHD patients' event-related potential (ERP) components in information processing, which they claim offer further support for this hypothesis. The P3 ERP component is thought to represent the updating of associations within a working-memory template and is elicited by exposure to a rare or meaningful stimulus. In ADHD, the amplitude of this P3 component is reduced (Ozdag, Yorbik, Ulas, Hamamcioglu, & Vural, 2004; Wiersema, van der Meere, Roeyers, Van Coster, & Baeyens, 2006; Du et al., 2006), Russell et. al., (2006) argue that this indicates that insufficient energy reserves are utilised in its formation and suggest that further evidence is evident in the fact that administration of methylphenidate increases the amplitude of the P3 component to normal levels (Hermens et al., 2005; Winsberg, Javitt, & Silipo, 1997; Ozdag et al., 2004) and also increases lactate production. However, this evidence does not provide proof for this theory, although these findings can be explained by the astrocyte dysfunction model, they can also be explained by different models, for example, it is equally plausible that the reduced amplitude of the P3 is caused by reduced effort allocated by ADHD patients (Kok, 2001).

2.2.4.3 *Evidence for insufficient myelination during development*

Myelination of axons in the human brain begins before birth and continues for up to 40 years, with the majority of myelination occurring in the first two years of life. Myelination by oligodendrocytes consumes the highest amount of energy in brain development and so

requires a large supply of lactate. Where this lactate is unavailable it is likely that myelination will be less efficient and consequently conduction of action potentials will be impaired (see Russell et. al., 2006, for further details). Volume of white matter (myelinated cells) has been shown to be an indicator of brain maturation and to be correlated with cognitive performance (Deary et al., 2006; Haier, Jung, Yeo, Head, & Alkire, 2004). MRI studies have shown a decrease – of up to 10% - in white matter volume in ADHD compared to healthy controls (Krain & Castellanos, 2006; Mostofsky, Cooper, Kates, Denckla, & Kaufmann, 2002; Durston et al., 2004; Ashtari et al., 2005; Filipek et al., 1997). Furthermore Ashtari et al., (2005) were able to show that myelination was associated with behavioural symptoms of ADHD. They demonstrated that in children with ADHD, the strength of myelination in the cerebellum (in terms of coherence and integrity) was negatively correlated with ratings of inattention. That is, weaker myelination in the cerebellum was associated with greater inattention.

However other research has presented less clear findings. Investigations of NNA concentrations (a metabolite that is associated with myelin synthesis) in ADHD have presented conflicting results. NAA is thought to be a marker for neuronal density and function (Kegeles, Humaran, & Mann, 1998) and decreases in NAA concentrations are associated with neuronal dysfunction (Sorensen et al., 2006; Kalra, Hanstock, Martin, Allen, & Johnston, 2006). However, some studies have reported increases in NAA concentrations in ADHD whereas others have reported reductions (Sun et al., 2005; Fayed & Modrego, 2005; Jin, Zang, Zeng, Zhang, & Wang, 2001; Hesslinger, Thiel, van Elst, Hennig, & Ebert, 2001). Nevertheless these studies, which are limited in number, have tended to involve small sample sizes and so further replications are necessary. Furthermore, animal studies have shown that methylphenidate treatment can affect NAA levels (Stoller, Garber, Tishler, & Oldendorf, 1994) and so it may be prudent to assess each patient's drug status (i.e. drug naivety) in future investigations that utilise NAA. To sum, there is some evidence supporting astrocyte dysfunction in ADHD, however at present this evidence is limited and requires replication, and furthermore does not exclusively account for this particular model.

2.2.5 The Default Mode Interference Hypothesis of ADHD

A further explanation of the increased response variability identified in ADHD is offered by the default-mode interference hypothesis. This hypothesis was developed by Sonuga-Barke & Castellanos (2007) as an explanation of the increased, periodic intra-individual variability seen in ADHD and suggests that fluctuations in attention occur –at least partly- because in some people, a default mode of a brain activity that is evident at rest intrudes into active states. Thus, the resting-state activity interferes with goal-directed task performance. This hypothesis stems from recent studies that have indicated that the resting brain consists of a certain type of activation, which involves spontaneous low-frequency oscillations (< 0.1 Hz - cycles longer than 10 seconds), synchronised across distant brain regions (e.g. Biswal, Yetkin, Haughton, & Hyde, 1995). This network of spontaneous activation has become known as the default-mode network (DMN) and is often referred to as

a task-negative network as it involves brain regions that are typically de-activated during goal-directed tasks. A second network, which is similarly characterised by very low frequency oscillations, is known as a task-positive network as it involves brain regions that are typically activated during goal-directed tasks. Fox et al.(2005) demonstrated that these two networks are tightly anti-correlated, so that as activation in the task-negative, DMN increases, activation in the task-positive network is attenuated.

2.2.5.1 *Default-mode interference in ADHD - hypotheses*

Sonuga-Barke & Castellanos (2007) suggested that ADHD in some patients may be characterised by intrusions of the DMN during goal-directed tasks. They hypothesised that, during goal-directed tasks, some patients with ADHD do not effectively attenuate the slow oscillations of the DMN and initiate focused task attention. This, they suggested, may allow the resting-state oscillations to intrude into task performance and cause periodic attention lapses and cycles of impaired performance. This is illustrated in Figure 2.4.

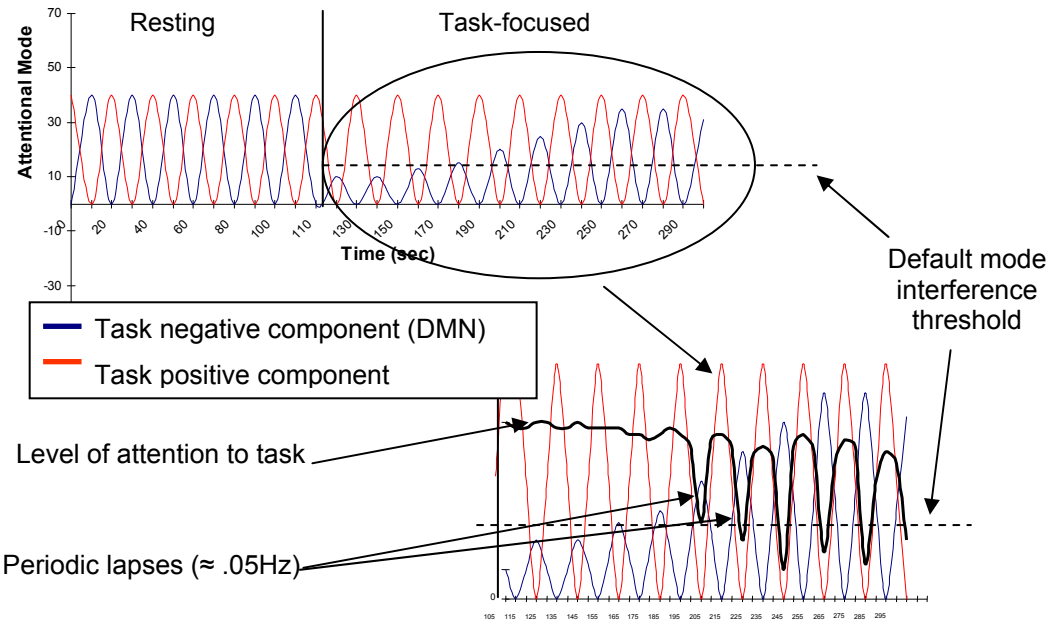

Figure 2.4: Resting-state intrusions in ADHD (From Sonuga-Barke & Castellanos, 2007). *Note.* The task negative (DMN) component is attenuated during a goal-directed task (above right) compared to rest (above left); however this activity re-emerges over time. If the power of the task negative component exceeds a particular threshold (the default-mode interference threshold) during the goal-directed task, a lapse in attention will occur (bottom), as the task negative component oscillates at low frequencies, these lapses in attention will occur periodically and at low frequencies

As shown in Figure 2.4, the default-mode interference hypothesis states that ineffective attenuation of the DMN may allow intrusion of this low frequency brain activity during goal-directed tasks which may result in attention lapses. However, it is likely that the interaction between the DMN and the task positive component is more complex than is illustrated in Figure 2.4. Due to the tightly anti-correlated nature of the DMN and the task-positive network, it will be difficult to determine whether ineffective attenuation of the DMN, or failure to maintain the task positive component during goal-directed tasks creates attention lapses. Furthermore, the extent to which the task positive and task negative components are anti-correlated in terms of phase and amplitude, and the behaviour of the task positive component in each condition is not yet certain and may differ from that illustrated in the figure.

2.2.5.2 *The default-mode interference hypothesis and predictions of response variability in ADHD*

This hypothesis offers several testable predictions:

- The attenuation of the very low frequency DMN from rest to goal-directed performance should occur irrespective of the nature of the task (except for general requirements such as for sustained attention and cognitive load).
- Factors of both state and task will affect the degree of attenuation of resting-state oscillations during goal-directed activity, e.g. fatigue or intrinsic motivation.
- A threshold should exist in the power of DMN oscillations, above which, impairment of attention will occur but below which no impairment will be evident.
- When the power of DMN oscillations exceeds this threshold, the individual will experience intrusions of introspective thoughts and a related decrease in task performance. Therefore, they will exhibit increased variability across the task.
- There will be synchrony between the fluctuations in the DMN, the intrusions of introspective thoughts, the lapses in attention and the declines in performance. These synchronised patterns will occur at low frequencies (.01-.1 Hz)

Although these hypotheses have not been explicitly tested, some evidence exists to support them. Evidence for the DMN in the resting brain and corresponding attenuation during task engagement will now be described. Research into the DMN in ADHD will also be briefly outlined, however the following chapter will give a much more comprehensive review of the literature associated with the default-mode interference hypothesis and corresponding methodological issues

2.2.5.3 *The DMN in the Resting Brain*

The network of brain regions involved in the ‘default mode’ of brain function at rest has mainly been investigated using functional magnetic resonance imaging (fMRI) methods. From such studies, it appears that distinct brain regions are associated with each of the task-negative and the task positive networks. The task positive network, which increases in activation during task engagement, includes the dorso-lateral prefrontal cortex, the parietal

cortex and the sensory motor areas. The task-negative network, which is attenuated during task engagement, includes the medial parietal and medial prefrontal cortices and the posterior cingulate cortex (e.g. Fransson, 2005; Fox et al., 2005). These two networks, although involved in distinct brain regions, are tightly anti-correlated temporally, so much so, that it is reasonable to consider that combined they may represent a single, complex network. Given this, it may be appropriate to describe both the task-positive and the task-negative networks as different elements of the DMN (see Broyd et al., 2009). However, it is likely that the different task components may have distinct functions. Fransson (2005) suggests that the task-negative network may represent an introspective mode that involves self-reflection, planning for the future and inner thought. The task positive network may conversely represent an extrospective, threat assessing mode that is characterised by increases in alertness and attention. Fransson (2005) suggests that toggling between these two modes at rest may afford evolutionary advantage for an individual, as intrusions of a threat-assessing mode in an otherwise introspective mode will identify dangers in the environment to which an individual should attend. Therefore as these two networks appear to have distinct functions, for clarity we shall we will use the term DMN to refer to the task-negative network only.

Additionally, the functional importance of the anti-correlation between the task-positive and task-negative components has recently been called into question. Murphy, Birn, Handwerker, Jones, & Bandettini (2009) claim that a common pre-processing technique - global signal regression- may artifactually introduce anti-correlations into the data, and thus the anti-correlation between the task-positive and task-negative networks may be artifactual. However, in response to this, Fox, Zhang, Snyder, & Raichle (2009) report that although global regression can introduce artificial anti-correlations, based on a combination of simulated data and applications of these simulations to human data, they believe that the task-positive/task-negative anti-correlations are a true representation of the physiological relationship between different brain regions. Nevertheless, until the impact of such pre-processing measures is properly understood it would be prudent to interpret the function of these anti-correlations with some caution and until then, it may be more appropriate to consider the DMN independently from the task-positive network.

2.2.5.4 *The DMN during Task Engagement*

The DMN does appear to be attenuated during task performance, however it is not completely extinguished and continues to be observed during goal-directed tasks - although at lower levels (e.g. Fransson, 2006; Greicius & Menon, 2004; Eichele et al., 2008). Furthermore, it appears the level of task demands affects the level of DMN attenuation: for example, Greicius & Menon (2004) showed that when participants were required only to passively view stimuli, there was little attenuation of this network. Furthermore, both McKiernan, D'Angelo, Kaufman, & Binder (2006) and Singh & Fawcett (2008) have reported that the level of task deactivation in brain regions implicated in the DMN is correlated with task difficulty. Moreover, it appears as if inefficient attenuation of DMN is associated with

poorer task performance: Drummond et al. (2005) reported that poorer performance on a vigilance task was correlated with increased activity in the midline brain structures that are associated with the DMN; Weissman, Roberts, Visscher, & Woldorff (2006) demonstrated that attentional lapses in healthy participants were characterised by less deactivation of the DMN; and Eichele et al. (2008) reported that up to 30 seconds prior to an error, brain regions associated with the DMN (e.g. precuneus, PCC, and retrosplenial cortex) showed an increase in activation; and periods of mind-wandering have been shown to be preceded by increased activation in the DMN (Christoff, Gordon, Smallwood, Smith, & Schooler, 2009).

An exception to this pattern of task related DMN deactivations occurs when the task requires participants to makes self-referential judgements. Gusnard, Akbudak, Shulman, & Raichle (2001), reported that the dorsal and ventral medial prefrontal cortex (MPFC) are differentially affected by tasks depending on whether the task requires self-referential judgement. When participants engaged in a task which required them to make a judgement (either self-referential - such as reporting how a picture made them feel -or not self-referential - for example to decide whether a picture represented an indoors or an outdoors scene), decreases in the ventral MPFC were observed: however, when the judgement was self-referential, this was also accompanied by an increase in dorsal MPFC activation. As self-referential thought is posited to be a function of the DMN, the authors suggest that tasks which require self-referential judgements may show differential DMN deactivations.

2.2.5.5 *Studies of the DMN and ADHD*

Research into DMN activity in ADHD will only briefly be outlined here, as it is reported in greater depth in the following chapter. However, generally, research into DMN brain activity in ADHD has been fairly limited. Investigations of the DMN in ADHD, typically using fMRI, have only recently been undertaken: the first published study of functional connectivity in ADHD using resting-state fMRI was by Tian et al. in 2006 who reported that patients with ADHD exhibited increased functional connectivity at rest between the dorsal anterior cingulate cortex and other brain regions, such as the thalamus, cerebellum and insula, than controls. However, later studies have failed to replicate these findings and instead tend to show decreased resting functional connectivity in ADHD in the structures of the DMN, particularly between the anterior and posterior components of the DMN, and those involving the precuneus (e.g.Castellanos et al. 2008; Uddin et al. 2008). A more detailed review of these studies and others that investigate DMN abnormalities in ADHD are reported in the following chapter –see section *3.2.1.1 Functional Magnetic Resonance Imaging in ADHD and DMN Research*. However, general findings indicate that differences may exist in the connectivity of the DMN between patients with ADHD and controls. Nonetheless, as coupling the intrusions of the DMN with periodic attention lapses in ADHD is key to the default-mode interference hypothesis of ADHD, it may be more appropriate to employ scalp electroencephalogram (EEG) rather than fMRI recordings, as scalp EEG, unlike fMRI, has excellent temporal resolution and also provides a more direct measure of neuronal activity than the BOLD signal.

In spite of this, resting-state EEG research in ADHD has not investigated very low frequency EEG activity (<.1 Hz) and instead has typically investigated group differences in higherfrequency neuronal oscillations, delta (1.5-4 Hz), theta (4-8 Hz), alpha (8 -12 Hz) and beta (12-25 Hz) frequency bands (e.g Yordanova, Banaschewski, Kolev, Woerner, & Rothenberger, 2001; Herrmann & Demiralp, 2005; Brenahan & Barry, 2002; Barry, Clarke, McCarthy, & Selikowitz, 2002; Barry et al., 2004). Such research has typically reported that patients with ADHD exhibit greater power in the low-frequency bands, specifically theta, and a decrease of power in the high frequencies, such as beta and alpha, than controls when at rest (e.g. Brenahan & Barry, 2002; Clarke, Barry, McCarthy, & Selikowitz, 2001b). Again these studies are reported in more detail in the following chapter - see section *3.2.2.1 Electrophysiology in ADHD Research*. Although these studies indicate that resting brain activity is likely to be abnormal in ADHD they do not explicitly test the predictions of the default-mode interference hypothesis.

In order to test the predictions of the default-mode interference hypothesis, it will be important i) to assess and localise low frequency DMN brain activity in ADHD, both at rest and during goal-directed tasks, ii) to examine whether periodic patterns exist in behavioural data, and iii) to determine whether there is synchrony between fluctuations in low frequency brain activity and declines in performance. Previous research which has investigated each of these questions and the methodological and analytical issues associated with this research will be addressed in greater depth in the following chapter. However, low frequency DMN brain activity has been investigated using fMRI and has been shown to be abnormal in ADHD. Furthermore, early research suggests that periodic patterns may exist in behavioural data: as described earlier in this chapter, response variability in ADHD has been shown to be temporally structured and RTs to oscillate at low frequencies, with a lapse in attention occurring every 20 seconds. However, it has not been shown whether these periodic attention lapses in ADHD are associated with intrusions of the DMN. Thus, in order to investigate the default-mode interference hypothesis of ADHD, temporally resolute EEG may be most appropriate for determining whether there is synchrony between fluctuations in low frequency brain activity and declines in performance.

2.2.6 Integration of Models and Response Variability in ADHD

To sum, although not all of the previously described models of ADHD explicitly attempt to describe response variability, they all offer predictions about how response variability might present in ADHD. A summary of these is shown in Table 2.1.

Table 2.1

Characteristics of response variability from different models of ADHD

Theory	Overview	Response Variability Predictions
ADHD as an EF deficit	ADHD results from global dysregulation of EF, possibly with a primary deficit in response inhibition.	Response variability will present as random variability.
ADHD as delay aversion	ADHD results from a motivational desire to avoid delay.	Response variability will occur when patients with ADHD are exposed to delay.
ADHD as a disorder of state regulation.	ADHD results from insufficient levels of effort or activation to meet task demands.	Response variability will occur in conditions that present very fast or very slow event rates.
ADHD as a disorder of astrocyte function.	ADHD results from a failure of astrocyte cells to produce enough lactate (energy) during demanding tasks.	Response variability will occur in conditions with high energy demands, specifically tasks with fast event rates.
ADHD as default-mode interference.	ADHD results from the intrusion of low-frequency resting-state oscillations into active state.	Response variability will have a periodic structure similar to that found in the resting-state brain activity (approximately one cycle every 20 seconds).

Note. EF = Executive Function

As illustrated in Table 2.1, each theory of ADHD offers specific, testable predictions about the presentation of response variability. However, as yet, few of these predictions have been examined. Furthermore, despite preliminary research, the temporal structure of response variability remains uncertain, understanding this will especially be a key issue in determining the feasibility of the Default-Mode Interference hypothesis.

2.3 Chapter Summary

Increased variability of RT responses is widely found in ADHD, however this has been under-researched and many key questions about the nature of this variability have remained unanswered. Different theories of ADHD offer different predictions about the causal processes in ADHD and correspondingly how this variability might be expressed. Theories of ADHD include; ADHD as a disorder of executive function, or as delay aversion, deficiencies in

state regulation, a disorder of astrocyte function, and inertia when transitioning from a resting-state to a goal-directed state. The default-mode interference hypothesis predicts that variability will be expressed by lapses in attention that occur periodically (approximately every 20 seconds). However, in order to test this hypothesis, more must be discovered about the form of the DMN in patients with ADHD, both during rest and during active, goal-directed states, to identify whether differences exist in this network between patients with ADHD and healthy controls. Furthermore, more appropriate tasks that allow the temporal variations in attention to be captured should be adopted. However, this will require novel methods to be employed, for example, in behavioural tasks, time series data must be examined and signal processing analyses will be necessary to decompose these data into their main frequency bands, which will elucidate any periodic nature of attention. Furthermore EEG, with its high temporal resolution, may be a more appropriate method for determining whether changes in the DMN are synchronised with attention lapses than fMRI.

Chapter 3 The default-mode interference hypothesis: A review of literature and methodology

This chapter will give a more comprehensive review of the literature associated with the default-mode interference hypothesis and the methodological issues associated with this research. The key issues associated with investigating the default-mode interference hypothesis will be: i) assessing and localising low frequency DMN brain activity in ADHD, both at rest and during goal-directed tasks, ii) examining whether periodic patterns exist in behavioural data, and iii) determining whether there is synchrony between fluctuations in low frequency brain activity and declines in performance. This chapter will assess each of these issues in turn, outlining the literature associated with each and highlighting methodological problems that must be considered in their investigation.

As the default-mode interference hypothesis makes specific predictions about resting-state brain activity, this chapter will begin by discussing 'what is rest?' and will outline different conditions that have been used to assess the resting-state in DMN investigations and will discuss the efficacy of these. The chapter will then outline the different methodologies that have been used in the investigation and examination of low frequency DMN brain activity in ADHD: it will outline these techniques, and review the literature about how they have typically been employed in ADHD research, it will then examine how they have been used in the localisation and examination of the DMN, and finally highlight each method's strengths and weaknesses. As mentioned in the previous chapter, investigations of DMN activation have predominantly adopted functional magnetic resonance imaging techniques (fMRI); however other methods such as electrophysiology (EEG), positron emission tomography (PET) and magnetoencephalography (MEG) have also been used. As they have been used extensively in both DMN and ADHD research, fMRI and EEG will be described in depth in this chapter, but as they have been used less often in DMN and ADHD research, PET and MEG will only be briefly outlined.

As the default-mode interference hypothesis suggests that periodic attention lapses are created by intrusions of spontaneous low-frequency brain activity (Sonuga-Barke & Castellanos, 2007), an important test of this hypothesis will be to examine whether periodic patterns do exist in behavioural data and whether there is synchrony between the fluctuations in low frequency brain activity and declines in performance. Therefore, this chapter will then describe how temporal patterns can be identified in behavioural data and the methodological considerations associated with designing behavioural tasks that ensure that the data obtained from these are suitable for signal processing analyses. Lastly, the chapter will describe attempts that have been made to co-register low frequency brain activity and lapses in attention.

3.1 What is rest?

The DMN is conceptualised as a resting-state network; it is active at rest and shows deactivations when participants engage in a goal-directed task. However, it is likely that DMN activity persists into non-rest states, as DMN activity appears to be attenuated rather than extinguished during goal-directed tasks and is still observed during task performance, although at lower levels (Eichele, et al., 2008; Fransson, 2006; Greicius, et al., 2003; Greicius & Menon, 2004). Therefore, although DMN activity is likely to be apparent outside of a resting-state, it will most probably be in an attenuated form and thus, DMN research typically investigates DMN brain activity during rest. However, a fundamental question when looking at DMN brain activity during rest is 'what is rest?' The term 'rest' may be misleading as the brain is constantly active even during sleep or anaesthesia and so never truly 'rests' (Greicius et al., 2008). In DMN research 'rest' is used to mean the absence of any specific goal-directed cognitive task and during these investigations participants are typically instructed simply to 'rest' or to 'relax' without falling asleep.

Greicius (2008) claims that a true measure of the DMN during the resting-state will involve a long task-free period during which the participant can rest, however, a large number of studies investigating this activity have now been performed on existing fMRI datasets which have not specifically included a task-absent condition. Instead, these studies have attempted to emulate the resting-state with existing data. For example, some studies have examined 'resting' brain activity while participants are performing simple tasks – such as Greicius, Srivastava, Reiss, & Menon (2004), who assessed DMN activity while participants performed a simple sensory motor-processing task, in which the participants were required to respond with a button press whenever a stimulus was presented. Other studies have 'cut' short periods of rest (normally 30 – 60 seconds duration) which fall between trials in longer cognitive tasks, and used these discontinuous segments to evaluate the resting-state (e.g. Fair et al., 2008). Further studies, that have not included resting blocks, have approximated the resting-state signal by removing the task-specific activation from the time-series signal - in this method the effect of the task is modelled (typically using a general linear model) and then regressed out of the signal, and this residual signal is then analysed (e.g. Meltzer, Negishi, Mayes, & Constable, 2007; Scheeringa et al., 2008b).

In order to determine whether these methods of 'near-rest' are in fact appropriately similar to the resting-state, Fair et al. (2007) compared the resting-state functional-connectivity of a continuous resting condition (a task-free period of rest), with resting epochs taken from blocks between trials in a visual choice task (32 - 45 seconds: total 640 seconds), and the residual time-series signal after task-activation had been regressed out from a event-related task. They showed that both of these methods resulted in reduced functional connectivity compared to the continuous resting condition, and this was particularly evident in the residual signal from the event-related task. They suggest that this may be because task-engagement is likely to attenuate the default-mode signal, and that attenuation of this signal

will reduce its functional connectivity: and therefore, the utility of the residual signal from an event-related task in exploring the resting-state is likely to be limited.

Greicius (2008) further asserts that resting-state measures taken from resting epochs between blocks of a task may also differ from a 'true' measure of rest, as these between-task blocks may be affected by anticipation of imminent task blocks or rumination over performance or mistakes made on previous task blocks. Greicius (2008) further suggests that the differences in this between-task rest and 'true' rest may be particularly salient in clinical groups, and thus any between-group differences in measures of resting-state that have not been obtained from task-free periods of rest may reflect differences in switching between tasks rather than resting-state related differences. Therefore, it does appear that 'rest' in a task-free period may be different from 'near-rest', such as resting epochs between blocks of a cognitive task, and is highly likely to be different from the residual time-series signal after task-activation is regressed out and so it will be important for future studies of resting brain activity to employ sufficiently long task-free resting periods.

Conversely, within these long resting periods, there does not appear to be a substantial difference between rest with eyes open and rest with eyes closed. For example, Raichle et al., (2001) showed that the brain regions activated while healthy participants rested quietly with eyes closed was highly comparable with those regions activated while participants rested with eyes open and passively viewing a fixation cross. The only notable difference in activations between these two rest conditions was that the visual cortex was deactivated in the eyes closed condition but activated in the eyes open condition. Therefore, either rest with eyes closed or rest with eyes open would be appropriate for DMN investigation. However for investigations which compare the resting-state with goal-directed activity, which is likely to require the participants to keep their eyes open as they attend to the task, it may be more appropriate to use rest with eyes open, as the visual cortex should be activated in both conditions.

3.2 Methodologies used in DMN investigation

The two main methodologies employed in DMN investigation are fMRI and EEG, however positron emission tomography (PET) and Magnetoencephalography (MEG) have also been used. Positron emission tomography is often used to describe blood flow: a radioactive isotope is injected into the blood supply of the participant and after a short delay (<1 minute) the gamma radiation emitted by this isotope can be detected by the scanner and regional changes in blood flow can be identified (Raichle, 1998). Positron emission tomography was used in early DMN research to delimit brain regions which exhibited task-induced deactivations (e.g. Raichle et al., 2001), in contrast, MEG, which measures the magnetic fields that are created by the brain's electrical signal, has only recently been employed in resting-state research, although it has focussed more on the faster frequency bands and not the correlates of the DMN (e.g. Bosboom et al., 2006; Osipova et al., 2006; Stam et al., 2006; Stoffers et al., 2008). As fMRI and EEG techniques have been extensively

used in both DMN and ADHD research, they will now be described: their role in ADHD research and in DMN research will be reviewed and their relative strengths and weaknesses will be highlighted.

3.2.1 Functional Magnetic Resonance Imaging

Functional magnetic resonance imaging measures the hemodynamic response, which reflects changes in the blood-oxygen level dependent signal (BOLD), as oxygen is released from the blood to the neurons. This hemodynamic response is thought to reflect neural activity and the difference in magnetic susceptibility between oxygenated blood (which contains oxyhemoglobin) and deoxygenated blood (which contains deoxyhemoglobin) is identified by the fMRI scanner. Traditionally these BOLD signal changes have been conceptualised as reflecting increased oxygen and glucose delivery to active neurons compared to inactive neurons, however this view had been criticised as oversimplified (Raichle & Mintun, 2006).

3.2.1.1 *Functional Magnetic Resonance Imaging in ADHD and DMN Research*

Traditionally in ADHD research, fMRI has been used to identify differences in task-induced increases in brain activation between patients with ADHD and controls. For example, patients with ADHD have been shown to exhibit decreased activation in the frontal lobes compared to controls during tasks that require inhibition, such as the Go/No-Go task (e.g. Durston, Mulder, Casey, Ziermans, & van Engeland, 2006; Durston et al., 2003; Booth et al., 2005), and the stop task (e.g. Rubia et al., 1999). However, in 2001, Raichle et al. reported that in fMRI and PET studies, certain brain areas rather than exhibiting task-induced activations, exhibited task-induced deactivations, i.e. certain brain regions showed decreases in activation when a participant engaged in a task compared to the baseline resting condition. Furthermore, the same brain regions exhibited task-related deactivations regardless of which task the participant engaged in. This implies that a network of brain regions exists which is a 'physiological baseline' or a 'default-mode' of brain activity, and this network is attenuated during task engagement (Gusnard & Raichle, 2001). The DMN, characterised by these task-induced deactivations, has since been extensively studied in healthy controls and also in abnormal populations, including Alzheimer's disease, schizophrenia, depression and anxiety, epilepsy, ASD and ADHD (see Broyd et al., 2009).

Localisation of the Default-Mode Network using fMRI

The BOLD response has also been used in a number of ways to identify and localise default-mode brain activity at rest. Two main approaches are: i) region-of-interest (ROI) analysis, and ii) independent component analysis (ICA) (ICA is described in more depth in section *4.2.6.2 Artifact Removal*). These methods are used to identify the spatial patterns of coherent BOLD activity, which is often described as the 'functional connectivity' between different brain regions (Fox & Raichle, 2007). ROI analysis determines the temporal correlation between the BOLD signal at a particular seed-region (the ROI) and the BOLD signal at all other brain voxels, this approach has been widely used to identify networks of

coherent brain activity at rest. However, this method requires the selection of an *a priori* seed-region and furthermore prevents analysis of more than one simultaneous network. ICA, in contrast, is data-driven and so is not constrained by *a priori* knowledge of particular seed-regions, moreover it decomposes the BOLD signal into maximally independent components which represent individual networks, this allows these networks to be examined simultaneously (Fox & Raichle, 2007). However, ICA is limited in terms of its reliance on subjective criteria for determining which extracted components reflect networks of brain activity and which represent artifacts (for further information see section *4.2.6.2 Artifact Removal*). Nevertheless, despite their respective limitations, both methods appear to produce similar results and both identify similar regions of resting brain activity (e.g. Greicius et al., 2004). Both of these methods have been used to identify spatial patterns of brain activity at rest that cohere at low-frequencies and the function of these networks is then inferred from the brain regions that they include, for example, a resting network that involved the bilateral primary visual cortices would be assumed to be implicated in vision (Greicius, 2008).

The Default-Mode Network in ADHD

Tian et al. (2006) were the first to investigate resting-state functional connectivity in ADHD. They mapped the functional connectivity patterns of the anterior cingulate cortex (ACC) in 8 adolescents with ADHD and 8 controls at rest. They chose the ACC as the seed region, as the ACC has previously been shown to function abnormally in ADHD and it has an important role in cognitive and autonomic control. Tian et al. (2006) report that the ACC of the patients with ADHD showed increased resting functional connectivity with various other brain regions, such as the thalamus, cerebellum, insula and brainstem, compared to the controls. Tian et al. (2008) find similar results in a re-analysis of this same data set using a method of analysis which they describe as a resting-state activity index. Tian et al. (2006) suggest that this pattern of increased functional connectivity in ADHD reflects the abnormalities in autonomic control expressed in ADHD, as many of these brain regions are implicated in autonomic arousal.

However, in a similar study, Castellanos et al. (2008) reported *decreased* functional connectivity in ADHD between ACC and brain regions associated with the DMN, such as the precuneus/posterior cingulate cortex (PCC). They further showed that using the precuneus/PCC as a seed-region, the ADHD group showed reduced connectivity within the DMN, notably between the precuneus/PCC and ventromedial prefrontal cortex i.e. between the anterior and posterior components of the DMN. They suggest that the precuneus/PCC is likely to be involved in the integration of anterior executive functions with posterior associations, and that abnormalities in this integrative process may represent a possible locus of dysfunction in ADHD.

Methodological differences may account for the contrasting findings of the two studies. For example, the studies employed different samples; Tian et al.(2006) used an adolescent sample but Castellanos et al. (2008) used an adult sample, therefore these differing findings may reflect developmental differences between the two groups. The studies

also adopted different methods of analysis - Tian et al.(2006) seeded the entire dorsal ACC and did not differentiate between the anti-correlated activations but Castellanos et al., (2008) seeded only a sub-region of the ACC and assessed the anti-phase activity between this area and other brain regions. However, other studies have also reported reduced DMN functional connectivity in ADHD. Cao et al. (2006) reported reduced regional homogeneity in the frontal-straital cerebella circuits in the resting BOLD signal of boys with ADHD compared to controls. Regional homogeneity assesses the similarity of the time series of a particular voxel with its neighbours (Zang, Jiang, Lu, He, & Tian, 2004). Adapting this method, Uddin et al. (2008) reported reduced *network homogeneity* within the DMN in ADHD compared to controls. Uddin et al., (2008) use the term network homogeneity to refer to long-range connectivity - in contrast to regional homogeneity, which is sensitive only to very local patterns of connectivity – and this measure gives a mean correlation of a particular voxel's time series with all other voxels in a particular network. Using this approach they report reduced network homogeneity within the DMN in ADHD, particularly between the precuneus and other DMN regions. Therefore it appears likely that reduced resting-state functional connectivity, particularly between the anterior and posterior components of the DMN, and those involving the precuneus may have a causal role in the attentional dysregulation observed in ADHD (Uddin et al., 2008).

In a different approach - following Greicius et al.(2004) who used a template of DMN activity to distinguish patients with Alzheimer's disease from those without (based on the spatial similarity between each participant's resting brain activity and the DMN template) - Zhu et al., (2008) showed that children with ADHD could be differentiated from controls by their resting-state fMRI. Zhu et al., (2008) used Fisher discriminative analysis to identify patterns of regional homogeneity in the resting-state fMRI data between children with ADHD and controls, they then employed permutation tests to identify which regions of brain activity were most able to discriminate between the two groups. These highly discriminative brain regions included the anterior cingulate gyrus, the prefrontal cortex, putamen and temporal cortex. Using these regions, they were able to correctly classify 85% of the children. Zhu et al., (2008) suggest that this classification algorithm may be able to be used in clinical diagnosis of ADHD.

Therefore, fMRI has been used to demonstrate differences in resting-state functional connectivity between patients with ADHD and controls, and has the potential to be useful in the clinical diagnosis of ADHD. However, the fMRI methodology has a number of weaknesses. For example, despite the high spatial resolution of fMRI, the hemodynamic response has poor temporal resolution. Furthermore, the relationship between the hemodynamic response measured by fMRI and underlying neuronal activity is unclear, as the BOLD signal does not directly measure neuronal activity but its delayed consequences, therefore it is uncertain precisely which element of neuronal activity is best associated with the BOLD signal, for example local field potentials, combined neural spiking etc (Huettel et al., 2004). Therefore the BOLD signal might not exactly fit with electrophysiological signals (Broyd

et al., 2009). Moreover, in fMRI, samples (scanning images) are typically taken once every 2-4 seconds; however brain activity operates on a much faster scale, and within the same brain regions, initial and re-entrant activity can occur very quickly (<100ms). Because of its infrequent sampling, fMRI is unable to differentiate between these two activations, and thus in isolation cannot give a complete picture of brain activity (Noesselt et al., 2002). Scalp electroencephalogram (EEG) recordings, however, have very good temporal resolution of less than a millisecond. This may be particularly important in determining whether changes in the DMN are synchronised with attention lapses.

3.2.1.2 *Summary of fMRI Research in ADHD and the DMN*

Functional magnetic resonance imaging has traditionally been used to identify task-induced increases in brain activation, however the concept of the DMN originated from the observation that task-induced decreases in brain activation also exist and these deactivations delimit a network of brain activity that is apparent at rest and is attenuated during goal-directed tasks. In DMN research, spatial patterns of resting brain activity are typically identified using ROI or ICA analysis. Such studies have typically reported that patients with ADHD exhibit decreased resting functional connectivity in the structures of the DMN, particularly between the anterior and posterior components of the DMN, and those involving the precuneus. Castellanos et al. (2008) and Uddin et al.(2008) suggest that this decreased functional connectivity between these structures may reflect difficulties in integration of executive functions with association processes and may underlie the attentional dysregulation observed in ADHD. However the poor temporal resolution, infrequent sampling and incongruence of the BOLD signal with underlying neural activity highlight the potential use of electrophysiology in DMN research.

3.2.2 Electrophysiology

Electroencephalogram is recorded from the scalp and measures the electrical signal produced by the brain: this electrical signal reflects post-synaptic potential changes from large groups of neurons that have a similar spatial orientation (Banaschewski & Brandeis, 2007). Electroencephalogram waveforms are typically divided into bands classified by their frequency, the location and function of these frequency bands are shown in Table 3.1

Table 3.1

The location and function of EEG frequency bands

Band	Frequency (Hz)	Location	Possible functions
Delta	1.5 – 4	Frontally in adults (particularly in the prefrontal cortex), posteriorly in children.	In adults, delta is normally found during sleep and is thought to suggest sensory disengagement (Anderson & Horne, 2003). In young children delta is prominent during waking but this declines with age. This is thought to be associated with cerebral maturation, (e.g. Taylor & Rutter, 2002).
Theta	4 – 7	Midline or frontal regions.	Power in the theta band is often considered to be a marker of sleep propensity (Vyazovskiy & Tobler, 2005). Power in the theta band is associated with subjective reports of sleepiness (e.g. Aeschbach et al., 1997) and sleep deprivation has been shown to increase power in this band (e.g. Makeig, Jung, & Sejnowski, 2000). However, frontal theta has also been associated with tasks that activate working memory (e.g. Buzsaki, 2005) and power in the theta band has shown to increase with cognitive load (e.g. Smith, Mcevoy, & Gevins, 1999).

Band	Frequency (Hz)	Location	Possible functions
Alpha	8 – 12	Particularly posterior regions.	Alpha is generally associated with restfulness, especially with eyes closed. It is normally attenuated with eyes opening and decreases with cognitive demand (e.g. Vanni, Revonsuo, & Hari, 1997). Furthermore, this decrease is proportional to cognitive load, i.e. when performing a working memory task with 2, 4 or 6 digits, the reduction in alpha power increases with the number of digits (Meltzer et al., 2007). Therefore it has been suggested that alpha may be an indicator of cognitive 'idling' (e.g. Miller, 2007)
Beta	12 – 30	Mainly frontal regions, although it is also found centrally and posteriorly, however these central and posterior activations are thought to represent faster versions of the alpha rhythm (Rangaswamy et al., 2002)	Beta is thought to be involved in processing at a cognitive level, such as during self-reflection and concentration, and tends to be coherent over large cortical regions. Power in the beta frequency is largely increased by benzodiazepines and barbiturates and increased resting beta power is found in alcoholics (e.g. Rangaswamy et al., 2002)
Gamma	30 – 70	Gamma is not normally able to be recorded by scalp electrodes due to distortions created by the conductivity of the skull and the scalp (Miller, 2007)	Gamma is thought to be associated with primary sensory processing (Miller, 2007) as well as conscious perception, memory and feature binding (Yordanova et al., 2002).

3.2.2.1 *Electrophysiology in resting-state ADHD Research*

In EEG research, resting-state assessments have traditionally investigated power in frequency bands much higher than those implicated in the DMN (i.e. >1.5 Hz). Between-group or between-condition comparisons are often made on the absolute or the relative power in each of these frequency bands or the ratio of power between two frequency bands (i.e. theta/beta ratio). These measures have been shown to have good test-retest reliability (John et al., 1980). In ADHD research, children with ADHD have fairly consistently been shown to have elevated frontal and central levels of theta power at rest compared to typically developing children (e.g. Clarke & Barry, 2001; Clarke, Barry, McCarthy, & Selikowitz, 2002; Chabot & Serfontein, 1996; Lazzaro et al., 1998; El-Sayed, Larsson, Persson, & Rydelius, 2002). Such theta activity is usually associated with under-arousal and suggests that children with ADHD may experience cortical hypo-arousal (Loo & Barkley, 2005). Abnormalities in the resting levels of higher frequency, alpha and beta power have been less consistently replicated: decreases in alpha and beta power in ADHD has been reported by some researchers e.g. (Clarke & Barry, 2001; Clarke et al., 2002; Chabot & Serfontein, 1996; Lazzaro et al., 1998) but not others (Janzen, Graap, Stephanson, Marshall, & Fitzsimmons, 1995; Kuperman, Johnson, Arndt, Lindgren, & Wolraich, 1996; Satterfield, Schell, Backs, & Hidaka, 1984). Theta/beta and theta/alpha ratios have also been shown to fairly consistently distinguish between children with ADHD and typically developing children. Children with ADHD are typically shown to exhibit higher ratios, especially in frontal locations e.g. (e.g. Clarke & Barry, 2001; Clarke et al., 2002; Monastra et al., 2001).

The inconsistency in findings (especially concerning alpha and beta power in ADHD) may be explained by differences between ADHD subtypes. Clarke et al. (2001a) attempted to determine whether ADHD subtypes can be differentiated by their EEG profile: they compared 40 children with ADHD combined subtype (ADHD-C), 40 children with ADHD- inattentive subtype (ADHD-I) and 40 typically developing controls. They showed that although the ADHD group (both subtypes) differed from the control group in the typical way, i.e. the ADHD group showed higher levels of theta, but lower levels of beta and alpha and higher theta/beta and theta/alpha ratios, the two ADHD groups also differed from each other, and the ADHD-C group showed higher levels of relative theta power and lower levels of relative alpha and beta than the ADHD-I group. Furthermore, the ADHD-C group showed higher theta/beta and theta/alpha ratios than then ADHD-I group. Clarke et al., (2001a) suggest that these results are indicative of a continuum model, in which the ADHD-I group would fall in between the control and the ADHD-C groups. However this finding was not replicated by Monastra, Lubar, & Linden (2001).

Clarke, Barry, McCarthy, & Selikowitz, (2001b) further attempted to determine whether the underlying structure of EEG impairment is heterogeneous within a large group of children with ADHD-C (N = 184). They performed cluster analysis on the total power and power in each of 4 frequency bands (delta, theta, alpha and beta) during an eyes-closed

resting condition. Three distinct EEG clusters emerged: the first, which contained 42% of the ADHD sample, was characterised by increased theta power, reduced delta and beta power and an increased theta/beta ratio; the second cluster, which contained 37% of the ADHD sample, was characterised by increased theta power, an increased theta/beta ratio and reduced alpha power; the third cluster, which contained 20% of the ADHD sample, was characterised by increased beta power and a reduced theta/beta ratio. This suggests that children with ADHD do not all display the same EEG profile and that clinical groups of children with ADHD are unlikely to be homogenous. This, Clarke et al., (2001b) claim, is likely to have implications for EEG research and the utility of EEG in the diagnosis of ADHD. Clarke, Barry, McCarthy, Selikowitz, & Brown (2002) replicated this analysis in a sample of children with ADHD-I (N = 100), and identified two clusters within this sample. One cluster, which contained 68% of the ADHD-I sample, was characterised by increased theta power, reduced beta power and normal alpha power: the second cluster was characterised by increased delta and theta power and reduced alpha power and contained 32% of the ADHD-I sample. Clarke et al., (2002) suggest that these two clusters may represent two different groups of children, with different underlying abnormalities: they suggest that the first cluster contains children with underlying cortical hypoarousal, and the second cluster consists of children with a central nervous system maturational lag. Therefore, observation of the behavioural characteristics and difficulties of children with ADHD is likely to be inadequate for determining their underlying cause, and EEG techniques may be useful in formulating more homogenous sub-groups of children with ADHD.

3.2.2.2 *Electrophysiology in Default-Mode Network Research*

Localisation of the Default-Mode Network using EEG

It is only very recently that EEG has been used to investigate default-mode brain activity, both in the traditional frequency bands and also in the lower frequencies that are more similar to those of the DMN (as identified by fMRI, i.e. <.1Hz). Chen, Feng, Zhao, & Yin (2008) identified EEG resting networks in the classic frequency bands, delta (.05 - 3.5 Hz), theta (4 - 7 Hz), alpha (alpha-1: 7.5 – 9.5 Hz; alpha-2: 10 – 12 Hz), beta (beta-1: 13 – 23 Hz; beta-2: 24 34 Hz) and gamma (35 – 45 Hz), in 15 healthy participants across two 3 minute rest sessions, one with eyes open and the other with eyes closed. These are shown in Figure 3.1. In both resting sessions delta was mainly located prefrontally, theta was located over the frontal-central area, alpha (both alpha-1 and alpha-2) was distributed across posterior regions, and alpha-1 was also distributed across anterior regions. Beta-1 was widely dispersed across frontal and posterior regions, and beta-2 and gamma both showed similar localised prefrontal distribution. The spatial locations across these frequency bands was fairly stable between the eyes open and eyes closed conditions, although there was some change in their power between these conditions. Chen et al., (2008) suggest that this pattern of brain activation should become known as the EEG default-mode network.

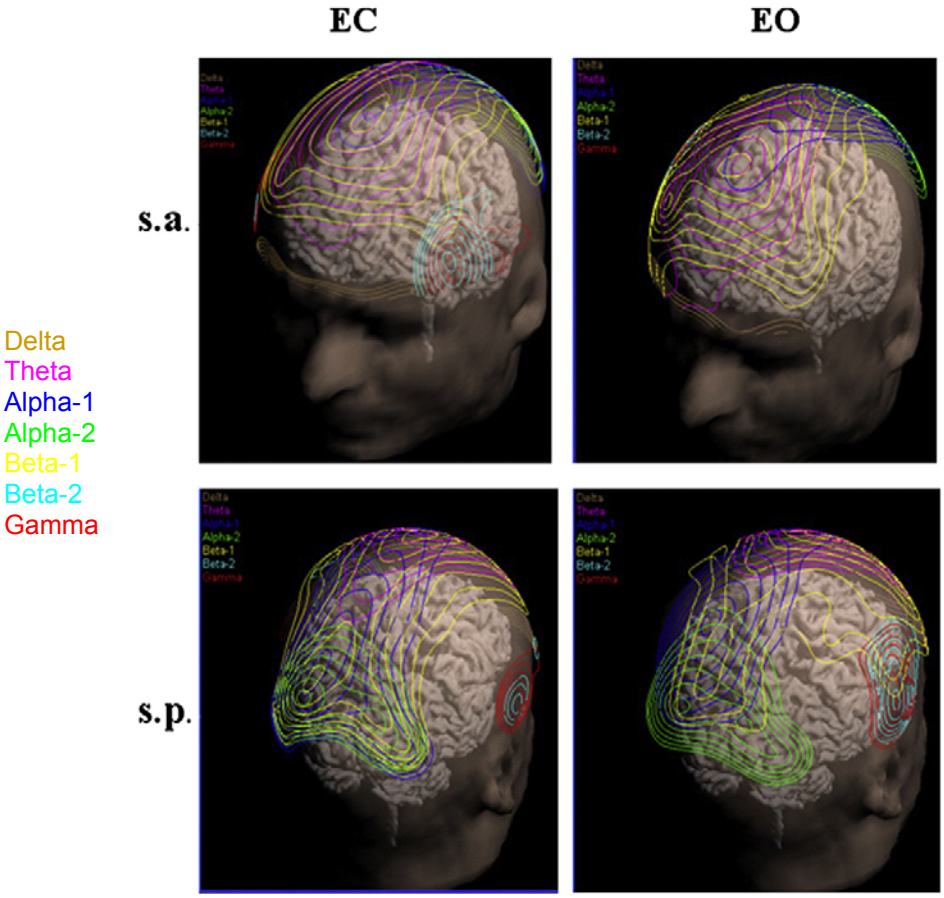

Figure 3.1: Distribution of traditional EEG frequency bands during rest with eyes closed (EC) and with eyes open (EO), shown in superior-anterior (s.a.) and superior posterior (s.p.) perspectives - from Chen. et. al. (2008).

However, these classic EEG bands oscillate at frequencies that are much higher than those of the DMN and it is not clear how they relate to the low frequency activity of the DMN (although recent combined EEG/fMRI research suggests that these classic EEG frequency bands may be moderated by the low frequency BOLD signal at rest, see section *Multi-modal Resting-state Research)*.

Identification of Low Frequency Brain Activity using EEG

Some research has investigated low-frequency resting brain activity (< 1Hz) using EEG but recording such low frequency oscillations using EEG has certain methodological considerations. Conventional EEG recordings use alternating current (AC)-coupled recording equipment, however such recordings typically automatically impose a high-pass filter on the data; this process removes all low frequency components from the data (typically oscillations lower than 0.1Hz), which obviously poses a problem when investigating low frequencies. An alternative method of recording, direct current (DC) recording, allows these lower frequencies to be recorded as it does not impose any filter on the data. However, as very low frequencies are not removed from the data, this method of recording is prone to drift artifacts, in which the mean of the signal changes over time. This loss of stationarity can be mediated by experimental design: drift rate can be stabilised in DC recordings by using sintered silver/silver chloride electrodes and high chloride gel as well as methods that prevent the chloride concentration of the gel from changing over time, such as sweating or drying, i.e. keeping the temperature constant (Tallgren, Vanhatalo, Kaila, & Voipio, 2005). However, any loss of stationarity in the data may violate assumptions of signal processing analyses. For example, FFT analysis assumes that the signal is stationary, and in order to overcome this, FFT analysis is often performed on overlapping segments or 'windows' of the entire data sequence, each of which will be stationary: an average FFT across these windows can then be calculated. Alternatively, wavelet analysis, which also provides details of amplitude and phase, but does not assume stationarity of the data can be performed (Broyd et al., 2009).

A further issue for DC-coupled recordings is that skin has an electrical charge - the transdermal epithelial potential (TEP). This TEP is largely generated by the sweat glands and is relatively high, in the range of +10 to -60 mV (Tallgren, 2005). Tallgren (2005) claims that the TEP must be 'short-circuited' prior to DC-EEG recordings, as this high voltage is likely to generate large amounts of low frequency noise. Tallgren (2005) compared different methods of short-circuiting the skin, such as scratching or puncturing the skin with needles and showed that scratching the skin was the most effective method. Similarly, abrasion has also been shown to 'short-circuit' the skin (e.g. Burbank & Webster, 1978). In a pilot study, we showed that abrasion with an abrasive electrode gel was comparable to scratching in 'short-circuiting' the TEP see Appendix A1.

Vanhatalo et al., (2004) used a DC-coupled EEG amplifier to record either overnight or daytime sleep for 16 participants (14 of whom had epilepsy). They identified very slow oscillations (.02 - .2 Hz) dispersed across the cortex, and the phase of these oscillations was

robustly correlated with the amplitude of higher frequencies i.e. in all of the higher frequencies (delta, theta and alpha), the highest amplitude of each frequency occurred during the negative deflection of the very slow oscillation. They suggest that the very slow oscillations might modulate the faster neuronal activity of the more traditional frequency bands. This research highlights the potential utility of EEG recordings in DMN research: research that employed fMRI, with its low sampling rate and poor temporal resolution, would be unable to reveal the associations between the activity in higher frequency bands and very slow brain oscillations.

However, although Vanhatalo et al., (2004) report that the low frequency oscillations were observed to be widespread across the cortex, they do not attempt to localise a pattern of low frequency brain activity. Localising a network of this low-frequency brain activity may be important for identifying an EEG DMN, which unlike the network identified by Chen et al., (2008), is more similar in frequency – and, thus, potentially also in function- to the fMRI DMN. Nevertheless, EEG has poor spatial resolution and even if a network of low frequency resting brain activity were identified using EEG, estimating the location of the sources of this scalp-recorded EEG (i.e. the inverse problem) would be difficult, and it might not be clear whether the pattern of low-frequency scalp-EEG activation is associated with the same brain regions involved in the DMN as identified by fMRI. This difficulty arises because the inverse problem does not yield a unique solution, but allows several different possibilities of where the source might be localised (e.g. Grech et al., 2008). Nevertheless, using appropriate source analysis measures, identifying the location of sources of EEG activity is reasonably accurate, and localisation errors tend to be smaller than 1cm: although this accuracy is reduced for deep brain sources, and localisation errors may increase to about 2cm (Banaschewski & Brandeis, 2007).

Multi-modal Resting-state Research

Recent multi-modal research has attempted to investigate default-mode activity using simultaneous fMRI and EEG, which takes advantage of each methodology's relative strengths: the high spatial resolution of fMRI and the high temporal resolution of EEG. Although this combined methodology has not been used to associate low-frequency EEG oscillations with the DMN, it has been used to determine associations between the resting BOLD signal and higher EEG frequencies. For example, a number of researchers have shown a negative association between EEG alpha power and the BOLD signal at rest, particularly in the occipital and frontal and parietal cortices (e.g. Laufs et al. 2003b; Laufs et al., 2006; Meltzer et al., 2007; Scheeringa et al., 2008a). Laufs et al. (2003a) suggest that as alpha power is known to decrease with cognitive load (either when processing external stimuli or performing internal operations), such a negative association between the BOLD signal and alpha power indicates that there is a heavy cognitive load on the cortical structures involved in the resting DMN – they suggest that this may be "abortive orienting reactions or loadings of working memory loops that occur (and subside) spontaneously during conscious rest" (Laufs et al., 2003a; p11057). Using a slightly different technique, Mantini, Perrucci, Del Gratta, Romani, & Corbetta (2007) first identified six resting networks in the fMRI BOLD signal using

ICA and then correlated the BOLD signal within each network with the EEG power in different frequency bands. They showed that the two networks which were associated with the DMN were the only ones to show positive correlations with EEG power in any of the frequency bands: this, they suggest is consistent with the fact that these two networks would be active in the resting-state and the others inactive. Furthermore, Mantini et al., (2007) showed that the BOLD signal in these DMN networks was positively correlated with gamma power (mainly in the ventro-medial prefrontal cortex) and also positively correlated with alpha and beta power (mainly in the PCC/precuneus, bilateral superior frontal gyrus and medial frontal gyrus). Although these authors report that alpha is negatively correlated with the BOLD signal outside of this resting network, such as with the dorsal attention activity network, which may account for this apparent contradiction with previous findings.

A similar negative relationship has also been identified between the BOLD signal in structures associated with the DMN and theta power, i.e. as the BOLD signal increased in the MPFC and ventral anterior cingulate, theta power decreased in these areas (e.g. Meltzer et al., 2007; Scheeringa et al., 2008a). To some extent, the negative correlation between the BOLD signal and theta power is surprising, as theta power –in direct contrast to alpha- is thought to *increase* with cognitive demand. Why both alpha and theta should then be anti-correlated with the resting BOLD signal is not clear. Scheeringa et al. (2008) suggests that actions performed by the DMN at rest - such as self-referential processing and mind wandering – are sufficiently different from those engaged during a goal-directed task to produce differing effects on theta power; and in fact the DMN in known to be attenuated and theta to increase during goal-directed performance, so they suggest that a negative correlation between the two is unsurprising. Positive correlations have been identified between beta power and the BOLD signal in the PCC and the dorso-MPFC – regions that have been implicated in the DMN (Laufs et al., 2003a; Mantini et al., 2007).This is perhaps unsurprising as beta has been associated with many of the same functions as the DMN i.e. self-reflection and concentration.

3.2.2.3 *Summary of Electrophysiology research*

In ADHD research, children with ADHD are typically shown to have elevated levels of lower frequency, theta brain activity than controls at rest. However the EEG profile is likely to be heterogeneous within ADHD and different profiles are likely to exist both between and within different ADHD subtypes. In DMN research, Chen et al. (2008) identified a network of resting EEG in terms of the classic frequency bands. However, it is not yet clear how these classic higher frequency bands relate to the lower frequencies of the DMN. Recording very low frequency EEG (< .1 Hz) poses certain methodological difficulties, however using appropriate methods, such as DC-coupled recording equipment, Vanhatalo et al. (2004) has identified very slow oscillations (.02 - .2 Hz) which correlate with the amplitude of the higher frequencies. However, due to the relatively poor spatial resolution of EEG and the difficulties in localising the sources of scalp-recorded EEG, research has begun to combine fMRI and

EEG methodologies. Although these simultaneous EEG-fMRI recordings have not yet been used to associate low-frequency EEG oscillations with the DMN, they are beginning to highlight associations between the low frequency BOLD signal and higher EEG frequencies: notably negative associations between BOLD and alpha and BOLD and theta and positive associations between BOLD and beta.

3.3 Periodicity in Behavioural Data and Synchrony with Low Frequency Brain Activity

One of the key hypotheses of the default-mode interference hypothesis is that periodic attention lapses are created by intrusions of spontaneous low-frequency brain activity. In order to test this hypothesis it will be important to i) examine whether periodic patterns do exist in behavioural data and ii) to determine whether there is synchrony between the fluctuations in low frequency brain activity and declines in performance. As described in Chapter 2, signal processing techniques such as FFTs and Power Spectral estimates can provide information about the power and amplitude of specific frequency bands in time series RT signals. However, these analyses have certain assumptions and any behavioural tasks used must be carefully designed or selected to ensure that the data obtained are suitable for these analyses. This chapter will now describe the methodological considerations associated with capturing temporal patterns in behavioural data and the methods and analytical approaches that have been used to co-register low-frequency brain activity and lapses in attention.

3.3.1 Capturing Temporal Patterns in Behavioural Data

Time series data, such as a series of RTs, can be examined using signal processing techniques to identify temporal patterns in behavioural data: although this is commonly done for EEG and other physiological measures, until recently, time series data has traditionally not been preserved or examined for behavioural RT data (Castellanos et al., 2005). However, the temporal structure and duration of behavioural tasks may constrain the oscillatory frequencies that can be investigated. When using signal processing techniques, the ISI determines the maximum frequency that can be investigated. The maximum frequency that can be observed in the data is equal to half the ISI. For example, if stimuli were presented every second, only frequencies up to .5Hz (a cycle every 2 seconds) could be investigated, information about any higher oscillations would be lost. Furthermore, as the duration between trial presentations constrains the participants' RTs, it is possible that the rhythmic presentation of trials may entrain oscillations of a particular frequency: frequent sampling is therefore essential and the use of continuous measures is ideal (Castellanos et al., 2005). So far, the tasks used to examine temporal patterns in behavioural data have failed to address this issue. Castellanos et al. (2005) and Di Martino et al.(2008) examined the time series of RT data sampled every 3 seconds from an Eriksen flanker task, this constrained their analysis of RT frequencies to those less than .17 Hz. Similarly, Johnson et al. (2007) and Johnson et al. (2008) employed a fixed sequence sustained attention to response task (SART), to obtain time series data. This task had an ISI of 1.5 seconds, which again limited their investigation to RT frequencies less

than .33 Hz. These narrow frequencies represent only a tiny part of the frequency spectrum that is normally investigated in biological rhythms (typically .1-70Hz) and are unlikely to be able to describe the periodic structure of RT variability in isolation from the higher frequencies. Investigating such a narrow frequency band also prevents other frequencies from being used as an 'internal control', i.e. to help examine whether children with ADHD are more variable specifically at these lower frequencies or whether they are more variable across the entire frequency spectrum. Tasks which employ more frequent sampling will help to answer this.

Furthermore, the SART task employed by Johnson et al., (2007; 2008) has the added confound of entraining a cyclical pattern in RTs. In this task, participants are shown the digits 1 – 9 in a fixed order, they must respond to each digit except the No-Go digit '3' by pressing a response button. Using this task, Johnson et al., (2007; 2008) report that children typically respond more quickly on the digit '2' compared to the other digits, in anticipation of the up-coming No-Go response. Using a task that creates a cyclical pattern of RT response, i.e. a faster RT every 9 responses or 13.5 seconds, is inappropriate as RT variability is constrained by this anticipatory effect and this entrained frequency is likely to obscure other frequencies in the data. Tasks which do not impose any cyclical pattern of RT response would be more appropriate for time series analyses.

A further issue is that shorter task durations may prevent very slow frequency oscillations from being identified. For example, an oscillation with a frequency of .05 Hz will take 20 seconds to complete a cycle, thus, in each minute of recording a maximum of three cycles will be identified. As biological oscillations are fundamentally variable and sufficient recordings are necessary to sample across such short-term variations, Bernston et al. (1997) recommend a recording period of at least 10 cycles of the target rhythm. This issue is now being considered and longer task durations are typically employed in investigations of RT frequencies, for example Di Martino et al. (2008) asked children to perform the Eriksen flanker task continuously for 15 minutes.

Further difficulties arise when the task allows a participant to make an incorrect response such as in a choice reaction time task; or if the task allows the participant to miss a response. The question of how to deal with missing data has not be adequately resolved (e.g. Widaman, 2006) and any method of data replacement may lead to biasing the data. Similarly, methods of dealing with incorrect compared to correct responses impose further constraints on data analysis. For example, DiMartino et al. (2008) reported that the trial type in the Eriksen flanker task impacted on RT (in this task they used three different stimulus types and two different directions for each stimulus), also participants made a number of missing or impossible responses (i.e. RT < 100ms). They attempted to control for this by interpolating the missing responses from the mean of the two closest responses, and regressing out the impact of trial type from the RT, and performing subsequent analyses on these regression residuals. However, the impact of these methods is unclear and a task that is used to identify temporal patterns in behavioural data should ideally avoid these issues by eliminating the

confound of trial type and by preventing the participants from making incorrect responses or omitting responses.

Therefore, an ideal task for measuring fluctuations in behavioural data should sample frequently or stimuli should be presented with a short ISI, the task should be of long enough duration to contain multiple cycles of the target rhythm, it should not entrain particular frequencies, and ideally should not allow missing or incorrect responses. An ideal task therefore may be a tracking task that, unlike RT data, could sample frequently and, if the outcome measure were distance from a tracked object, this would not result in different trial types or missing data or incorrect responses. For example, the task that we designed to measure fluctuations in attention is a tracking task presented as a 'road' on a computer screen for 10 minutes. When performing this task, participants are instructed to keep a central marker as close as possible to white lines on the centre of this 'road' by pressing the right and left arrow keys. The distance of the marker from the white lines is used as a near-continuous measure of the participants' sustained attention. This task is able to take 28 samples (measures of the distance of the marker) each second, which is much more frequent than is possible in RT tasks. Therefore it allows examination of a larger part of the frequency spectrum - frequencies up to 14 Hz. Furthermore, our measure of the degree of deviation from the central marker prevents the participants from making missing responses, as the distance from the marker is recorded automatically 28 times each second rather than in response to every button press. Similarly, this measure prevents participants from making incorrect responses; in this task, 'error' is measured on a continuous rather than a dichotomous scale and so rather than being a potential confound, this error is the outcome variable and does not need to be adjusted, which prevents bias from being introduced into the data. This task, with its high temporal resolution will also assist the co-registration of brain activity with fluctuations in attention (see following section).

3.3.2 Co-registering Low-frequency Brain Activity and Attention Lapses

Very little research has attempted to determine whether low frequency patterns of brain activity are associated with attention lapses. Eichele et al.(2008) recorded fMRI data while 15 healthy participants performed a speeded flanker task. They investigated the patterns of brain activations that proceeded errors on a trial-by-trial basis, and identified a pattern of brain activity that occurred prior to an error – in fact this pattern of brain activity was evident up to 30 seconds before the error was made. Specifically, prior to an error, the brain regions associated with attention and task engagement, which have previously been identified as being activated during flanker task performance (e.g. the inferior frontal gyrus, posterior orbital gyrus and the superior MPFC) showed a decrease in activation and brain regions associated with the DMN (e.g. precuneus, PCC, and retrosplenial cortex) showed an increase in activation. After error detection, DMN activity decreased and the task-relevant brain activity increased. However, Eichele et al., (2008) reported that they did not identify a relationship between the phase of the low frequency oscillation and errors; i.e. more errors were not made

at either the peak or the trough of the low frequency BOLD signal. In contrast, Monto, Palva, Voipio, & Palva (2008) recorded DC-EEG from two electrode sites (Fpz and Cz) and investigated the association between low-frequency EEG oscillations from these sites and participants' ability to detect a sensory stimulus (an electrical stimulation to their index finger): they found an association between errors and the phase of the low-frequency oscillations. They showed that in 11 healthy participants, the hit rate was much higher during the rising phase of a low-frequency oscillation (.01-.1 Hz) than during the falling phase. However, they found no association between the amplitude of the LFO and hit rate.

It is somewhat surprising that although both studies showed a relationship between low frequency brain activity and errors, Eichele et al., (2008) found no relationship between the phase of the low frequency oscillation and errors, while Monto et al., (2008) found that temporal positioning of errors was strongly associated with the phase of the low frequency oscillation. These contrasting findings may be due to the different methodologies of fMRI and EEG. As mentioned earlier, the BOLD signal response has poor temporal specificity and it is not clear exactly how it relates to underlying neural processes, whereas the EEG signal has excellent temporal specificity and directly measures neural activity. In fact, Sauseng & Klimesch (2008) argue that EEG phase reflects the exact timing of brain processes and, as such, is the most appropriate measure of neural communication at both global and local network scales. Therefore, it is perhaps unsurprising that EEG would be better able to elucidate the relationship between brain activity and behavioural measures (i.e. errors). However, there has been very little research attempting to determine whether low frequency patterns of brain activity are able to predict attention lapses, and replication of these studies is necessary before sound conclusions can be made.

Furthermore, the tasks adopted by these two studies have constrained co-registration analyses to assessing the relationship between the dichotomous variable *error* and the phase of the low frequency oscillations. If attention were recorded as time-series data, for example using the tasks described previously, the phase of the two signals could be compared directly i.e. the phase of the low frequency EEG data could be compared to low frequency fluctuations in attention. This would allow a more sophisticated comparison of the two signals. A number of different analytical techniques can be employed to this end. Firstly, the cross correlation of the two signals can be determined, this measure assesses the 'similarity' between two signals and has the advantage of allowing one of the signals to be shifted in time (i.e. for these analyses to be performed at different time lags) (Wijewerdena-Gamalath, 2004). This is important as there may be some small lag between brain and behavioural activity due to signal conduction or measurement error, by performing these analyses at small lags (i.e. +/- 1 second), this measure is able to control for this error (see section *5.2.5.3 Temporal synchrony of behavioural and EEG oscillations* for further information about cross-correlation analysis). Alternatively, coherence analysis determines the correlation of two signals at a particular frequency. However, neither the coherence measure nor the cross-correlation measure is specific to a signal's phase and these measures are unable to separate the effects of

amplitude from the effects of phase. Coherence increases with amplitude covariance – thus if two signals have a high amplitude covariance, their magnitude squared coherence would be high. However this does not mean that they are necessarily phase locked. This is because the relative importance of amplitude and phase covariance in the coherence value is not clear. Phase synchrony, in contrast, is independent of amplitude and assesses whether the phase shift between two signals remains constant over time (Broyd et al., 2009). Thus, unless phase synchrony is adopted in analyses that attempt to co-register behavioural and brain activity, it will be important to control for any effects that amplitude may have on the analyses. This effect of amplitude could be controlled by normalising the signals, i.e. subtracting the mean and dividing by the standard deviation of the signal: this would ensure that all signals have the same mean and standard deviation (zero and one respectively) and thus, these measures would be independent of the signals' amplitude.

3.4 Chapter Summary

This chapter addressed three key methodological and analytical issues associated with investigating the default-mode interference hypothesis: i) assessing and localising low frequency DMN brain activity in ADHD, both at rest and during goal-directed tasks ii) examining whether periodic patterns exist in behavioural data and iii) determining whether there is synchrony between fluctuations in low frequency brain activity and declines in performance. The key points raised for each of these issues will now be summarised.

i) *Assessing and localising low frequency DMN brain activity in ADHD, both at rest and during goal-directed tasks.*

When assessing resting-state brain activity, conditions of 'near-rest' are unlikely to accurately emulate true rest, and therefore future studies of resting brain activity should employ sufficiently long task-free resting periods. However, abnormal resting brain activation in ADHD has been identified using both fMRI and EEG methodologies. In fMRI research, the spatial pattern of brain activity at rest has been shown to exhibit less functional connectivity in ADHD than in controls, and in EEG research abnormal activation in higher frequencies (> 1.5 Hz) in the resting brain has been observed in children with ADHD. However, patterns of resting EEG are normally assessed in higher frequency bands than those identified in the DMN (e.g. theta, alpha and beta) and very low frequency EEG oscillations (< .1 Hz) have not been examined in ADHD. Chen et al. (2008) identified EEG resting networks in the classic frequency bands and suggested these become known as the EEG DMN, however a network of low-frequency resting EEG brain activity has not yet been identified.

ii) Examining whether periodic patterns exist in behavioural data

Temporal patterns in RT data are beginning to be investigated, and preliminary research indicates that RTs are likely to be periodic and to oscillate at low frequencies, however the tasks used to elicit time series data for this are not always appropriate for the

signal processing analyses. An ideal task for this analysis should sample frequently, be of a long duration and prevent the participant from making incorrect or missing responses: we suggest that a tracking task would meet these criteria

iii) Determining whether there is synchrony between fluctuations in low frequency brain activity and declines in performance.

Very few studies have attempted to co-register very low frequency brain activity and attention lapses, however, both studies investigating this have shown a relationship between low frequency brain activity and errors, although they report contrasting findings about whether the *phase* of the low frequency oscillation is associated with errors. Therefore, replication of these studies is necessary and EEG, with its excellent temporal specificity and more direct measure of neuronal activity may be important in elucidating this effect. Furthermore, if tasks that were able to record attention as time-series data were employed, the phase of the two signals could be compared: that is, the phase of the low frequency EEG data could be compared to low frequency fluctuations in attention, using methods such as cross-correlation, coherence analysis or phase synchrony analysis.

3.5 Thesis Aims

In the present thesis we aimed to address these three key issues and to test the predictions of the default-mode interference hypothesis. The specific aims of the present thesis were:

1) To identify the spatial distribution of low frequency EEG at rest
2) To determine whether low frequency EEG is attenuated from rest to task
3) To identify whether periodicity is evident in RT data
4) To identify whether there is synchrony between low frequency EEG and low frequency fluctuations in RT data.
5) To examine whether these factors are associated with ADHD.

In Chapter four we explore these first two aims, we try to identify the spatial distribution of low frequency EEG at rest and investigate whether this low frequency EEG is attenuated from rest to task, we also examine whether these factors are associated with ADHD as we compare between a high-ADHD symptom group and a low ADHD-symptom group. We replicate and extend these investigations in a clinic referred sample of boys with ADHD in Chapter six. In Chapter five we explore the third and fourth aims, we examine whether there is any periodicity in RT data and whether there is synchrony between low frequency fluctuations in RT data and low frequency fluctuations in EEG. Again, we examine whether these factors are associated with ADHD as we compare between a high-ADHD symptom group and a low ADHD-symptom group. In Chapter seven we again replicate and extend these investigations in a clinic referred sample of boys with ADHD. A summary of the findings

in relation to these aims as well as a discussion of the implication of these findings is given in Chapter eight.

Chapter 4 Low-frequency EEG oscillations at rest and during goal-directed task performance

4.1 Introduction

During focussed goal-directed activity, the periodic slow oscillations of the resting-state – the DMN - may be replaced with more specific task-related brain activity, characterised by low amplitude, desynchronised patterns (Buzsaki & Draguhn, 2004). The default-mode interference hypothesis (Sonuga-Barke & Castellanos, 2007) suggests that during goal-directed tasks, some patients with ADHD may not effectively attenuate the slow oscillations of the DMN and initiate focused task attention in this way. This may cause the resting-state oscillations to intrude on task performance and thus cause periodic attention lapses. Accordingly, Sonuga-Barke & Castellanos (2007) suggested that the inattentive symptoms of ADHD may be characterised by intrusions of the DMN during goal-directed tasks in some ADHD patients. The study reported in this chapter represents the first test of this hypothesis using EEG DC recordings.

4.1.1 Study Aims

The study had several general and specific aims. The first general aim was to explore low frequency EEG oscillations at rest. More specifically the aims were to i) identify a network[2] of resting slow 3 (S3; .06-.2Hz) activity across the scalp using DC-EEG - the S3 frequency band was selected to determine this network as this frequency band most closely resembled the frequency of oscillations involved in the DMN; ii) to examine the stability of this resting network of S3 activity over a one week test-retest period and iii) to determine intra-individual differences in variation in low frequency EEG (from slow 4 to delta: slow 4 (S4) .02-.06Hz; S3 .06-.2Hz; slow 2 (S2) .2-.5Hz; slow 1 (S1) .05-1.5Hz; delta, 1.5-4Hz, as defined in Penttonen & Buzsaki, 2003) within and outside of this network between a *high-ADHD* symptom group and a *low-ADHD* symptom group.

2) The second general aim of the study was to explore low frequency EEG during goal-directed task performance. More specifically the aims were to: i) identify the spatial distribution of S3 power during goal-directed task performance; ii) to examine the test-retest reliability of this distribution over a one week period; and iii) to explore variation between

[2] Throughout this study, the term network will be used to loosely refer to a consistent pattern of scalp activation in a particular frequency band –slow 3- however it is not intended to describe the functional connectivity of these regions and is not assumed to relate to specific brain localisations.

ADHD symptom groups in low frequency EEG within and outside of the S3 resting network while participants performed a goal-directed task.

3) The third general aim of the study was to determine the extent to which the power within low frequency EEG bands was attenuated as one moves from rest to goal-directed task performance. More specifically the aims were to: i) determine differences in power between these two tasks across the whole scalp; ii) to examine differences in S3 power between these two tasks within and outside of the resting S3 network, and variation in this between ADHD symptom groups; and iii) to investigate the level of attenuation of S3 power from rest to the goal-directed task between ADHD symptom groups.

4.1.2 Predictions

1) Exploring low frequency EEG oscillations at rest

Firstly, it was predicted that a network of low frequency S3 oscillations would be identified at rest. This activation should be stable over a 1 week test-retest period. It was also predicted that intra-individual differences in variation in power in this network, between the *high-ADHD* and the *low-ADHD* symptom groups, would be identified. More specifically, it was predicted that these differences would be related to symptoms of inattention rather than symptoms of hyperactivity and impulsiveness, as the default-mode interference hypothesis specifically predicts that default-mode abnormalities will cause lapses in attention rather than hyperactive or impulsive symptoms.

2) Exploring low frequency EEG during goal-directed task performance

It was further predicted that the spatial distribution of S3 oscillations during goal-directed task performance would differ from the resting network, and would be less directed along the frontal midline and posterior scalp regions as S3 activity throughout a goal-directed task should be less localised to the S3 network. This activation should be stable over a one week test-retest period. It was also predicted that intra-individual differences in variation in power in this network would be identified, and related to symptoms of inattention. Specifically, it was predicted that inattentive participants would exhibit higher power of low frequency EEG than the other groups during goal-directed performance, as the default-mode interference hypothesis assumes that low-frequency activity intrudes into goal-directed task performance in this group.

3) Attenuation of low frequency EEG oscillation bands as one moves from rest to goal-directed task performance

It was predicted that S3 power across the scalp would be lower while participants were performing the goal-directed task than at rest, as S3 oscillations should be attenuated during goal-directed performance. It was also predicted that the attenuation of S3 power from rest to a goal-directed task within the S3 network would be associated with inattention, and participants with high inattention ratings would be less effective at attenuating S3 power between tasks than the other two groups. The relationship between low frequency EEG activity and performance will be explored in the following chapter.

4.2 Methods

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

4.2.1 Participants

4.2.1.1 *Initial Participant Screening*

All year 1 and 2 undergraduate psychology students enrolled at the University of Southampton (N = 241) were screened with an adult ADHD rating scale (Barkley & Murphy, 1998). This scale is a self-report measure that contains 18 questions which are derived from the 18 ADHD symptom criteria reported in the DSM-IV. Each of the 18 items on the scale are rated on a 4 point Likert-scale (occasionally, never, often, very often). Exemplar questions are '[I] fail to give attention to details or make careless mistakes at work' and '[I] have difficulty awaiting turn' (see Appendix A2). This scale contains two correlated factors, inattention and hyperactivity/impulsivity, which have demonstrated stability in factor analysis and possess high internal consistency, furthermore the scale has been shown to posses good construct validity and test-retest reliability (construct validity .35-.85, 4 week test-retest reliability .78-.86; see Collett, Ohan, & Myers, 2003 for a review). Participants who scored in the top 80th percentile on the ADHD rating scale and reported six or more symptoms were included in the *high-ADHD* symptom group and were invited to participate in the study. Similarly, participants who scored in the bottom 20th percentile on the ADHD rating scale and reported zero or one symptoms were included in the *low-ADHD* symptom group and were invited to participate in the study.

4.2.1.2 *Participant Sample Characteristics*

13 *high-ADHD* symptom participants and 11 *low-ADHD* symptom participants were recruited for the study. In addition to the student participants, one participant with a diagnosis of ADHD was recruited from the researcher's personal contacts (male, aged 16).[3] All participants were screened for neurological disorders, none were taking medications or reported any sleep disturbance, and all were asked to refrain from caffeine or nicotine for at least 2 hours prior to the testing sessions. In order to corroborate the self ratings - given the possibility of bias - we also gathered independent ratings of participants' ADHD from a close

[3] Although this participant was from a different referral source, and the inclusion of a single participant with ADHD does not add specific information about ADHD, we were interested in individual differences of participants with high and low ADHD symptoms. This participant was included in the study as he is an individual who experiences many ADHD symptoms, and would therefore increase the range of ADHD symptoms experienced in our sample. However, to ensure that the inclusion of this participant had not affected our results, all analyses were re-run without including his data. All of the main results of the study remained the same when he was not included in the analyses.

friend, parent or partner of each participant using an adapted version of the adult ADHD rating scale about their ADHD behaviours. Thus, questions were adapted from '[I] talk excessively' to '[He/she] talks excessively' and '[I] don't listen when spoken to directly' to '[He/she] doesn't listen when spoken to directly' so that they rated the participant's behaviour on the same 4 point Likert-scale (see Appendix A3). This was collected for all but one of the participants. There was a strong correlation between the self-and friend or relative-reported total ADHD scores ($r(21)$ = .69, p<.001), hyperactive symptoms ($r(21)$ = .57, p<.01) and inattentive symptoms ($r(21)$ = .73, p<.001). As the self-ratings were highly correlated with friend/relative-ratings and they were more complete, self-ratings were used to determine group membership.

Participant demographics are shown in Table 4.1. As expected, the *high-ADHD* symptom group were reported as having significantly more ADHD symptoms, hyperactivity and inattention than the *low-ADHD* symptom group, in both the self- and the friend or relative-report (using independent samples t-tests[4]). The two groups did not differ in age or gender[5] and so these were not entered as covariates in further analyses.

Table 4.1

Demographics

	Low-ADHD symptoms	*High-ADHD* symptoms
Total participants	11	13
Age (years) – mean (SD)	23.27 (5.57)	21.54 (3.91)
Number (%) males[6]	2 (18%)	6 (46%)
Self report - mean (SD)		
Total score	10.64 (3.53)	31.62 (8.73) **
Total inattention	5.18 (2.36)	16.38 (5.61) **
Total hyperactivity	5.45 (1.96)	15.23 (4.66) **
Friend or relative report- mean (SD)		
Total Score	10.00 (5.29)	24.00(13.59) *
Total inattention	3.91 (2.66)	12.00 (7.31)*
Total hyperactivity	6.09 (4.18)	11.92 (6.78)*

*p<.05, **p<.001

[4] Where variance between groups was not equal, the equal variance not assumed test statistic was used.

[5]Although the two groups were not found to statistically differ in gender, this result should be viewed with some caution, as the small sample size may not yield sufficient power to determine group differences.

[6] As the variable *gender* is categorical and sample sizes were small, Fisher's exact test was used to assess group differences.

4.2.2 Design

The study had a within groups repeated-measures design. Participants completed two testing sessions, approximately one week apart (mode 7 days; range 4-73 days). Twenty four participants completed the initial test session. Of these, 20 participants returned for the retest; all of the participants who were unable to return for a retest were in the *high-ADHD* symptom group. In each testing session, the participants completed identical tasks; however in order to reduce order effects, for each participant, the sequence of task presentation was reversed for the second session.

4.2.3 Procedure

After informed consent was obtained from the participant (see Appendix A4), they were seated on a comfortable chair in front of a computer screen and an electrode cap was fitted.

4.2.4 Assessments

Each participant then completed four assessments (however data will only be presented here for two of the assessments – rest with eyes open and the two-choice reaction time task – as the data from the other two tasks were not usable). Two of the assessments measured resting-state activity and two assessed activity while performing a goal-directed task. The four assessments were presented in a pseudo-counterbalanced order. The resting-state assessments were always presented first and fourth and the goal-directed state assessments were always presented second and third. The rationale for the duration of each assessment period is explained in Appendix A4.

For the rest with eyes open condition, time 2 data segments for three participants, all of who were in the *low-ADHD* symptom group, were excluded as they contained excessive movement artifacts; for the goal-directed (simple 2-choice RT) task, time 2 data segments for one participant in the *high-ADHD* symptom group, and both time 1 (T1) and time 2 (T2) data segments for three participants, two of whom were in the *low-ADHD* symptom group, were excluded as they contained excessive movement artifacts. Therefore, for the rest with eyes open condition, T1 data were available for 24 participants and retest data were available for 17 participants, 8 *low-ADHD* symptom and 9 *high-ADHD* symptom participants; and in the goal-directed (simple RT) task, T1 data were available for 21 participants and retest data were available for 16 participants, 7 *low-ADHD* symptom and 9 *high-ADHD* symptom participants.

4.2.4.1 *Resting-state Assessments*

Each resting period lasted 5 minutes. During one of the resting-state assessments participants were instructed to keep their eyes closed throughout the testing session (although this data is not reported here; see section *2.2.6.6 Problems with the analysis of the data obtained during the rest with eyes closed assessment*). During the other resting assessment the participants were instructed to keep their eyes open and fixed on the centre

of the computer screen throughout. Prior to each resting period, participants were instructed to rest and to try to refrain from any specific cognitive activity during this period.

4.2.4.2 *Assessments During Goal-Directed Task Performance*

Both tasks were developed specifically for the purposes of the current study. During one of the goal-directed state assessments, the participants undertook a 2-choice response reaction-time (2-CR RT task) attention task for 10 minutes. This task involved attending to and responding to a computer presentation of a green target "arrow" that pointed left or right. The target arrow was presented in the centre of the computer monitor. Participants were instructed to respond, by pressing the right or left mouse button, to indicate the direction of each arrow. Each trial lasted one second (stimulus presentation time 400ms, inter-stimulus interval 600ms). The task duration was 10 minutes and a total of 600 trials were presented. Data collected included reaction time for each trial and correct and incorrect responses. In the other goal-directed state assessment, the participants undertook a visual tracking task presented as a driving task for 10 minutes. In this, they were instructed to keep a central marker as close as possible to the centre of a track by pressing the right and left arrow keys. The track was pseudo-randomly generated within certain difficulty limits and was identical for each participant. The track was designed to have a consistent level of difficulty (set by certain parameters such as maximum angle of each successive track segment) so that a low frequency bias was not introduced onto the error data. That is, if the track became more difficult, for example if there was a sharp bend, every 10 seconds, a 10 second cycle of error may be introduced to the data (however data from this task were unusable and will not be presented here; see section *5.2.4.2.1 Problems with the data collected by the tracking task*). As the behavioural data for this task was not useable, it was deemed inappropriate to analyse the EEG data from this task and so this task was discarded from further analyses.

4.2.5 Electrophysiological Acquisition

All data were recorded using Neuroscan Synamps^2 68 channel EEG system. The data were recorded using direct current (DC) coupled recording equipment, they were sampled with a 70 Hz low pass filter at a rate of 250 Hz. An electrode cap (Easycap, Herrsching, Germany) was fitted to the participant and EEG data were recorded from twenty-seven silver/silver chloride electrodes placed according to the extended 10/20 system (Fp1, Fpz, Fp2, Afz, F7, F3, Fz, F4, F8, FCz, C7, C3, Cz, C4, T8, Cp5, Cp3, Cp1, Cpz, Cp2, Cp4, Cp6, P3, Pz, P4, O1, O2), see Figure 4.1. These positions were chosen to broadly cover the scalp but also to give emphasis to scalp regions that may be associated with activity of the DMN.

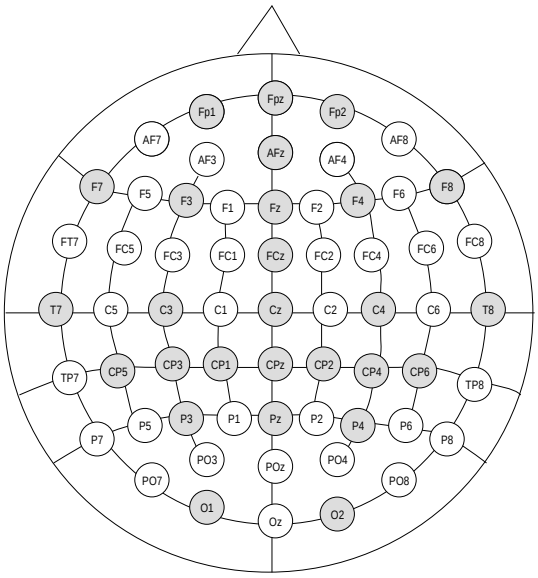

Figure 4.1: Position of scalp electrodes: electrodes included in the montage for the present study are shown in grey.

Furthermore, a ground electrode was positioned on Af7 and an active (reference) electrode at Fc6: a reference electrode was also placed on each mastoid. Horizontal electro-oculogram (HEOG) was recorded from bipolar electrodes placed on the outer canthi of each eye. Vertical electro-oculogram (VEOG) was recorded from bipolar electrodes placed above and below the right eye. All impedances were kept below 10 kΩ. Electro-cardiogram (ECG) data were recorded from a negative reference electrode placed on the right shoulder and a positive electrode placed on the centre of the chest, however these data will not be discussed in the present study.

4.2.6 EEG Data Processing

4.2.6.1 *Pre-processing*

All data were analysed and processed using MATLAB (version 7.0.1). The data were initially re-referenced off-line to the two mastoid channels. Due to the nature of DC-coupled recording, significant drift was evident in the data. In order to overcome this, the linear trend caused by drift was removed from the EEG data using the 'detrend' command in MATLAB. This command removes the best-fit straight line linear trend from the data. The data were also down-sampled from 250 to 10 samples per second to increase the speed of data processing. Although this prevents frequencies higher than 5Hz from being investigated (as the maximum frequency that can be observed in the data is half of the sampling frequency and so down-sampling the data to 10Hz would only allow investigation of frequencies up to 5Hz), the lower frequencies (<1Hz), that are of interest to the present study, were unchanged by this analysis.

4.2.6.2 *Artifact Removal*

Ocular and other artifacts were removed from the data using independent component analysis (ICA) using the Fast ICA algorithm (James & Hesse, 2005). ICA is a data-driven tool that extracts independent components from a complex or 'mixed' signal. The scalp signals recorded by EEG can be modelled by distinct signals from independent (or near-independent) brain networks, locally synchronised field activities and non-brain artifacts such as ocular artifacts, movement artifacts and line noise. ICA 'unmixes' these signals to recover the independent source signals: thus, artifacts, which are identified as independent signals, can be identified and removed from the original signal. ICA has been successfully used to remove eye movements, eye blinks and electrode artifacts from both EEG and fMRI data (e.g. Debener, Makeig, Delorme, & Engel, 2005; Melissant, Ypma, Frietman, & Stam, 2005; Mantini et al., 2007; Onton, Westerfield, Townsend, & Makeig, 2006).

However, ICA operates using a termed complete method, i.e. ICA will recover the same number of components as the number of input channels. In the present study, input is given from 29 channels (27 scalp electrodes and two bipolar EOG channels) and so 29 components will be recovered by ICA. This can result in some components being separated, by ICA, into more than one sub-component. Principal components analysis (PCA) can be used to moderate this effect of ICA by reducing the dimensions in the data set. This dimensional reduction reduces the number of data channels that can then be used as inputs for ICA. PCA identifies dimensions that are able to successively explain as much of the outstanding data variance as possible. Unlike ICA, each dimension identified by PCA need not be independent from other sources and so each dimension is likely to be the sum of numerous independent components. Once PCA has identified a number of dimensions, that explain the majority of the variance in the data and is smaller than the original number of input EEG channels, these can be used as the input for ICA. Using a smaller number of inputs for ICA will reduce the number of components that are recovered and thus, reduces the likelihood of single components being reduced into separate components by ICA (Onton et al., 2006).

In this manner, in the present study, after down-sampling and detrending the data, PCA was performed to extract fifteen dimensions from the data (this number of dimensions was deemed appropriate after inspection of a scree plot that showed that the majority of the variance in the data set was explained in fewer than 15 dimensions). ICA was then performed on this output. As fifteen inputs were entered from PCA, a maximum of fifteen components would be recovered by ICA for each data analysis. This method of analysis was individually performed on the data segment for each participant, 1) during rest with eyes open (5mins), 2) during rest with eyes closed (5 mins) and 3) during 2-CR RT task (10mins), at both the test and the retest sessions. Thus, for each participant, up to fifteen components were extracted for each task and for each test session. Each component recovered by ICA is expressed both temporally and spatially (see Figure 4.2).

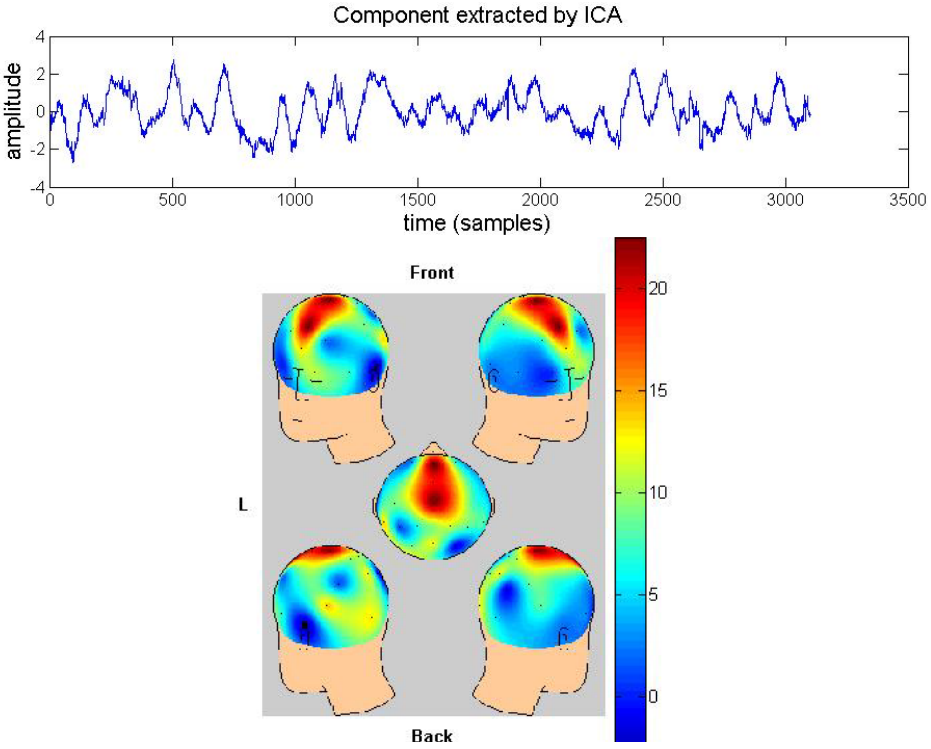

Figure 4.2: A component extracted for participant 13, shown temporally (above) and spatially (below).

Note. The amplitude of components extracted by ICA is expressed in arbitrary values determined by ICA.

The components were then inspected to identify those that represented eye blinks or other eye movements and other artifacts, such as faulty leads.

4.2.6.3 *Ocular Artifacts*

A component was considered to be an ocular artifact; 1) if its spatial element was located around the eyes and 2) if its temporal element closely resembled the EOG channels. For example, Figure 4.3 shows the temporal element of a component that was extracted by ICA for participant 1 and the recordings from the EOG channels (VEOG is shown in blue and HEOG in green) for the same participant. The VEOG recording is very similar to the extracted component.

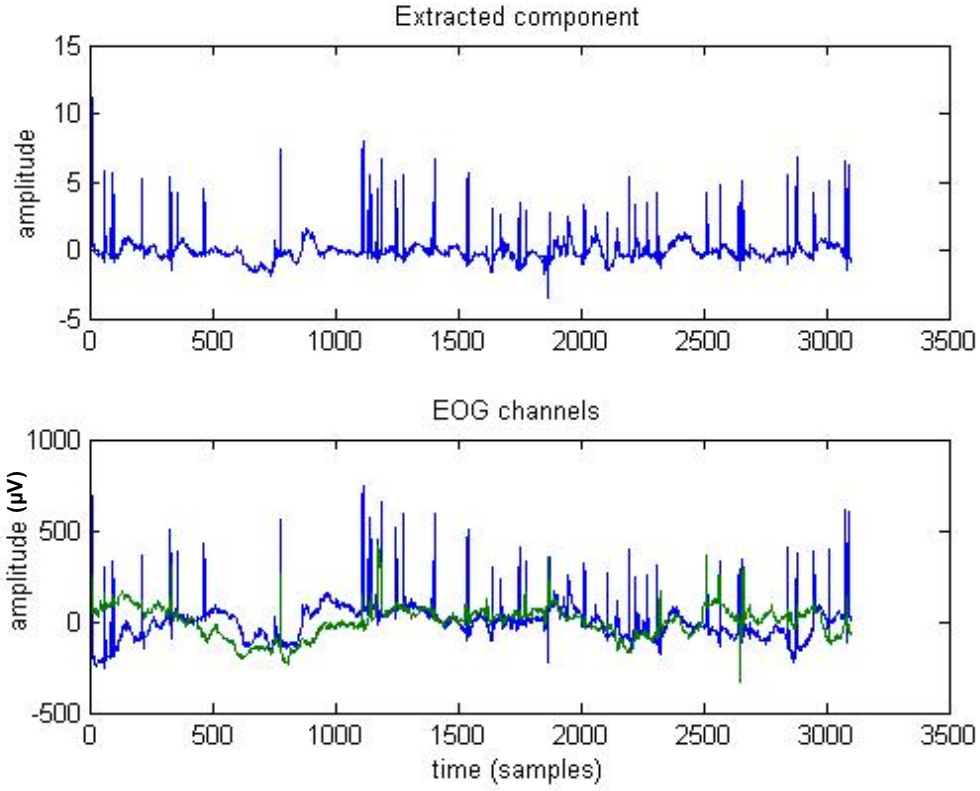

Figure 4.3: Temporal element of a component extracted by ICA (above) and EOG channels (below), for participant 1.

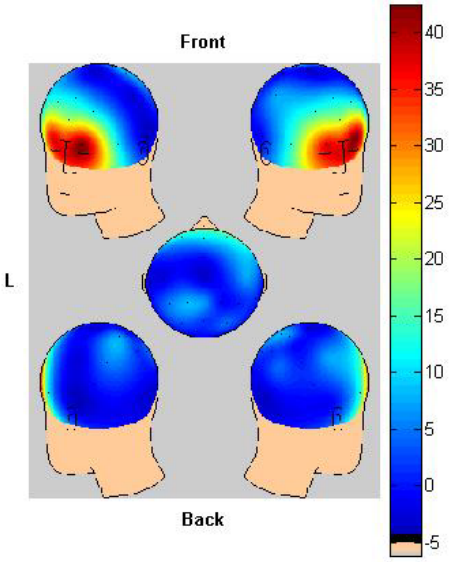

Figure 4.4: Spatial element of component.

Furthermore, Figure 4.4 shows the spatial location of this component, and this clearly indicates that the component is located around the eyes. Thus, this component was deemed to represent an ocular artifact and was excluded from further analysis.

4.2.6.4 *Other Artifacts*

Other artifacts may include line noise, movement or faulty leads. He, Clifford, & Tarassenko (2006) describe typical artifacts identified by ICA, which manifest as an abrupt change in the signal. This is illustrated in Figure 4.5.

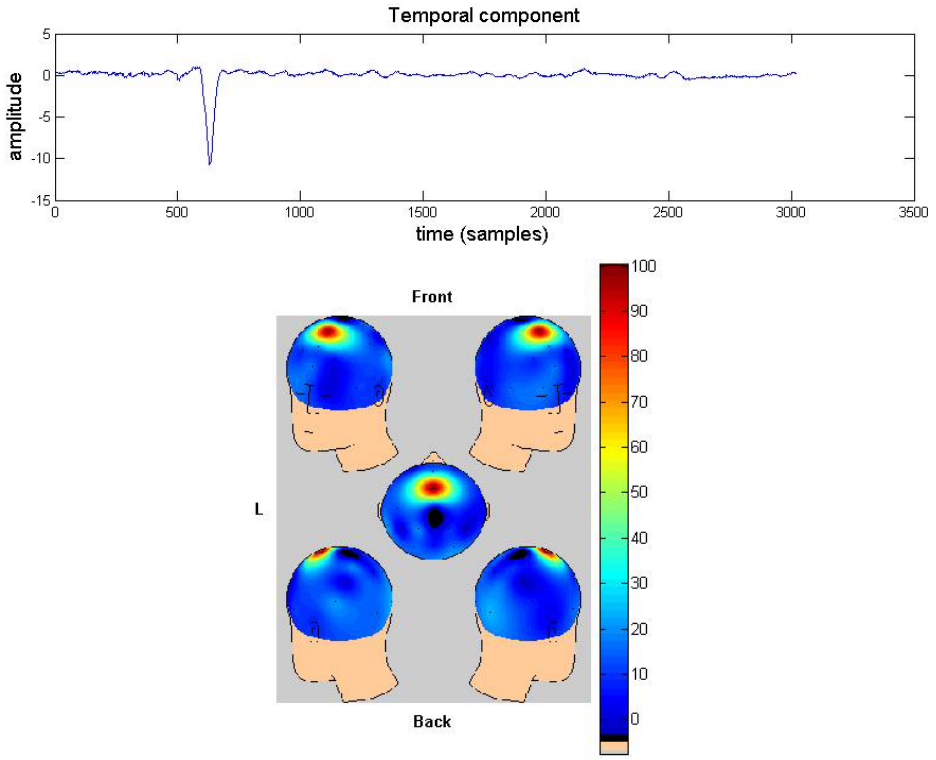

Figure 4.5: A component extracted for participant 5, shown temporally (above) and spatially (below) that illustrates an abrupt change artifact.

The temporal element of this component shows a large abrupt change at approximately 500ms, furthermore the spatial element of the component shows that this is centred on a single channel and thus, is likely to be an artifact. If the temporal element of a component contained an abrupt change, it was considered to be an artifact and was excluded from further analysis.

4.2.6.5 *Signal reconstruction*

Ocular and other artifacts were removed by back-projection of all but those components. The outcome of this method of data cleaning is demonstrated in Figure 4.6. Figure 4.6 shows a recording at channel Fz from participant 1 during rest with eyes open. Prior to artifact removal, eye blink artifacts are clearly evident in the data segment but after the artifact components have been excluded from the signal, these are no longer apparent.

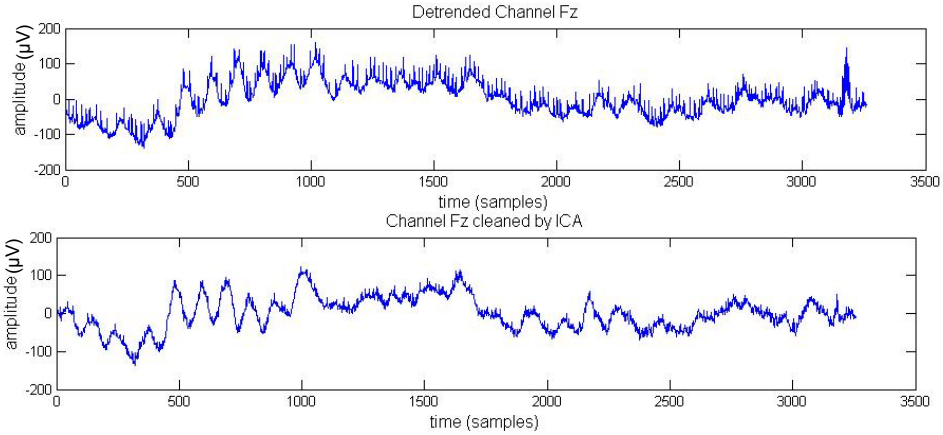

Figure 4.6: Channel Fz before (above) and after (below) data cleaning by ICA

After the signal was reconstructed, data from all channels for each participant were visually inspected. Any channels that still appeared artifactual i.e. they had greater power than all other channels and their signal was uncorrelated with neighbouring channels, were replaced by the mean of their four closest neighbours (see Figures 4.7 and 4.8).

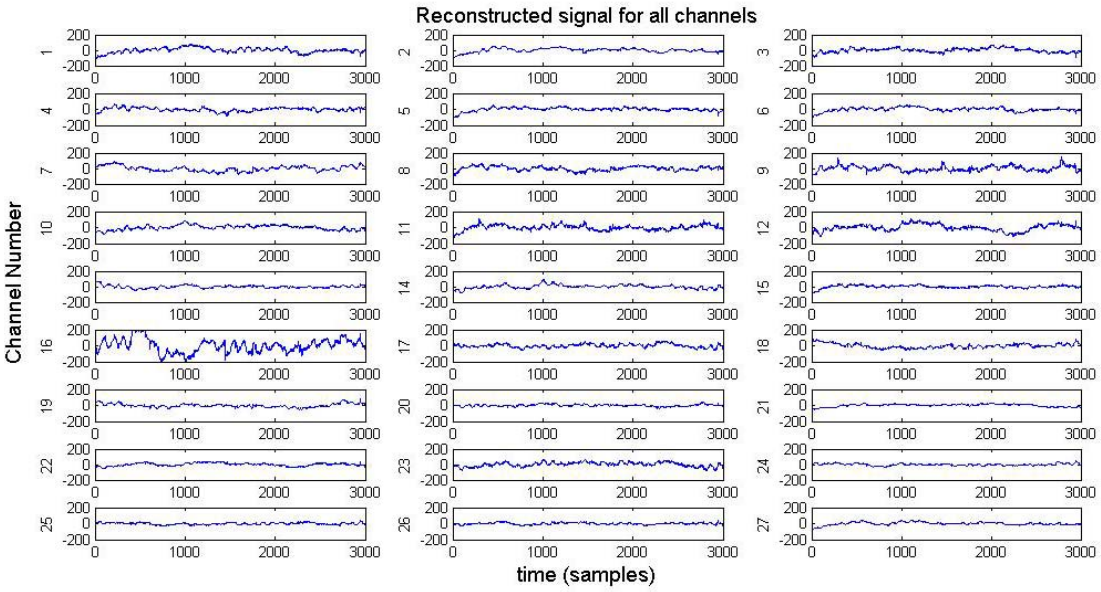

Figure 4.7: Reconstructed signal for all channels for participant 20; channel 16 shows increased power and no correlation with neighbouring channels.
Note. The y-axis indicates the amplitude (*μV)* of each channel.

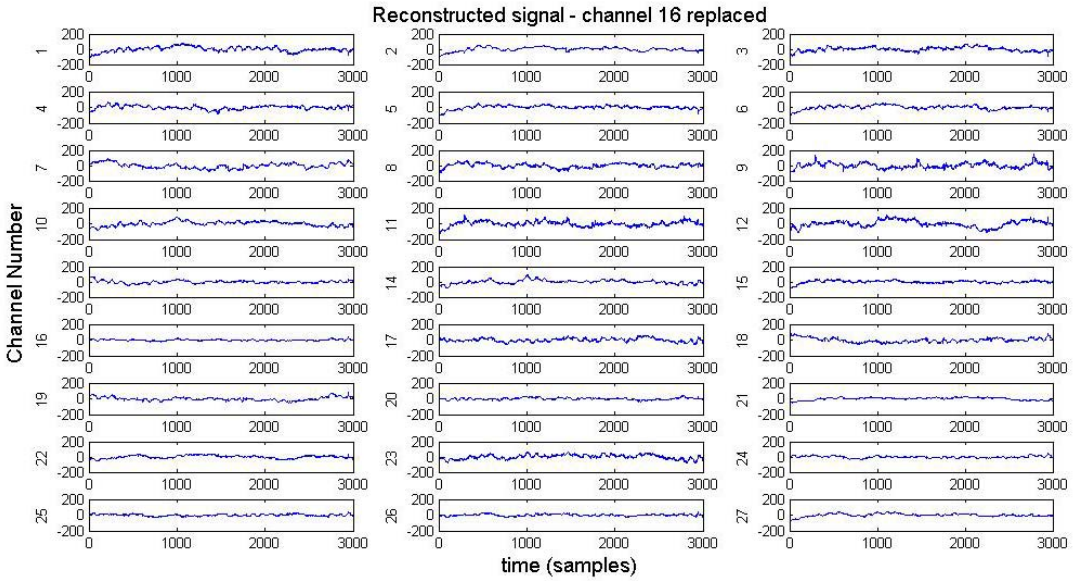

Figure 4.8: Reconstructed signal across all channels for participant 20 after channel 16 has been replaced with the mean of the four closest channels.
Note. The y-axis indicates the amplitude (*μV)* of each channel.

Only 6 channels of data across all participants in both testing sessions (i.e from a total of 1188 channels of data) were replaced in this way.

This method of data processing was performed on the EEG data obtained from the rest with eyes open, rest with eyes closed and the simple RT goal-directed task. However, removal of ocular artifacts from the rest with eyes closed condition using this method was very problematic and despite numerous attempts, a satisfactory solution did not emerge.

4.2.6.6 *Problems with the analysis of the data obtained during the rest with eyes closed assessment*

During this testing session, the participants were instructed to rest with their eyes closed for 5 minutes. Throughout this, as with the other tasks, EEG, EOG and ECG data were recorded (see section *4.2.5 Electrophysiological Acquisition* for further details). As with the data recorded from the other tasks, considerable drift and other artifacts were evident in the raw data. The same artifact removal techniques that were used for the other tasks were employed on these data – such as ICA for artifact removal. As described previously, when using ICA, ocular artifacts are identified by comparing the components extracted by ICA with the data recorded from the EOG channels; ocular artifact components can then be excluded. Eye blinks are easily identified in the data as sharp vertical spikes, both in the ICA components and in the EOG channels. This allows accurate identification of ICA components that contain eye blink artifacts in conditions in which the participants have their eyes open; however in the resting with eyes closed condition, ocular artifacts are less apparent – as no eye blinks are present.

Examples of EOG data from the eyes open and eyes closed resting conditions are shown in Figure 4.9, VEOG is shown in blue and HEOG is shown in green. As is evident in Figure 4.9, eye blinks are very easily identifiable in the rest with eyes open condition but in the rest with eyes closed condition there is a much less palpable EOG pattern. Consequently when comparing these EOG data to the extracted ICA components, ocular artifact components are easily identified in the rest with eyes open condition but less easily identified in the rest with eyes closed condition.

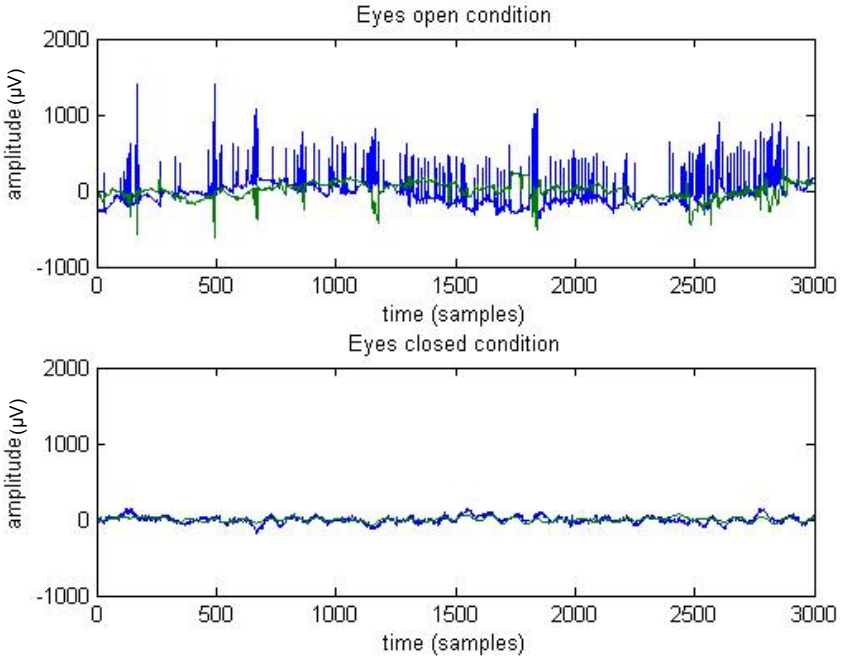

Figure 4.9: EOG data for eyes open resting condition (above) and eyes closed resting condition (below), for participant 1.

Although ICA was run on the data obtained during the rest with eyes closed condition for all participants, identification of ICA components that contained ocular artifacts was problematical as these were not clearly apparent. Subsequently after the 'non-artifact' ICA components had been back projected to reconstruct the signal, substantial power was still observed around the eyes (see Figure 4.10). This indicates that removal of ocular artifacts was unlikely to have been successful, and muscle activity, which is likely to reflect the participant's attempts to keep their eyes firmly closed throughout the resting session, was still evident in the data.

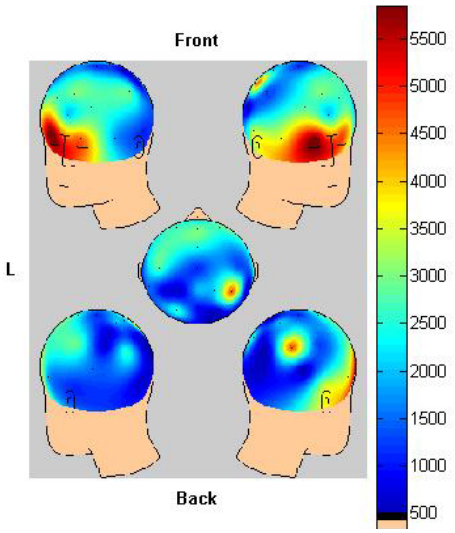

Figure 4.10: Slow 3 power during the eyes closed resting condition, after ICA artifact removal -participant 20.

This method of artifact removal using ICA was run twice on the data from this testing session - rest with eyes closed - for all participants, and both times a substantial amount of ocular muscle activity remained after signal reconstruction. As ICA is a very time consuming technique and two attempts at this procedure had been unable to exclude ocular artifacts, attempts to analyse this data further were discontinued.

4.2.7 Data analysis

4.2.7.1 *Fast Fourier Transformation*

After the signal was reconstructed, fast fourier transformation (FFT) analysis was performed on the data segments from each of the 27 scalp electrodes for each participant in each test condition 1) rest with eyes open and 2) goal-directed (2-CR RT) task. FFT analysis describes the frequency content of the signal and thus, illustrates the relative strength of different oscillations within the EEG signal. FFTs are often performed on segments or 'windows' of the entire data sequence so that an average of the FFTs for each window can then be calculated, this makes the analysis suitable for non-stationary signals and reduces random error. These windows are usually overlapped to further reduce random error (Simpson & Stefano, 2004). In the present study, each data segment was divided into one minute windows that overlapped by 10 seconds, thus the FFTs of these overlapping windows were averaged to give a single FFT for each data segment.

Different window shapes can be used in FFT analysis; two common ones are the hanning window and the boxcar window. Hanning windows are tapered at the ends and boxcar windows have straight edges. In the present study, hanning windows were used as they are less affected by 'spectral leakage' than boxcar windows. Spectral leakage describes the process by which power from a particular frequency band can 'leak out' or affect the power in neighbouring frequency bands. This was deemed important for the present study as

if spectral leakage occurred, the low frequencies of interest may be contaminated by power from the DC component.

The FFT plot is illustrated in Figure 4.11; the upper part of the figure shows the data segment for channel Cz (participant one, during rest eyes open). Slow oscillations are clearly present and from visual inspection appear to be at a frequency of approximately one every ten seconds. A corresponding FFT of this data segment would be expected to exhibit a peak of power at about .1Hz. This is shown in the lower part of the figure – a peak of power is evident at about .1Hz (for ease of reading, the FFT plot has been shown only up until 1 Hz although frequency data exists up to 5Hz).

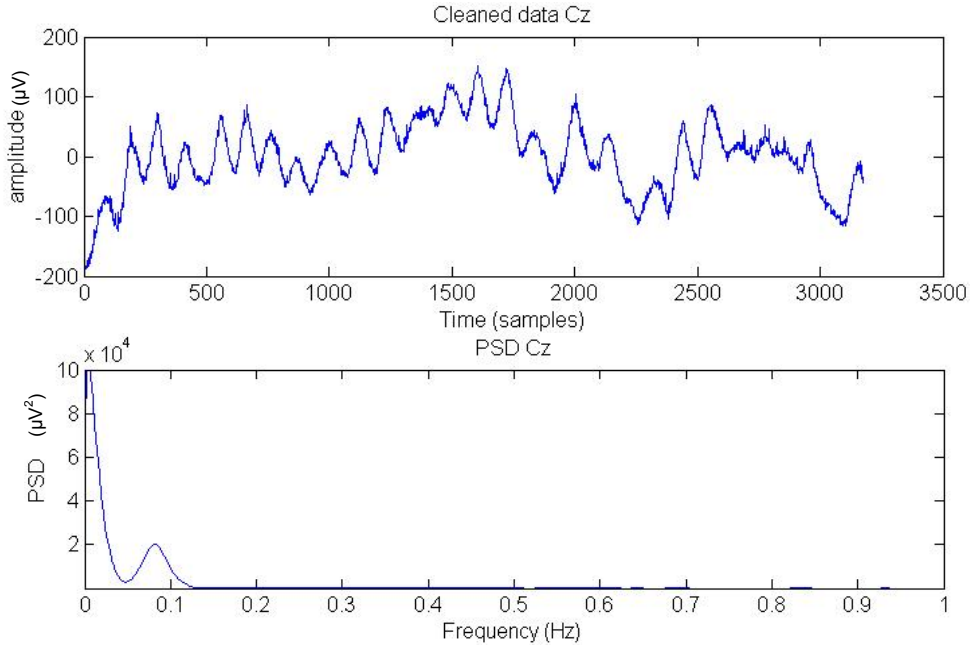

Figure 4.11: Data from channel Cz (above) and corresponding FFT (below).

4.2.7.2 *Spatial localisation of the resting S3 network*

After the FFT for each data segment across each of the 27 scalp electrodes was determined, the power in each of five frequency bands (as area under the FFT curve) was calculated for each participant, see Figure 4.12.

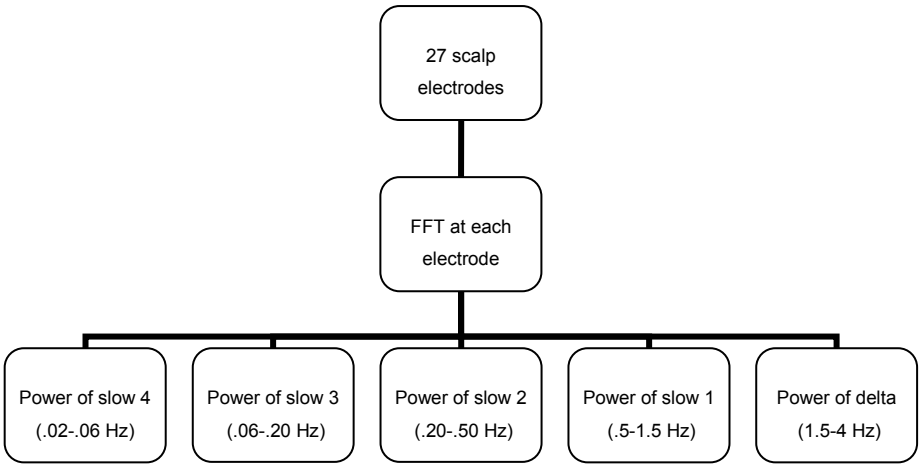

Figure 4.12: Flow diagram showing data analysis for each participant in each condition.

Thus, for each participant during each task, at each of the 27 scalp electrodes, five frequency measures were obtained. The spatial localisation of the resting S3 network was determined using power in the slow 3 frequency band only from data segments from the rest with eyes open condition (at both the test and the re-test sessions). The spatial location of this network was established using only data from the *low-ADHD* symptom group as it is assumed that this network may be abnormal in the *high-ADHD* symptom group. Time 1 data were available for 11 of the *low-ADHD* symptom group and T2 data were available for 8 of the *low-ADHD* symptom group. The network was established by calculating the mean slow 3 power for each scalp electrode across these 19 data segments. The overall mean across all electrodes was then calculated and any electrodes with slow 3 power that was higher than the overall mean across all electrodes was considered to be part of the network of slow 3 power.

This mean cut off was fairly arbitrary and other cut offs could have been used. For example, it would be equally feasible to have used electrodes with power in the highest 40th centile or electrodes with power higher than the median as the cut off that defined the S3 network. In order to ensure that the results obtained in the present study were not an artifact of the cut off used, some analyses were run on these data using alternative cut offs. The results, including the pattern of S3 activation at rest and the group differences identified within this resting network, remained relatively unchanged regardless of which cut off was used to identify the electrodes with the highest S3 power. Therefore this mean cut off, although arbitrary, appeared to be a useful method of delimiting a S3 network that can be used in subsequent analyses.

Subsequently, for each condition, in each frequency band, the mean power across all of the electrodes within this network was calculated for each participant. This gave an individual single power value for each frequency band within this network per participant. Similarly the mean power of all the electrodes not in the network was calculated to give the power of each frequency band outside of the network, for each participant. Since power is not normally distributed, the values were natural log transformed (Gasser, Bacher, & Mocks,

1982); from now on the power in each of these frequency bands will refer to the natural log transformed data – ln(μV^2).

The stability of this network over time was calculated by a correlation of all participants' test and retest power scores.

4.2.7.3 *Associations with symptoms of inattention*

Group comparisons (*high-ADHD* symptom group vs. *low-ADHD* symptom group) for T1 only were made on power scores in each of the five frequency bands in the resting network of low-frequency oscillations and outside of this resting S3 network. Because of participant attrition and exclusion of participants with excessive movement artifacts, there was insufficient power to perform these analyses at T2.

To investigate the association between self-reported inattentive symptoms and power in this network, the *high-ADHD* symptom group were split, by a median split, into those with high inattentive symptoms (N = 7) and those with low inattentive symptoms (N = 6). Thus, comparisons were also made between three groups; *low-ADHD* symptom group, *high-ADHD* symptom group with low inattention and *high-ADHD* symptom group with high inattention. The *high-ADHD* with high inattention self-reported more inattention (M = 20.6) than the *high-ADHD* with low inattention group (M = 11.5). This difference was shown to be statistically significant using an independent samples t-test ($t(11) = 5.13$, $p<.001$). However an independent samples t-test showed that the *high-ADHD* with high inattention group (M = 16.1) did not differ from the *high-ADHD* with low inattention group (M = 14.2) in their self-reported hyperactivity/impulsivity ($t(11) = .75$, *ns*).

These group comparisons were made using repeated-measures ANOVAs for data collected during the rest with eyes open condition and the 2-CR RT task condition. Furthermore, comparisons between these two conditions were made, again using repeated-measures ANOVAs and between groups.

4.2.7.4 *Statistical Power*

Given the small sample size adopted in the present study (N = 24), there is insufficient power to detect statistically significant small or medium effects. For example, for a significance test of Pearson's r at α =.05, an N of 85 would be necessary to detect a medium sized effect ($r \approx .3$); a sample of N = 24 would only be able to detect large effects ($r \approx .5$) (Cohen, 1992). Due to the exploratory nature of the present study and its small sample size, it is inappropriate to disregard associations between variables that fail to reach statistical significance; therefore, for each statistical test the test statistic and exact *p* value will be reported, and medium sized effects will be highlighted, even if they fail to reach statistical significance at $p = .05$. Furthermore, the issue of whether or not to adjust for multiple testing is a complex one and has been widely debated. Perneger (1998) argues that such adjustments are overly conservative and unnecessary unless testing for significant associations in the absence of pre-established hypotheses. Given that we are testing a-priori hypotheses, we will

not employ these corrections; however, we will report the test statistic and exact *p* value for each statistical test to make our results transparent.

4.3 Results

4.3.1 Low frequency oscillations during rest

A network of resting S3 activity was identified, its test re-test stability was assessed and intra-individual variation in low-frequency oscillations within and outside of this network at rest was calculated.

4.3.1.1 *Identification of a network of resting slow 3 power using DC-EEG*

Low frequency oscillations were clearly present in the raw data both before and after data cleaning.

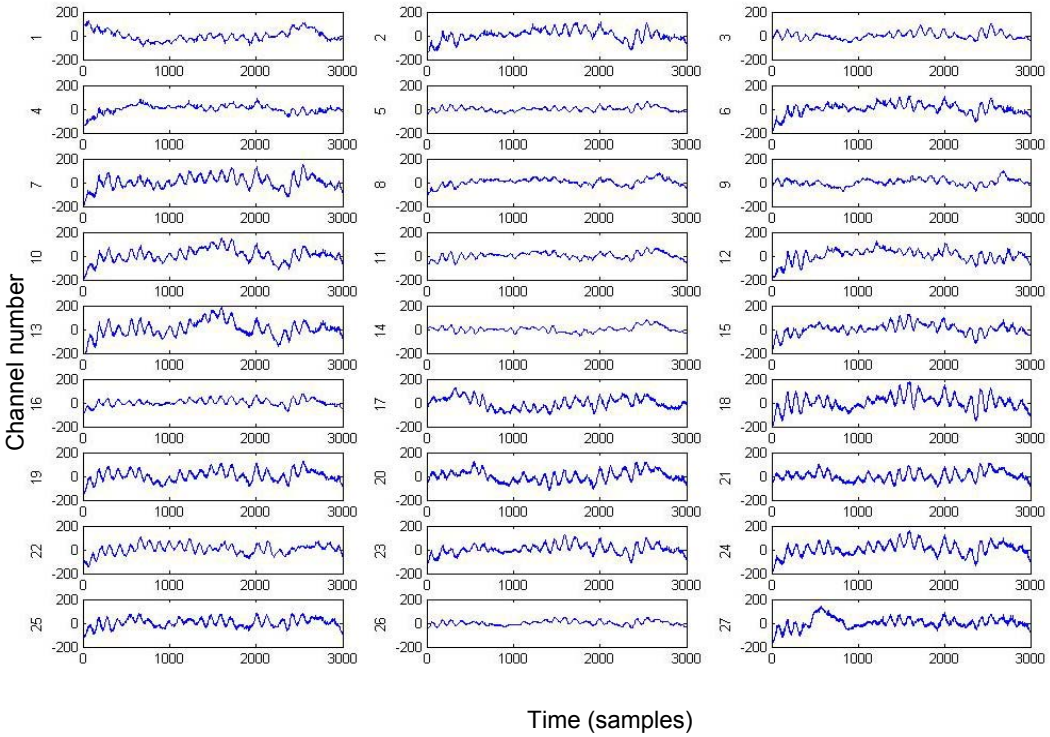

Figure 4.13: All electrodes after ICA, participant 1.
Note. The y-axis indicates the amplitude (*μV)* of each channel.

Figure 4.13 shows 5 minutes of data from each channel across the scalp of an individual participant, during the rest with eyes open condition; this clearly demonstrates that across all electrodes, some level of periodic fluctuation in EEG power exists. The relative power of these low frequency oscillations are shown in Figure 4.14, which demonstrates the corresponding FFT for each electrode (for ease of reading the FFT has been shown only until .25 Hz).

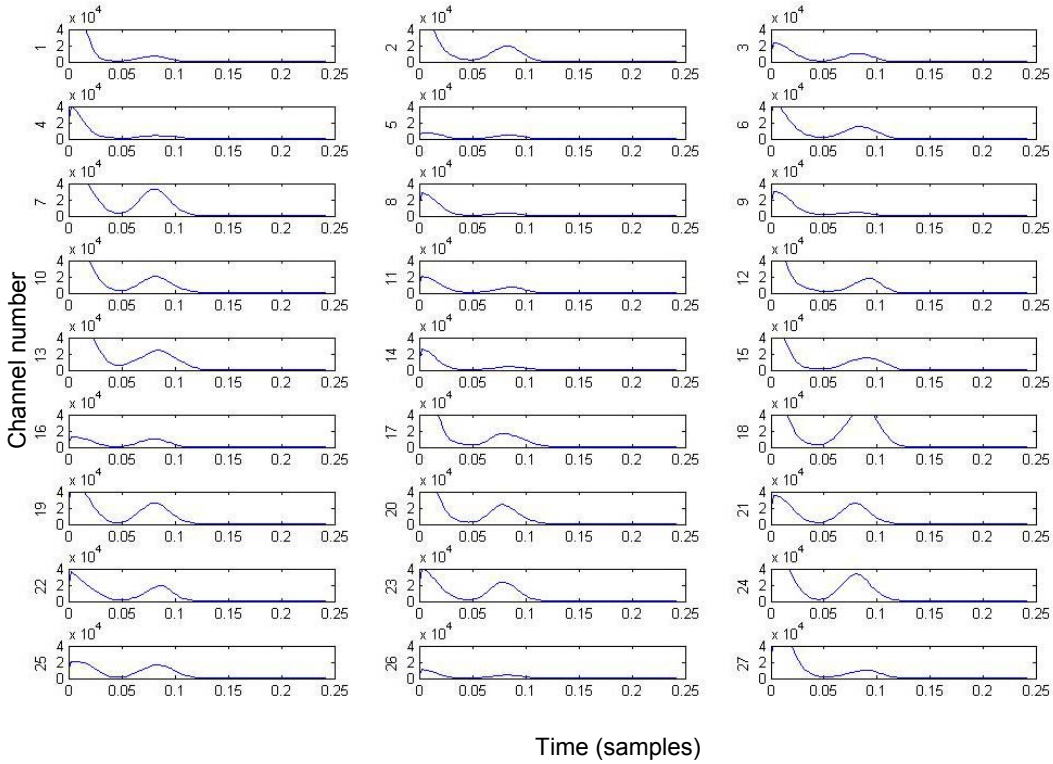

Figure 4.14: FFT for each electrode, participant 1.
Note. The y-axis indicates the power (μV^2) of each channel.

From Figure 4.14, it is evident that in the majority of electrode channels from this individual there is a peak of power between .05 and .1Hz. However it is also clear that the relative strength of this peak varies between channels. Topographical diagrams are better able to describe the spatial distribution of this power. Such diagrams can be drawn by plotting the mean power (as area under the FFT curve) in a particular frequency band at each electrode site. An example of this is shown in Figure 4.15; the topographical diagram shows the spatial distribution of the power in slow 3 band for participant 1.

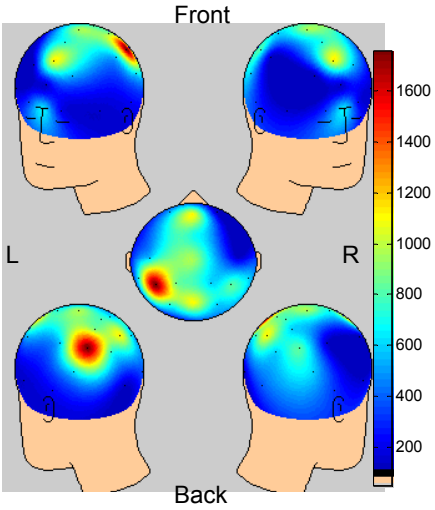

Figure 4.15: Spatial distribution of slow 3 power for participant 1.

The averaged spatial distribution of power in the slow 3 frequency band during rest with eyes open, across all of the *low-ADHD* symptom participants (both test and re-test testing sessions) is shown topographically in Figure 4.16. The location of electrodes with slow 3 power that was higher than the mean – those determined as comprising the resting slow 3 network are also shown in Figure 4.16.

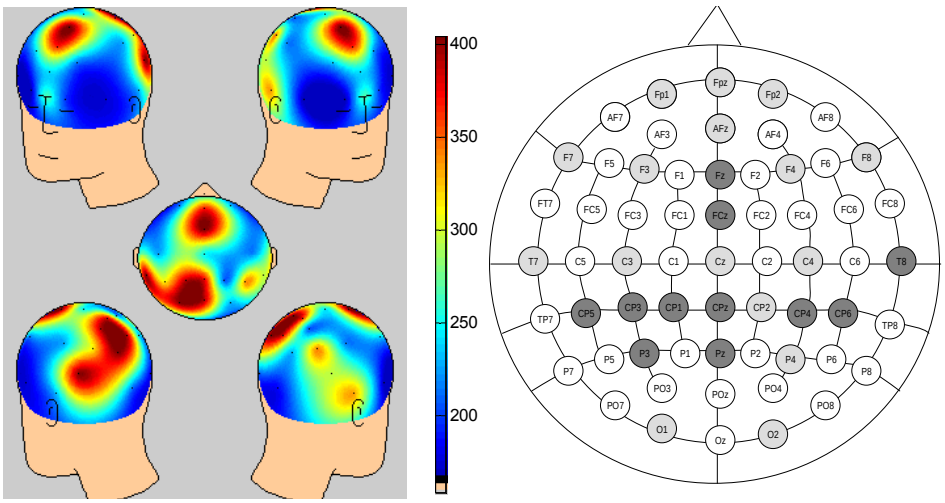

Figure 4.16: Slow 3 power across the entire low-ADHD symptom group (left) and electrodes selected for network (right). Electrodes selected for network are shown in dark grey, all other electrodes in the montage are shown in light grey.

Individual topographical maps for all the *low-ADHD* symptom participants are shown in Appendix A6, these indicate that substantial variation exists between participants.

4.3.1.2 *Stability of the resting slow 3 network over time*

Although the network was determined using a combination of both T1 and T2 data, considerable overlap existed in the spatial location of slow 3 power at each time point, see Figure 4.17.

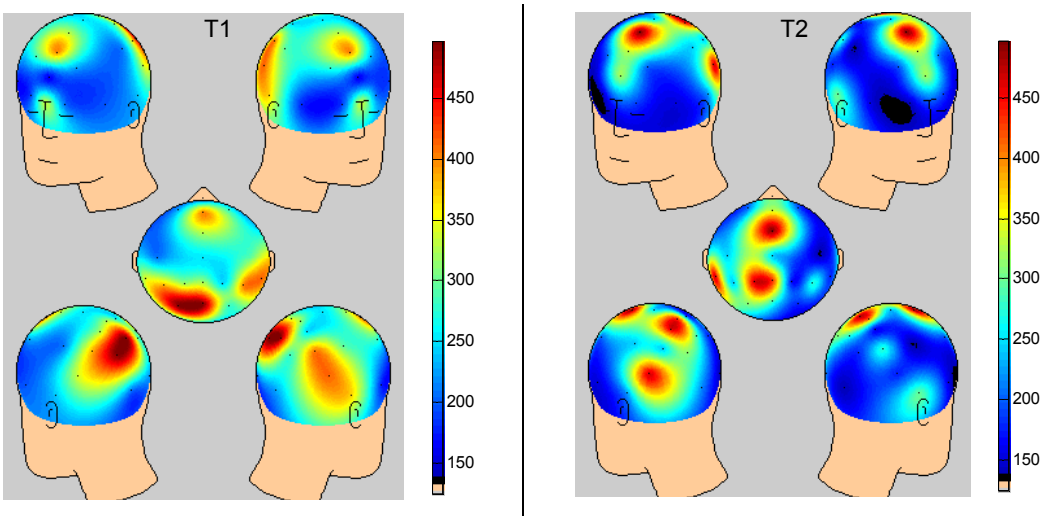

Figure 4.17: Spatial location of slow 3 power at T1 (left) and T2 (right).

Likewise, the electrodes that exhibited the most slow 3 power at T1 and T2 were largely similar, see Figure 4.18.

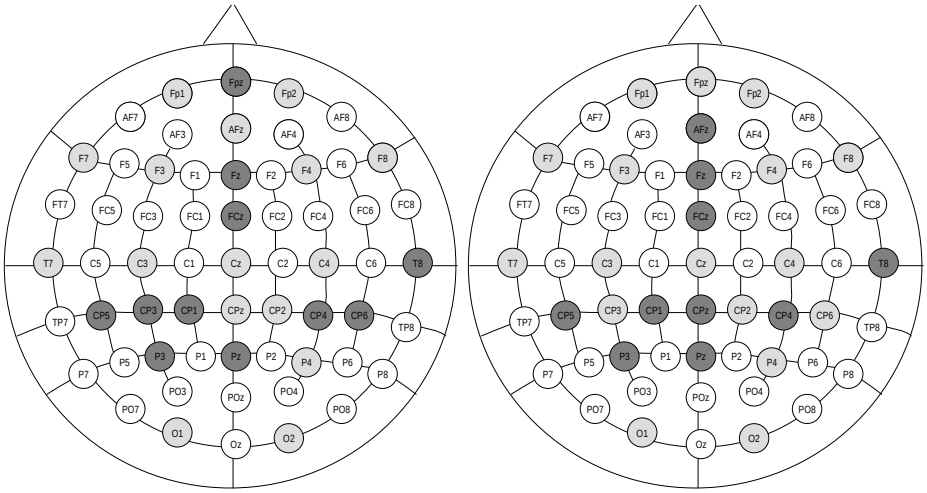

Figure 4.18: Electrodes exhibiting the most power shown in dark grey at T1 (left) and T2 (right), all other electrodes in montage shown in light grey.

Therefore, the spatial location of the network appeared to be relatively stable over time and was predominately located along the frontal and posterior midline and central posterior cortex.

The stability of this network for each frequency band was further assessed by correlating the power in each of these frequency bands within this network at T1 and T2. Thus, between frequency band correlations at T1 (N = 24) and T2 (N = 17) as well as test-retest correlations between these two testing sessions (N = 17) were performed. These

correlations (Pearson's r) are shown in Table 4.2. Between band correlations at each time point are very high, particularly between neighbouring frequency bands. For example, the correlation between the S4 and S3 frequency bands is *r(24)* =.860 at T1 and *r(17)* = .843 at T2; and the correlation between S2 and S1 is *r(24)* = .908 at T1 and *r(17)* = .966 at T2. Test-retest correlations between the same frequency band at each of the two testing sessions are not as high. However, in the lower frequencies, S4 and S3 correlations of about *r* = .4 to.5 are identified. Although these correlations do not reach statistical significance, they are medium to large effects (Cohen, 1992).

Table 4.2

Correlations of power at each frequency band within the S3 network at T1 and T2.

	1	2	3	4	5	6	7	8	9	10
1.S4 time 1	--	.860**	.554**	.456*	.490*	.418†	.580*	.267	.244	.257
2.S3 time 1		--	.458*	.394†	.446*	.261	.465†	.172	.181	.195
3.S2 time 1			--	.908**	.789**	.277	.251	.294	.203	.166
4.S1 time 1				--	.885**	.319	.300	.376	.300	.257
5.Delta time 1					--	.228	.384	.250	.232	.263
6.S4 time 2						--	.843**	.839**	.840**	.870**
7.S3 time 2							--	.617**	.632**	.695**
8.S2 time 2								--	.966**	.912**
9.S1 time 2									--	.966**
10.Delta time 2										--

** $p<.01$, *$p<.05$, †$p<.1$

4.3.1.3 *Specificity of the resting slow 3 network*

Thus far, the S3 network has been defined by activation only in the slow 3 frequency band; however, it is not clear whether this network is distinct from the other slow frequency bands or whether it is one element of a broader sub-delta network. The previous section showed that within this network, very strong correlations were apparent between the sub-delta frequency bands, especially between neighbouring frequencies such as S4 and S3, and, S1 and S2. Topographical diagrams that show the averaged spatial distribution of power in these other sub-delta frequencies during rest with eyes open, across all of the *low-ADHD* symptom participants (both test and re-test testing sessions) indicate that the overall pattern of scalp activation was broadly similar across all of these frequency bands -see Figure 4.19. Across all of these frequencies, the main activation occurred across the frontal midline and posterior scalp regions.

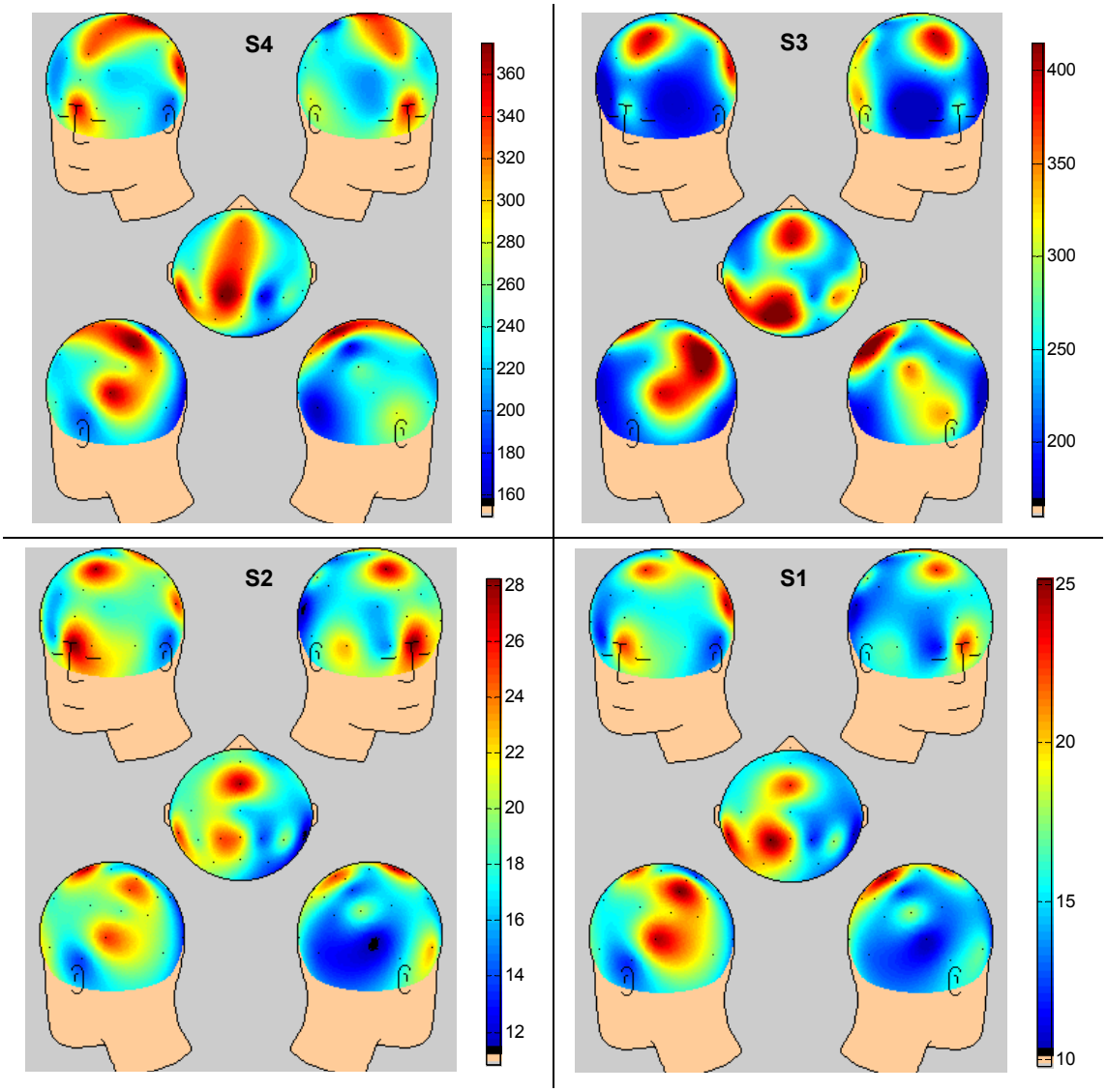

Figure 4.19: Scalp activations of S4 (top left), S3 (top right), S2 (bottom left) and S1 frequency bands (bottom right), in low-ADHD symptom participant during rest with eyes open (all maps are shown on individual best-fit scales).

4.3.1.4 *Intra-individual variation in very low frequency oscillations within this network at rest*

Figure 4.20 illustrates group (*low-ADHD* symptom group vs. *high-ADHD* symptom group) differences in power across the five frequency bands at rest.

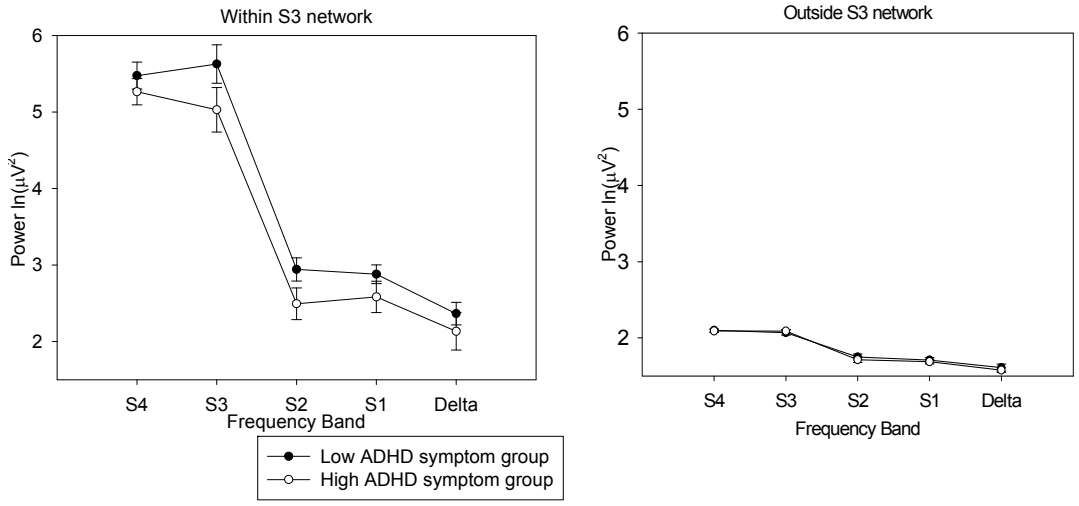

Figure 4.20: Power across all frequency bands for low-ADHD symptom group and high-ADHD symptom group within (left) and outside of network (right), error bars represent +/- 1 standard error.

The difference in power between these groups and in each location (within and outside of the slow 3 network) for each of these frequency bands was tested using a 2 x 2 repeated measures ANOVA. Location (within and outside of the network) was entered as the within subjects factor and group (*low-ADHD* symptom group vs. *high-ADHD* symptom group) was entered as the between subjects factor.

No effects of group were identified for any of the five frequency bands (delta $F(1,22) = .32$, $p = .574$, *ns*; S1 $F(1,22) = .96$, $p = .337$, *ns*; S2 $F(1,22) = .26$, $p = .616$, *ns*; S3 $F(1,22) = 2.12$, $p = .160$, *ns*; S4 $F(1,22) = .57$, $p = .459$, *ns*). However for each frequency band a significant effect of location emerged and within the network there was higher mean power than outside of it (delta $F(1,22) = 25.56$, $p<.001$; S1 $F(1,22) = 86.33$, $p<.001$; S2 $F(1,22) = 96.65$,$p<.001$; S3 $F(1,22) = 324.98$, $p<.001$; S4 $F(1,22) = 814.38$, $p<.05$). No significant group by location interactions emerged for any of the frequency bands (delta $F(1,22) = 1.05$, $p = .318$, *ns*; S1 $F(1,22) = 2.04$, $p = .167$, *ns*; S2 $F(1,22) = 1.01$, $p = .325$, *ns*; S3 $F(1,22) = 2.57$, $p = .123$ *ns*; S4 $F(1,22) = .92$, $p = .348$, *ns*).

In order to further clarify the effect of inattention on differences in power across the five frequency bands, these analyses were repeated entering the three groups (in which the *high-ADHD* symptom group are median split into those with high inattention and those with low inattention) as the between subjects factor, this is illustrated in Figure 4.21.

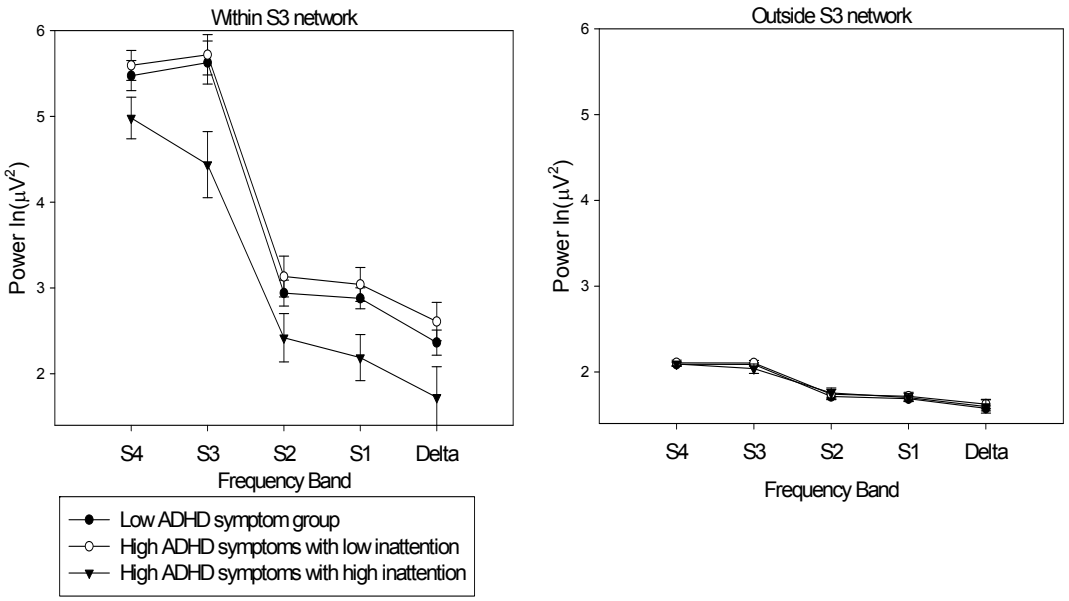

Figure 4.21: Power across all frequency bands between low-ADHD symptom group, high-ADHD with low inattention and high-ADHD with high inattention groups, within (left) and outside of network (right), bars represent +/- 1 standard error.

Thus, the difference in power between groups and in each location for each of these frequency bands was tested using a 2 x 3 repeated measures ANOVA. Location (within and outside of the network) was entered as the within subjects factor and group (*low-ADHD* symptom group, *high-ADHD* with low inattention and *high-ADHD* with high inattention) was entered as the between subjects factor.

A significant effect of group was identified in both the S3 and the S1 frequency bands ($F(1,21) = 4.81$, $p = .019$; $F(1,21) = 3.79$, $p = .039$, respectively). In both of these frequency bands the *high-ADHD* with high inattention group exhibited significantly less power than the other two groups. However the effect of group was not significant for any of the other frequency bands, (delta $F(1,21) = 2.38$, $p = .118$, *ns*; S2 $F(1,21) = 1.67$, $p = .212$, *ns*, S4 $F(1,21) = 1.95$, $p = .167$, *ns*). For each frequency band a significant effect of location emerged and within the network there was higher mean power than outside of it (delta $F(1,21) = 29.36$, $p<.001$; S1 $F(1,21) = 112.34$, $p<.001$; S2 $F(1,21) = 112.62$, $p<.001$; S3 $F(1,21) = 389.63$, $p<.001$; S4 $F(1,21) = 870.94$, $p<.001$). Furthermore, significant group by location interactions emerged for all frequency bands except slow 4(delta $F(2,21) = 4.54$, $p = .023$; S1 $F(2,21) = 7.15$, $p = .004$; S2 $F(2,21) = 4.22$, $p = .029$; S3 $F(2,21) = 5.77$, $p = .010$; S4 $F(2,22) = 2.67$, $p = .093$, *ns*). In these frequency bands, the *high-ADHD* with high inattention group exhibited less power than the other two groups within the network but power equal to the other two groups outside of the network.

The significant effect of group and the significant group by location interaction in the S3 frequency band survived the covarying of power of all other frequency bands within the S3 network ($F(2,22) = 4.03$, $p = .038$; $F(2,22) = 4.00$, $p = .037$ respectively) and the covarying of power of all other frequency bands outside of the S3 network ($F(2,22) = 9.97$, $p = .002$; $F(2,22)$

= 9.71, *p* =.001 respectively). This suggests that this effect of the S3 frequency is independent of the other frequencies.

4.3.1.5 *Summary*

A resting network of S3 power was identified that showed a relatively stable pattern of activation in terms of its location and its frequency. However it is not clear whether this S3 network is distinct from other sub-delta frequencies as high between frequency band correlations were evident and similar spatial patterns of activation were identified at other sub-delta frequencies. Nevertheless, power across frequencies in this network at rest appeared to be associated with self-reported symptoms of attention, and the association between symptoms of inattention and S3 power was independent of power in frequencies other than S3 either within or outside of the S3 network.

4.3.2 Low frequency oscillations during goal-directed task (2-CR RT task) performance

The localisation of S3 power during goal-directed task performance and intra-individual variation within and outside of the resting S3 network during performance of a goal-directed task performance was then assessed.

4.3.2.1 *Localisation of S3 power*

The averaged spatial distribution of power in the slow 3 frequency band during this goal-directed task (simple RT task), across the entire *low-ADHD* symptom group is shown overall (across both test and re-test testing sessions - left), at T1 (centre), and at T2 (right) in Figure 4.22.

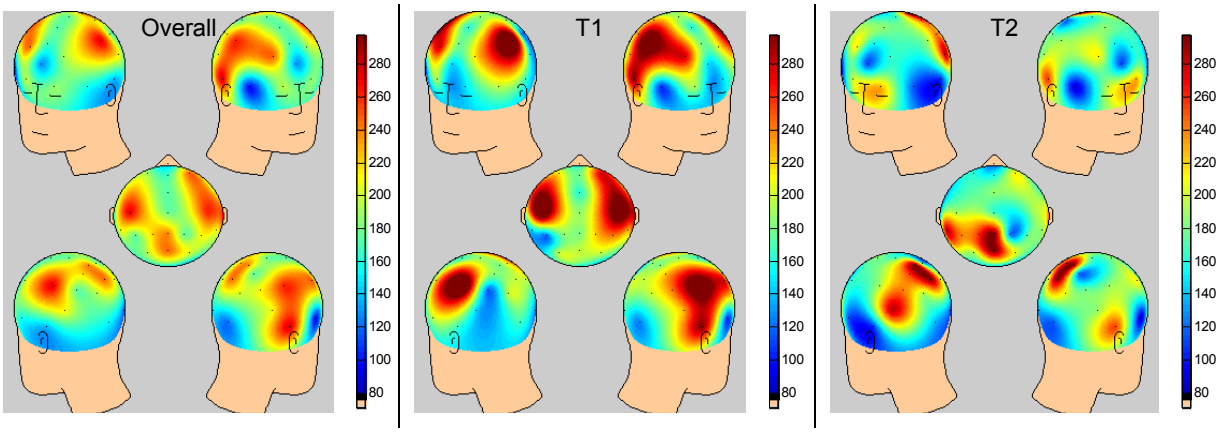

Figure 4.22: Spatial location of S3 power in the low-ADHD symptom group throughout the goal-directed task, overall (left), at T1 (centre), and at T2 (right).

The electrodes that showed higher than the mean of power in the slow 3 frequency band during the goal-directed task, overall, at T1, and at T2 are shown in Figure 4.23.

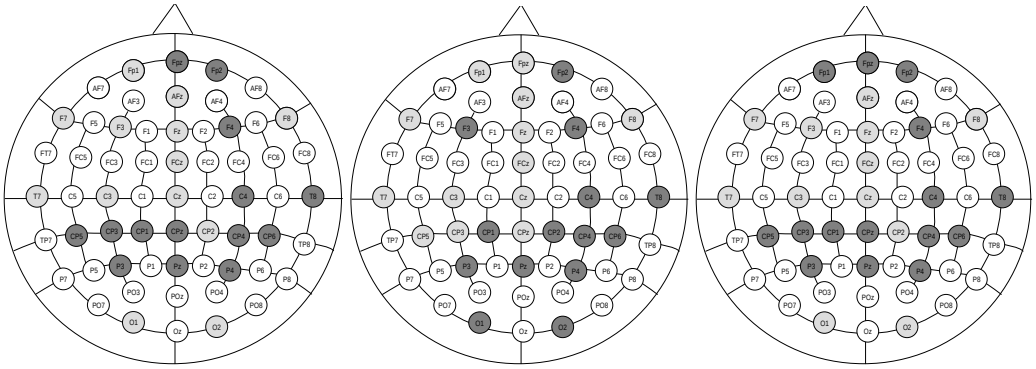

Figure 4.23: Electrodes that showed higher than the mean of S3 power in the low-ADHD symptom group throughout the goal-directed task are shown in dark grey, overall (left), at T1 (centre), and at T2 (right), all other electrodes in the montage are shown in light grey.

Some overlap is evident between these two time points, in both the topographical and electrode maps. The spatial location of this S3 power during the goal-directed task was predominately along the central posterior cortex and frontally. In contrast to the localisation of S3 power during the rest session, there is no frontal midline activation at any of the time points.

The stability of each frequency band during this task was assessed by correlating the power in each of these frequency bands across the whole scalp, within this network, and outside of the network at T1 and T2. Thus, between frequency band correlations at T1 (N = 21) and T2 (N = 16) as well as test-retest correlations between these two testing sessions (N = 16) were performed, for power across the whole scalp, within the network and outside of the network. These correlations (Pearson's r) are shown in Tables 4.3, 4.4 and 4.5 respectively. As with the resting condition, between band correlations tended to be strong, particularly between neighbouring frequency bands and at T1: for example at T1, the correlation between the S2 and S1 frequency bands was $r(21) = .881$ across the whole scalp, $r(21) = .862$ within the S3 network and $r(21) = .897$ outside of the S3 network. However, test-retest correlations between the same frequency band at each of the two testing sessions were much weaker and often negative, in each of these locations. Only the S3 and S4 frequency bands had positive test-retest correlations at each of the locations, and although statistically non-significant, the S3 test-retest correlation was moderately strong and ranged from $r(16) = .343$ to $r(16) = .406$ between these locations.

Table 4.3

Correlations of different frequency bands across the whole scalp during goal-directed task (2-CR RT task)

	1	2	3	4	5	6	7	8	9	10
1.S4 time 1	--	.583**	.597**	.484*	.400†	.165	.234	-.237	-.262	-.343
2.S3 time 1		--	.458*	.454*	.330	-.324	.401	-.300	-.387	-.531*
3.S2 time 1			--	.881**	.825**	-.491†	.052	.098	.029	-.238
4.S1 time 1				--	.908**	-.431†	-.097	-.139	-.209	-.408
5.Delta time 1					--	-.412	-.075	-.009	.020	-.117
6.S4 time 2						--	-.013	-.001	.052	.239
7.S3 time 2							--	.301	.271	.229
8.S2 time 2								--	.919**	.748**
9.S1 time 2									--	.914**
10.Delta time 2										--

** $p<.01$, * $p<.05$, † $p<.1$

Table 4.4

Correlations of different frequency bands within the S3 network during goal-directed task (2-CR RT task)

	1	2	3	4	5	6	7	8	9	10
1.S4 time 1	--	.679**	.609**	.459*	.336	.228	.233	-.227	-.224	-.272
2.S3 time 1		--	.495*	.444*	.375†	-.017	.406	-.185	-.270	-.405
3.S2 time 1			--	.862**	.811**	-.409	.055	.075	.202	-.225
4.S1 time 1				--	.909**	-.360	-.197	-.263	-.294	-.459†
5.Delta time 1					--	-.447†	-.106	-.068	-.028	-.184
6.S4 time 2						--	.161	.068	.083	.199
7.S3 time 2							--	.392	.376	.337
8.S2 time 2								--	.909**	.714**
9.S1 time 2									--	.908**
10.Delta time 2										--

** $p<.01$, * $p<.05$, † $p<.1$

Table 4.5

Correlations of different frequency bands outside of the S3 network during goal-directed task (2-CR RT task)

	1	2	3	4	5	6	7	8	9	10
1.S4 time 1	--	.543*	.556**	.518**	.518*	.182	.180	-.155	-.201	-.312
2.S3 time 1		--	.463*	.488*	.329	-.281	.343	-.369	-.445†	-.604*
3.S2 time 1			--	.897**	.831**	-.437†	.049	.125	.049	-.200
4.S1 time 1				--	.897**	-.342	-.020	-.062	-.144	-.340
5.Delta time 1					--	-.309	-.041	.024	.034	-.061
6.S4 time 2						--	.086	.334	.244	.350
7.S3 time 2							--	.282	.236	.196
8.S2 time 2								--	.936**	.791**
9.S1 time 2									--	.912**
10.Delta time 2										--

** $p<.01$, * $p<.05$, † $p<.1$

4.3.2.2 *Intra-individual variation in very low frequency oscillations within and outside of the S3 network during the goal-directed task*

The difference in power across all frequency bands during the goal-directed task, within and outside of the S3 network, and between groups was assessed using a 5 x 2 x 3 repeated-measures ANOVA. Frequency band (S4, S3, S2, S1 and Delta) and location (within and outside of the S3 network) were entered as the within subject factors and group (*low-ADHD* symptom group, *high-ADHD* low inattention and *high-ADHD* high inattention) was entered as the between subject factor. A significant main effect of frequency ($F(4,72)=202$, $p<.001$) emerged and greater power was observed in the lower frequency bands (as expected due to the 1/f distribution of power), however, no main effects of location ($F(1,18) = .232$, $p = .636$, *ns*) or of group ($F(1,18) = .306$, $p = .697$, *ns*) were found. Similarly, there were no significant interactions between frequency, location and group (see Figure 4.24).

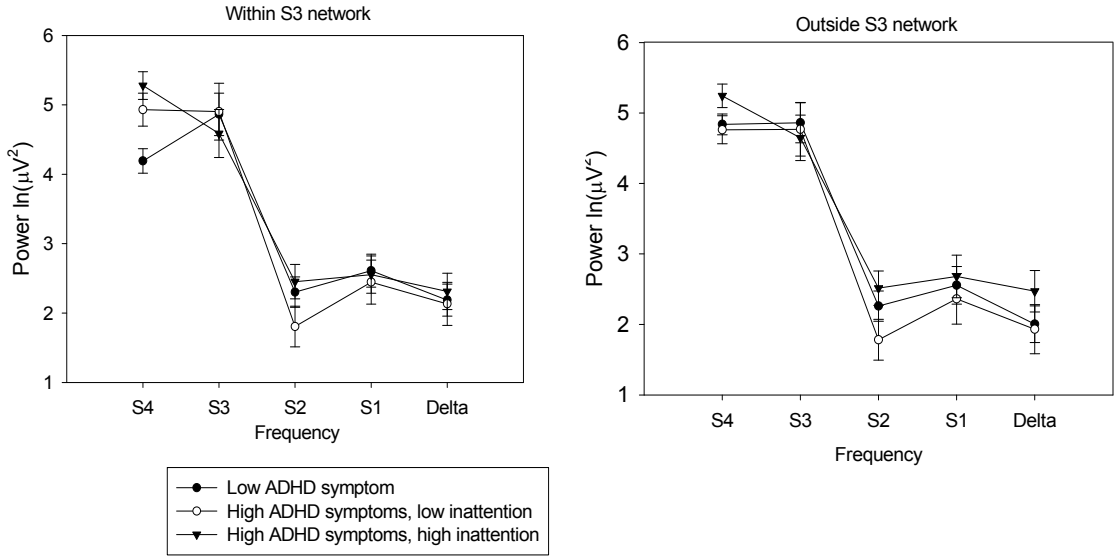

Figure 4.24: Power across all frequency bands within (left) and outside of the S3 network (right) during the goal-directed task, between groups, bars represent +/- 1 standard error.

4.3.3 Comparison of low frequency oscillations at rest and during goal-directed task performance

Comparisons were then made between these low frequency oscillations at rest (N = 23) and those observed during performance of goal-directed tasks (N = 21). Correlations (Pearson's r) between these two conditions for the power of different frequency bands are shown within the S3 network in Table 4.6 and outside of the S3 network in Table 4.7. As is evident from Table 4.6, within the S3 network, power in all of the frequency bands were highly correlated while the participants were performing each condition. However the between-condition correlations of each frequency band tended to be less strong, particularly among the higher frequency bands (S2, S1 and delta), which tended to be characterised by weak and often negative correlations. However, the power of the S3 frequency band between the two conditions was fairly strongly positively correlated (*r(21)* = .528); this indicates that within the

S3 network participants who exhibited high levels of S3 power while they were resting also exhibited high levels of S3 power while they were performing the goal-directed task.

Outside of this S3 network, the power in all of the frequency bands was again, strongly correlated within each condition. Again, a positive, although this time statistically non-significant, correlation in the S3 frequency band between the two conditions also emerged (*r(21)* = .366). However, outside of this network, fairly strong negative correlations emerged between power in the lowest frequencies at rest (S4 and S3) and the higher frequency bands during the goal-directed task (especially S1 and delta) (*r(21)*= -.264 to -.437), although these did not all reach statistical significance – see Table 4.7)

Table 4.6

Correlations between conditions for power of different frequency bands within the S3 network

	1	2	3	4	5	6	7	8	9	10
1.S4 rest	--	.860**	.554**	.456*	.490*	.259	.464*	-.157	-.082	-.169
2.S3 rest		--	.458*	.394†	.446*	.169	.528*	-.047	.081	-.016
3.S2 rest			--	.908**	.789**	.224	.338	-.041	.038	-.043
4.S1 rest				--	.885**	-.037	.131	-.088	.054	-.061
5.Delta rest					--	-.134	.018	-.153	-.058	-.056
6.S4 RT task						--	.679**	.609**	.459*	.336
7.S3 RT task							--	.495*	.444*	.375†
8.S2 RT task								--	.862**	.811**
9.S1 RT task									--	.909**
10.Delta RT task										--

** p<.01, *p <.05, †p<.1

Table 4.7

Correlations between conditions for power of different frequency bands outside the S3 network

	1	2	3	4	5	6	7	8	9	10
1.S4 rest	--	.736**	.677**	.560**	.540**	.151	.116	-.307	-.396†	-.437*
2.S3 rest		--	.396†	.227	.292	.080	.366†	-.220	-.264	-.398†
3.S2 rest			--	.909**	.790**	.253	.085	-.103	-.261	-.165
4.S1 rest				--	.879**	.042	-.115	-.150	-.325	-.278
5.Delta rest					--	-.179	-.276	-.248	-.426†	-.333
6.S4 RT task						--	.543*	.556**	.518*	.518*
7.S3 RT task							--	.463*	.488*	.329
8.S2 RT task								--	.897**	.831*
9.S1 RT task									--	.897**
10.Delta RT task										--

** p<.01, *p <.05, †p<.1

4.3.3.1 *Low-frequency rest-task attenuation across all participants*

A repeated measures ANOVA with condition (rest *vs*. 2-CR RT task) and frequency band (S4, S3, S2, S1 and delta) entered as within subject effects was run for each location (inside and outside of the S3 network). Within the S3 network there was a general trend towards attenuation of EEG power when participants engaged in a goal-directed task, and greater EEG power was observed during the resting state (M = 3.63) compared to the goal-directed task (M = 3.37), however this failed to reach statistical significance ($F(1,20) = 2.50$, $p = .130$, *ns*). A significant main effect of frequency emerged ($F(4,80) = 305$, $p<.001$) and greater power was observed in the lower frequencies (i.e. S2, S3 and S4). A significant condition by frequency band interaction also emerged ($F(4,80) = 5.65$, $p <. 001$) and paired t-tests showed that significant differences (i.e. attenuation of power in the goal-directed task compared to the resting condition) only emerged for the S3 and S2 frequency bands not in S4, S1 or delta, although S4 just missed statistical significance (S4 $t(20) = 2.06$, $p =.053$, ns; S3 $t(20) = 2.57$, $p = .018$; S2, $t(20) = 2.43$, $p = .025$; S1 $t(20) = .371$, $p = .715$, ns; Delta $t(20) = -.218$, $p = .830$, ns).

In contrast, outside of the S3 network greater power was observed during the 2-CR RT task (M=3.33) compared to rest (M = 1.83), this difference was statistically significant ($F(1,20) = 128$, $p < .001$). A significant main effect of frequency also emerged ($F(4,80) = 247$, $p<.001$) and again greater power was observed in the lower frequencies. A condition by frequency band interaction was also found to be statistically significant ($F(4,80) = 144$, $p < .001$). Paired t-tests showed that significant differences (i.e. increased power in the goal-directed task compared to the resting condition) emerged for all frequency bands, however this difference was greater for the lower frequencies (S4 $t(20) = -28.3$, $p < .001$; S3 $t(20) = -15.8$, $p < .001$; S2, $t(20) = -3.43$, $p = .003$; S1 $t(20) = -4.96$, $p < .001$; Delta $t(20) = -3.12$, $p = .005$).

4.3.3.2 *Rest-task S3 attenuation between groups defined by inattentive symptoms*

In order to specifically investigate the level of attenuation of S3 power from rest to the goal-directed task between groups defined by their self-reported symptoms of inattention , a 2 x 3 (location x group) repeated measures ANOVA was performed on the individual change scores (that describe the change or difference in S3 power between rest and goal-directed conditions). A main effect of location emerged ($F(1,18) = 277$, $p<.001$) and an increase in power between conditions occurred outside of the network (M = 2.76), whereas within the S3 network a smaller decrease in power occurred (M = -.51). No main effect of group emerged ($F(1,18) = .91$, $p = .42$, *ns*), however a statistically significant location x group interaction was found ($F(2,18) = 4.20$, $p = .032$) and the *high-ADHD* with high inattention group exhibited an small increase in S3 power whereas other two groups showed a decrease in this power within the S3 network, but outside of network all three groups exhibited similar increases in power (see Figure 4.28).

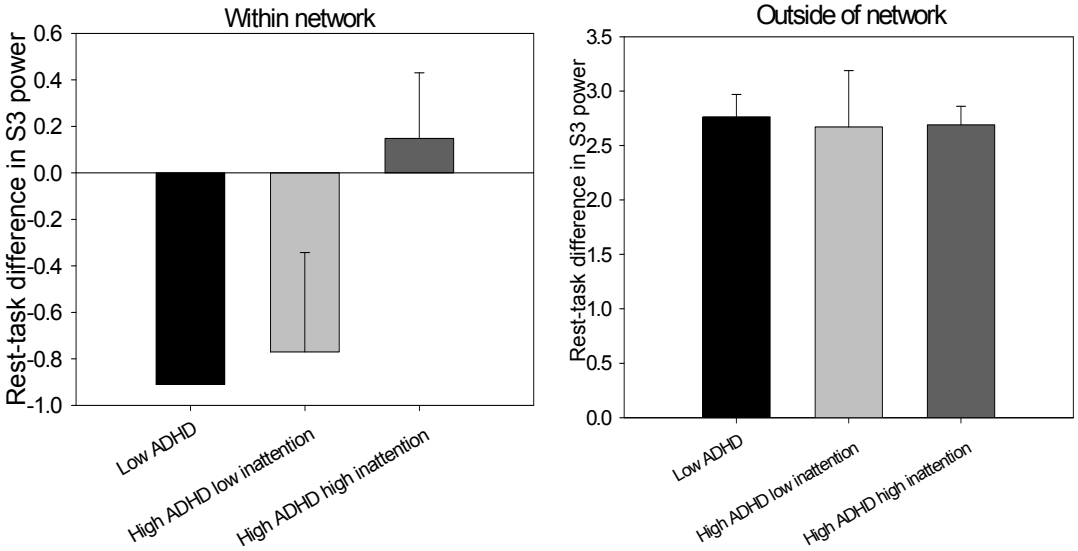

Figure 4.25: Attenuation of S3 power from rest to goal-directed task, within and outside of S3 network between groups split by inattention, bars represent +/- 1 standard error.

4.4 Discussion

In this study we were able to identify a resting-state slow 3 network of very low frequency electrophysiological oscillations. This network was mainly located along the frontal and posterior midline and the central posterior cortex and showed a good degree of stability over time, in both its location and its frequency. Furthermore, slow 3 power in this network at rest appeared to be associated with attention. Participants with high self-report ratings of inattention exhibited lower power across all frequencies within the network compared to the *low-ADHD* symptom group or the *high-ADHD* symptom group with lower self-report ratings of inattention. Outside of the network at rest, the power in any of the measured frequency bands did not differ between these three groups. The association between symptoms of inattention and S3 power was independent of power in frequencies other than S3 either within or outside of the S3 network.

When participants engaged in a goal-directed task, the slow 3 power was more widely dispersed across the scalp than at rest, and greater power was observed outside of the S3 network. Furthermore, across all participants, S3 power within the S3 network was lower while performing the goal-directed task than at rest, which indicates that S3 oscillations are attenuated during goal-directed performance. Furthermore, the attenuation of S3 power from rest to a goal-directed task within the S3 network was associated with inattention. Participants with high self-report ratings of inattention did not exhibit the same reduction in slow 3 power within the network compared to *low-ADHD* symptom group or *high-ADHD* symptom group with lower self-report ratings of inattention. Outside of the network at rest, however, the increase in S3 power from rest to the goal-directed task did not differ between these three groups.

4.4.1 Localisation of a resting S3 network

The network in the present study was characterised by power in the slow 3 frequency band. However it is not clear whether this network is distinct from the other slow frequency bands: other sub-delta frequency bands demonstrated very similar spatial patterns of activation at rest to the S3 frequency band and very strong correlations between all of the low-frequency bands were evident both within and outside of the network, this was especially the case between neighbouring frequencies. As the functional importance of the distinction between these low-frequency bands is not known - their limits were suggested by Penttonen & Buzsaki (2003) and are based on the assumption of a natural logarithmic relationship between successive frequency bands - the bands used in the present study may not be segmenting distinct physiological phenomenon, instead they may be dividing or combining real boundaries between frequencies.

Furthermore, the different frequency bands are unlikely to be distinct from each other. Buzsaki & Draguhn (2004) report that several different frequency bands are able to co-exist within the same cortical area and moreover, the slower, more powerful oscillations appear to moderate the activation of faster, more local events. Therefore the power in each frequency band is unlikely to be independent of the other frequency bands and alterations in the power in the S3 frequency band may affect the power in other frequency bands. However, despite this inherent colinearity between frequency bands, the group effect of inattention at rest for the S3 frequency was shown to be independent of the other frequencies. Thus it appears as though inattention is specifically associated with the S3 frequency band within and outside of the S3 network at rest.

Identifying a low frequency resting-state network using EEG may have important consequences for linking default-resting-state activity with behaviours such as attention lapses. The temporal resolution of EEG is much higher than fMRI and EEG more directly measures neuronal activity than fMRI, which has been previously adopted in such investigations, and so EEG is likely to be better able to synchronise low-frequency resting oscillations with moment-to-moment fluctuations in behaviour. However, it is important to consider that although this pattern of activation has been referred to as a ‘network’, the analysis in the present study has been unable to describe the functional connectivity of the identified scalp locations. The analysis merely identified areas that exhibited high power in a particular frequency band; it did not show that these areas are oscillating together. It is possible that the identified network may consist of numerous independent sources that are oscillating at the same frequency but a different phase and so are not necessarily functionally connected. Other analyses such as phase-synchrony or coherence analyses will be necessary to elucidate this. Furthermore, the sample size used to determine the network is small (N = 19) and so replication of its localisation is essential, both within other conditions, and with other participants.

4.4.2 Associations with symptoms of inattention

Only the *high-ADHD* symptom group who rated themselves as inattentive showed reduced power in the identified network at rest when compared to either *low-ADHD* symptom group or to *high-ADHD* symptom group that did not rate themselves to be inattentive. It is interesting that these differences appeared to be specific to the identified S3network. At rest, the group that reported high symptoms of inattention were only found to exhibit differences in power within the network; outside of the network the power that they exhibited across frequency bands was equal to that of the *low-ADHD* symptom group and the *high-ADHD* scores who did not rate themselves to be inattentive. This indicates that at rest, this group was not simply exhibiting an overall reduction in power across the whole scalp but rather, that this reduction in power was specifically found in the resting network. Thus it is likely that some element of this network at rest differs between those with high self-reported inattention and healthy controls.

It is also interesting that no differences between these groups occurred during performance of a goal-directed task, either within or outside of the resting network. Rather, group differences were evident in the attenuation of resting S3 activity when participants engaged in a goal-directed task. Participants with high self-reported ratings of inattention did not exhibit the same reduction of S3 power within the resting S3 network compared to *low-ADHD* symptom group or *high-ADHD* symptom group with lower self-report ratings of inattention; however, outside of the network, these three groups all exhibited similar increases in S3 power from rest to the goal-directed task. These findings offer some support for the hypotheses proposed by Sonuga-Barke & Castellanos (2007), which predicts that participants with ADHD will be less effective at attenuating low frequency brain activity from rest to task, as we showed that participants with high inattention experienced less attenuation of their resting brain activity when they engaged in a goal-directed task than other participants. However, in the present study, inattentive participants were also found to have lower levels of resting-state brain activity within the identified network; this does not follow the predictions of Sonuga-Barke & Castellanos (2007). Furthermore, this pattern of findings might also indicate that the inattentive participants found resting more challenging than the other participants did. Prior to the rest condition, participants were instructed to rest for 5 minutes and to try to keep as still as possible. It is possible that this may be particularly difficult for inattentive participants and thus, for these participants, the ‘rest’ condition may have been comparable to a goal-directed task: this would account for the similarity in S3 power between the two conditions in this group. However, the group of inattentive participants did not differ from the high-ADHD low inattention group in self-reported hyperactivity, and it seems more likely that hyperactive rather than inattentive symptoms would contribute to difficulties resting. Furthermore, although the inattentive participants exhibited similar S3 power between the rest condition and the goal-directed task within the S3 network, outside of the S3 network they exhibited large differences between the two conditions. Therefore, although individual differences in the ease with which a participant is able to ‘rest’ may impact on brain activity,

S3 activation was substantially different in all groups (at least outside of the S3 network) between rest and the goal-directed task to indicate that the rest condition was distinct from the goal-directed task. Therefore, although the present study offers some support for the default-mode interference hypothesis, its results are not entirely consistent with this hypothesis and further research is necessary to elucidate the function of default-mode brain activity in ADHD and inattention.

4.4.3 Limitations

It is important to consider that this study is clearly limited in terms of its small sample size and non-clinical sample. Specifically, the group effect of inattention is based on very small subgroups (N = 6 and 7) and clearly replication with larger groups is necessary before sound conclusions can be made. Future studies should employ a larger sample and also clinical cases.

Furthermore, although the network of S3 oscillations identified in this chapter might be consistent with the DMN, Debener et al. (2005) report that the relationship between fMRI and EEG is complicated and not well understood and so comparisons between such electrophysiological correlates and the BOLD signal should not be made without direct testing. Including a wider and more even distribution of electrodes will allow other methods of data analysis to be performed, such as distributed source modelling and dipole source seeding. This will address the question as to whether the pattern of low-frequency scalp-EEG activation is associated with the brain regions involved in the DMN (identified by fMRI). Additionally, these EEG signals should be coregistered with methods that offer better structural specificity such as fMRI or MEG (Debener, Ullsperger, Siegel, & Engel, 2006).

A further limitation of the present study is that it has focussed only on very slow, sub-delta, frequencies. This was designed to act in accordance with previous research, which has shown that the DMN is characterised by very low frequency oscillations. However, it is possible that higher neuronal oscillations are also involved in the resting network. For example, Chen et. al., (2008) propose that an EEG DMN can be described in terms of higher frequencies, which comprises of delta frequencies distributed across the prefrontal area, theta (4-7Hz) over the frontal-central area and alpha (7.5-12 Hz) distributed bilaterally over the posterior areas. It may be important for future research to investigate resting EEG across the whole frequency spectrum, so that the role of both sub-delta and super-delta frequencies in the DMN is elucidated.

4.4.4 Problems associated with data collection and analysis

Furthermore, a number of problems are associated with data collection and analysis of this type. One of the main issues is that the EEG signal is very ‘noisy’ and contains numerous artifacts, such as ocular and movement artifacts as well as hardware induced artifacts, such as malfunctioning electrode channels, in addition to the brain signals. DC-EEG recordings also tend to experience substantial ‘drift’. Removing these artifacts is necessary

prior to data analysis. In the present study, ICA was used to identify, and then remove artifacts from the brain signal. However ICA is very time consuming (as well requiring a long computational time) as each of the extracted components must be visually inspected to determine whether they are likely to be artifactual. In the present study, ICA extracted up to 15 components for each participant, while they were performing each condition, for each of the test and the re-test conditions. As 24 participants were involved in the study, 21 of whom returned for the re-test session, and data from three of the conditions were analysed, this meant that over 2000 components needed to be inspected and compared to the data recorded from the specific participant's EOG channels. This was obviously a lengthy and computationally demanding process.

A further issue relates to the vast quantity of data available for analysis in the present study. Recordings were made for each participant in both the test and the re-test sessions from 27 scalp electrode channels, throughout each of 4 conditions (although only two were analysed in their entirety – see section *5.2.4.1 Problems with the data collected by the tracking task* and section *5.2.6.6 Problems with the analysis of the data obtained during the rest with eyes closed assessment*). After artifact removal, FFT analysis was performed on each of these data recordings and the power in each of five frequency bands was calculated. From only the two conditions described in this chapter, this resulted in over 240 variables for each participant: determining appropriate methods of data reduction that made this dataset more manageable but did not lose any of the quality of the data was crucial to the data interpretation process. By determining a network of S3 power, data were reduced to 10 key variables per participant, for a particular testing session and for a particular condition – the power in each of the five frequency bands within this S3 network and outside of it. This made the dataset much more manageable and reduced the need for multiple comparisons, which would increase the likelihood of Type I errors.

4.5 Conclusions

In the present study, DC-EEG was able to identify very slow frequency oscillations and a network of these slow 3 oscillations at rest was identified and found to be stable over time. Furthermore, power in the S3 network differentiated an inattentive high ADHD subgroup at rest. During goal-directed task performance, S3 power was generally attenuated and more widely dispersed across the scalp than at rest. However, inattentive participants did not show the same attenuation of resting S3 power within the S3 network as other participants when they engaged in a goal-directed task.

Chapter 5 The associations between intra-individual variability in task performance, symptoms of ADHD and low frequency EEG

5.1 Introduction

Patients with ADHD have consistently been shown to be more variable than controls in the speed of their reaction time (RT) responses on neuropsychological tasks. It has been argued that this variability is caused by occasional attentional lapses (Sonuga-Barke & Castellanos, 2007). Some recent research has attempted to establish the temporal structure and frequency of these attention lapses using signal processing techniques on time-series RT data. For example, Castellanos et al. (2005) reported that the time-series RT data obtained from controls' and ADHD patients' performance on a Flanker task oscillated at a specific frequency, .05 Hz (representing a cycle every 20 seconds), and that the power of this oscillation was significantly higher in the ADHD group than in the control group. A further study by the same group replicated this finding, and again showed that patients with ADHD exhibited greater power in RT fluctuations at this frequency than controls, and further extended this by showing that power in this frequency band predicted the diagnosis of ADHD above and beyond the normal measure of variability - SD of RT (Di Martino et al., 2008).

The default-mode interference hypothesis, introduced by Sonuga-Barke & Castellanos (2007), proposes that these periodic attention lapses are created by intrusions of brain activity that is normally characteristic of rest, into goal-directed tasks. Thus, these attention lapses should occur periodically and at low frequencies (specifically the slow 3 frequency band, S3, .06-.2 Hz). Moreover, there should be synchrony between the fluctuations in the default mode EEG oscillations and the declines in performance.

5.1.1 Study Aims

This chapter had two main aims. First it aimed to determine the associations between intra-individual variability in task performance and symptoms of ADHD. Specifically it aimed: i) to determine the test-retest reliability of measures of variability over a one week test-retest period; ii) to establish the associations between standard measures of variability (such as SD of RT and normalised variability), errors, and symptoms of ADHD; iii) to decompose intra-individual variability into its constituent power components using FFT analysis and to establish the associations between these frequency domain measures of variability and ADHD, and also to determine whether these frequency domain measures of variability are able to improve the prediction of group membership (high-ADHD or low-ADHD) beyond the global measures of variability; and iv) to establish changes in intra-individual variability over time.

Secondly it aimed to determine the association between oscillations in behavioural data and low frequency brain activity. Specifically it aimed to i) assess whether there is temporal synchrony between low frequency EEG and low frequency fluctuations in RT data; and ii) to determine whether temporal synchrony of low frequency RT and EEG is greater in participants who do not attenuate low frequency EEG from rest to a goal-directed task or in participants with high ratings of ADHD. For these analyses, the synchrony of the EEG and RT signals was specifically focussed on the S3 frequency band, as power in this frequency band has previously been identified as associated with ADHD in RT signals (e.g. Castellanos et al., 2005; Di Martino et al., 2008) and our previous research suggested that inattentive participants do not attenuate power in the S3 EEG frequency band to the same extent as other participants. This chapter further aimed to iii) establish whether the degree of attenuation from rest to task is associated with task performance.

5.1.2 Predictions

1) The associations between intra-individual variability and symptoms of ADHD

It was predicted that:

- The task measures should be stable over a one week test-retest period, suggesting that they are tapping a stable aspect of task performance.
- Both global measures of variability and frequency domain measures of variability as well as the number of errors would be associated with symptoms of ADHD, and participants who reported more ADHD symptoms would make more errors and also be more variable.
- Consistent with Di Martino et al. (2008), frequency domain measures of variability should contribute above and beyond the global measures of variability in the prediction of group membership (high-ADHD symptoms vs. low-ADHD symptoms). The RT frequency band that would show the greatest improvement to the prediction of group membership should be S3, as this band is most closely related to the frequencies of the DMN, which Sonuga-Barke & Castellanos (2007) suggest might intrude into goal-directed task activity and create lapses in attention.
- Variability should change as a function of time on task and as time on task increases, state factors such as boredom or fatigue would cause increased variability. This should be evident in frequency domain measures of variability as well as global measures of variability such as SD of RT. This is consistent with Johnson et al. (2007), who demonstrated that an impaired group of children with ADHD (defined as impaired by the number of commission errors they made on a sustained attention task), became slower and more variable on both global measures of variability and low frequency measures of variability but did not make more errors over the course of a 5.5 minute task.

2) The temporal synchrony of behavioural and EEG oscillations

As the default-mode interference hypothesis predicts that people who do not effectively attenuate their low frequency resting EEG oscillations are likely to experience intrusion of these low frequency oscillations onto attention in goal-directed tasks, it was predicted that:

- In general there would be a significant degree of synchronization between very low frequency oscillations (VLFOs) in EEG and RT data, as RT fluctuations may be constrained by underlying neural EEG VLFOs. However, as the scalp EEG is a complex signal, which is influenced by multiple cortical sources, and the RT time series data is an imperfect measure of attention, the overall level of synchrony between these two signals would be low.
- The synchrony between the S3 EEG and the S3 RT signals should be associated with the degree of attenuation of the S3 EEG signal from rest to goal-directed task as participants who do not effectively attenuate their very low frequency EEG should experience intrusion of this into their goal-directed task performance. Thus, participants who do not attenuate low frequency EEG from rest to task should experience a greater degree of synchrony between S3 EEG and S3 RT signals than those who do effectively attenuate S3 EEG from rest to task.
- Similarly, as the default-mode interference hypothesis has been proposed as a causal mechanism for ADHD, participants with high-ADHD symptoms should also experience greater synchrony between S3 EEG and S3 RT than participants with low-ADHD symptoms.
- The degree of attenuation from rest to task should be associated with measures of task performance, so that people who do not attenuate this low frequency EEG from rest to task will perform more poorly on the task than those who do attenuate. This is because the default-mode interference hypothesis suggests that people who do not effectively attenuate their low frequency EEG from rest to task may experience impaired performance.

5.2 Methods

5.2.1 Participants

As in 4.2.1 Participants

5.2.2 Design

As in 4.2.2 Design

5.2.3 Procedure

As in 4.2.3 Procedure

5.2.4 Assessments

Two tasks were designed specifically for the purpose of this study: they were both designed to obtain time-series data of participants' responses and to allow decomposition of this into power in different bands within the frequency domain. These tasks are described in *4.2.4.2 Assessments during goal-directed task performance* – briefly, they were i) a two choice response RT attention task (2-CR RT task) that required participants to respond by

indicating the direction of an arrow presented on the computer screen (right or left) and ii) a visual tracking task that required participants to keep a central marker as close as possible to the centre of a track by pressing the right and left arrow keys on a computer keyboard.

As the maximum frequency that can be identified in the data is dependent upon the sampling frequency of the data (the inter-stimulus interval in RT tasks), more frequent sampling allows a larger proportion of the frequency domain, i.e. higher frequencies, to be investigated. The RT task in the present study was designed to sample frequently; each trial lasted one second (stimulus presentation time 400ms, inter-stimulus interval 600ms): this allowed frequencies up to .5Hz to be examined in the RT data. Furthermore, both tasks were designed to have a long duration and were 10 minutes long. It is important for data intended for frequency domain analyses to be of a long duration, as shorter task durations may prevent very slow frequency oscillations from being identified (see *1.4.1 Capturing Temporal Patterns in Behavioural Data*). A 10 minute task would allow 30 cycles of .05Hz, which should be sufficient to allow for short-term variations in these cycles.

However, the RT task allowed participants to make incorrect and missing responses, which is not ideal for a task that is used to identify temporal patterns in behavioural data, as dealing with these missing or incorrect responses can lead to bias in the data. Therefore the second task, the tracking task was designed to eliminate this problem. In this task, participants were instructed to keep a central marker as close as possible to white lines on the centre of the track by pressing the right and left arrow keys. A continuous measure of deviation from this central line was taken as a measure of the participants' sustained attention. This outcome measure ensured that participants were unable to make incorrect or missing responses, and avoids any issues of bias that may arise when dealing with this.

Furthermore, when analyses such as FFTs are performed on time series data it is normally necessary to use an anti-alias filter as the data are sampled – this is a low pass filter that prevents high frequency components from contaminating low-frequency components of the signal. However, using an anti-alias filter is not possible when looking at behavioural RT data, as the time series of this data has already been sampled; and so it is not possible to automatically impose an anti-alias filter onto it. The tracking task was designed to anti-alias the data before FFTs were performed: the data were collected at a very high sampling rate and an anti-alias filter was performed on these data as they were later down-sampled in software (MATLAB version 7.0.1). Down-sampling in software, unlike manual down-sampling, applies an anti-alias filter to the data, which makes it suitable for FFT analyses. Therefore, in the present study, the data were initially sampled at a rate of 512 samples per second and these were then down-sampled to 28. This down-sampled rate was still substantially higher than is possible in RT data and thus, this task was able to produce a much larger frequency interval range – up to 14Hz – and allowed much higher frequencies to be examined than has been possible in RT data. However, the data collected by this task proved to be unusable (see following section).

5.2.4.1 *Problems with the data collected by the tracking task*

Throughout the task, a track, which comprised of a number of successive straight track segments subtended at an angle of between 165 and 195 degrees, and a triangular, central marker were presented on the computer screen (see Figure 5.1). Deviation from this central line was frequently recorded (512 Hz) throughout the task. A number of versions of this task were designed, and each contained errors in the programming code that prevented the data from being used.

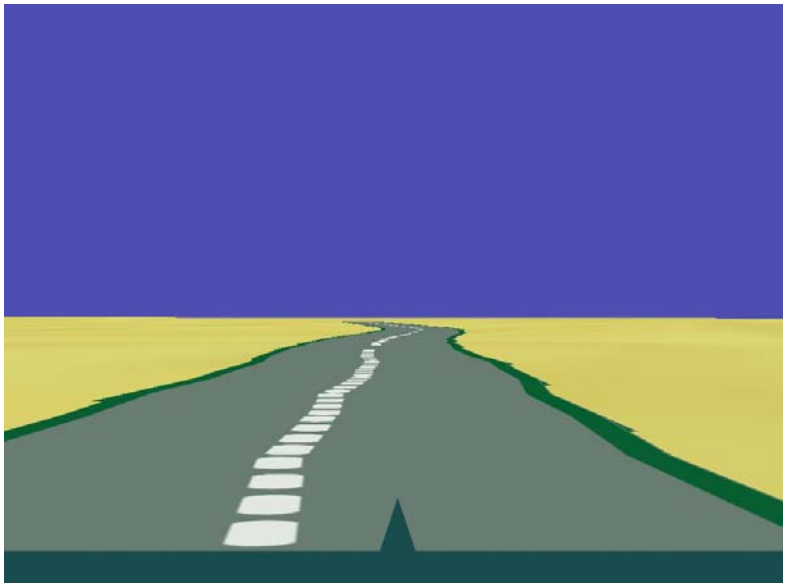

Figure 5.1: The track, which comprises of successive straight track segments and white lines indicating the centre of the track and a triangular centre marker.

An example of the data obtained from the version of the task used in the present study is shown in Figure 5.2. An inverse 'saw tooth' pattern is clearly evident in the data, this pattern was also evident in the tracking data obtained from all other participants.

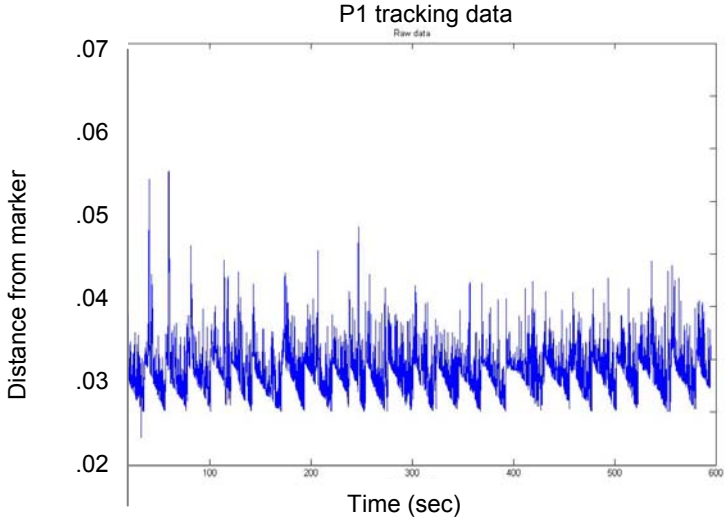

Figure 5.2: An example of the raw data obtained from the tracking task, a 'saw tooth' artifact is evident.

This saw tooth pattern represents a linearly decreasing error which is periodically zeroed. This pattern is an artifact; it would not be created by participants' behavioural responses. Investigation of the task data showed that this error was associated with the segment changes in the track, which occurred each second and the linear decrease was associated with the code that recorded the 'camera change' as each segment of the track changed. This artifact could not be removed from the data using filters in software.

In order to overcome this problem for future versions of the task, the straight track segments were subdivided into sub-segments and each of these sub-segments was curved, this prevented any abrupt change between segments, which would cause the participants to make a periodic error and introduce an artifact into the data. The computer code for recording the camera angle of the task was also adjusted to remove the error associated with this. However as the data recorded for the present study were unusable, data from this task was dropped from further analysis.

5.2.5 Data Analysis

As the data from the tracking task were unusable, data were only analysed from the 2-CR RT task. Data obtained from this task included the RT for each of the 600 trials as well as the number of omission errors (missing responses) and directional errors made by each participant (in which the participant incorrectly indicated the direction of the arrow).

5.2.5.1 *Time Domain*

Impossible responses (<100ms) for each participant were removed. Then the number of omission errors and directional errors for each participant was calculated. Following Di Martino et al. (2008), participants who made >15% omission errors were excluded from further analysis, as they were not considered to be sufficiently engaged in the task. One participant with a 19% omission rate (116 omissions from 600 trials) was excluded on this basis. This participant was in the high-ADHD symptom group.

The mean RT and the SD of RT across all correct responses as well as across all incorrect responses was then calculated for each participant. Paired t-tests showed that mean RT was slower across correct responses (M = 345 ms, SD = 33.8ms) than across incorrect responses (M = 339ms, SD = 33.8ms) ($t(43) = 7.79$, $p<.001$) and that SD of RT was less variable across correct responses (M = 70.5 ms, SD = 23.5ms) than across incorrect responses (M = 73.4 ms, SD = 24.8ms) ($t(43) = 7.11$, $p<.001$). As response type (correct or incorrect) impacted on the RT and SD of RT, general measures of mean RT and SD of RT were calculated from only the correct responses. Furthermore, as mean RT and SD of RT were found to be highly correlated ($r(43) = .684$, $p<.001$), and Salthouse (1993) reports that slower RTs are often associated with increased variability, simply because they are not constrained by the same ceiling effects as the faster RTs, a measure of normalised variance was also calculated (SD of RT / mean RT). This measure corrects for the effect of mean RT on SD of RT.

5.2.5.2 *Frequency Domain*

In order to remove the potential confound of response type (correct or incorrect) from the time series data, errors were regressed out of the RT data. For each participant, a linear regression was performed – RT was entered as the dependent variable and response (correct or incorrect) was entered as the independent variable – the unstandardised residuals were saved from this regression. These regression residuals represent the portion of each RT score that is independent of response type (see Di Martino et al., 2008). The time series of these residuals were then used in frequency domain analyses. In order to make the time series data suitable for frequency analyses, missing responses were interpolated using a linear interpolation (SPSS version 15). As there were no practice trials in the task, the first two responses made by each participant were excluded, i.e. the time series of 598 rather than 600 RTs was analysed. FFT analyses were then performed on these data (see section *4.2.7.1 Fourier Transformation*) using 60 point Hamming windows that overlapped by 10 samples. This window size was deemed appropriate as it was sufficiently large to encompass the lowest frequency of interest in the study (.02 Hz – which corresponds to a cycle of 50 seconds). The power in each of S4 (.02-.06 Hz), S3 (.06-.2Hz) and S2 (.2-.5Hz) RT frequency bands was then calculated as area under the FFT curve for each participant.

In order to examine the effect of time on task, the time series data was divided into 2 segments (1st half segment 298 seconds; 2nd half segment 300 seconds) and the same FFT analyses were performed on each of these individually, so that for each segment, RT power in each of the three frequency bands was calculated. Furthermore, for each of these time segments, the SD of RT (for correct only responses), and number of errors was calculated.

5.2.5.3 *Temporal synchrony of behavioural and EEG oscillations*

We created an index of the temporal S3 synchrony between the brain (EEG) and behavioural data by performing cross-correlations between each participant's RT time series and their EEG signal while they were performing this RT task. This index represented the 'similarity' between the EEG and RT signal for each participant. Cross-correlation, which is equivalent to statistical co-variance, determines the similarity of two signals: it can be used for pattern recognition, as it essentially looks for one time-series pattern that might be reflected in another. As these patterns might be shifted in time, cross-correlations can be performed at different time lags (shifts along the x axis) (Wijewerdena-Gamalath, 2004). The present study assumed that the brain and behavioural activity would be tightly synchronised temporally as the conduction of signals in both the brain and central nervous system is very fast (typically > 70m/second), however there may be some small lag between brain and behavioural activity due to measurement error and electrode capacitance, therefore, the peak cross-correlation between +/- 1 second (i.e. +/- 10 lags) between each channel of EEG data within the S3 network (N = 27) and the RT time series data was calculated for each participant.

The EEG data were prepared as described in section *4.2.6 EEG Data Processing* and the RT time series was prepared as described in the previous section. Further to this, the

EEG signal was truncated so that its length exactly corresponded to the length of the RT time series signal (for each participant) and both the EEG and the RT time series were band-pass filtered to leave only the S3 frequency component of the signal (.06-.2Hz). As the cross-correlation analysis may be affected by the amplitude of the signals, i.e. a high amplitude EEG signal may artifactually increase the value of the cross-correlation coefficient, prior to the cross-correlation, each channel of EEG data and the RT time series for each participant was normalised (i.e. the mean was subtracted from the signal and it was divided by the standard deviation of the signal). This ensured that for each participant the cross-correlation was calculated for signals that were independent of amplitude (as all signals had a mean of 0 and a SD of 1); this meant that the cross-correlation measure assessed the similarity of the signals' shape rather than the signals' amplitude.

As the EEG signal and the RT time series had different sampling rates (the EEG was sampled at 10Hz and the RT time series was sampled at 1Hz), and cross-correlation analysis requires both signals to have the same sampling rate, the RT time series was interpolated using the 'interp' function in Matlab (version 7.0.1) to increase its sampling rate to 10Hz. Separately, the EEG sampling rate was also down-sampled to 1Hz using the 'decimate' function in Matlab (version 7.0.1) and the same cross-correlation analyses were run on both of these data. The cross-correlations from these two methods of adjusting the sampling rate of the signals – up-sampling the RT time series and down-sampling the EEG - were then compared. Very similar patterns and values of cross-correlation were identified from the two methods (see Appendix A7). Therefore, although either method would have been suitable for the cross-correlation analysis, only the up-sampled RT time series was used in subsequent cross-correlation analyses.

An example of the EEG and RT time series signals for a single participant at one electrode site (Cp3) is shown in Figure 5.3, for visual clarity a segment of the two signals that shows weak cross-correlation between the signals is highlighted (bottom left) and a section that shows strong cross correlation between the two signals is highlighted (bottom right).

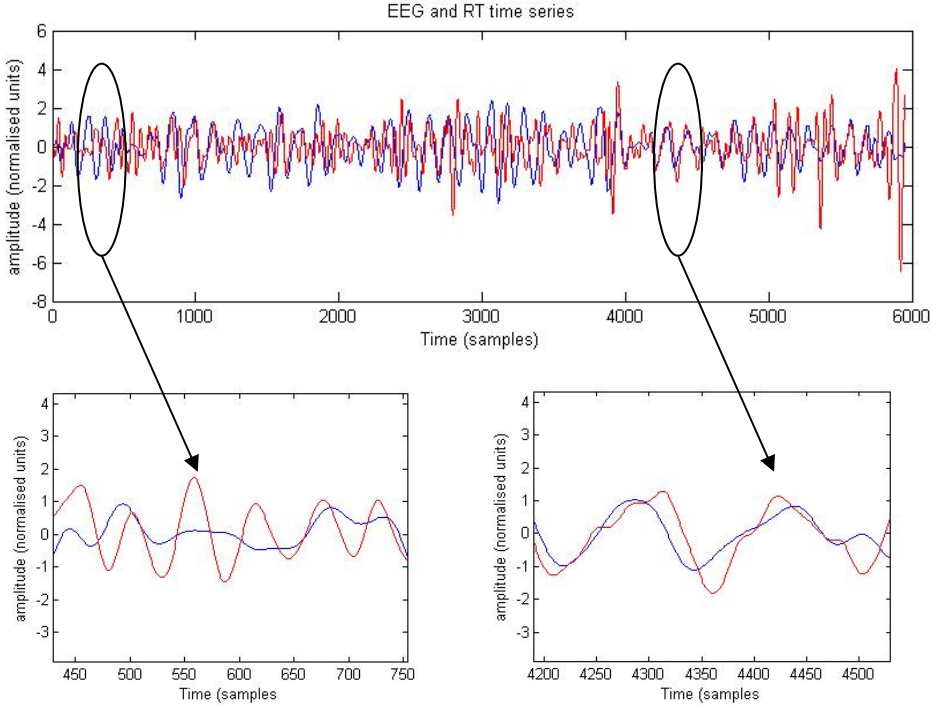

Figure 5.3: Filtered Cp3 EEG signal (blue) and RT time series (red) for participant 23 (above) - sections of weak (left) and strong cross-correlation (right) are highlighted for visual clarity (below).

The cross correlation between these two signals was then calculated using the '*xcorr'* function in Matlab (version 7.0.1) for 200 lags (up to a 20 second shift in time). Figure 5.4 illustrates the cross-correlation between the EEG and the RT time series signals shown in Figure 5.3. As is evident from Figure 5.4, the cross correlation between the two signals varies as a function of the lags, however in this example a cross-correlation peak of about .16 is observed at 0 lags (i.e. when the two signals have not been shifted in time).

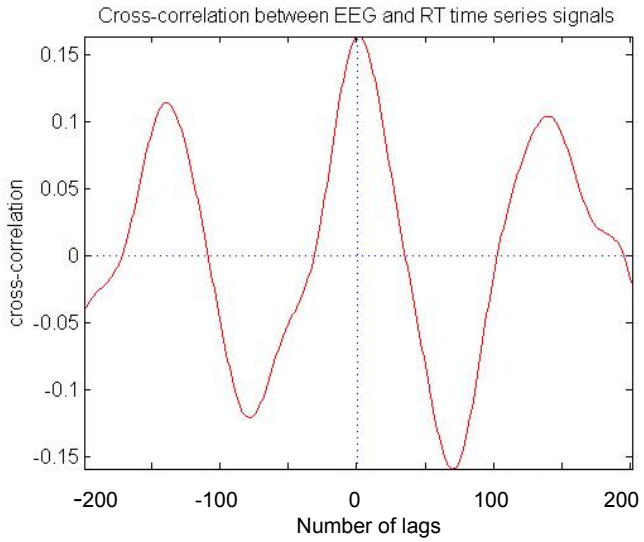

Figure 5.4: The cross-correlations between the EEG and RT time series signals: the number of lags is shown on the x axis and the strength of the cross correlation is shown on the y axis.

The peak cross-correlation between each channel of EEG data (N= 27) and the RT time series data between +/- 10 lags (+/- 1 second) was calculated for each participant. This is illustrated in Figure 5.5: for one participant, a single channel of EEG data (Cp3) is shown in blue and the RT time series is shown in red (for clarity only a small section of the entire signal is shown). The RT time series is also shown shifted forwards in time by 1 second (10 lags) by the dashed red line, and shifted backwards in time by 1 second (10 lags) by the dotted red line. The peak cross-correlation of the EEG and the RT signals between these two different lags was calculated between each channel of EEG data (N= 27) and the RT time series data for each participant.

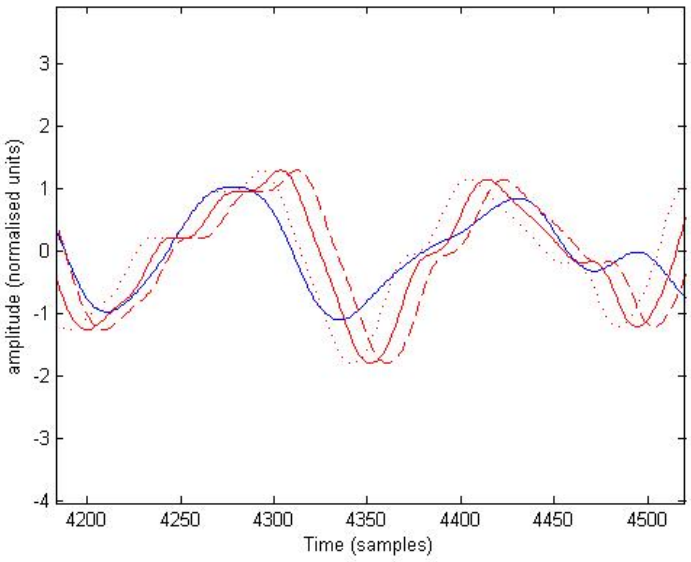

Figure 5.5: EEG signal (blue) and RT time series (red) for participant 23, RT time series is also shown at +1 sec (dashed) and -1 sec (dotted) lags.

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Subsequently, the mean peak cross-correlation across all of the electrodes within the S3 network (as defined in *4.3.1.1 Identification of a network of resting slow 3 power*) was calculated to obtain an index of S3 RT-EEG synchrony for each participant within the S3 network; and the mean cross-correlation across all of the electrodes outside of the S3 network was calculated to obtain an index of S3 RT-EEG synchrony for each participant outside of the S3 network.

In order to ensure that this analysis, i.e. filtering both signals to leave only the narrow S3 frequency band, did not artifactually induce some degree of synchrony between the two signals, we investigated whether uncorrelated simulated signals would show synchrony after both signals were filtered to leave only the S3 component. Cross-correlations between pairs of filtered white noise signals were not found to differ significantly from zero, so it seems unlikely that this analysis would artifactually induce synchrony, and thus, it was deemed an appropriate measure to employ in our present study (see Appendix A8).

5.2.5.4 *Normality of Data Distribution*

The normality of the distribution of data for each variable was assessed across all cases (test and retest) using the Kolmogorov-Smimov test of normality (K-S). Neither the number of omission errors nor power in the S4, S3 or S2 RT frequency bands were normally distributed (K-S(42) = .180, p = .002; K-S(42) = .239, p < .001; K-S(42) = .153, p = .014; K-S(42) = .176, p = .002, respectively). Natural log transformations of the power in the S4, S3 and S2 RT frequency bands normalised their distribution (K-S(42) = .118, p = .158 *ns* ; K-S(42) = .094, p = .200 *ns* ; K-S(42) = .119, p = .114 *ns* respectively). A natural log transformation did not normalise the distribution of omission errors (K-S(42) = .191, p = .001: as omission errors contained some zero values, the natural log transformation was performed on *50 – number of omission errors* for each participant), however, a square root transformation was able to obtain normality of the distribution (K-S(42) = .134, p = .051, *ns*). Subsequent analyses using these variables were performed on these transformed data.

5.2.5.5 *Statistical Analyses*

Associations between measures of variability, errors and symptoms of ADHD

Associations between measures of variability, errors and symptoms of ADHD were assessed using correlations (Pearson's r) between the number of omission errors, the number of directional errors and the total number of errors (the sum of these two), global measures of variability – SD of RT and normalised variability – as well as more specific frequency measures – power in the S4, S3 and S2 RT frequency bands – and symptoms of ADHD. For each of these measures, data were available for 23 participants (24 participants with one exclusion >15% omission errors), and retest data were available for 20 participants. Therefore, group comparisons were made on T1 data (N = 23) - due to participant attrition

there was insufficient power to perform these analyses at T2. Test-retest correlations were performed where retest data were available (N = 20).

Predicting group membership

The contribution of power in each RT frequency band to predicting group membership (*high-ADHD* or *low-ADHD*) was assessed using binary logistical regression with group as the dependent variable. The contribution of power in each frequency band beyond the model that contained either SD of RT or normalised variance was expressed by the number of cases correctly classified and the χ^2 change to the model by each step.

Changes in intra-individual variability over time

In order to examine the effect of time on task, the number of errors made, the SD of RT, normalised variance and power in each of the three RT frequency bands (S4, S3 and S2) in each task segment (1st half, 2nd half) was individually compared using repeated measures ANOVAs. In each of these, the error or variability measure over time was entered as the within subjects factor. In order to assess differences in performance between groups these analyses were run with group characterised by ADHD symptoms (i.e. high ADHD symptom group vs. low ADHD symptom group) entered as the between subjects factor. Group x segment interactions were also examined. In order to assess whether the associations between these variables changed across the task, correlations (Pearson's r) between the task measures, intra-individual variability and ADHD ratings were performed separately for the first segment of the task and the second segment of the task.

Associations between low frequency EEG and low frequency fluctuations in RT data, and the association between rest-task attenuation and task performance

The degree of synchronisation between the S3 RT and S3 EEG signals was determined using a one sampled t-test to assess whether S3 RT-EEG synchrony differed from 0. The S3 RT-EEG synchrony of participants who attenuated their S3 EEG power from rest to goal-directed task (S3 rest-task attenuators) (N = 12) was compared to the S3 RT-EEG synchrony of participants who did not attenuate their S3 EEG power from rest to goal-directed task (S3 rest-task non-attenuators) (N = 8). Correlations between rest-task attenuation, task performance and ADHD symptoms were performed (Pearson's r). T1 data were available for 20 participants (EEG data were available for 21 participants, but one of these participants was excluded from the analyses of the behavioural data as they made >15% omission errors), therefore these correlations were performed with N = 20.

5.3 Results

5.3.1 Test-Retest reliability of task variables

The test-retest reliability for each of the task variables was assessed by a Pearson's r correlation between the scores at T1 and at T2. However, visual inspection of scatter plots of these data showed that for each of the directional and omission errors a single participant appeared to be an outlier and to have an atypical pattern of response (e.g. they made 131 errors at T1 but only 24 errors at T2). Therefore the outlier participant was removed from the

analysis of the test-retest correlations (N = 19); these correlations are shown in Table 5.1. All of these three error measures showed good test-retest reliability, $r > .4$. The global measures of variance - SD of RT and normalised variance - showed only small and statistically insignificant correlations between T1 and T2. However, the frequency domain measures of variability showed much stronger correlations between T1 and T2 and these reached statistical significance. Notably, the test-retest correlation between S3 RT power at T1 and at T2 was the strongest of all the variables and was substantially higher than the test-retest reliability of SD of RT.

Table 5.1

Test-retest reliability of task variables, Pearson's r (N=19)

Variable	Pearson's r	*p*
Number of omission errors[a]	.422	.072†
Number of directional errors	.627	.004**
Total number of errors	.609	.006**
Mean RT	.249	.289
SD of RT	.169	.488
Normalised variance	.182	.456
S4 RT power	.422	.072†
S3 RT power	.708	<.001**
S2 RT power	.584	.009**

**, $p<.01$, *$p<.05$, †$p<.1$

Note. a) When split into T1 and T2 data, the number of omission errors at T2 was no longer normally distributed - even after a square root transformation- therefore, for this variable, the non-parametric test, Spearman's Rho, rather than the parametric Pearson's r test was used and reported.

5.3.2 The associations between intra-individual variability and symptoms of ADHD

5.3.2.1 *Periodic variability within the RT time series data*

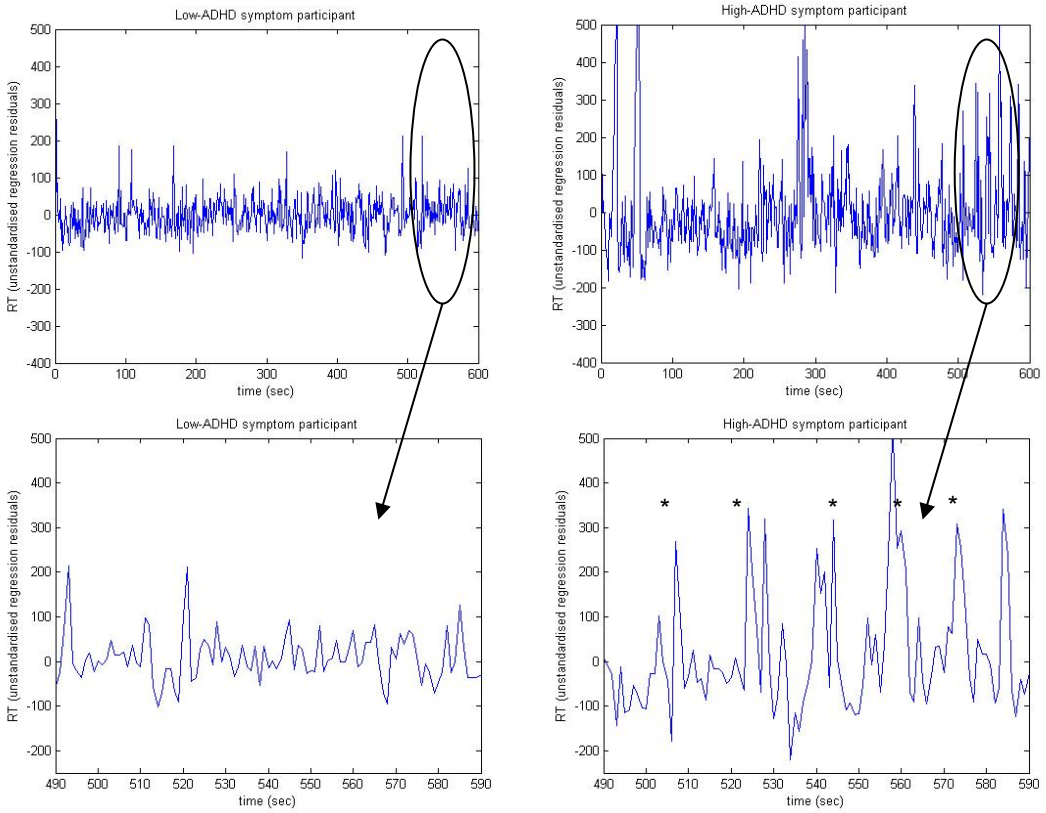


Figure 5.6: RT time series for a low-ADHD (left) and a high-ADHD symptom participant (right), throughout the entire task (above) and for a 100 sec section of the task (below).

Examples of the variability exhibited by two participants, a low-ADHD and by a high-ADHD symptom participant are shown in Figure 5.6. These examples are shown for the entire task (above) and, for visual clarity, for a smaller (100 sec) section of the task (below). As is evident from this figure, intra-individual differences in the amount of variability were apparent across participants. In the example shown above, the high-ADHD participant exhibited greater variability in their RTs across the task than the low-ADHD participant. Furthermore, this variability appeared to exhibit some degree of periodicity, particularly in the high-ADHD symptom participant; as is shown in the lower part of the figure, the high-ADHD symptom participant made slower responses at fairly regular intervals (specifically at approximately 505, 525, 540, 560 and 575 seconds – shown by *). This periodic variability would correspond to cycles of about .07 Hz – within the S3 frequency band. RT time series for all other low-ADHD symptom participants as well as all other high-ADHD symptom participants are shown in Appendix A9.

5.3.2.2 *Associations between time domain measures of variability, frequency domain measures of variability, errors and ADHD symptoms*

Correlations between the different task measures and symptoms of ADHD at T1 are shown in Table 5.2. The number of omission errors and number of directional errors made throughout the task were positively correlated – and participants who made more omission errors were also more likely to make more directional errors, although this did not reach statistical significance. Participants who made more omission errors were also more variable in their RTs: the number of omission errors was highly positively correlated with both SD of RT and normalised variance. However the correlation between the number of directional errors and RT variability, although positive, was less strong than the correlation between the number of omission errors and RT variability, for either SD of RT or for normalised variance. Mean RT was significantly negatively correlated with total number of errors, indicating a speed accuracy trade-off as participants who made slower responses made fewer errors – although this only applied to the number of directional errors and not the number of omission errors.

ADHD scores were positively correlated with the number of errors made, which indicates that participants with higher ADHD scores made more errors than those with lower ADHD scores; this applied to both the number of omission errors and the number of directional errors. No statistically significant correlations emerged between ADHD scores (total ADHD score as well as inattention and hyperactivity) and either mean RT or measures of variability. However, non-significant trends emerged showing that ADHD symptoms were negatively correlated with mean RT ($r(23) \approx -.2$) but positively correlated with measures of variability (SD of RT $r(23) \approx .2$; normalised variance $r(23) \approx .3$); so that participants with higher ADHD scores were faster and more variable than those with lower ADHD scores.

Although they were very strongly positively correlated with each other ($r(23) = .953$), normalised variance was more strongly positively correlated with all ADHD scores than SD of RT was, however none of these correlations reached statistical significance. Similarly, normalised variance was more strongly positively correlated with all of the error measures (omission errors, directional errors, and total errors) than SD of RT was. Power in all RT frequency bands (S4, S3 and S2) was significantly correlated with global measures of variability - both SD of RT and normalised variance. Power was also highly positively correlated between all the RT frequency bands. Furthermore, power in all three RT frequency bands was significantly correlated with the number of omission errors. However, neither the number of directional errors nor the total number of errors was associated with power in any of these RT frequency bands. Although the global measures of variability - SD of RT and normalised variance - were positively, although not significantly, correlated with ADHD scores (total ADHD score, inattention or hyperactivity), none of the frequency domain RT measures – i.e. RT power in S4, S3 or S2 bands – showed any correlation with the ADHD scores ($r < .1$).

Table 5.2

Correlations between different task measures and ADHD symptoms (N = 23)

	2	3	4	5	6	7	8	9	10	11	12
Error Measures											
1. Omission errors	.365†	.512*	.109	.507*	.589**	.500*	.522*	.456*	.369†	.504*	.456*
2. Directional errors	--	.981**	-.534**	.071	.307	.055	-.031	-.087	.444*	.515*	.503*
3. Total Errors		--	-.458*	.182	.416*	.161	.084	.025	.484*	.574**	.555**
Variability Measures											
4. Mean RT			--	.691**	.444*	.609**	.721**	.744**	-.187	-.216	-.211
5. SD of RT				--	.953**	.914**	.959**	.942**	.128	.243	.191
6. Normalised Variance					--	.881**	.891**	.866**	.246	.402†	.336
7 S4 RT power						--	.930**	.874**	.041	.080	.062
8 S3 RT power							--	.950**	-.031	.088	.025
9 S2 RT power								--	.072	.191	.134
ADHD symptoms											
10 Inattention									--	.790**	.955**
11 Hyperactivity										--	.937**
12 ADHD score											--

** p<.01, *p <.05, $^{\dagger}p$<.1

5.3.2.3 *Predicting group membership*

The contribution of power in each of the S4, S3 and S2 RT frequency bands, in predicting group membership, above and beyond either SD of RT or normalised variance on the 2-CR RT task is shown in Table 5.3. It is clear from this table that the initial models that contained the global measures of variability were not very accurate in classifying the cases into the correct groups, these initial models were only able to correctly classify about half of the cases and neither model was statistically significant. In both models, the addition of power in any of the RT frequency bands improved the model i.e. increased the percentage of cases correctly classified. Furthermore, for both SD of RT and normalised variance, the addition of S3 RT power into the regression model made the most significant contribution to the model, and increased correct classification to 87% in the model containing SD of RT and to about 74% in the model containing SD of RT.

Table 5.3

Contributions of S4, S3 and S2 RT power to classification of group (high-ADHD or low-ADHD), above SD of RT or normalised variance on the 2-CR RT task

Model	Added variable	% correctly classified	χ^2 model	*p*	χ^2 step	*p*
SD of RT		47.8	.071	.790		
SD of RT +	S4 RT power	60.9	2.85	.241	2.77	.096†
SD of RT +	S3 RT power	87.0	6.24	.044*	6.17	.013*
SD of RT +	S2 RT power	69.6	1.46	.481	1.39	.238
Normalised variance		52.2	.118	.731		
Normalised variance +	S4 RT power	69.6	7.39	.025*	7.28	.007**
Normalised variance +	S3 RT power	73.9	8.85	.012*	8.73	.003**
Normalised variance +	S2 RT power	65.2	4.06	.131	3.94	.047*

**p<.001, *p <.05, $^{\dagger}p$<.1

Changes in the number of errors made and intra-individual variability in each segment of the task

Repeated measures ANOVAs were run separately entering the number of errors and the variability measures during each of two segment (1st half, 2nd half) as the within subjects factor and group (high ADHD symptom group vs. low ADHD symptom group) as the between subjects factor, these are shown in Table 5.4.

Table 5.4

Group Differences on 2-choice RT task, in the first and second segment of the task

	First segment Mean (SD)		Second Segment Mean (SD)		*Main Effect (Segment)*		*Group Effect*		*M X G*	
	Low-ADHD	High-ADHD	Low-ADHD	High-ADHD	*F*	*p*	*F*	*p*	*F*	*p*
Omission errors[a]	.522 (.730)	2.30 (5.55)	1.26 (1.71)	2.10 (3.09)	1.98	.184	1.64	.214	.304	.587
Directional errors	15.7 (9.64)	29.3 (18.9)	17.9 (9.49)	32.5 (16.7)	1.57	.223	7.04	.015*	.055	.817
Mean RT (ms)	349 (36.0)	332 (26.6)	363 (37.3)	336 (22.2)	2.43	.127	3.34	.075†	.011	.917
SD of RT (ms)	66.0 (16.5)	63.2 (17.9)	69.3 (22.9)	67.0 (16.1)	5.24	.033*	.054	.818	.018	.896
Normalised variance	.187 (.036)	.190 (.048)	.193 (.049)	.198 (.040)	2.81	.109	.217	.646	.023	.880
S4 RT power	9.37 (.640)	8.49 (.591)	9.14 (.723)	9.05 (.711)	.047	.830	.894	.355	.574	.457
S3 RT power	9.19 (.509)	8.92 (.456)	9.15 (.702)	8.97 (.544)	1.38	.253	.985	.332	.152	.701
S2 RT power	8.95 (.529)	8.78 (.402)	8.97 (.611)	8.88 (.514)	5.18	.033*	.695	.414	.318	.579

*p <.05, †p <.01

Note. [a] the mean number of omission errors for each group is shown in this table for illustrative purposes, however as this variable was not normally distributed, analyses were performed on the square root transformed data.

Main Effect = effect of segment, M X G = Segment by Group interaction

The only significant main effects to emerge were for SD of RT and S2 power, and participants exhibited greater variability on these measures in the second segment of the task than in the first segment. Participants were not found to make more errors in the second segment of the task compared to the first segment. The only statistically significant group effect to emerge was for the number of directional errors made and the high-ADHD symptom group made more directional errors than the low-ADHD symptom group. No group x segment interactions were identified for any of the variables.

5.3.2.4 *Associations between intra-individual variability, errors, and ADHD symptoms in each segment of the task*

The correlations (Pearson's r) between errors, intra-individual variability and ADHD ratings are shown for the first segment of the task in Table 5.5 and for the second segment of the task in Table 5.6. In both segments of the task, the measures of intra-individual variability (both global measures and frequency domain measures) were all highly positively inter-correlated. The correlation between omission errors and SD of RT was only positive and statistically significant in the second segment of the task. Similarly, power in the S4 and S3 RT frequency bands was positively correlated with the number of omission errors in both segments of the task, but this only reached statistical significance in the second segment of the task, power in the S2 RT frequency band showed a similar pattern but did not reach statistical significance. In contrast, normalised variance showed comparable sized positive correlations with the number of omission errors at each segment of the task. Both normalised variance and SD of RT were more highly correlated with directional errors in the second segment of the task than the first segment; however frequency domain measures of variability did not show much correlation with directional errors at either segment of the task.

All correlations between the number of errors made and ADHD scores were positive at both segments of the task. However, the correlations between the number of directional errors and ADHD scores (inattention, hyperactivity and total ADHD score), were stronger and reached statistical significance in the second segment of the task. The associations between measures of intra-individual variability (both global and frequency domain measures) and ADHD scores were broadly similar in each of the two segments of the task.

Table 5.5

Correlations between different task measures, intra-individual variability and ADHD ratings during the first segment of the task (N = 23)

	2	3	4	5	6	7	8	9	10	11
Error Measures										
1. Omission errors[a]	.444*	.498*	-.016	.152	.051	.134	.129	.091	.240	.155
2. Directional errors	--	.971**	-.060	.235	.047	-.036	-.259	.307	.398†	.369†
3. Total Errors		--	.086	.387†	.123	.088	-.148	.366†	.488*	.446*
Variability Measures										
4. SD of RT			--	.937**	.770**	.835**	.817**	.176	.269	.231
5. Normalised Variance				--	.732**	.788**	.693**	.287	.448*	.382†
6. S4 RT power					--	.844**	.712**	-.126	-.065	-.103
7. S3 RT power						--	.858**	-.078	.114	.011
8. S2 RT power							--	-.043	.047	-.002
ADHD Symptoms										
9 Inattention								--	.790**	.955**
10 Hyperactivity									--	.937**
11. ADHD score										-

** $p<.01$, * $p<.05$, † $p<.1$

Note. [a] When split into the two segments of the task, the number of omission errors was no longer normally distributed at either segment, therefore, for this variable, the non-parametric test, Spearman's Rho, rather than the parametric Pearson's r test was used and reported.

Table 5.6

Correlations between different task measures, intra-individual variability and ADHD ratings during the second segment of the task (N = 23)

	2	3	4	5	6	7	8	9	10	11
Error Measures										
1. Omission errors[a]	.213	.299	.441*	.495*	.526*	.462*	.335	.164	.186	.161
2. Directional errors	--	.988**	.243	.433*	.179	.028	.078	.563**	.618**	.622**
3. Total Errors		--	.320	.503*	.268	.109	.145	.591**	.645**	.651**
Variability Measures										
4. SD of RT			--	.961**	.817**	.873**	.858**	.087	.223	.158
5. Normalised Variance				--	.779**	.794**	.783**	.204	.352	.287
6. S4 RT power					--	.847**	.767**	.158	.151	.163
7. S3 RT power						--	.896**	-.030	.021	-.007
8. S2 RT power							--	.056	.193	.126
ADHD Symptoms										
9. Inattention								--	.790**	.955**
10.Hyperactivity									--	.937**
11.ADHD score										-

** $p<.01$, * $p<.05$, $^{\dagger}p<.1$

Note. [a] When split into the two segments of the task, the number of omission errors was no longer normally distributed at either segment, therefore, for this variable, the non-parametric test, Spearman's Rho, rather than the parametric Pearson's r test was used and reported.

5.3.2.5 *Summary*

The frequency domain measures of variability showed good test-retest reliability, particularly in the S3 RT frequency band, and these showed better test-retest reliability than the global measures of variability. ADHD scores were positively correlated with the number of errors but not with measures of variability (especially frequency domain measures, which typically exhibited correlations of $r < .1$ with ADHD symptoms). Power in the S3 RT frequency band was able to make the greatest improvement to the prediction of group membership, beyond SD of RT or normalised variance Participants tended to be more variable in the second segment of the task than in the first segment of the task, although the only frequency domain measure of variability to show this effect was S2 RT, and this did not differ between groups defined in terms of ADHD symptoms. The association between measures of variability and errors also changed over time, and both SD of RT and the frequency domain measures of variability were more strongly correlated with the number of omission errors at the second segment of the task, than in the first segment.

5.3.3 Temporal synchrony of behavioural and EEG oscillations

Across all participants, the mean S3 RT-EEG synchrony was small overall (M = .0501) but significantly different from zero ($t(19) = 4.27$, $p < .001$; 95% CI .0255 - .0747). Furthermore, *rest-task S3 non-attenuators* exhibited greater S3 RT-EEG synchrony (M = .0889) than *rest-task S3 attenuators* (M = .0234), and independent samples t-tests demonstrated that this difference in S3 RT-EEG synchrony was statistically significant both within ($t(18) = 3.34$, $p = .004$) and outside of the S3 network ($t(18) = 2.21$, $p = .041$). Similarly, high-ADHD participants were found to exhibit greater S3 RT-EEG synchrony (M = .0618) than low-ADHD participants (M = .0370), however, this did not reach statistical significance in independent samples t-tests either within ($t(18) = 1.17$, $p = .257$, *ns*) or outside of the S3 network ($t(18) = .934$, $p = .363$).

5.3.4 Associations between rest-task attenuation and task performance

Table 5.7 shows the correlations (Pearson's r) between the rest-task attenuation of EEG, performance on the 2-CR RT task and symptoms of ADHD. As expected, rest-task attenuation within the S3 network was significantly negatively correlated with ADHD symptoms, but not outside of the S3 network; and participants who self-reported the most ADHD symptoms exhibited the least attenuation of S3 EEG power within the S3 network when they engaged in the RT task compared to rest. Also as predicted rest-task attenuation was associated with task performance and greater attenuation was generally associated with better task performance, i.e. fewer errors and less variability, although this did not reach statistical significance for any of the variables.

Table 5.7

Correlations between rest-task attenuation, performance on the 2-CR RT task and ADHD symptoms

	2	3	4	5	6	7	8	9	10
Rest-task attenuation									
1. Rest-task attenuation within S3 network	.552**	-.235	-.150	-.100	-.079	-.264	-.591**	-.412†	-.537*
2. Rest-task attenuation outside S3 network	--	-.106	-.214	-.387†	-.324	-.213	-.102	-.129	-.151
Task Performance									
3. Omission errors		--	.356	.109	.507*	.589**	.369†	.504*	.456*
4. Directional errors			--	-.534**	.071	.307	.444*	.515*	.503*
5. Mean RT				--	.691**	.444*	-.187	-.216	-.211
6. SD of RT					--	.953**	.128	.243	.191
7. Normalised variance						--	.246	.402†	.336
ADHD Symptoms									
8. Inattention							--	.790**	.955**
9. Hyperactivity								--	.937**
10. ADHD score									--

** p<.01, *p <.05, $^{\dagger}p$<.1

5.4 Discussion

The purpose of this chapter was to determine the associations between intra-individual variability, symptoms of ADHD and low frequency EEG. Although we showed that participants who rated themselves as having more ADHD symptoms were likely to make more errors on the RT task we did not find that they exhibited greater intra-individual variability than participants who rated themselves as having fewer ADHD symptoms. However we did find that power in the S3 RT frequency band made the greatest improvement to the prediction of group membership (high-ADHD or low-ADHD) beyond SD of RT or normalised variance. Throughout the course of a 10 minute RT task, participants became more variable and the associations between errors and intra-individual variability became stronger: in the second half of the task, SD of RT and frequency domain measures of variability were more strongly positively correlated with the number of errors than in the first half of the task.

We also investigated the association between low frequency EEG and low frequency fluctuations in RT data. We found that there was small but significant synchrony between low frequency EEG and low frequency RT and furthermore, participants who exhibited least attenuation of the S3 EEG signal when engaging in the RT task (compared to rest) showed greater similarity between their S3 EEG and S3 RT signals. There was a similar, but statistically insignificant trend for participants who self-reported the most ADHD symptoms to show greater synchrony between the S3 EEG and the S3 RT signals than participants who reported fewer ADHD symptoms. We also found that there was an association between rest-task attenuation and task performance, and participants who exhibited least rest-task attenuations tended to perform more poorly on task measures, although this did not reach statistical significance.

5.4.1 The associations between intra-individual variability and lapses in attention

These results are broadly consistent with previous literature. We showed that power in the S3 RT frequency band made the greatest improvement to the prediction of group membership (high-ADHD or low-ADHD) beyond global measures of variability. This is consistent with the findings of Di Martino et al., (2008), who demonstrated that an ADHD group could be differentiated from a control group by their SD of RT and the power exhibited in another similar RT frequency band (.03-.07 Hz) on a Flanker task- although this group were unable to examine the entire range of the S3 frequency band as they were constrained by their long inter-trial interval, which prevented them from examining the higher frequencies. Similarly, Johnson et al. (2007) showed that a group of impaired-ADHD children (defined by the number of commission errors made) were distinguishable from an unimpaired-group of children with ADHD and controls by the power they exhibited in a RT frequency band very similar to S3 (.07-.33Hz) on a continuous performance task (CPT). As these effects are specific to a particular low frequency band and power in this RT frequency band operates above and beyond that of SD of RT, it will be important to consider this RT frequency band in future measures of variability.

Similarly, we showed that participants became more variable over the course of the task but did not make more errors, which again is consistent with Johnson et al., (2007), who demonstrated that an impaired group of children with ADHD became more variable on both global measures of variability and low frequency measures of RT variability, but did not make more errors, over the course of a CPT. However, we also showed that the associations between these measures of variability and errors changed throughout the course of the task: such that, in the second half of the task, SD of RT and frequency domain measures of RT variability were more strongly positively correlated with the number of errors made than in the first half of the task. This suggests that the association between variability and errors may be contextually dependent on state factors such as boredom or fatigue, and it may be important to examine the relationships between these measures of performance over time.

Furthermore, both the number of errors and frequency domain measures of RT variability showed a reasonable degree of stability over a one week test-retest period, ($r \approx .6$) and these correlations were of similar magnitude to the test-retest reliabilities reported by Johnson et al., (2008) for these same measures – although the RT frequency bands reported by Johnson were slightly different from those used in the present study, they divided their FFT spectra into fast (> .77 Hz) and slow frequencies (< .77 Hz). This suggests that these measures are tapping into a stable aspect of task performance. However, we also predicted that the global measures of variability should show a similar degree of stability over time, but in this chapter test-retest correlations for SD of RT and normalised variance were very small and statistically insignificant ($r \approx .15$), which is in contrast to the findings of Johnson et. al., (2008) who reported a test-retest correlation of $r = .75$ for SD of RT. However, there are some differences between our study and the study of Johnson et. al., (2008), for example, although both studies adopt similar sample sizes for their test-retest correlations (N = 22 and N = 19), Johnson et. al., (2008) calculated the test-retest reliability of task measures using data only from control children; we used data from both the low-ADHD and the high-ADHD groups. Indeed, when data from only the low-ADHD participants are used to calculate test-retest reliability of RT variability measures in our study, correlations substantially increase, (SD of RT, $r(11) = .89$; mean RT $r(11) = .73$). Although it would be inappropriate to make firm conclusions from such a small sample, this result highlights the variability inherent in ADHD; it is possible that high-ADHD symptom participants may be more affected by context and state and thus, are more variable in expressions of intra-individual variability than low ADHD symptom participants; and accordingly, SD of RT would be a less stable construct in high-ADHD symptom participants.

It is surprising however that none of the measures of variability were strongly associated with ADHD symptoms: the global measures of variability were moderately associated with ADHD symptoms (SD of RT $r \approx .2$; normalised variance $r \approx .3$) but none of the frequency domain RT measures – i.e. RT power in S4, S3 or S2 bands – showed any correlation with the ADHD scores ($r < .1$). Intra-individual response variability, as SD of RT, has often been found to be strongly correlated with ADHD symptoms (Epstein et al., 2003;

Kuntsi et al., 2001) and the size of group differences for SD of RT between patients with ADHD and controls are typically about d = .7 (Nigg et al., 2005). Furthermore, Johnson et al., (2007) showed that a group of impaired-ADHD children were distinguishable from an unimpaired-group of children with ADHD and controls by the power they exhibited in a frequency band very similar to S3 (.07-.33Hz). Although it is important to bear in mind that this study did not employ a clinical sample of ADHD, and replication with a clinical sample may yield different results, it is possible that the fast event rate adopted by the present study may have affected the patterns of response variability exhibited by the participants. Although patients with ADHD typically perform more poorly than controls on tasks with a slow event rate, their performance on tasks with fast event rates has not been found to be impaired (e.g. Scheres et al., 2001). Furthermore, Andreou et al., (2007) showed that under fast event-rate conditions, RT variability (SD of RT) was significantly reduced in a large group of children with ADHD, compared to a slow event rate condition; although the authors do not report whether the new level of RT variability in children with ADHD reached the level of the control group. It may be that the fast event rate, which was adopted by the present study to allow higher frequencies of RT variability to be examined, caused RT variability to be reduced in the participants. As event rate is likely to impact on RT variability, it will be important to use tasks with slower event rates in future studies, even though this will constrain the RT frequencies that are able to be examined.

5.4.2 Implications for the default-mode interference hypothesis

This chapter also aimed to directly test the predictions of the default-mode interference hypothesis (Sonuga-Barke & Castellanos, 2007), which suggests that during goal-directed tasks some patients with ADHD may not effectively attenuate the slow oscillations of the resting DMN and initiate focused task attention, which would allow resting-state oscillations to intrude on task performance and cause periodic attention lapses and cycles of impaired performance. The default-mode interference hypothesis further suggests there should be synchrony between the fluctuations in low frequency EEG oscillations, and lapses in attention or declines in performance. The findings of this chapter were consistent with this: we demonstrated a small but significant degree of synchrony between moment-to-moment fluctuations in behavioural performance (as indexed by RT VLFO) and EEG VLFO. Synchrony was, as predicted, low due to the complexity of the RT and EEG time series. However, such an analysis has important implications for current conceptualisations of DMN interference during goal-directed performance.

The findings in this chapter also offered some support for the notion that inefficient attenuation of VLF EEG from rest to task will result in impairment of attention. Participants, who did not attenuate their S3 EEG signal when they went from rest to the RT task, exhibited poorer task performance and also showed greater similarity between their S3 EEG and their S3 RT signals during the goal-directed task than participants who did attenuate this S3 EEG signal. This is consistent with the assertion of the default-mode interference hypothesis, that if

task-negative EEG oscillations are not effectively attenuated when one engages in a goal-directed task, they may intrude into attention and will be synchronised with fluctuations in behaviour.

The default-mode interference hypothesis is offered as an account of ADHD. We found that participants who rated themselves as having higher ADHD symptoms experienced less attenuation of their resting S3 EEG oscillations and also showed greater synchrony between their S3 EEG and the S3 RT signals (although this difference in S3 RT-EEG synchrony failed to reach statistical significance). This suggests that participants with higher ADHD symptoms are less likely to effectively attenuate their low frequency EEG in the transition from rest to task than participants with fewer ADHD symptoms, and that this might interfere with goal-directed brain activity. Therefore, it is possible that this may be a characteristic of ADHD. However, the group differences in S3 EEG-RT synchrony did not reach statistical significance and therefore, in order to understand the role of this in ADHD, it will be important to replicate these findings in a clinical sample of ADHD participants.

5.4.3 Limitations

Many of the limitations identified in the previous chapter are also relevant here; this study is clearly limited in terms of its small sample size and non-clinical sample. Similarly, the issue of the large quantity of data available for analysis in the present study is also pertinent: EEG data were available from 27 scalp electrode channels for each participant, and the cross-correlation between the RT signal and each of these EEG data channels was performed for each participant, which resulted in 27 measures of signal synchrony for each participant. Again, in order to make this dataset more manageable and to reduce the need for multiple comparisons, these were reduced into two key synchrony variables for each participant: the mean cross-correlation across all of the electrodes within the S3 network and the mean cross-correlation across all of the electrodes outside of the S3 network.

A further limitation of this study is that the RT task used by the present study allowed participants to make missing and incorrect responses. Incorrect responses were found to be faster and more variable than correct responses. While we attempted to resolve this by using linear regression residuals to represent the portion of each RT score that is independent of response type and interpolating missing responses with a linear interpolation of neighbouring responses, this may have inadvertently introduced bias into the data. As described in *5.2.4 Tasks*, a task that does not allow participants to make incorrect or missing responses would avoid any issues of introducing bias into the data. Although the data from the tracking task in the present study were unusable, this task would provide a continuous measure of participants' sustained attention that is not affected by incorrect or missing responses and, furthermore, would allow a much greater portion of the frequency spectrum to be examined. Future studies that attempt to investigate the frequency components of behavioural data should utilize similar continuous tasks.

5.5 Conclusions

Participants who rated themselves as having more ADHD symptoms were likely to make more errors on the RT task; however we did not find an association between ADHD symptoms and intra-individual variability. Nonetheless, we also showed that power in the S3 RT frequency band made the greatest improvement to the prediction of group membership (high-ADHD or low-ADHD) beyond SD of RT or normalised variance. Furthermore, we found that there was small but significant synchrony between low frequency EEG and low frequency RT. Importantly, participants who exhibited the greatest synchrony between S3 EEG and S3 RT were those that did not effectively attenuate their resting low-frequency EEG. This is consistent with the default-mode interference hypothesis.

Chapter 6 Low-frequency EEG oscillations in a clinic-referred ADHD sample at rest and during goal-directed task performance

6.1 Introduction

In Chapter four we showed that a stable network of slow 3 oscillations was evident in healthy controls at rest. Furthermore, power in this S3 network at rest differentiated an inattentive high ADHD subgroup. During goal-directed task performance, S3 power was generally attenuated compared to rest, however inattentive participants did not show the same degree of attenuation within the S3 network as other participants when they engaged in a goal-directed task. In this chapter we aimed to replicate these findings in a clinic referred sample of boys with ADHD. Further, we aimed to extend the previous work by including a task with a slower event rate. As described previously, tasks that include fast event rates may constrain variability in ADHD as although patients with ADHD typically perform more poorly than controls on tasks with a slow event rate, their performance on tasks with fast event rates has not been found to be impaired (e.g. Scheres et al., 2001). However as the ISI directly affects the frequencies that are able to be examined in the RT data (the maximum frequency that can be investigated is half the sampling frequency, see section *3.3.1 Capturing Temporal Patterns in Behavioural Data*), and we are interested in examining the frequency components of RT variability, we included a condition with a moderate (3 second ISI) rather than a slow event rate, which would limit the proportion of the RT frequency spectrum that we could investigate.

6.1.1 Study Aims

This chapter aimed to replicate and extend the findings of our previous study. Firstly it aimed to replicate the identification of a network of low frequency EEG oscillations at rest in a clinical sample of adolescent boys with ADHD. Specifically it aimed to: i) identify a network of resting slow 3 (.06-.2Hz) EEG activity across the scalp and to compare this to the S3 network location identified in Chapter 4; ii) to determine whether this network is specific to the S3 frequency band; and iii) to determine whether adolescent boys with ADHD exhibit differences in resting VLF EEG within and outside of this network compared to age- and gender-matched controls.

Secondly, this chapter aimed to replicate the findings of differences in the location and power of low frequency EEG during goal-directed task performance compared to rest in a clinical sample. The chapter aimed to extend these previous findings by including a moderate as well as a fast event rate condition of the task. The chapter specifically aimed: i) to identify the spatial distribution of S3 power during goal-directed task performance; and ii) to explore

variation in power of VLF EEG between adolescents with ADHD and age- and gender-matched controls while participants performed a goal-directed task.

Third, the chapter aimed to replicate the group differences (ADHD vs control) in attenuation of power within low frequency EEG bands as one moves from rest to goal-directed task performance, and again to extend these findings by determining whether the degree of attenuation varies as a context of event-rate. Specifically, the aims were: i) to compare VLF EEG power at rest and during goal-directed task performance; ii) to examine the level of attenuation of these VLFOs from rest to task and between groups and event-rate condition (i.e. 1 second ISI and 3 second ISI).

6.1.2 Predictions

1) Exploring low frequency EEG oscillations at rest

Firstly, it was predicted that the location of resting low frequency S3 oscillations would be similar to the S3 network identified in Chapter 4, and that maximal S3 power should mainly be located along the frontal midline and posterior scalp regions. It was also predicted that, consistent with the previous chapter, the ADHD group should exhibit reduced VLFO power in this network at rest when compared with controls.

2) Exploring low frequency EEG during goal-directed task performance

Also, in line with the findings of Chapter 4, it was predicted that the spatial distribution of S3 oscillations during goal-directed task performance would differ from the resting network. Furthermore, across all participants, S3 power within the S3 network should be lower while performing the goal-directed task than at rest, as S3 oscillations should be attenuated during goal-directed performance.

3) Attenuation of low frequency EEG oscillation bands as one moves from rest to goal-directed task performance

Furthermore, also consistent with Chapter 4, it was predicted that the ADHD group should exhibit a lower degree of S3 attenuation than the control group from rest to a goal-directed task. Task-induced deactivation from the default mode has been shown to be associated with event-rate, for example, McKiernan et al. (2006) showed that greater task induced deactivations from a resting baseline were observed in a fast- compared to a moderate- or a slow-event rate. Therefore, it was also predicted that the degree of attenuation would be associated with event-rate condition, and that greater attenuation would be evident in the fast condition of the 2-CR RT task compared to the moderate condition.

The relationship between low frequency EEG activity and performance will be explored in the following chapter.

6.2 Methods

All methods were approved by the by the University of Southampton School of Psychology Ethics Committee and by the Southampton & South West Hampshire Research Ethics Committee B (see Appendix A10).

6.2.1 Participants

Sixteen boys with a clinical diagnosis of ADHD-combined type aged between 13 and 16 years (mean age 14 years 7 months) and 16 age-matched control boys (mean age 14 years 8 months) participated in the study (see Table 6.1). A further four boys took part in the study but were excluded as they did not meet the study entry criteria (see following sections).

6.2.1.1 *Clinical Cases*

Participants with ADHD were recruited from two clinics from the Southampton City Primary Care Trust Child and Adolescent Psychiatry Mental Health Service (the Ashurst Child and Family Health Centre and the Brookvale Adolescent Service). Children were invited to participate in the study if they met the following criteria: a) a formal clinical diagnosis of ADHD from their psychiatrist; b) no other developmental disorder other than oppositional defiant disorder (ODD) or conduct disorder (CD); c) IQ > 70 (see section *6.2.1.5 Measure of IQ*); and d) no medication other than methylphenidate (which must be discontinued 24 hours prior to testing). Eligible cases for the study were identified by one of the psychiatrists involved with their care.

6.2.1.2 *Typically Developing Controls*

Control cases were recruited from two local schools. An advert for the study was placed in the weekly school newsletter and interested children contacted a designated member of staff who then passed their details onto the researcher. Inclusion criteria for controls were; a) no developmental disorder; b) IQ > 70 (see section *6.2.1.5 Measure of IQ*); and c) no medication. One control was excluded because of the presence of tic disorder.

6.2.1.3 *Recruitment*

Eligible clinical and control cases were sent an information pack about the study (see Appendices A11-A17). The information packs for both the clinical cases and the controls contained:

1) A cover letter addressed to both parents and young people.
2) An information letter for parents
3) An information letter for young people
4) A reply slip
5) A freepost envelope

After receiving the information packs, interested parties were asked to return the reply slip in the freepost envelope giving permission for the researcher to contact them. The researcher then phoned the participant and arranged a date for the testing session. All participants received £30 to reimburse their travel expenses.

6.2.1.4 *Validation of the Diagnosis*

All participants were screened with the following questionnaires:

1) The ADHD rating scale (Dupaul et al., 1998) (see Appendix A18). This was completed by both parents and teachers about the child and is a parent- or teacher-report measure of ADHD symptoms experienced by the child. It is similar to the self-report ADHD measure described in section 4.1.1, and contains 18 questions which are derived from the 18 ADHD symptom criteria reported in the DSM-IV and which fall onto two correlated factors, inattention and hyperactivity/impulsivity. Each item is rated on a 4 point Likert-scale (occasionally, never, often, very often). The scale has been shown to posses good construct validity and test-retest reliability (construct validity .35-.85, 4 week test-retest reliability .78-.86; see Collett et al., 2003 for a review).

2) The strengths and difficulties questionnaire (SDQ) (Goodman, 1997) (see Appendix A19). This was completed by parents of the children. The SDQ is a 25-item questionnaire, which comprises of 5 scales: emotional problems, conduct problems, hyperactivity/inattention, peer relationship problems and prosocial behaviour. The SDQ can be used a screening measure for child psychiatric disorders and has been shown to have good sensitivity and specificity (Goodman, Ford, Simmons, Gatward, & Meltzer, 2000). Furthermore, the hyperactivity/inattention subscale of this questionnaire has been shown to have moderate sensitivity to identify ADHD cases (Banaschewski, Woerner, Becker, & Rothenberger, 2004)

Parents and teachers of children who did not take stimulant medication were asked to complete these questionnaires about the child's behaviour in the last six months. Parents and teachers of children who did take stimulant medication were asked to rate the last medication free period. Children with ADHD were included in the study if they were reported to experience a clinical degree of ADHD symptoms, i.e. 12 or more overall ADHD symptoms or more than 6 symptoms from either the hyperactivity/impulsivity or the inattention subscales. Two children in the ADHD group were excluded as they did not meet these criteria. Controls were included in the study only if they scored less than 5 on the hyperactivity/impulsivity subscale of the SDQ and they did not experience a clinical degree of ADHD symptoms as reported on the ADHD rating scale. No control cases were excluded on this basis.

6.2.1.5 *Measure of IQ*

An estimation of full-scale IQ was assessed in all children using the Wechsler Intelligence Scales for children (WISC-III, Wechsler, 1991). The vocabulary and block design subsets were used; this short form of the WISC-III is frequently used as a screening measure in research and has been shown to have good reliability (r = .911) and validity (r = .862) (Sattler, 1992). The sum of the scaled score from these two subtests was converted into an estimated full-scale IQ deviation quotient using the conversion reported in Sattler (1992) Children were excluded from the study if their estimated IQ was less than 70. One participant in the ADHD group was excluded on this basis, IQ = 67.

6.2.2 Design

The study had a within-groups design. Participants completed a single testing session, all participants completed identical assessments, however the order of these was counterbalanced (see section *6.2.4 Assessments*).

6.2.3 Procedure

Written informed consent was obtained from the parents themselves, from the parents on behalf of the children and also from the children themselves. The child then completed the WISC-III IQ assessment. After this, they were seated on a comfortable chair in front of a computer monitor in the testing cubicle and an electrode cap was fitted: the researcher video-monitored the participant in an adjacent room throughout the experiment.

6.2.4 Assessments

Each participant then completed three assessments. One assessment measured resting-state activity. The others assessed activity while performing a goal-directed task, of these goal-directed assessments, one was a 2-CR RT task, with two conditions, a fast and a moderate event-rate condition, and the other assessment was a continuous tracking task. The four assessments were presented in a counterbalanced order. The resting-state assessment was presented to be equally likely to occur before or after the goal-directed assessments. Within the goal-directed assessments, the tracking task was presented with equal likelihood of occurring either before or after the 2-CR RT task; and within this 2-CR RT task, the fast condition was presented equally often before and after the moderate condition. Thus, one of eight orders was presented to each participant.

6.2.4.1 *Resting-state Assessments*

The resting-state assessment lasted 5 minutes. During this assessment participants were instructed simply to ‘rest’ and to keep their eyes fixated on a fixation cross in the centre of the computer screen.

6.2.4.2 *Goal-Directed Assessments*

Two-choice RT Task

Each condition of the 2-CR RT task lasted 10 minutes. One of these conditions was identical to the RT task described in *section 4.2.4.2 Assessments During Goal-Directed Task Performance*. Briefly, green arrows were presented in the centre of the computer screen and pointed either right or left, participants were asked to respond by pressing the right or left mouse button to indicate the direction of the arrow. In this condition the ISI was 1 second. The other condition was identical to this except that the ISI was 3 seconds. The stimulus presentation time was identical in both tasks (400ms).

Tracking Task

The tracking task was a modified version of the tracking task used in the previous chapter. Briefly, a track and a central marker were presented on the computer screen.

Participants were instructed to keep the central marker as close as possible to the centre of the track using the right and left arrow keys on the computer keyboard. In order to prevent the previous problems that had rendered the data obtained from this task unusable, i.e. error associated with the segment changes in the track, which occurred each second, the task had been redeveloped to prevent abrupt changes between successive track segments. Thus, rather than the track comprising of a number of rectangular segments, as it had in the previous study, the track was designed to comprise of arcs. In order to ensure a consistent level of difficulty throughout the task, the arc radius was kept within 1-2˚, however, in order to prevent periodicity in the track, the arc radius varied randomly within these limits. In a further measure to prevent periodicity in the track, the length of each arc was designed to vary randomly, by randomly varying the number of fixed-length sub-segments which comprised each arc. Again the number of sub-segments was set to be consistent over certain difficulty levels (i.e. to vary between 12 and 32 sub-segments per arc). However despite these modifications, error was again introduced into the data by the code used to record movement along the track. This is illustrated in Figure 6.1, which shows simulated task data from an 'ideal' user. This simulation automatically adjusts the target course at each sample point to the ideal course, this allows the application to correct itself in the way that an ideal user could and so represents 'intrinsic' error in the task. It is very clear from this figure and its corresponding FFT that the task is introducing low frequency variability into the data (at approximately .06 Hz). As the data recorded for the present study were unusable, data from this task, both behavioural and EEG data, was dropped from further analysis

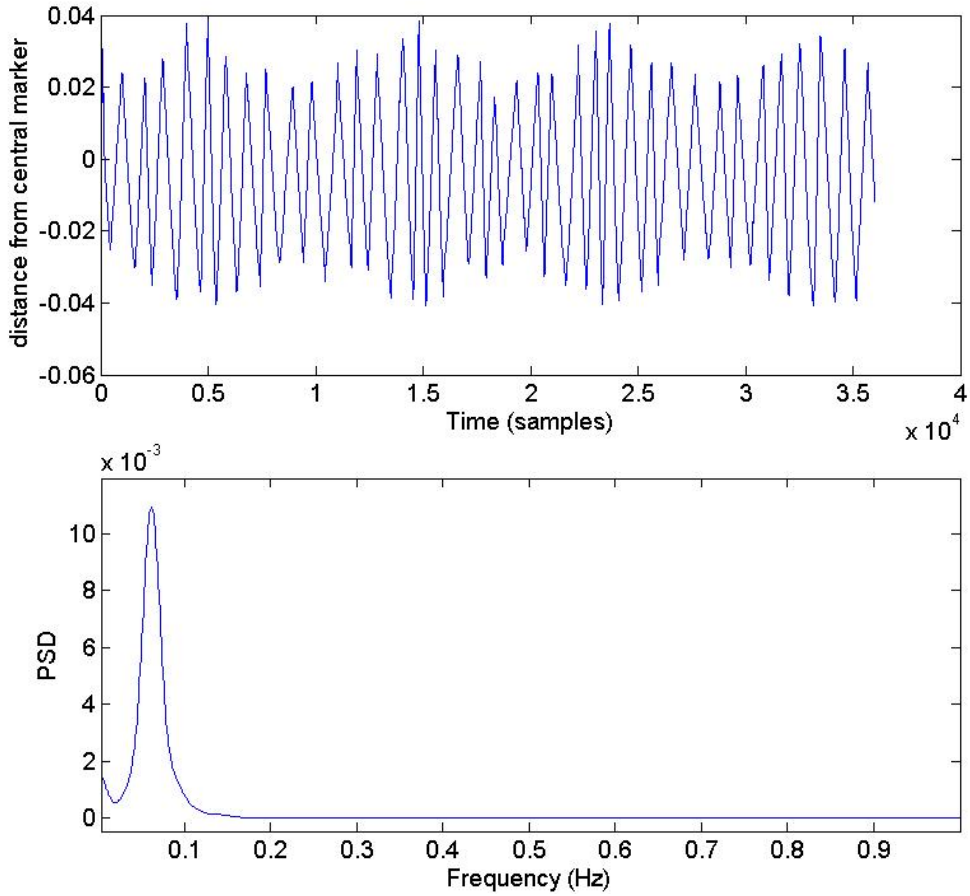


Figure 6.1: Simulated data that illustrates intrinsic error in the task (above) and corresponding FFT (below).

6.2.5 Electrophysiological Acquisition

All data were recorded in the same manner as described in Chapter 4 (see section *4.2.5 Electrophysiological Acquisition*). Briefly, the data were recorded using Neuroscan Synamps[2] 68 channel EEG system, DC-coupled recording equipment, they were sampled with a 70 Hz low pass filter at a rate of 250 Hz. An electrode cap (Easycap, Herrsching, Germany) was fitted to the participant and EEG data were recorded from twenty-seven silver/silver chloride electrodes placed according to the extended 10/20 system (Fp1, Fpz, Fp2, Afz, F7, F3, Fz, F4, F8, FCz, C7, C3, Cz, C4, T8, Cp5, Cp3, Cp1, Cpz, Cp2, Cp4, Cp6, P3, Pz, P4, O1, O2). Furthermore, a ground electrode was positioned on Fc6 and an active (reference) electrode at Af7: a reference electrode was also placed on each mastoid. Horizontal electro-oculogram (HEOG) was recorded from bipolar electrodes placed on the outer canthi of each eye. Vertical electro-oculogram (VEOG) was recorded from bipolar electrodes placed above and below the right eye. All impedances were kept below 10 kΩ. Electro-cardiogram (ECG) data were recorded from a negative reference electrode placed on the right shoulder and a positive electrode placed on the centre of the chest.

6.2.6 EEG Data Processing

6.2.6.1 *Pre-processing*

All data were analysed and processed using MATLAB (version 7.7.0) and in a similar manner to that described in Chapter 4 (see sections *4.2.6 EEG Data Processing*). The data were initially re-referenced off-line to the mean mastoid signal, the linear trend caused by drift was removed from the EEG data using the 'detrend' command in MATLAB and data were downsampled to 10 Hz. Again, ocular and other artifacts were removed from the data using ICA. However as a greater number of movement artifacts were evident in this data than was observed in the previous chapters, PCA was not used to reduce the dimensions in the data set prior to ICA. This allowed ICA to recover 29 components for each participant in each condition. The components were then inspected to identify those that represented eye blinks or other eye movements and other artifacts, such as faulty leads. Ocular and other artifacts were removed by back-projection of all but those components. This method of data processing was performed separately on the EEG data obtained from the rest with eyes open session, and each condition from the 2-CR RT task.

6.2.6.2 *Exclusion of Participants*

Excessive movement artifacts

EEG data across all conditions from one participant from the control group and three participants from the ADHD group contained too many movement artifacts and so were excluded. EEG data for one participant from both the resting condition and the moderate event rate condition of the 2-CR RT task and from just the moderate event-rate condition of the 2-CR RT task of another participant contained excessive movement artifacts and were excluded. Both of these participants were in the high ADHD group.

Insufficient Task Engagement

As described in Chapter 5, participants who made >15% omission errors on the 2-CR RT task were excluded from further analysis as they were not considered to be sufficiently engaged in the task. On this basis, two participants were excluded from the fast event-rate condition and one participant was excluded from the moderate event-rate condition, all of these participants were in the ADHD group. As these participants were not considered to be sufficiently engaged in the task it was inappropriate to include their EEG data for analysis.

6.2.6.3 *Final Sample Numbers*

Therefore, for the purposes of this chapter, for the control group all comparisons were performed on a sample of N = 15 for all conditions, but for the ADHD group, the resting condition contained a sample of N = 12, the fast condition of the 2-CR RT task comprised of a sample of N = 11, and the moderate condition of the 2-CR RT task sample contained a sample N = 10.

6.2.7 Data analysis

6.2.7.1 *Fourier Transformation*

After the signal was reconstructed, data were analysed as described in Chapter 4. Briefly, FFT analysis was performed on the data from each of the 27 scalp electrodes for each participant in each test condition 1) rest with eyes open and 2) fast event rate condition of the 2-CR RT task and 3) moderate event-rate condition of the 2-CR RT task. One minute Hanning windows that overlapped by 10 seconds were used and power in each of the S4, S3, S2, S1 and Delta frequency bands were calculated for each condition. Since power is not normally distributed, the values were natural log transformed (Gasser et al., 1982).

6.2.7.2 *Spatial location of S3 Network*

In the same manner as in Chapter 4, the spatial location of the resting S3 network was assessed using data only from the control group as it was assumed that the network may be abnormal in the ADHD group. Electrodes with S3 power higher than the mean were selected and considered to comprise the S3 network.

6.2.7.3 *Statistical Analyses*

Comparisons between groups (patients with ADHD and controls) and conditions (rest, fast condition and moderate condition of the 2-CR RT task) were made using repeated-measures ANOVAs.

6.3 Results

6.3.1 Clinical characteristics

Table 6.1 illustrates the clinical characteristics of the control and ADHD groups. The two groups did not differ in age. However, consistent with previous literature (e.g. Kuntsi et al., 2004;Mariani & Barkley, 1997), the ADHD group was found to have a significantly lower IQ than the control group. Therefore main analyses were run with and without IQ as a covariate to control for its effect. Parents reported that the ADHD group displayed more ADHD symptoms than controls using both the ADHD rating scale and the SDQ. Also according to parental report on the SDQ, patients with ADHD displayed more emotional and conduct problems, had more difficulties in peer relationships and exhibited less pro-social behaviour than controls. Teacher response rate was 75% for control cases and 69% for ADHD cases. Teachers also reported that the ADHD group displayed more ADHD symptoms than controls using the ADHD rating scale.

Table 6.1

Group Characteristics

	Control (N = 16) Mean (SD)	ADHD (N = 16) Mean (SD)	*F*	*p*
Age	14y 8 m (11m)	14y 7m (11m)	.072	.791
WISC-III IQ				
Block Design (scaled score)	11.25 (2.99)	8.31 (2.35)	9.57	.004**
Vocabulary (scaled score)	10.69 (2.63)	7.50 (2.19)	13.90	.001**
Full	105.6 (14.5)	88.1 (11.26)	14.52	.001**
Number of Parent Reported ADHD Symptoms				
Inattention	.81 (1.22)	7.88 (1.41)	229.38	<.001**
Hyperactivity	.38 (.619)	6.81 (2.29)	118.14	<.001**
Total Score	1.19 (1.22)	14.69 (3.18)	251.56	<.001**
Parent Reported SDQ				
Emotion	.50 (1.10)	4.75 (2.76)	32.59	<.001**
Conduct	.88 (1.147)	5.94 (2.17)	67.83	<.001**
Peer Relationships	1.25 (1.69)	4.25 (2.41)	16.62	<.001**
Prosocial Behaviour	9.25 (.77)	6.19 (2.51)	21.76	<.001**
Impact	.06 (.25)	5.00 (2.97)	44.01	<.001**
Hyperactivity	1.69 (1.49)	8.81 (1.37)	196.90	<.001**
Number of Teacher Reported ADHD Symptoms	**N = 12**	**N = 11**		
Inattention	1.33 (2.27)	6.64 (2.01)	34.9	<.001**
Hyperactivity	.420 (.900)	5.55 (2.42)	46.9	<.001**
Total Score	1.75 (2.60)	12.18 (2.31)	71.3	<.001**

**, $p<.01$, *$p<.05$

Note. WISC-III = Wechsler Intelligence Scales for children, SDQ = Strengths and Difficulties Questionnaire

6.3.2 Low frequency oscillations during rest

6.3.2.1 *Identification of a network of resting slow 3 power*

As in Chapter 4, low frequency oscillations were clearly present in the raw data both before and after data cleaning.

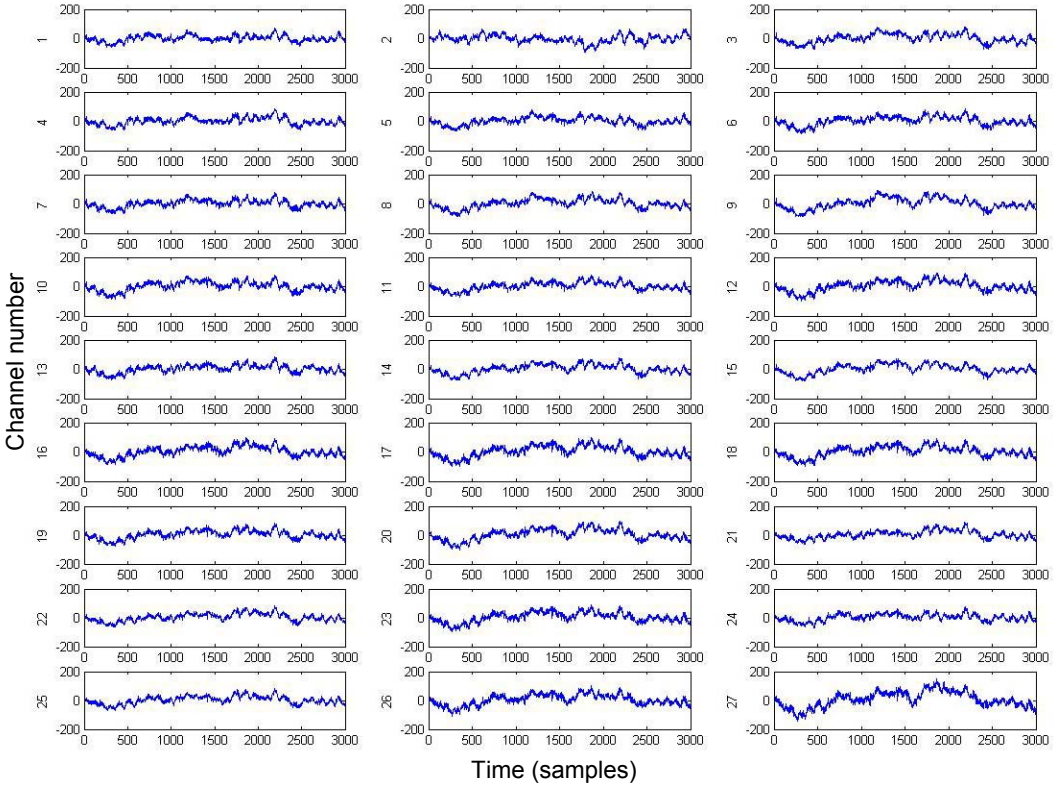


Figure 6.2: Cleaned data from all channels for a single participant
Note. The y axis indicates the amplitude (*μ*V) of each channel.

Figure 6.2 shows 5 minutes of data from each channel of EEG data for an individual participant, during the rest with eyes open condition; as demonstrated in Chapter 4, periodic fluctuation in low frequency EEG power is again evident. The relative power of these low frequency oscillations are shown in Figure 6.3, which demonstrates the corresponding FFT for each electrode (for clarity the FFT has been shown only until .25 Hz).

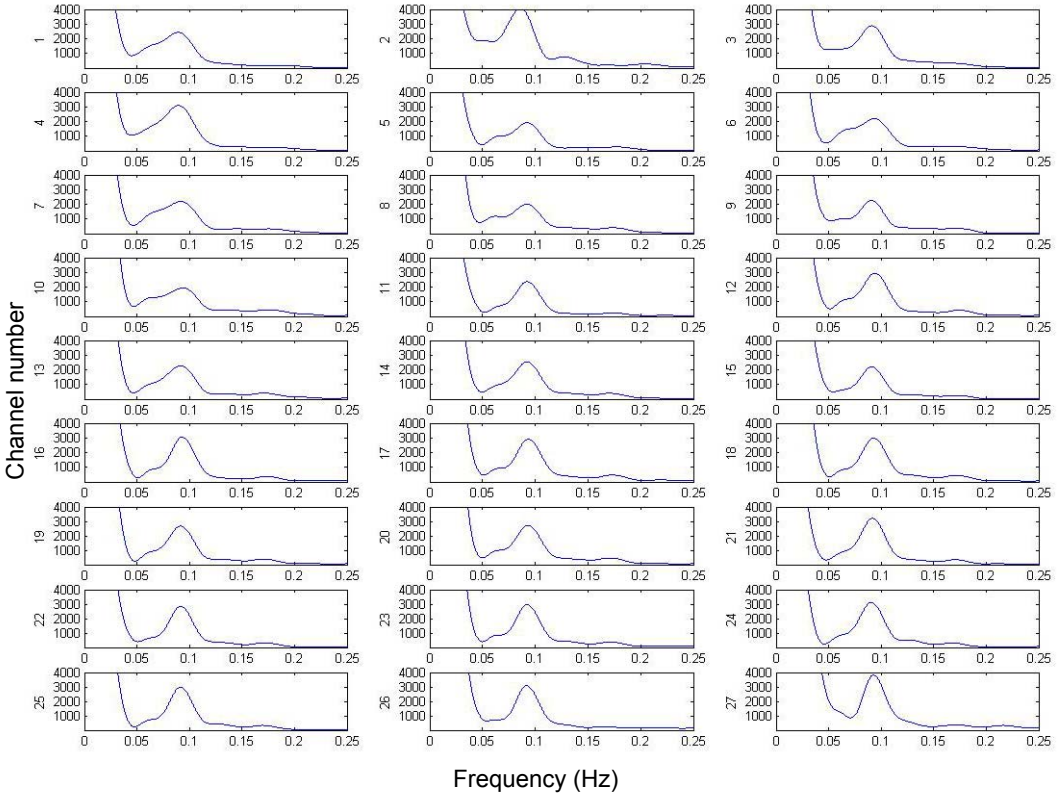


Figure 6.3: FFT for each electrode

Note. The y axis indicates the power (μV^2) of each channel.

From Figure 6.3, it is evident that, again, a peak of power is apparent at about .1 Hz. In order to determine whether this slow 3 power showed a similar spatial distribution to the S3 network which was identified in the previous chapters, the averaged spatial distribution of power in the slow 3 frequency band across all of the control participants and the spatial distribution of slow 3 power identified in the previous study are shown topographically in Figure 6.4. It is clear from this figure that although absolute values of power varies between the two samples, the spatial distribution of slow 3 power identified in this chapter is broadly similar to that which was identified in the previous chapter, and was located mainly along the frontal midline and posterior regions.

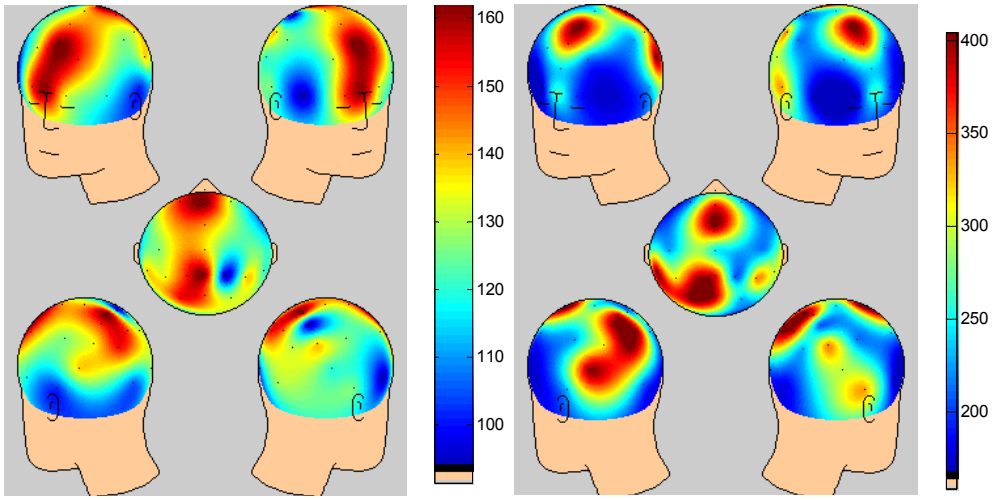


Figure 6.4: Slow 3 power across the entire control group (left) and slow 3 resting network identified in the previous chapter (right).

As in the previous chapter, a resting slow 3 network was determined by identifying electrodes with slow 3 power that was higher than the mean across all control participants. The electrodes identified as comprising the S3 network in this sample as well as the electrodes which had been identified as comprising the S3 network in the previous chapter are shown in Figure 6.5. Again, there is substantial overlap between the electrodes identified as comprising the S3 network in both samples.

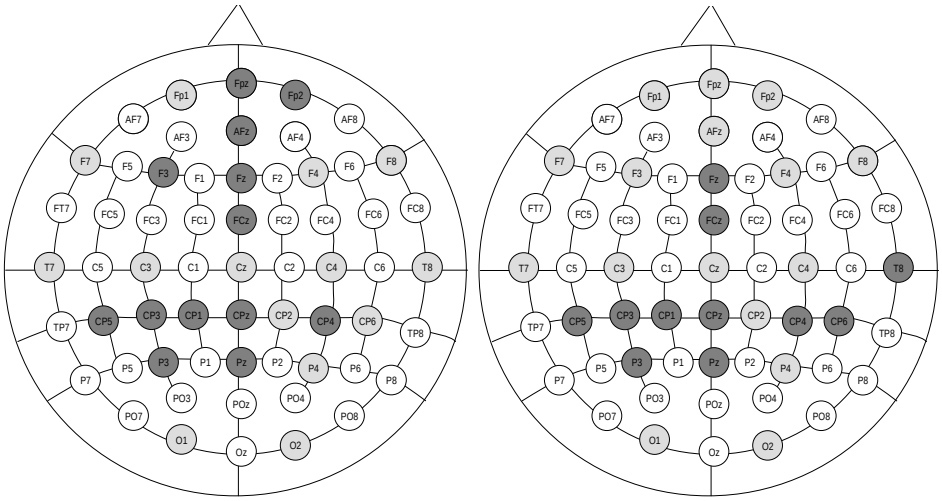


Figure 6.5: Electrodes selected for S3 network shown in dark grey in the present sample (left) and in the previous chapter (right), all other electrodes in the montage are shown in light grey

6.3.2.2 *Specificity of the resting slow 3 network*

Table 6.2 shows that both within and outside of the S3 network, very strong correlations were apparent between all sub-delta frequency bands, especially between neighbouring frequencies, so for example S4 power within the S3 network was more strongly correlated with S3 power (r = .868) than with S2 (r = .657), S1 (r = .649) or delta power (r = .574) within the S3 network, although all correlations were statistically significant.

Table 6.2

Correlations of power at each frequency band within and outside of the S3 network.

	1	2	3	4	5	6	7	8	9	10
1.S4 within network	--	.868**	.657**	.649**	.574**	.917**	.778**	.638**	.641**	.553**
2.S3 within network		--	.760**	.687**	.634**	.823**	.899**	.694**	.641**	.595**
3.S2 within network			--	.925**	.872**	.550**	.610**	.917**	.867**	.827**
4.S1 within network				--	.953**	.499**	.502**	.835**	.940**	.910**
5.Delta within network					--	.407*	.429*	.755**	.870**	.947**
6.S4 outside network						--	.890**	.651**	.579**	.465*
7.S3 outside network							--	.707**	.591**	.503**
8.S2 outside network								--	.908**	.827**
9.S1 outside network									--	.936**
10.Delta outside network										--

** $p<.01$, * $p<.05$, † $p<.1$

Figure 6.6 illustrates the topographical diagrams that show the averaged spatial distribution of power in all sub-delta frequencies during rest with eyes open, across all of the control participants. As in Chapter 4, the overall pattern of scalp activation was broadly similar across all of these frequency bands and across all of the frequencies the main activation occured across the frontal midline and posterior scalp regions.

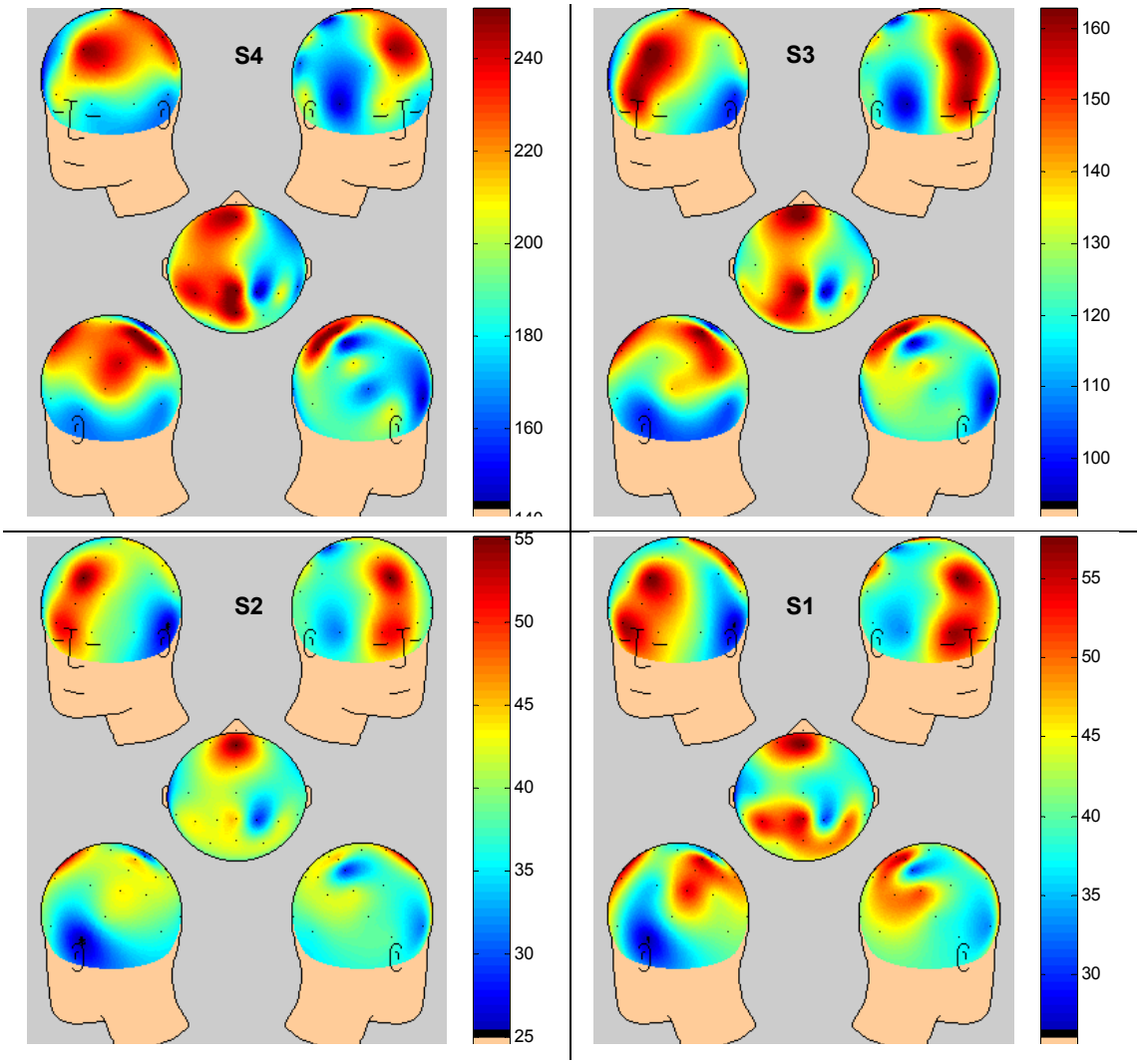


Figure 6.6: Scalp activations of S4 (top left), S3 (top right), S2 (bottom left) and S1 frequency bands (bottom right), in low-ADHD symptom participant during rest with eyes open (all maps are shown on individual best-fit scales).

6.3.2.3 *Intra-individual variation in very low frequency oscillations within this network at rest*

Figure 6.7 illustrates group (control vs ADHD group) differences in power across the five frequency bands at rest.

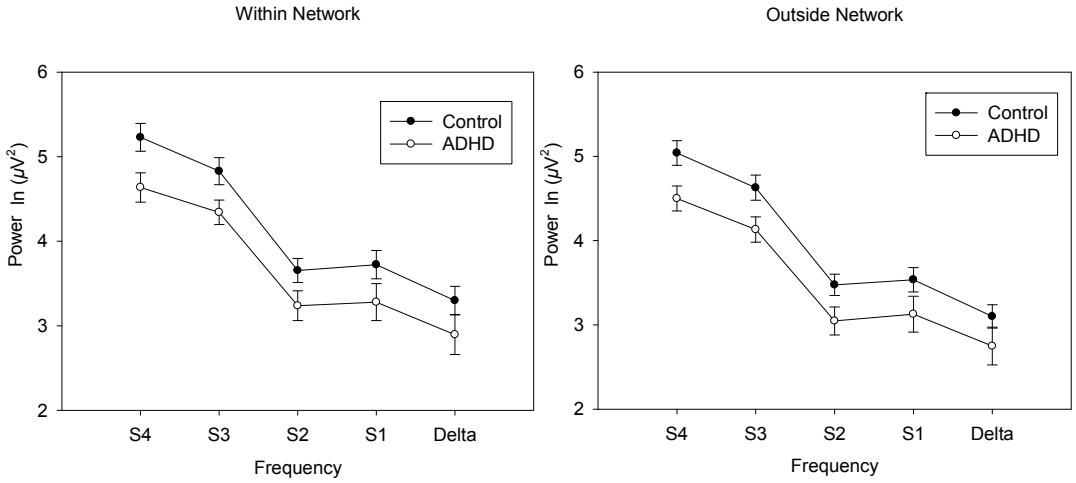


Figure 6.7: Power across all frequency bands at rest for control and ADHD groups within (left) and outside of network (right), error bars represent +/- 1 standard error.

The difference in power between these groups and in each location (within and outside of the slow 3 network) for each of these frequency bands was tested using a 2 x 2 repeated measures ANOVA. Location (within and outside of the network) was entered as the within subjects factor and group (control vs. ADHD) was entered as the between subjects factor. A significant effect of group was identified in the S4 and S3 frequency bands ($F(1,25) = 6.62$, $p = .016$; $F(1,25) = 5.41$, $p = .028$, respectively). In both of these frequency bands the ADHD group exhibited significantly less power than the controls. The effect of group did not reach statistical significance for any of the other frequency bands, although there was a non-significant trend for in the S2 frequency band (S2 $F(1,25) = 4.07$, $p = .055$, *ns*; S1 $F(1,25) = 2.78$, $p = .108$ *ns*, delta $F(1,25) = 2.04$, $p = .165$, *ns*). For each frequency band a significant effect of location emerged and within the network there was higher mean power than outside the network (delta $F(1,25) = 13.16$, $p = .001$; S1 $F(1,25) = 12.12$, $p = .002$; S2 $F(1,25) = 14.79$, $p = .001$; S3 $F(1,25) = 14.63$, $p = .001$; S4 $F(1,25) = 8.93$, $p = .006$). However these differences between locations were much less strongly pronounced than in the previous sample. No significant group by location interactions emerged for any of the frequency bands (delta $F(1,25) = .306$, $p = .585$, *ns*; S1 $F(1,25) = .122$, $p = .730$, *ns*; S2 $F(1,25) = .015$, $p = .903$, *ns*; S3 $F(1,25) = .007$, $p = .937$, *ns*; S4 $F(1,22) = .256$, $p = .617$, *ns*).

When IQ was included as a covariate, the significant effects of group for each of the S4 and S3 frequency bands was reduced to a non-significant trend (IQ: S4 $F(1,24) = 4.05$, $p = .055$, *ns*; S3 $F(1,24) = 3.26$, $p = .084$). Furthermore, unlike in the previous chapter, the effect of group did not survive the covarying of power of all other frequency bands either inside of the S3 network (S4 $F(1,21) = 1.45$, $p = .242$, *ns*; S3 $F(1,21) = .054$, $p = .818$, *ns*) or outside of the S3 network (S4 $F(1,21) = 1.14$, $p = .298$, *ns*; S3 $F(1,21) = .009$, $p = .923$, *ns*).

6.3.3 Low frequency oscillations during goal-directed task performance

6.3.3.1 *Localisation of S3 power*

The spatial location of S3 power across all control participants, while they were performing each condition of the 2-CR RT task is shown in Figure 6.8.

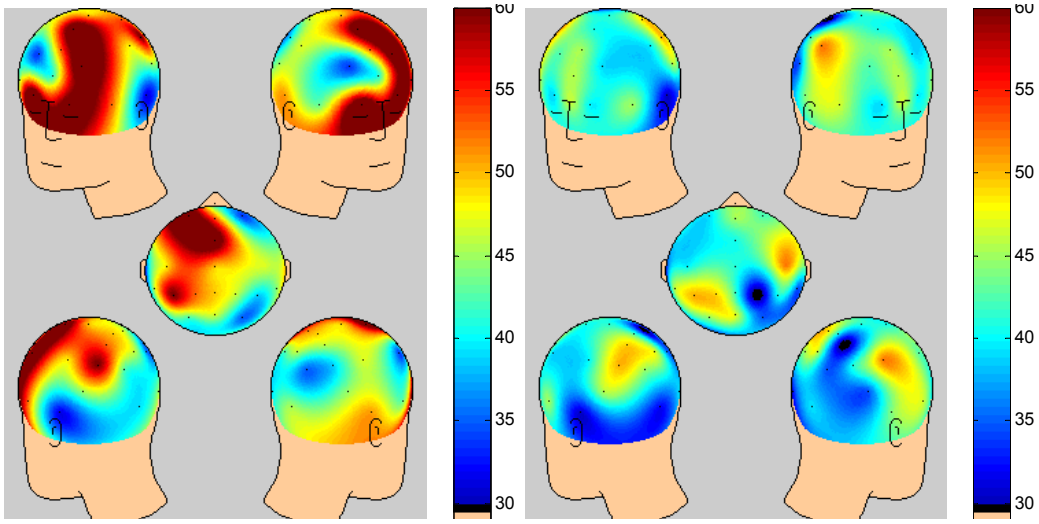


Figure 6.8: Localisation of S3 power across all controls during the 2-CR RT task fast condition (left) and moderate condition (right).

The spatial location of S3 power appeared to differ from the resting S3 network, and there appeared to be greater frontal activation and less posterior activation during the goal-directed task than at rest. However there were also differences between conditions: generally there appears to be less S3 activation across the moderate condition than across the fast condition, furthermore there was greater frontal activation during the fast condition than the moderate condition. These spatial locations of S3 activation differed from those identified in during goal-directed task performance in Chapter 4, which showed no frontal midline activation.

6.3.3.2 *Intra-individual variation in very low frequency oscillations within and outside of the S3 network during the goal-directed task*

Fast event-rate condition

The difference in power across all frequency bands during the fast condition of the RT goal-directed task, within and outside of the S3 network, and between groups was assessed using a 5 x 2 x 2 repeated-measures ANOVA. Frequency band (S4, S3, S2, S1 and Delta) and location (within and outside of the S3 network) were entered as the within subject factors and group (control vs ADHD) was entered as the between subject factor. A significant main effect of frequency ($F(4,92) = 89.7$, $p<.001$) emerged and greater power was observed in the lower frequency bands, however, no main effects of location ($F(1,23) = .406$, $p = .530$, *ns*) or of group ($F(1,23)=.185$, $p =.671$, *ns*) were found (see Figure 6.9). The only significant

interaction to emerge was a frequency by group interaction (F(4, 92) = 3.63, p = .009) and the control group tended to exhibit least power in the lowest frequency bands (S4 and S3) but most power in the highest frequency bands (S1 and delta).

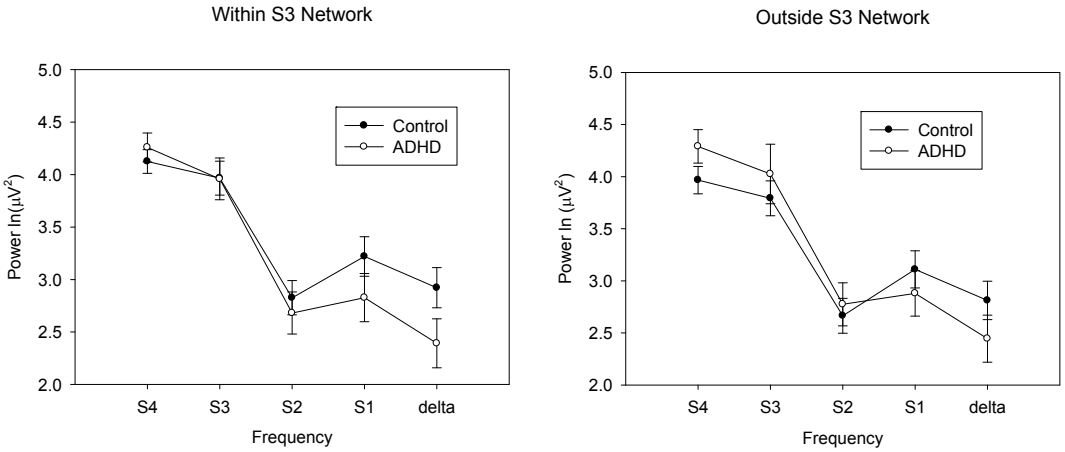


Figure 6.9: Power in each frequency band during the fast condition of the 2-CR task, between groups, within the S3 network (left) and outside of the S3 network (right), bars represent +/- 1 standard error.

Moderate event-rate condition

The difference in power during the moderate condition of the RT goal-directed task across all frequency bands was then assessed in the same manner. Again, a 5 x 2 x 2 (frequency X location X group) repeated-measures ANOVA was performed. As in the fast condition, a significant main effect of frequency emerged (F(4,92) = 78.7, p<.001) and greater power was observed in the lower frequency bands (see Figure 6.10), again, no main effects of location (F(1,23) = 1.10, p = .350, *ns*) or of group (F(1,23)=.1.76, p =.198, *ns*) were found to be statistically significant. In this condition no statistically significant interactions emerged.

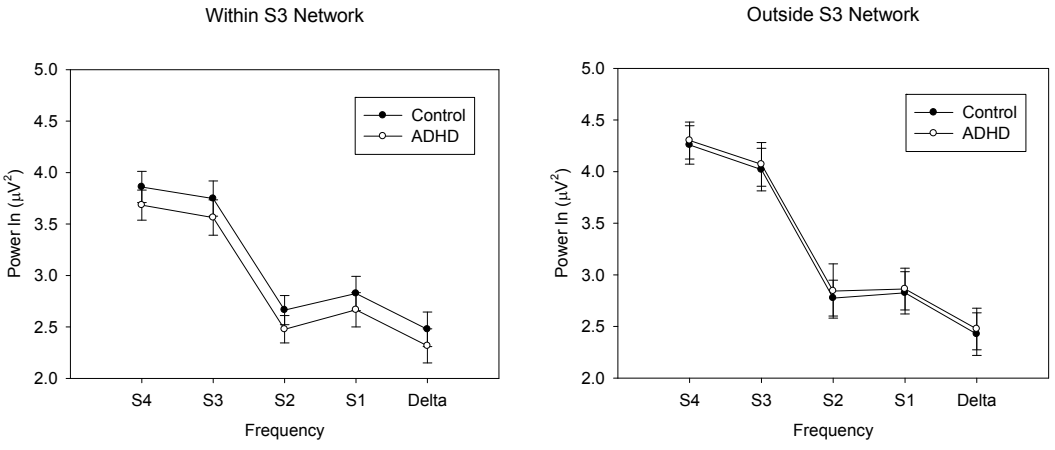


Figure 6.10: Power in each frequency band during the moderate condition of the 2-CR RT task, between groups, within the S3 network (left) and outside of the S3 network (right), bars represent +/- 1 standard error.

6.3.4 Comparison of low frequency oscillations at rest and during goal-directed task performance

Fast event-rate condition

Comparisons were then made between these low frequency oscillations at rest and those observed during performance of the fast condition of the 2-CR RT task. Correlations (Pearson's r) between these two conditions for the power of different frequency bands are shown within the S3 network in Table 6.3 and outside of the S3 network in Table 6.4. Both within and outside of the S3 network, within-condition correlations were positive and highly statistically significant between all frequency bands. However between-condition correlations for each frequency band tended to be less strong and in contrast to the previous chapter, the higher frequency bands (particularly S1 and delta), were the only frequencies for which significantly positive between-condition correlations emerged.

Table 6.3

Correlations between power of different frequency bands within the S3 network during the fast event-rate and rest conditions

	1	2	3	4	5	6	7	8	9	10
1.S4 rest	--	.867**	.690**	.696**	.659**	-.031	-.032	-.134	-.005	-.031
2.S3 rest		--	.790**	.731**	.709**	.046	.037	-.129	-.003	-.003
3.S2 rest			--	.923**	.878**	-.082	-.017	.170	.369†	.312
4.S1 rest				--	.957**	-.103	.019	.167	.363†	.305
5.Delta rest					--	-.012	.150	.261	.466*	.457*
6.S4 RT task						--	.833**	.638**	.476*	.503*
7.S3 RT task							--	.592**	.485*	.517**
8.S2 RT task								--	.919**	.893**
9.S1 RT task									--	.968**
10.Delta RT task										--

** $p<.01$, * $p<.05$, † $p<.1$

Table 6.4

Correlations between power of different frequency bands outside of the S3 network during the fast event-rate and rest conditions

	1	2	3	4	5	6	7	8	9	10
1.S4 rest	--	.889**	.691**	.635**	.562**	.008	-.025	-.140	-.004	-.017
2.S3 rest		--	.750**	.636**	.593**	-.037	-.059	-.194	-.029	-.033
3.S2 rest			--	.908**	.839**	-.130	-.149	.133	.372†	.326
4.S1 rest				--	.944**	-.106	-.091	. 168	.409*	.342*
5.Delta rest					--	-.019	.015	.243	.510**	.482*
6.S4 RT task						--	.847**	.705**	.512**	.532**
7.S3 RT task							--	.576**	.439*	.453*
8.S2 RT task								--	.902**	.894**
9.S1 RT task									--	.975**
10.Delta RT task										--

** $p<.01$, * $p<.05$, † $p<.1$

Moderate event-rate condition

These same comparisons were then made between these low frequency oscillations at rest and those observed during performance of the moderate condition of the 2-CR goal-directed task. Again, correlations (Pearson's r) between these two conditions for the power of different frequency bands are shown within the S3 network in Table 6.5 and outside of the S3 network in Table 6.6. As with the fast condition, both within and outside of the S3 network, within-condition correlations were positive between all frequency bands and, again, between-condition correlations of each frequency band tended to be less strong except in the higher frequency bands (S1 and delta). Notably, in this condition, S3 power also showed a positive between-task correlation both within and outside of the S3 network, although this just failed to reach statistical significance in either location ($p < .1$).

Table 6.5

Correlations between power of different frequency bands within the S3 network during the moderate event-rate and rest conditions of the 2-CR RT task

	1	2	3	4	5	6	7	8	9	10
1.S4 rest	--	.867**	.690**	.696**	.659**	.045	.276	.110	.206	.155
2.S3 rest		--	.790**	.731**	.709**	.123	.371†	.051	.138	.099
3.S2 rest			--	.923**	.878**	-.136	.046	.107	.285	.282
4.S1 rest				--	.957**	-.086	-.081	.106	.392†	.401*
5.Delta rest					--	-.089	.048	.152	.372†	.432*
6.S4 RT task						--	.898**	.569**	.432*	.326
7.S3 RT task							--	.459*	.372†	.242
8.S2 RT task								--	.925**	.846**
9.S1 RT task									--	.961**
10.Delta RT task										--

** p<.01, *p <.05, †p<.1

Table 6.6

Correlations between power of different frequency bands within the S3 network during the moderate event-rate and rest conditions of the 2-CR RT task

	1	2	3	4	5	6	7	8	9	10
1.S4 rest	--	.889**	.691**	.635**	.562**	-.077	.158	-.088	-.018	-.104
2.S3 rest		--	.750**	.636**	.593**	-.089	.339†	-.003	.030	-.041
3.S2 rest			--	.908**	.839**	-.142	.025	.173	.307	.301
4.S1 rest				--	.944**	-.121	.027	.254	.426*	.429*
5.Delta rest					--	-.080	.036	.242	.416*	.428*
6.S4 RT task						--	.874**	.556**	.420*	.317
7.S3 RT task							--	.417*	.287	.209
8.S2 RT task								--	.921**	.850**
9.S1 RT task									--	.961**
10.Delta RT task										--

** p<.01, *p <.05, †p<.1

6.3.4.1 *Low-frequency rest-task attenuation across all participants*

Fast event-rate condition

A repeated measures ANOVA with condition (rest *vs*. fast event rate condition) and frequency band (S4, S3, S2, S1 and delta) entered as the within subject factors, was run for each location (inside and outside of the S3 network). Within the S3 network, a statistically significant effect of condition emerged ($F(1,23) = 13.12$, $p = .001$) and EEG power was attenuated from rest (M = 3.94) to task (M = 3.35). Again, a significant main effect of frequency emerged ($F(4,92) = 151$, $p<.001$) and greater power was observed in the lower frequencies (i.e. S2, S3 and S4). A significant condition by frequency band interaction also emerged ($F(4,92) = 8.42$, $p <. 001$) and paired t-tests showed that significant differences (i.e. attenuation of power in the goal-directed task compared to the resting condition) only emerged for the S4, S3, S2 and S1 frequency bands but not for delta (S4 $t(24) = 4.83$, $p <.001$; S3 $t(24) = 3.32$, $p = .003$; S2, $t(24) = 3.89$, $p = .001$; S1 $t(24) = 2.18$, $p = .039$; Delta $t(24) = 1.86$, $p = .075$, *ns*).

In contrast to the previous chapter, attenuation was also observed outside of the S3 network from rest (M = 3.76) to task (M = 3.31) ($F(1,23) = 8.59$, $p = .007$). A significant main effect of frequency also emerged ($F(4,96) = 138$ $p<.001$) and again greater power was observed in the lower frequencies. A condition by frequency band interaction was also found to be statistically significant ($F(4,96) = 10.1$, $p <. 001$). Paired t-tests showed that significant differences (i.e. attenuation of power in the goal-directed task compared to the resting condition) emerged only for the three lowest frequency bands S4, S3 and S2 (S4 $t(24) = 4.55$, $p < .001$; S3 $t(24) = 2.61$, $p = .016$; S2, $t(24) = 3.35$, $p = .003$; S1 $t(24) = 1.72$, $p = .099$, *ns*; Delta $t(24) = 1.30$, $p = .207$, *ns*).

Moderate event-rate condition

These analyses were repeated for the moderate condition of the 2-CR RT task. Again a 2 X 5 (condition X frequency band) repeated measures ANOVA was run for each location (inside and outside of the S3 network). As with the fast condition, within the S3 network, a statistically significant effect of condition emerged ($F(1,24) = 28.9$, $p < .001$) and EEG power was attenuated from rest (M = 3.94) to task (M = 3.17). Again, a significant main effect of frequency emerged ($F(4,96) = 150$, $p < .001$) and greater power was observed in the lower frequencies (i.e. S2, S3 and S4) and a significant condition by frequency band interaction also emerged ($F(4,96) = 3.08$, $p =. 020$). Paired t-tests showed that attenuation of power in the goal-directed task compared to the resting condition emerged for all frequency bands, however this difference was larger in the lower frequency bands i.e. S4 and S3 (S4 $t(24) = 5.51$, $p <.001$; S3 $t(24) = 5.27$, $p <.001$; S2, $t(24) = 4.70$, $p <.001$; S1 $t(24) = 4.43$, $p <.001$; Delta $t(24) = 4.39$. $p <.001$).

As with the fast condition, attenuation was again observed outside of the S3 network from rest (M = 3.76) to task (M = 3.09) ($F(1,23) = 23.8$, $p < .001$). A significant main effect of frequency also emerged ($F(4,96) = 133$, $p < .001$) as well as a significant condition by

frequency band interaction (F(4,96) = 3.93, p =. 005). Once again, paired t-tests showed that attenuation of power in the goal-directed task compared to the resting condition emerged for all frequency bands, however this difference was larger in the lower frequency bands i.e. S4, S3 and S2 (S4 t(24) = 5.04, p <.001; S3 t(24) = 4.27, p <.001; S2, t(24) = 4.46, p <.001; S1 t(24) = 4.16, p <.001; Delta t(24) = 4.16. p <.001).

6.3.4.2 *Does rest-task S3 attenuation differentiate between groups? Does this differ between conditions?*

The difference in attenuation of S3 power from rest to the goal-directed task between groups and also between conditions (fast vs. moderate) was assessed using a 2 X 2 X 2 (condition X location X group) repeated measures ANOVA on attenuation scores (difference in S3 power between rest and goal-directed conditions). A main effect of group emerged and the ADHD group exhibited less attenuation from rest to task than the controls (F(1,21) = 19.7, p < .001). The group difference in attenuation survived the co-varying of IQ (F(1,20) = 10.1, p = .001). No effect of condition emerged (F(1,21) = 1.45, p = .236, *ns*) and equal attenuation was observed in the fast and the moderate conditions compared to rest. A non-significant trend for an effect of location was found (F(1,21) = 4.09, p = .056, *ns*) and less attenuation was observed outside of the S3 network (M = -.525) compared to inside the S3 network (M = -.378). No condition by group or location by group interactions emerged (see Figure 6.11)

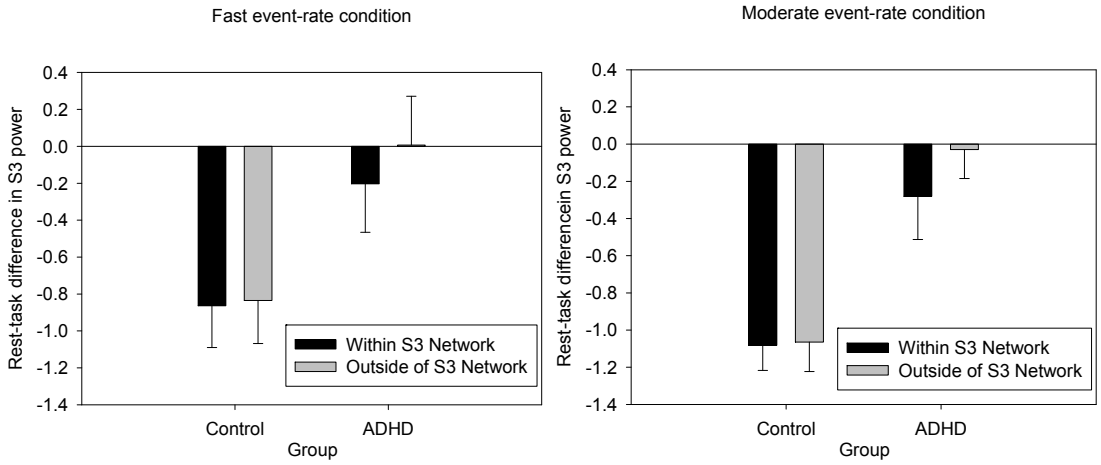


Figure 6.11: Group differences in attenuation from rest to goal-directed task, fast condition (left) and moderate condition (right) within and outside of the S3 network, bars represent +/- 1 standard error.

The group difference in attenuation also survived the covarying of resting S3 power within and outside the S3 network (F(1,19) = 11.8, p =.003).Therefore it appears as if the group differences in rest-task S3 attenuation are not driven by range effects due to differences in the baseline (resting) condition.

6.4 Discussion

In this chapter we identified a network of a resting-state slow 3 oscillations which was broadly similar to the S3 network that we identified in Chapter 4, and again this network was mainly located along the frontal and posterior midline and the central posterior cortex. Also consistent with Chapter 4, we found that participants with ADHD exhibited less very low frequency power (S4 and S3) in this network at rest than controls. However, unlike in the previous study, we did not find that these group differences were independent from power in all other frequency bands.

We also showed that when participants engaged in a goal-directed task, low frequency EEG power was generally attenuated and became more widely dispersed across the scalp than at rest. Again, consistent with our findings in Chapter 4, the ADHD group were found to exhibit less attenuation than the control group. However, we did not find any difference in attenuation between the two RT task conditions, so that greater attenuation was not evident in the fast condition compared to the moderate condition

6.4.1 Localisation of a resting S3 network

The results of this chapter revealed many similarities with our previous findings. Firstly the spatial location of S3 power while participants were resting was very similar in both samples, and was predominantly located along the frontal midline and posterior regions. Similarly, in both samples there was found to be greater low frequency power within this network than outside of it at rest; and furthermore, both inattentive participants and adolescents with ADHD exhibited reduced EEG power at rest within this network compared to controls.

However there were also a number of differences between the findings in the present study and in our previous study. A notable difference is the discrepancy in the magnitude of EEG power within compared to outside of the S3 network at rest. In Chapter 4 we reported that within the S3 network there was much greater low frequency EEG power than outside of the S3 network: although we find this same effect in the present sample, and again we find that within the network there was higher mean power than outside the network, the difference between locations was much less strongly pronounced than in the first sample. There are a number of possible explanations for this, firstly it is possible that these differences reflect differences in development, the first sample comprised of adults (mean age 22 years 4 months) but the present sample consisted of adolescent boys (mean age 14 years 8 months). It is possible that the S3 network is less well developed in the adolescent sample than in the adult sample and that low frequency EEG power is less localised to this resting network in adolescents compared to adults. For example Fair et al. (2008) report that in childhood, default-mode regions are only sparsely connected but with development, these mature in the coherent, default-mode network.

However there were also slight differences in the methods used for data cleaning between the two studies, is it possible that these different methodologies may have

contributed to these different findings. In the first study, prior to data cleaning by ICA, PCA was used to reduce the number of dimensions in the dataset, i.e. so that a maximum of 15 rather than 29 components were extracted from the data, these components were then examined and artifactual components were removed. However in the present study, many more movement artifacts were present in the data and performing PCA for dimension reduction prior to ICA would be inappropriate as a greater number of sources were present in the data. Therefore, in the present study, ICA was performed on the raw EEG data and not on data that had been transformed by PCA. It is possible that this PCA analysis may have impacted on the data and may have reduced the amount of low frequency power identified outside of the S3 network. In order to examine this further, data from a small subset of participants from the first study were re-examined using the same methodology as in the present study. These results are shown in Appendix A20 and demonstrate that using PCA does appear to impact on the data and to affect the magnitude in the difference in S3 power within and outside of the S3 network, however, the direction of this effect remained the same and highly significant ($p < .001$) in both samples.

A further difference was identified in the specificity of the resting S3 network. In both studies, S3 power at rest was found to differ between groups: in the first study an inattentive subgroup was found to exhibit less S3 power at rest than the other groups and in the present study the ADHD group was found to exhibit less S3 power at rest than the control group. In our previous study, this group difference remained after covarying the power in all other frequency bands either within or outside of the S3 network, which suggested that this group difference was independent of power in any of the other frequency bands. However, in the present study, covarying power in the other frequency bands reduced the group difference to statistical insignificance. Again this difference between the two samples could either reflect differences in the development of the two samples – for example, in an adult resting network the S3 frequency band may be more distinct from the other frequencies, but in an adolescent resting network, the distinction of this particular frequency band may not have fully developed. Alternatively, this difference could again reflect variation in the analysis techniques used. In order to clarify this, it will be important to replicate this finding using different analysis techniques and in different developmental samples.

6.4.2 Low frequency oscillations during goal-directed task performance

There were also many similarities between the low frequency activation identified during goal-directed task performance in this study (during either condition of the 2-CR RT task) and during goal-directed task performance in our previous study. In both samples when participants engaged in a goal-directed task there was no difference in the amount of low frequency EEG power within the S3 network compared to outside of the S3 network, so it appears that during goal-directed task performance, low frequency EEG is less confined to the S3 network. Similarly there were no group differences in the amount of low frequency EEG exhibited during goal-direct task performance. However we did find that there were

differences in the spatial location of S3 power during the goal-directed task between samples. In our first study we showed that during the goal-directed task, S3 power did differ from rest and was predominately located along the central posterior cortex and frontally, and notably there was no frontal midline activation at any of the time points. In the present study we again identified a different pattern of S3 activation during the goal-directed task compared to rest, however during both the fast and the moderate event rate conditions of the task, frontal midline activation of S3 power was evident. Furthermore, there were also differences between conditions and there was greater frontal activation during the fast condition than the moderate condition. Therefore it is difficult to determine the spatial location of S3 EEG power during goal-directed performance: this may be due to differences between samples and task conditions, however given that we have not been able to identify a consistent spatial pattern of S3 activation, it appears likely that the spatial location of low frequency EEG may be less stable during task performance than it is during rest. It will be important to assess the spatial location of these low frequency EEG bands across different tasks and different samples before any sound conclusions can be made.

6.4.3 Rest-task attenuation

As in our previous study, we found that there was attenuation of low frequency EEG power from rest to task; also consistent with our previous study we showed that this attenuation was greatest in the lowest frequency bands – S4, S3 and S2. However in contrast to the previous study, we showed that this attenuation was not limited to within the S3 network but also occurred outside of the S3 network: although in the present study we did show that the degree of attenuation was greater within the S3 network than outside of the S3 network. This difference in attenuation outside of the S3 network between samples is likely to be closely linked to the difference in power during rest outside of the S3 network between samples, as the sample in the first study were found to have much lower power outside of the S3 network than the sample in our present study. Again this difference is likely to be due to the analysis techniques employed by the first study – however replication of these findings will be necessary to clarify this. Nevertheless, consistent with our first study, in which inattentive participants were found to exhibit least attenuation of low frequency EEG from rest to task, in the present study we showed that patients with ADHD exhibited less rest-task attenuation than controls. Again these findings offer some support for the default mode interference hypothesis (Sonuga-Barke & Castellanos, 2007), which suggests that patients with ADHD may not effectively attenuate resting low frequency EEG when they engage in a goal-directed task and this may then intrude into goal-directed performance.

6.4.4 The impact of event-rate

In the present study we employed two conditions of the 2-CR RT task, one with a fast- (1 second ISI) and one with a moderate-event rate (3 second ISI). We predicted that the degree of attenuation from rest to task would be associated with event rate, so that greater attenuation would be evident in the fast condition of the task compared to the moderate

condition. However we did not find this, there was no difference in the degree of attenuation from rest to task between the fast and the moderate event rate condition. This is somewhat surprising as attenuation of resting brain activity has been shown to be proportional to task difficulty in fMRI research. For example, McKiernan et al. (2006) showed that the degree of task induced deactivations from a resting baseline were proportional to event rate, and that greater task induced deactivations were observed in a fast- (600ms) compared to a moderate- (1000ms) or a slow-event rate condition (2000ms). However it is important to note that the ISI of the conditions in the McKiernan et al. (2006) study differed from those we adopted in our present study. In fact, the moderate event rate of the McKiernan study was equivalent to the fast event rate adopted by our study and our moderate event rate was actually slower than their slow event rate. McKiernan et al. (2006) report no difference in the degree of task induced deactivations between their moderate- (1000ms) and their slow-event rate conditions (2000ms), which would be the most comparable to the two conditions employed by our present study. Therefore, it is possible that our fast event rate was insufficiently fast to induce a difference in attenuation from rest to task. Future investigations that employ a range of event rates will help to elucidate whether the degree of rest-task EEG attenuation is associated with event-rate.

6.4.5 The impact of IQ

In the present study, the children with ADHD were found to have lower IQs than the controls, therefore all analyses of group differences were run with and without IQ entered as a covariate. Both of the group differences identified in this chapter (rest-task attenuation and power of resting S3 EEG) were found to remain intact after IQ was entered as a covariate (although the difference in resting S3 power just missed significance when IQ was controlled, $p = .055$). This suggests that the group differences observed are not an artifact of IQ but do represent valid differences in patients with ADHD.

6.4.6 Limitations

Many of the limitations described in section *4.4.3 Limitations* also apply here, for example group sample sizes were small – especially after participants with excessive movement artifacts were excluded from the analyses - also the number and arrangement of scalp electrodes does not allow for source analysis, which would determine whether these low frequency EEG data were associated with the structures of the default mode network. Similarly by focussing only on the low frequencies, we are unable to determine associations between these low frequencies and higher frequency neuronal bands such as alpha and theta. However, we did attempt to run these analyses on the full frequency spectrum, and ran ICA analysis for data cleaning on the full-band EEG data from a small subset of participants. But as the maximum number of components extracted by ICA is equal to the number of input channels, a limited number of components can be extracted by ICA - 29 in our present study. When ICA was performed on the full-band rather than filtered (down-sampled) data, many more sources were present in the data, for example higher frequency artifacts, such as mains

noise (50 Hz), as well as higher frequency brain activity such as alpha and theta: each of these sources was then extracted by ICA as an independent component. ICA is not appropriate when there are a greater number of sources than inputs, and in participants with a large number of movement artifacts, on the full-band EEG there were a greater number of sources than could be extracted by ICA, therefore it was not appropriate to use this method of data cleaning. For consistency with the previous study, we again downsampled the data to 10 Hz and only investigated the lower frequencies (< 5 Hz).

6.5 Conclusions

We replicated many of the findings from our previous study, a broadly similar resting network of S3 EEG was identified, and patients with ADHD exhibited lower power in this network than controls at rest. Furthermore, patients with ADHD exhibited less attenuation of low frequency EEG from rest to task, however the degree of attenuation did not differ between event rates. Differences in the magnitude of EEG power outside of the S3 network at rest were observed in our present study compared to our previous study but these differences are likely to be the result of differences in data cleaning methods adopted in each study.

Chapter 7 The associations between intra-individual variability in task performance, ADHD and low frequency EEG

7.1 Introduction

In Chapter 5 we assessed the associations between intra-individual variability in task performance, ADHD and low frequency EEG. In an attempt to understand whether variability has a temporal pattern we decomposed intra-individual variability into its constituent power components using FFT analysis. We found that power in the S3 RT frequency band made the greatest improvement to the prediction of group membership (high-ADHD or low-ADHD) beyond SD of RT or normalised variance. We also found that participants who rated themselves as having more ADHD symptoms were likely to make more errors on the RT task; however they did not exhibit greater intra-individual variability than participants who rated themselves as having fewer ADHD symptoms. As we described in Chapter 5, the lack of significant between-group differences in intra-individual variability may have been caused by the fast event rate of the task employed by the study, and so in this chapter we also adopted a moderate event rate condition of this task (3 second ISI).

In Chapter 5, we also found that participants who exhibited least attenuation of the S3 EEG signal when engaging in a goal-directed task (compared to rest) showed greater synchrony between their S3 EEG and S3 RT signals, which indicates that the S3 EEG may be impacting on the RT signal. Similarly, participants who self-reported the most ADHD symptoms also showed greater synchrony between these two signals, although this did not reach statistical significance. In this chapter, we aimed to replicate these findings in a clinical sample of adolescent boys with ADHD.

7.1.1 Aims

This chapter aimed to replicate and extend the findings of the previous study. Firstly it aimed to determine the associations between intra-individual variability in task performance and ADHD in a clinical sample of adolescents with ADHD. Specifically it aimed: i) to establish the associations between ADHD and both standard measures of variability – such as SD of RT and normalised variability – and frequency domain measures of variability; ii) to establishing whether frequency domain measures of variability contribute to the prediction of group membership (ADHD or control) beyond the standard measures of variability; and iii) to determine whether these associations are more apparent in a moderate- compared to a fast-event rate condition.

Secondly the chapter aimed to clarify the association between oscillations in behavioural data and intrusions of low frequency brain activity by replicating the findings of Chapter 5 in a clinical sample of ADHD cases. Specifically, it aimed: i) to determine the

association between the temporal synchrony of low frequency RT and EEG (as described by their cross-correlation) and the degree of attenuation of this low frequency EEG from rest to a goal-directed task and to ii) establish whether the degree of temporal synchrony between the S3 EEG and the S3 RT signals is greater in ADHD than in controls.

7.1.2 Predictions

1) The associations between intra-individual variability and lapses in attention

Consistent with previous literature (e.g. Nigg et al., 2005), we predicted that the ADHD group would be slower, more variable and would make more errors than the controls. However, we further predicted that there would be a group by event rate interaction for measures of variability and the group differences in variability would be less pronounced in the high event rate condition than in the moderate event rate (e.g. Scheres et al., 2001). Furthermore, consistent with our previous findings and the findings of Di Martino et al. (2008) we predicted that the RT frequency band that would make the greatest improvement to predictions of group membership (ADHD or control) beyond global measures of variability would be S3.

2) The temporal synchrony of behavioural and EEG oscillations

Also consistent with the findings of Chapter 5, we predicted that there would be a small but significant degree of synchronisation between the S3 RT and S3 EEG signal across all participants. Furthermore, we predicted that participants who do not effectively attenuate their S3 EEG from rest to task and participants with ADHD would exhibit a greater degree of synchrony between EEG and RT as these participants should be most likely to experience intrusions of low frequency EEG into their task performance.

7.2 Methods

7.2.1 Participants

As in 6.2.1 Participants

7.2.2 Design

As in 6.2.2 Design

7.2.3 Procedure

As in 6.2.3 Procedure

7.2.4 Data Processing

7.2.4.1 *Behavioural Data*

Time Domain

As described in the previous chapter, participants who made >15% omission errors on the 2-choice RT task were excluded from further analysis. Impossible responses (<100ms) for each participant were removed. The number of omission errors and directional errors that each participant made during each condition was calculated, but as the number of trials differed between the fast and the moderate condition of the task, the percentage of trials which were omission errors and the percentage of trials which were directional errors were then calculated for each participant in each condition.

As in the previous chapter, paired t-tests showed that in both the fast- and the moderate-event rate conditions, mean RT was slower across correct responses than across incorrect responses (fast: *correct RT* M = 335 ms, SD = 35.4ms, *incorrect RT* M = 265 ms, SD = 37.5ms, $t(30) = 13.89$, $p<.001$) (moderate: *correct RT* M = 390 ms, SD = 78.1 ms, *incorrect RT* M = 341 ms, SD = 93.68 ms, $t(31) = 5.08$, $p<.001$). As response type (correct or incorrect) impacted on the RT and SD of RT, general measures of mean RT and SD of RT were calculated from only the correct responses. Furthermore, as mean RT and SD of RT were found to be highly correlated within each task (fast $r(30) = .559$, $p = .001$; moderate $r(31) = .843$, $p<.001$), a measure of normalised variance was also calculated (SD of RT / mean RT). For each of these measures, any individual's score that lay outside of 3 standard deviations from the group mean was considered to be an outlier and was replaced by the group mean for that measure.

Frequency Domain

The data were prepared for frequency domain analysis in the same way as described in Chapter 5 (section *5.2.5 Data Analysis*). Briefly, errors were regressed out of the RT data using linear regressions, missing responses were interpolated using a linear interpolation (SPSS version 15) and the first two responses made by each participant were excluded. FFT analyses were then performed using 60 second Hamming windows that overlapped by 10 seconds. The power in each of S4 (.02-.06 Hz) and S3 (.06-.2Hz) RT frequency bands was then calculated as area under the FFT curve for each participant. Due to the constraints imposed by the sampling rate, power in the S2 frequency band (.2 - .6Hz) could only be calculated for the fast condition and not the moderate event-rate condition.

7.2.4.2 *Temporal synchrony of behavioural and EEG oscillations*

We then created an index of the temporal S3 synchrony between the EEG and RT data for each of the fast and the moderate conditions in the same manner as described in Chapter 5 (section *5.2.5 Data Analysis*). Briefly, the EEG data were prepared as described in section *6.3.1 EEG Data Processing* and the RT time series was prepared as described in the previous section and then upsampled to 10 Hz. Both signals were normalised and bandpass

filtered to leave only the S3 frequency component. Cross-correlations were then performed between each participant's RT time series and their EEG signal. The peak cross-correlation between +/- 1 second (i.e. +/- 10 lags) between each channel of EEG data (N = 27) and the RT time series data was calculated for each participant. Subsequently, the mean peak cross-correlation across all of the electrodes within the S3 network was calculated to obtain an index of S3 RT-EEG synchrony for each participant within the S3 network; and the mean cross-correlation across all of the electrodes outside of the S3 network was calculated to obtain an index of S3 RT-EEG synchrony for each participant outside of the S3 network.

7.2.4.3 *Normality of Data Distribution*

The normality of the distribution of data for each variable was assessed across all cases using the Kolmogorov-Smimov test of normality (K-S). As in the previous chapter, the percentage of omission errors was not normally distributed for either the fast or moderate conditions (K-S(33) = .259, p = .001; K-S(33) = .321, p < .001 respectively), however, a square root transformation was able to obtain normality of these distributions (K-S(33) = .189, p = .129, *ns:* K-S(33) = .191, p = .098 *ns*). Furthermore no frequency domain measures of variability were normally distributed, for any of the tasks; however a natural log transformation was able to obtain normality of distribution. Subsequent analyses using these variables were performed on these transformed data.

7.2.4.4 *Statistical Analyses*

Associations between the 2-CR RT task dependent variables, ADHD and event rate

Intra-task correlations were used to assess the associations between dependent variables and repeated measures ANOVAs were used to assess group and condition differences for each dependent variable from the 2-CR RT task.

Predicting group membership

The contribution of power in each RT frequency band to predicting group membership (ADHD or Control) was assessed using binary logistical regression with group as the dependent variable. The contribution of power in each frequency band beyond the model that contained IQ and either SD of RT or normalised variance was expressed by the number of cases correctly classified and the χ^2 of the change for each step.

Associations between low frequency EEG and low frequency fluctuations in RT data and the association between rest-task attenuation and task performance

Following the analyses of Chapter 5, the degree of synchronisation between the S3 RT and S3 EEG signals was determined using a one sampled t-test to assess whether S3 RT-EEG synchrony differed from 0. The difference in S3 RT-EEG synchrony between groups and between conditions was assessed using repeated measures ANOVA. The association between attenuation and task performance were assessed by correlations between rest-task attenuation and task performance in each condition of the 2-CR RT task.

7.3 Results

7.3.1 Associations between task variables and IQ

As the ADHD group was found to have lower IQ than the control group, the association between output variables from the 2-CR RT task and IQ were assessed (see Table 7.1). All of the variables except mean RT were significantly negatively correlated with IQ and participants with lower IQs tended to be more variable and to make more errors than those with high IQs. As IQ was associated with the output variables from the 2-CR RT task and IQ was also found to differ between groups (see section *6.4.1 Clinical Characteristics*), all analyses were run with and without IQ entered as a covariate.

Table 7.1

Correlations (Pearson's r) between variables from 2-CR RT task and IQ

	Pearson's r
Fast event-rate condition	
1. Mean RT	-.267
2. SD of RT	-.604**
3. Normalised variance	-.597**
4.% Directional errors	-.512**
5. % Omission errors	-.540**
Moderate event-rate condition	
6. Mean RT	.021
7. SD of RT	-.438*
8. Normalised variance	-.535**
9. % Directional errors	-.561**
10.% Omission errors	-.352†

** p<.01, *p <.05, $^{\dagger}p$ <.1

7.3.2 Time-domain measures of variability

Intra-task correlations for the 2-CR RT task are shown in Table 7.2. All measures were positively correlated between conditions, so participants who responded more slowly during the fast condition also responded more slowly during the moderate condition, participants who were more variable during the fast condition also exhibited greater variability during the moderate condition, and participants who made more errors in the fast condition

also tended to make more errors in the moderate condition. Within each condition (fast- and moderate event-rate condition) mean RT and SD of RT were highly positively correlated, and participants who were slower also tended to be more variable. Furthermore, both measures of variance - SD of RT and normalised variance - were positively correlated with measures of error (% directional errors and % omission errors) both within and between conditions. Thus, participants who were more variable in the fast condition tended to make more errors in both this condition and the moderate condition. Similarly participants who were more variable in the moderate condition tended to make more errors during both conditions. There was no correlation between mean RT and number of errors, so participants who tended to be slower were no more accurate than faster participants

Table 7.2

Two-CR RT task intra-task correlations

	1	2	3	4	5	6	7	8	9	10
Fast condition										
1. Mean RT	--	.521**	.262	-.016	.174	.720**	.731**	.619**	.476**	.465*
2. SD of RT		--	.954**	.743**	.733**	.200	.691**	.777**	.799**	.701**
3. Normalised variance			--	.827**	.826**	.011	.538**	.670**	.722**	.620**
4.% Directional errors				--	.736**	-.259	.266	.439*	.733**	.419*
5. % Omission errors					--	.007	.510**	.626**	.588**	.575**
Moderate condition										
6. Mean RT						--	.635**	.367*	-.091	.187
7. SD of RT							--	.944**	.478**	.512**
8. Normalised variance								--	.636**	.550**
9. % Directional errors									--	.414*
10.% Omission errors										--

**, $p<.01$, *$p<.05$

Repeated measures ANOVAs with condition (fast vs moderate) entered as the within subjects factor and group (ADHD vs controls) as the between subjects factor were run for each dependent variable from the 2-CR RT task. Mean performance on each variable for each group, as well as the ANOVA main effects (difference between conditions), group effects and condition by group interactions for each variable are shown in Table 7.3. Significant main effects of condition were identified for each variable, and participants made fewer omission and directional errors, were slower and less variable in the moderate condition compared to the fast condition. Furthermore, patients with ADHD made more omission errors, were slower, and more variable than controls; however, there were no significant condition by group interactions. Table 7.4 illustrates that after controlling for the effects of IQ, all of the main effects of condition remained statistically significant except for the number of directional errors made, and furthermore the group differences in variability and mean RT remain intact. Although neither measure of error remained statistically significant between groups, the group difference in the number of omission errors just fails to reach statistical significance (p = .07). A statistically significant condition by group interaction also emerged for SD of RT and when IQ is controlled, so that controls showed a marked reduction in variability in the moderate condition (M = 57.6) compared to the fast condition (M = 81.9) but patients with ADHD displayed slightly greater variability in the moderate condition (M = 111) compared to the fast condition (M = 108).

Table 7.3

Group Differences on 2-CR RT task, fast and moderate event-rate conditions

	Fast condition Mean (SD)		Moderate condition Mean (SD)		*Main Effect (Condition)*		*Group Effect*		*M X G*	
	Control	ADHD	Control	ADHD	*F*	*p*	*F*	*p*	*F*	*p*
% Omission errors[a]	.844 (1.24)	4.07 (4.43)	.094 (.271)	2.23 (3.97)	28.25	<.001**	9.89	.004**	1.18	.287
% Directional errors	15.5 (8.82)	20.6 (10.7)	4.72 (3.74)	8.67 (6.27)	73.07	<.001**	2.59	.119	.283	.604
Mean RT	321 (29.7)	356 (35.1)	361 (45.5)	401 (56.4)	38.15	<.001**	7.69	.010**	.444	.513
SD of RT	74.6 (27.5)	117.1 (34.7)	57.3 (11.4)	110 (30.2)	4.84	.037*	30.0	<.001**	1.01	.324
Normalised variance	.233 (.088)	.327 (.086)	.159 (.030)	.273 (.056)	22.15	<.001**	21.5	<.001**	.332	.547

**, p<.01, *p <.05

Note. [a] the mean percentage of omission errors for each group is shown in this table for illustrative purposes, however as this variable was not normally distributed, analyses were performed on the square root transformed data.

Main Effect = Effect of condition, M X G = Condition by Group interaction

Table 7.4

Main and group differences and their interaction between 2-CR RT task at fast and moderate conditions, when IQ is controlled

	Main Effect (Condition)		*Group Effect*		*M X G*	
	F	*P*	*F*	*p*	*F*	*p*
% Omission errors	5.64	.025*	3.46	.074	.936	.342
% Directional errors	7.70	.010*	<.001	.985	.155	.697
Mean RT	1.59	.218	8.26	.008**	3.04	.093
SD of RT	8.19	.008**	15.49	.001**	5.25	.030*
Normalised variance	10.54	.003**	10.52	.003**	2.76	.108

**, p<.01, *p <.05

Note. Main Effect = Effect of condition, M X G = Condition by Group interaction

7.3.3 Frequency domain measures of variability

The mean FFT for each group (ADHD and Control) for each of the fast and the moderate conditions of the 2-CR RT task are shown in Figure 7.1. Low frequency peaks were evident in the control FFT at approximately .04 Hz and .08 Hz in each condition and in the ADHD FFT at about .08 Hz in the moderate condition but not in the fast condition. The ADHD group appeared to be more variable across the whole frequency spectrum than the control group for each condition.

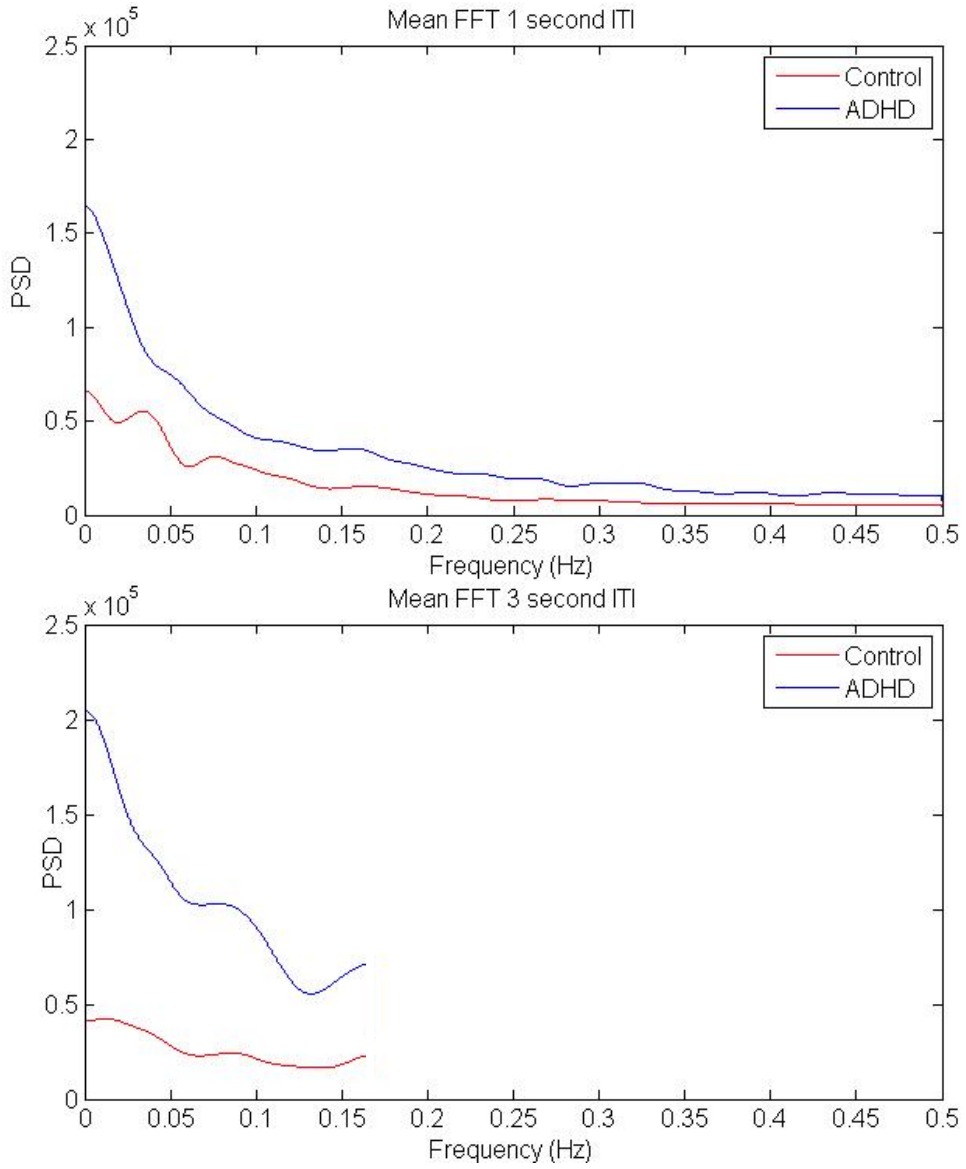


Figure 7.1: Mean FFT for each group for the 2-CR RT task for the fast condition (above) and the moderate condition (below).

Note. Due to the lower sampling rate, a smaller proportion of the frequency spectrum is available for the moderate event-rate condition of the task.

Intra-task correlations on the 2-CR RT task for frequency domain variability and error measure are shown in Table 7.5. Frequency domain measures of variability were highly positively correlated, both within and between each condition (fast and moderate), particularly within neighbouring frequency bands. Furthermore, within each condition all frequency domain measures of variability were positively correlated with the number of errors made, so that participants who were more variable also made more errors: although within the moderate condition the strength of this correlation was higher for omission errors than for directional errors.

Table 7.5

Two-CR RT task frequency domain variability and error intra-task correlations

	1	2	3	4	5	6	7	8	9
2-CR RT task 1 sec ISI									
1. S4 RT power	--	.939**	.805**	.644**	.823**	.505**	.581**	.628**	.525**
2. S3 RT power		--	.907**	.673**	.774**	.575**	.645**	.681**	.581**
3. S2 RT power			--	.635**	.727**	.679**	.756**	.749**	.643**
4.% Directional errors				--	.736**	.145	.240	.733**	.419*
5. % Omission errors					--	.459*	.551**	.588**	.575**
2-CR RT task 3 sec ISI									
6. S4 RT power						--	.933**	.398*	.653**.
7. S3 RT power							--	.467**	.590**
8. % Directional errors								--	.414*
9.% Omission errors									--

**, p<.01, *p <.05, †p<.1

Repeated measures ANOVAs with condition (fast vs moderate) entered as the within subjects factor and group (ADHD vs controls) as the between subjects factor were run for each of the S4 and S3 RT frequency measures of variability from the 2-CR RT task. As S2 RT power could not be calculated for the moderate condition due to the lower sampling rate, repeated measures ANOVA was not suitable for this variable, therefore group differences in S2 power were calculated using a one-way ANOVA. Mean performance on each variable for each group, as well as the ANOVA main effects (difference between conditions), group effects and condition by group interactions for each variable are shown in Table 7.6. No significant main effects of condition were identified for either S4 or S3 RT power, which suggests that participants exhibited equal variability in these frequency domain measures in the fast and the moderate event-rate conditions. However, for all frequency measures of variability S4, S3 and S2 RT power, patients with ADHD were more variable than controls. There were no significant condition by group interactions. However, Table 7.7 illustrates that not only did these group differences in variability remain intact after controlling for the effects of IQ, when IQ is controlled, a main effect of condition emerged for both the S4 and S3 RT frequency bands, and participants were more variable in the moderate condition compared to the fast condition. Also a statistically significant condition by group interaction emerged for S3 power: so that when IQ is controlled, control participants show a reduction in S3 RT variability in the moderate condition compared to the fast condition, but patients with ADHD conversely show an increase in S3 RT variability in the moderate condition compared to the fast condition. A similar trend for a condition by group interaction also emerged for S4 power, although this just failed to reach statistical significance (p = .066).

Table 7.6

Group Differences on frequency domain measures of variability for the 2-CR RT task at fast and moderate event rate conditions

	Fast condition Mean (SD)		Moderate condition Mean (SD)		*Main Effect (Condition)*		*Group Effect*		*M X G*	
	Control	ADHD	Control	ADHD	*F*	*p*	*F*	*p*	*F*	*p*
S4 RT power	6.67 (1.167)	7.71 (.932)	6.79 (.796)	8.18 (.760)	1.14	.269	16.5	<.001**	.267	.609
S3 RT power	7.51 (.863)	8.40 (.667)	7.58 (.553)	8.81 (.686)	2.08	.160	21.0	<.001**	.939	.341
S2 RT power[a]	7.54 (.461)	8.33 (.467)					22.0	<.001**		

Table 7.7

Group Differences on frequency domain measures of variability for the 2-CR RT task at fast and moderate event rate conditions when IQ is controlled

	Main Effect (Condition)		*Group Effect*		*M X G*	
	F	*p*	*F*	*p*	*F*	*p*
S4 RT power	6.37	.018*	7.27	.012*	3.69	.066†
S3 RT power	7.19	.013*	10.39	.003**	6.15	.020*
S2 RT power[a]			8.35	.008**		

**, p<.01, *p <.05, †p< .1

Note. [a]S2 power could not be calculated for the moderate condition due to the lower sampling rate, therefore main effects and M X G interactions could not be calculated for this variable.

Main Effect = Effect of condition, M X G = Condition by Group interaction

7.3.3.1 *Predicting group membership*

The contribution of power in each of the S4, S3 and S2 RT frequency bands, in predicting group membership, above that of IQ as well as SD of RT or normalised variance on the 2-CR RT task fast condition is shown in Table 7.8 and on the 2-CR RT task moderate condition in Table 7.9. It is clear from both of these tables that the initial models that contained IQ and the global measures of variability were able to correctly classify the majority of the cases into the correct groups. In the fast condition 70% of cases were correctly classified by this initial model, however in the moderate condition, this initial model was able to correctly classify nearly all of the cases (96.8%). In the fast condition, only the addition of S2 RT power significantly improved the model and improved classification from 70% to 86.7%. In the moderate condition, the addition of S4 RT power was able to improve the model from 96.8% to 100% correct classification. This pattern of findings was very similar when IQ was not included into the model (see Appendix A21).

Table 7.8

Contributions of S4, S3 and S2 RT power to classification of group (ADHD or Control), above IQ and SD of RT and normalised variance on the fast event-rate condition

Model	Added variable	% correctly classified	χ^2 model	*p*	χ^2 step	*p*
IQ + SD of RT		70.0%	14.96	.001		
IQ + SD of RT +	S4 RT power	73.3%	16.14	.001	1.18	.278
IQ + SD of RT +	S3 RT power	73.3%	16.07	.001	1.11	.293
IQ + SD of RT +	S2 RT power	86.7%	21.70	<.001	6.74	.009**
IQ + Normalised variance		70.0%	12.65	.002		
IQ + Normalised variance +	S4 RT power	66.7%	12.68	.005	.030	.862
IQ + Normalised variance +	S3 RT power	73.3%	13.26	.004	.607	.436
IQ + Normalised variance +	S2 RT power	86.7%	24.03	<.001	11.38	.001**

*p <.05, $^{\dagger}p$<.1

Table 7.9

Contributions of S4 and S3 RT power to classification of group (ADHD or Control), above IQ and SD of RT and normalised variance on the moderate event rate condition

Model	Added variable	% correctly classified	χ^2 model	*p*	χ^2 step	*p*
IQ + SD of RT +		96.8%	37.13	<.001		
IQ + SD of RT +	S4 RT power	100%	42.94	<.001	5.82	.016*
IQ + SD of RT +	S3 RT power	96.8%	37.77	<.001	.312	.576
IQ + Normalised variance		96.8%	33.78	<.001		
IQ + Normalised variance +	S4 RT power	96.8%	38.02	<.001	3.68	.055†
IQ + Normalised variance +	S3 RT power	93.5%	35.27	<.001	1.15	.285

*p <.05, †p<.1

7.3.3.2 *Summary*

Participants were generally slower, less variable and made fewer errors on the moderate compared to the fast event rate condition of the choice RT task. Children with ADHD were slower, more variable (on both global measures of variability and frequency domain measures of variability) and made more errors than controls on this choice RT task. These effects of group remained after IQ was statistically controlled. The power in one RT frequency band - S4 - improved the classification of group membership beyond global measures of variability and IQ similarly, S4 power improved classification of ADHD and control cases beyond global measures of variability and IQ in the moderate event rate condition, however in the fast event rate condition, only power in the S2 RT power uniquely improved classification of ADHD and control cases.

7.3.4 Temporal synchrony of behavioural and EEG oscillations

7.3.4.1 *Fast event-rate condition*

Table 7.10 shows the mean S3 RT-EEG synchrony within groups. Consistent with the findings of Chapter 5, mean S3 RT-EEG synchrony was small overall both within and outside of the S3 network but significantly different from zero. However, when S3 RT-EEG synchrony was calculated within groups, i.e. separately for ADHD and control cases, only the control S3 RT-EEG synchrony was found to be significantly different from zero, the S3 RT-EEG synchrony of the ADHD group did not differ from zero in either location.

Table 7.10

Mean S3 RT-EEG synchrony within groups for the fast condition of the 2-CR RT task

					95 % Confidence Interval	
Group	Mean	*t*	df	*p* (2-tailed)	Upper	Lower
Overall within network	.0337	3.27	24	.002**	.0137	.0537
Overall outside network	.0279	2.92	24	.007**	.0082	.0476
Control within network	.0534	4.12	14	.001**	.0256	.0811
Control outside network	.0449	3.36	14	.005**	.0162	.0735
ADHD within network	.0069	.643	10	.535	-.0170	.0307
ADHD outside network	.0048	.463	10	.654	-.0182	.0277

**$p<.01$

S3 RT-EEG synchrony was also found to be significantly negatively correlated with the number of errors made (within S3 network, $r(26) = -.508$, $p = .008$; outside of S3 network $r(26) = -.454$ $p = .020$) so participants who made more errors tended to demonstrate the least S3 RT-EEG synchrony. As described previously, response type (correct or incorrect) impacted on the RT and error responses were typically faster than correct responses: in an attempt to control for the impact of error on RT, error was regressed out of the RT data using linear regression residuals (see section *7.2.4 Data Processing*). However, it is possible that the use of these regression residuals may have introduced some bias into the data and therefore data that contained many errors are likely to be less reliable indicators of attention than data with fewer errors. If this were the case we would expect to observe lower synchrony between RT and EEG data in participants who made a greater number of errors and this may be particularly salient for the ADHD group who were found to be less accurate in this task. When all cases with > 25% error rate were excluded from the analysis, S3 RT-EEG synchrony was significantly different from zero overall and in each group (see Table 7.11).

Table 7.11

Mean S3 RT-EEG synchrony within groups when cases with > 25% error rate are excluded

					95 % Confidence Interval	
Group	Mean	*t*	df	*p* (2-tailed)	Upper	Lower
Overall within network	.0449	4.74	15	<.001**	.0247	.0651
Overall outside network	.0386	3.65	15	.002**	.0160	.0612
Control within network	.0534	3.96	9	.003**	.0229	.0840
Control outside network	.0465	2.96	9	.016*	.0109	.0826
ADHD within network	.0307	3.00	5	.030*	.0044	.0571
ADHD outside network	.0255	2.54	5	.052	-.0003	.0513

**p<.01, *p<.05

Furthermore, when all cases with > 25% error rate were excluded from the analysis *rest-task S3 non-attenuators* exhibited greater S3 RT-EEG synchrony (M = .0723) than *rest-task S3 attenuators* (M = .0347), however this just failed to reach statistical significance in independent samples t-tests either within (t(13) = 1.77, p = .101, *ns*) or outside of the S3 network (t(13) = 1.01, p = .333, *ns*). Furthermore, although the ADHD group appeared to exhibit reduced S3 RT-EEG synchrony (M = .0290) compared to the control group (M = .0496) this was not statistically significant either within (t(14) = 1.18, p = .259, *ns*) or outside of the S3 network (t(14) = .955, p = .356, *ns*).

7.3.4.2 *Moderate event-rate condition*

Mean S3 RT-EEG synchrony in the moderate event-rate condition was also found to be small overall but to differ from zero - both within and outside of the S3 network - and this was the case for both the ADHD and the control groups (see Table 7.12)

Table 7.12

Mean S3 RT-EEG synchrony within groups during 2-CR RT task moderate condition

					95 % Confidence Interval	
Group	Mean	*t*	df	*p* (2-tailed)	Upper	Lower
Overall within network	.0585	4.12	24	< .001**	.0292	.0878
Overall outside network	.0509	4.07	24	< .001**	.0250	.0767
Control within network	.0520	3.12	14	.008**	.0162	.0878
Control outside network	.0434	3.14	14	.007**	.0137	.0730
ADHD within network	.0681	2.62	9	.028*	.0094	.1269
ADHD outside network	.0621	2.59	9	.029*	.0079	.1163

***p*<.01, **p*<.05

No participants made greater than 25% errors in this condition and S3 RT-EEG synchrony was not found to be significantly correlated with the number of errors made in this condition (within S3 network, $r(25) = -.093$, $p = .659$, *ns*; outside of S3 network $r(25) = -.135$, $p = .519$, *ns*) so it seemed unlikely that errors were impacting on the synchrony analyses in this condition, therefore the analyses were not re-run excluding cases with a high error rate.

In this condition, the ADHD group exhibited greater S3 RT-EEG synchrony (M = .0651) than the control group (M = .0477), however this did not reach statistical significance either within ($t(23) = .547$, $p = .589$, *ns*) or outside of the S3 network ($t(23) = .735$, $p = .476$, *ns*). Similarly, *rest-task S3 non-attenuators* (N = 4) exhibited greater S3 RT-EEG synchrony (M = .1125) than *rest-task S3 attenuators* (N = 21) (M = .0437). This difference was found to be statistically significant in an independent samples t-test outside of the S3 network ($t(23) = 2.44$, $p = .023$) and just failed to reach statistical significance within the S3 network ($t(23) = 1.66$, $p = .111$, *ns*). To overcome the large difference in group size between the *rest-task S3 non-attenuators* (N = 4) and *rest-task S3 attenuators* (N = 21), participants were median-split into those that showed greater than mean attenuation and those that showed less than mean attenuation. These two groups were found to significantly differ in degree of S3 RT-EEG synchrony, and those who attenuated least exhibited greater synchrony (M = .0839) than those who attenuated most (M = .0277), this was shown to be statistically significant both within ($t(23) = 2.20$, $p = .038$) and outside of the S3 network ($t(23) = 2.38$, $p = .026$). This difference remained when IQ was controlled (inside S3 network, $F(1,22) = 4.39$, $p = .048$; outside S3 network $F(1,22) = 5.39$, $p = .030$).

7.3.4.3 *Is there a differential effect of event-rate on ADHD and controls?*

The difference in S3 RT-EEG synchrony between groups and also between conditions (fast vs. moderate) was assessed using a 2 X 2 X 2 (condition X location X group) repeated measures ANOVA. No main effect of group emerged ($F(1,21) = .293$, $p = .594$, *ns*) and the ADHD group exhibited the same degree of synchrony as controls. However a main effect of condition did emerge ($F(1,21) = 4.49$, $p = .046$) and S3 RT-EEG synchrony was greater in the moderate condition (M = .063) than in the fast condition (M = .025); as well as a main effect of location ($F(1,21) = 5.10$, $p = .035$) and S3 RT-EEG synchrony was higher within the S3 network (M = .047) than outside the S3 network (M = .040). Furthermore a condition by group interaction was found to be statistically significant ($F(1,21) = 4.83$, $p = .039$) and the ADHD group were found to exhibit lower S3 RT-EEG synchrony compared to controls in the fast condition but higher S3 RT-EEG synchrony in the moderate condition of the 2-CR RT task (see Figure 7.2). No condition by location or location by group interactions emerged.

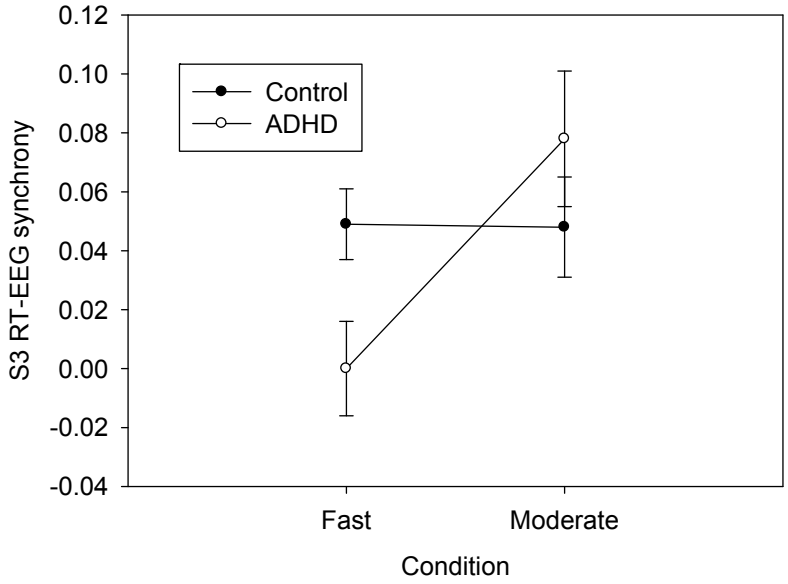


Figure 7.2: S3 RT-EEG synchrony between groups in the fast and the moderate conditions of the 2-CR RT task, bars represent +/- 1 standard error

The condition by group interaction survived the co-varying of IQ ($F(1,20) = 5.26$ $p = .033$), however the main effects of condition and location were reduced to statistical insignificance.

7.3.5 Associations between attenuation and task performance

7.3.5.1 *Fast event-rate condition*

Table 7.13 shows the correlations between the rest-task attenuation of EEG power and task performance. Consistent with our previous findings, rest-task attenuation tended to be negatively correlated with task performance measures, so that participants who attenuated least made more errors, and were slower and more variable than those who attenuated most: however this only reached statistical significance for mean RT.

Table 7.13

Correlations between S3 RT-EEG synchrony, rest-task attenuation, and task performance in the fast condition of the 2-CR RT task

	1	2	3	4	5	6	7
Rest-task attenuation							
1. Rest-task attenuation within S3 network	--	.893	-.171	-.032	-.343†	-.232	-.251
2. Rest-task attenuation outside S3 network		--	-.169	-.100	-.458*	-.378†	-.266
Task Performance							
3. % Omission errors			--	.736**	.174	.773**	.826**
4. % Directional errors				--	-.016	.743**	.827**
5. Mean RT					--	.521**	.262
6. SD of RT						--	.954**
7. Normalised variance							--

** p<.01, *p <.05, $^{\dagger}p$<.1

7.3.5.2 *Moderate event-rate condition*

Table 7.14 shows these same correlations for the moderate condition i.e. between the rest-task attenuation of EEG power and task performance. In this condition, again rest-task attenuation was negatively correlated with task performance measures, and participants who attenuated least tended to make the most errors and to be slower and more variable than those who attenuated most, this association was statistically significant for omission errors and measures of variability.

Table 7.14

Correlations between S3 RT-EEG synchrony, rest-task attenuation, and task performance in the moderate condition of the 2-CR RT task

	1	2	3	4	5	6	7
Rest-task attenuation							
1. Rest-task attenuation within S3 network	--	.853**	-.346†	-.214	-.150	-.354†	-.340†
2. Rest-task attenuation outside S3 network		--	-.411*	-.504*	-.109	-.562**	-.587**
Task Performance							
3. % Omission errors			--	.414*	.187	.512**	.550**
4. % Directional errors				--	-.091	.478**	.636**
5. Mean RT					--	.635**	.367*
6. SD of RT						--	.944**
7. Normalised variance							--

** p<.01, *p <.05, $^{\dagger}p$<.1

7.3.5.3 *Summary*

Although synchrony between S3 EEG and S3 RT data was small, we showed that it was significantly greater than zero and rest-task S3 non-attenuators exhibited greater S3 RT-EEG synchrony than rest-task S3 attenuators. Furthermore, we also found that participants who exhibited least rest-task attenuation performed most poorly on the choice RT task, they made the most errors, and were slower and more variable than those who attenuated most. Moreover, children with ADHD exhibited less S3 RT-EEG synchrony than controls during the moderate event rate condition but greater S3 RT-EEG synchrony than controls in the fast event rate condition.

7.4 Discussion

Consistent with previous literature, we showed that children with ADHD were slower, more variable and made more errors than controls on a choice RT task. When RT data were decomposed into frequency domain measures of variability, peaks were evident at about .04 and .08 Hz, and again children with ADHD were found to exhibit greater variability in these frequency domain measures than controls (S4, S3 and S2 RT frequency bands). Unlike in Chapter 5, in which power in the S3 RT frequency band made the greatest improvement to predictions of group membership, it was unclear which RT frequency band best predicted group membership as S2 RT power uniquely improved classification of ADHD and control cases beyond IQ and SD of RT in the fast event rate condition but only S4 RT power improved classification in the moderate event rate condition.

Consistent with our findings in Chapter 5, we found that there was small but significant synchrony between S3 EEG and S3 RT data. Again, we also found that participants who exhibited least attenuation of the S3 EEG signal when engaging in the RT task (compared to rest) showed greater similarity between their S3 EEG and S3 RT signals. Furthermore we found that the S3 RT-EEG synchrony exhibited by children with ADHD varied as a function of event rate and during the fast event rate condition children with ADHD exhibited less S3 RT-EEG synchrony than controls but during the moderate event rate condition, children with ADHD exhibited greater S3 RT-EEG synchrony than controls. Moreover, we showed that rest-task attenuation was negatively correlated with task performance measures, and participants who attenuated least tended to make the most errors and to be slower and more variable than those who attenuated most.

7.4.1 The associations between ADHD, intra-individual variability and lapses in attention

Our results were largely consistent with previous research: children with ADHD were slower and made more errors than controls. Also consistent with previous research (e.g. Kalff et al., 2005;Klein et al., 2006; Scheres et al., 2001; van Meel et al., 2005) children with ADHD were more variable than controls, on both global measures of variability such as SD of RT and normalised variance, and also on frequency domain measures of variability. These findings contrast with our findings in Chapter 5, which failed to show a strong association

between any of the measures of variability and ADHD symptoms. In Chapter 5 we suggested that this null finding may have been caused by the fast event rate of the 2-CR RT task, as we only used a fast condition, however in the present study we identified group differences in variability in both a fast and a moderate event-rate condition of the same choice RT task, and so this seems unlikely. It is more probable that the non-clinical sample in Chapter 5 was insufficient to yield sufficient group differences in behavioural data.

Also consistent with previous research - both our previous study and research by other groups (e.g. Di Martino et al., 2008) - we showed that power in individual RT frequency bands was able to improve classification of group membership beyond the global measures of variability (and IQ). This suggests that power in individual RT frequency bands can contribute to predictions of group classification above and beyond the global measures of variability. However, the frequency band which made the most improvement to the model differed between conditions in the present study and also in our previous study. In the present study, S2 RT power uniquely improved classification of ADHD and control cases beyond IQ and SD of RT in the fast event rate condition but only S4 power improved classification the moderate event rate condition. In Chapter 5 the addition of power in the S3 RT frequency band made the greatest improvement to the prediction of group membership. However, it is not clear whether these frequency bands are functionally distinct, as they are based on the theoretically designated limits by Penttonen & Buzsaki (2003) and if these bands were not distinct but instead shared a common source, it would not be surprising that neighbouring frequency bands may show similar patterns. It is difficult to directly assess the relative impact of the S4 and S3 frequency bands in other samples as there has been little consistency regarding the frequencies used to delimit the low frequency bands. Therefore, much of the previous research into frequency domain measures of variability has adopted frequency bands which cross the S4 and S3 frequencies that we have employed in these studies. For example, in the research by Johnson et al., (2007; 2008) they divided their FFT spectra into fast (> .077 Hz) and slow frequencies (< .077 Hz), our S3 frequency band (.06 -.2 Hz) falls across both of these bands. Adopting a consistent approach to low frequency limits would be beneficial for comparison across studies, and this would help to clarify whether a particular frequency band contributes further beyond the global measures of variability than other frequency bands.

7.4.2 The associations between ADHD, rest-task attenuation, S3 RT-EEG synchrony and task performance

Consistent with our previous findings, synchrony between S3 RT and S3 EEG was again low but significantly different from zero. Furthermore, also consistent with our previous research, rest-task non-attenuators showed greater similarity between their S3 EEG and their S3 RT signals during the goal-directed task than rest-task attenuators, although unlike in Chapter 5, this was only the case in the moderate event rate condition. Also consistent with our previous research, rest-task attenuation was found to be associated with task performance and participants who exhibited greater attenuation of S3 power from rest to task

tended to perform better on the 2-CR RT task, i.e. to make fewer errors, and to be less variable. Again, these findings are consistent with the assertions of the default-mode interference hypothesis that inefficient attenuation of low frequency EEG oscillations when one engages in a goal-directed task, may interfere with goal-directed brain activity causing impaired performance, and that there should be synchrony between the fluctuations in low frequency EEG oscillations declines in performance.

7.4.3 The impact of event rate

Participants were found to be slower, less variable and to make fewer errors in the moderate- compared to the fast- event rate condition of the choice RT task, which is consistent with previous research (e.g. Van der Meere, Vreeling, & Sergeant, 1992; Andreou et al., 2007), however there were no differences in the frequency domain RT bands between conditions. Also, in contrast to our predictions, we did not find any group by event rate interactions. This may be for a number of reasons, for example the difference in event rates in our present study may not have been sufficiently large to elicit a group by condition interaction, for example the group by event rate interaction reported by Van der Meere et al. (1992) was found between a one second ISI- and a four second ISI-condition, it is possible that if we had included a slower condition, the interaction may have been more evident. However, in our present study, group by event rate interactions did emerge for SD of RT and for each of the frequency domain RT measures when IQ was statistically controlled, therefore, it appears that in our sample that group differences in IQ suppressed the interaction effect.

We also showed that in the fast condition, the addition of S2 RT made the only significant improvement to predicting group membership beyond the global measures of variability (and IQ) and the addition of S2 RT power increased correct classification from 70% to 86.7% of all cases, but, in the moderate event-rate condition, only the addition of S4 RT power significantly improved the prediction of group membership, from 96.8% to 100% correct classification. The relative impact of the S4 and S2 RT frequency bands between the different conditions may reflect a frequency by condition interaction, and in faster event rates, the ADHD group is better differentiated by faster RT frequency bands and in moderate event rates, the ADHD group is better differentiated by slower RT frequency bands. However it is important to consider that the event rate also directly impacts on the frequencies in the RT data that are able to be examined. Only frequencies up to half of the ISI can be observed in the data, therefore in the fast (one second ISI) condition, frequencies up to .5Hz can be examined in the RT data but in the moderate (three second ISI) event-rate condition only frequencies up to .16Hz can be examined. Thus, the S2 RT frequencies were not accessible in the moderate event rate condition. This creates an obvious difficulty when comparing RT frequencies between event rates, as a very slow event rate condition, with, for example a 9 second ISI, would only allow a tiny portion of the frequency spectrum to be investigated - in this example up to .05Hz. A further difficulty also arises as RT data are not anti-aliased as they are sampled, therefore it is possible that higher frequencies may present as lower

frequencies in the data. As a result any low frequency differences in tasks with very slow event rates, which sample very infrequently, should be interpreted with caution as it is possible that these low frequencies are aliased higher frequencies. We tried to combat this possible confound by designing our tracking task which is capable of a very fast sampling rate and also allows the data to be anti-aliased before processing, however the data from this task proved to be unusable. Nonetheless, future versions of this task or similar tasks will be very useful in establishing more definitely whether low frequency variations do exist in behavioural data.

We also showed that S3 RT-EEG synchrony varied between event rates, and furthermore that a group by condition interaction emerged, so that the ADHD group were found to exhibit lower S3 RT-EEG synchrony compared to controls in the fast condition but higher S3 RT-EEG synchrony in the moderate condition of the 2-CR RT task. As outlined in the results section, rather than reflecting a difference in the event rate per se, this difference is likely to reflect differences in the reliability of the RT measure as an index of attention in the ADHD group between conditions. In the fast event rate condition, the ADHD group made a large number of errors; about half of the children with ADHD made more than 25% errors in this condition. We tried to control for the impact of error (error responses were generally faster than correct responses) by using regression residuals, however, this may have introduced some bias into the data. Data from the moderate event rate condition typically contained many fewer errors and so was likely to be a more reliable index of attention. Therefore, it is unsurprising that S3 RT-EEG synchrony should be higher when a more reliable index of attention was used.

7.4.4 The impact of IQ

As the ADHD group were shown to have lower IQs than controls, analyses of group differences were run with and without IQ entered as a covariate. Generally most of the group differences identified in this chapter remained after IQ was controlled, for example, the group differences in global measures of variability, of mean RT and of frequency domain measures of variability remained after IQ was controlled. The difference in S3 RT-EEG synchrony between rest-task attenuators and rest-task non-attenuators was also found to remain after IQ was controlled. In fact the only group differences which did not survive covarying of IQ were differences in the number of errors made (both omission errors and directional errors), and after IQ was controlled, the ADHD group was not found to differ from the control group in the number of errors made. This suggests that the group differences observed in variability are not an artifact of IQ but do represent valid differences in patients with ADHD compared to controls, and furthermore that the differences in S3 RT-EEG synchrony between attenuator groups are not likely to be an artifact of IQ. However group differences in the number of errors made are likely to be associated with IQ.

7.4.5 Limitations

Many of the limitations described in section *5.4.3 Limitations* also apply here, for example group sample sizes were small – especially after participants with excessive movement artifacts were excluded from the analyses. Due to this small sample size, we may not have sufficient statistical power to detect small or medium sized effects. Therefore, we have reported the test statistic and exact *p* value for all statistical tests and have highlighted medium sized effects even if they fail to reach statistical significance at $p = .05$. Furthermore, as described in Chapter 5, we have not adjusted for multiple testing as we have tested a-priori hypotheses (see Perneger 1998). However, replicating these results in a larger sample may highlight further smaller sized effects.

Moreover, as described in section *5.4.3 Limitations*, and also in section *7.4.3 The impact of event rate,* the RT task was not ideal for investigations of the frequency components of behavioural data as it allowed participants to make missing and incorrect responses, which may introduce error into the data, and furthermore, it restricted the portion of the frequency spectrum which could be investigated. Future studies that attempt to investigate the frequency components of behavioural data should combat this by utilizing continuous tasks which sample at a higher rate.

7.5 Conclusions

In this chapter we showed that children with ADHD were more variable than controls. We also showed that power in particular RT frequency bands was able to improve the prediction of group membership beyond normal global measures of variability. We were also able to replicate our previous findings that participants who exhibited least attenuation of the S3 EEG signal when engaging in the RT task (compared to rest) showed greater similarity between their S3 EEG and S3 RT signals, and we showed that rest-task attenuation was negatively correlated with task performance, so that participants who attenuated least tended to make the most errors and to be slower and more variable than those who attenuated most.

Chapter 8 General Discussion

8.1 Introduction

Increased response variability in ADHD is one of the most consistent findings in ADHD research. However, until recently this phenomenon has largely been ignored and its role within the causal processes of ADHD has, for the most part, been unexamined. Castellanos et. al., (2005) suggested that developing a better understanding of the nature of response variability in ADHD, and clarifying the temporal and contextual characteristics of response variability may help to explain the underlying pathophysiology of ADHD. In 2008, the default-mode interference hypothesis of ADHD was introduced by Sonuga-Barke and Castellanos as a biologically plausible account of this increased variability in ADHD. This hypothesis suggests that some patients with ADHD might not effectively attenuate low frequency resting EEG during the transition from rest to task and that these low frequency oscillations may then intrude onto and interfere with task performance and cause periodic attention lapses. These periodic attention lapses would manifest as increased variability in RT data and would be synchronised with the low frequency EEG.

The aim of the present thesis was to test the predictions of the default-mode interference hypothesis and to investigate the possible role of very low frequency, spontaneous brain activity in the aetiology of ADHD. The specific aims of the present thesis were:

1) To identify the spatial distribution of low frequency EEG at rest
2) To determine whether low frequency EEG is attenuated from rest to task
3) To identify whether periodicity is evident in RT data
4) To identify whether there is synchrony between low frequency EEG and low frequency fluctuations in RT data.
5) To examine whether these factors are associated with ADHD.

This final chapter of the thesis will provide a summary of the findings relating to these aims and then address the issues that arise from these findings by answering a number of key questions.

8.2 Summary of Findings

8.2.1 Low frequency EEG oscillations at rest and during goal-directed task performance

Low frequency EEG at rest and during goal-directed task performance was assessed in a sample of adults who self-reported either high- or low-ADHD scores in Chapter 4 and in a sample of adolescent boys with ADHD (aged 13 to 16) and age and gender-matched controls in Chapter 6. A summary of the main findings from each chapter is shown in Table 8.1.

Table 8.1

Summary and comparison of main findings from Chapter 4 and Chapter 6

	Chapter 4	Chapter 6
A S3 resting network was identified in healthy controls along the frontal midline and central posterior cortex.	✓	✓
At rest, greater low frequency EEG power was identified within this S3 network than outside of it.	✓	✓[a]
Reduced S3 EEG power was evident in the S3 network in inattentive or ADHD participants at rest.	✓	✓
This group difference was independent from power in all other low frequency bands.	✓	✗
An altered spatial pattern of S3 activation was identified during goal-directed performance compared to rest.	✓	✓[b]
No difference in low frequency EEG power was identified within the S3 network compared to outside of the S3 network during goal-directed task performance.	✓	✓
Attenuation of low frequency EEG was evident from rest to task.	✓	✓[c]
Reduced rest-task S3 attenuation was found in inattentive or ADHD participants.	✓	✓

Note. a) The magnitude of this difference was notably reduced in Chapter 6 compared to Chapter 4; b) although both studies identified altered patterns of S3 activation during the goal-directed task, we did not find a consistent spatial pattern of goal-directed task S3 activation between the two chapters, or between conditions of Chapter 6; c) although rest-task S3 attenuation was identified in both studies, in Chapter 4 this was found only within the S3 network and in Chapter 6, it was found both within and outside of the S3 network.

It is clear from Table 8.1 that a number of consistent finding emerged across the two chapters. In both chapters, a resting network of S3 EEG was identified and inattentive or ADHD participants were found to exhibit less power in this network than controls at rest. During goal-directed task performance, an altered pattern of S3 activation was evident, and S3 EEG was less confined to the S3 network. Furthermore, attenuation of low frequency EEG was generally evident from rest to task, but ADHD and inattentive participants exhibited less rest-task attenuation than controls. However, the magnitude of the difference in resting power within and outside the S3 network, the spatial pattern of goal-directed S3 activation and attenuation of low frequency EEG outside of the S3 network were not consistent between the two chapters.

8.2.2 The association between intra-individual variability, low-frequency EEG and ADHD

The association between intra-individual variability, low-frequency EEG and ADHD was assessed in the same sample of adults with either high- or low-ADHD ratings in Chapter 5 and in the same sample of adolescent boys with ADHD in Chapter 7. Again, a summary of the main findings from each chapter is shown in Table 8.2.

Table 8.2

Summary and comparison of main findings from Chapter 5 and Chapter 7

	Chapter 5	Chapter 7
ADHD was associated with greater errors.	✓	✓
ADHD was associated with greater variability.	✗	✓
Power in individual RT frequency bands was found to contribute to the prediction of group membership (ADHD or control) beyond global measures of variability.	✓	✓[a]
S3 RT-EEG synchrony was significantly different from zero.	✓	✓
Rest-task non-attenuators exhibited greater S3 RT-EEG synchrony than rest-task attenuators.	✓	✓[b]
Greater rest-task attenuation was associated with better task performance.	✓	✓

Note. a) Although the particular RT frequency band that made the greatest improvement to the model differed between the two studies; b) in Chapter 7, this effect was only found in the moderate event-rate condition of the 2-CR RT task, ~ = N/A

Again, there are clearly a number of consistent findings across the two chapters. In both chapters, ADHD was associated with greater errors, and power in frequency domain measures of RT contributed to the prediction of group membership beyond global measures of variability. Furthermore, synchrony was found between low frequency EEG and low frequency oscillations in RT data, and participants who failed to attenuate S3 EEG from rest to task exhibited greater synchrony between these measures, these rest-task non-attenuators also performed more poorly on the choice-RT task than participants who effectively attenuated S3 EEG. However, which RT frequency band best predicted group membership was inconsistent between the two chapters, and furthermore, in Chapter 7, the association between attenuation and S3 RT-EEG synchrony was only evident during the moderate event-rate condition of the choice-RT task.

8.3 Implications of these results

The results of this thesis raise a number of important issues. These issues will now be addressed by answering a number of key questions.

8.3.1 Is there a VLF EEG network?

We identified a very similar spatial pattern of resting S3 activation in healthy adults (Chapter 4) and in healthy adolescent boys (Chapter 6). This spatial pattern was also found to be stable over a one week test-retest period. This is an important finding as no resting pattern of VLF EEG has previously been identified. However, throughout this thesis, we have referred to this pattern of activation as a S3 'network', yet, we have not performed analyses that are able to show whether there is functional connectivity between the different scalp locations. A coherent network would exhibit not only the same oscillatory frequency, but also the same phase (or a consistent phase lag) between these oscillations: phase-synchrony analysis, which assesses whether the phase shift between two signals remains constant over time will be necessary to clarify whether the spatial pattern of S3 activity that we have identified is really a coherent network. However, such measures of scalp coherence are heavily affected by volume conduction (the spread of current through the tissues of the head) and large EEG coherence can arise from volume conduction alone (Srinivasan et al., 2007). For example, Nunez et al. (1997) report that less than 5% of the measured scalp potential comes from sources directly below an electrode. Nunez et al., (1999) further suggest that different EEG coherence measures – such as Spline-Laplacian and dura imaging methods – each introduces different error into the coherence estimate and that studies of coherence should include multiple analysis techniques. Further as different methods of referencing the data also affects the coherence estimate multiple methods should also be used (Nunez et al., 1997). Therefore, identifying and performing the methods that are able to give the most accurate measures of coherence for our data is beyond the scope of this thesis; however this remains an important issue for future studies.

8.3.2 Could the S3 network mirror the DMN?

Both the DMN and the S3 network are characterised by very low frequency oscillations and both are evident in the resting brain. Therefore it is possible that the S3 EEG network mirrors the DMN. However, as mentioned in Chapter 4, the relationship between fMRI and EEG is complicated and not well understood; therefore, it is difficult to relate the spatial location of the low frequency scalp EEG that we have identified in this thesis, to the sources implicated in the DMN by the fMRI BOLD signal. Although the resting S3 network that we identified does show a number of similarities with the DMN, for example attenuation of low frequency activity from rest to goal-directed task occurs in both the DMN and the S3 EEG network, no direct comparisons can be made between the two without directly testing their relationship. This relationship can be tested by recording EEG from a wider and more evenly distributed montage of scalp electrodes, so that distributed source modelling and dipole

source seeding analyses can then be performed. Alternatively, the EEG signals could be co-registered with methods that offer better structural specificity such as fMRI or MEG.

8.3.3 The DMN has anti-correlated components - where are they in the EEG network?

Furthermore, the DMN has been shown to contain two anti-correlated components, the task positive and the task negative components, if the S3 network did mirror the DMN, it is likely that the S3 network would also contain these two anti-correlated components. Again, as the analyses that we performed to identify the S3 network did not take into account the phase of the S3 oscillation we have not been able to assess this, and again phase synchrony analysis will be important in clarifying this issue. However, as described in Chapter 2, Murphy et al. (2009) claim that the anti-correlations between the task positive and the task negative components may be artifactually introduced by pre-processing measures (specifically by global signal regression). Although we did not use global mean regression in our analyses, we did re-reference the EEG data offline to paired mastoid references; it is unclear what impact this pre-processing measure may have on the associations between different components of this network. Therefore, if phase-synchrony analyses were employed on our or a similar EEG dataset, it will be very important to carefully consider the impact that any pre-processing measures may have on the relationship between different brain regions, and until more research has clarified the specific effects of pre-processing methods, it would be prudent to interpret the function of these anti-correlations with some caution.

8.3.4 How distinctive is the S3 component of this network?

Throughout this thesis we have focussed on a particular frequency band described by Penttonen & Buzsaki (2003) as slow 3 (S3, .06 -.2Hz). This band was used to delimit a network of low frequency oscillations, to determine attenuation from rest to task and as a focus for the synchrony between EEG and RT data. There were two main reasons for focussing on this particular frequency band, firstly it most closely resembled the frequencies of the DMN, and secondly this particular band contained an oscillatory peak that was evident in the EEG data (at approximately .1 Hz). However, it is not clear whether this S3 frequency is distinct from other low frequency bands. In both Chapter 4 and Chapter 6 we report that at rest the spatial pattern of other low frequency bands, S4, S2 and S1 look very similar to the resting S3 network and in both chapters, very strong correlations were evident between all of the frequency bands (although the strongest correlations tended to be between neighbouring frequency bands). Furthermore, although in Chapter 4 we showed that the group difference in resting S3 power was independent from power in all of other low frequency bands, which does suggest that S3 power is distinct from other frequency bands, we were unable to replicate this in Chapter 6, and when power in all of the other low frequency bands was entered as a covariate, the group difference in resting S3 EEG power was reduced to statistical insignificance. Also we found that attenuation from rest to task was not unique to the S3 frequency band, in Chapter 4, rest-task attenuation occurred in both the S3 and S2 frequency bands and just missed significance in the S4 frequency band. In Chapter 6,

attenuation from rest to task occurred in all frequency bands, but was greatest in the S4, S3 and S2 frequencies. As we suggested in the discussion section of Chapter 4, the limits of the S3 frequency band were theoretically determined and were based on the assumption of a natural logarithmic relationship between successive frequency bands, therefore this S3 frequency band may not represent a band that is functionally distinct from its neighbours but instead may be dividing a genuine functional boundary. Given the similarity in attenuation and spatial distribution of S3 with its neighbouring frequency bands S4 and S2, this is a likely possibility. It will be important for future research into very low frequency EEG to determine functionally distinct frequency bands.

8.3.5 Could this be a spurious finding or a signal processing artifact?

It is possible that our findings may be spurious or may be an artifact of the signal processing techniques that we used. However, many of our key findings were replicated in two different samples, which makes it is unlikely that they would be completely spurious. Furthermore, the two studies were conducted in different labs, and using different equipment, which makes it unlikely that the findings would be the result of technical artifacts created by the EEG equipment. However, as described previously, pre-processing methods can impact heavily on the results obtained from the EEG data, for example using a global signal reference can artifactually create anti-correlations in the data. Furthermore, in Chapter 6 we showed that when we used a slightly different method of data cleaning (i.e. not using PCA prior to ICA), although the general pattern for greater low frequency EEG power within- compared to outside- the S3 network remained, the magnitude of this difference was greatly reduced. Therefore it is necessary to clearly report all pre-processing methods so that replication can take place.

However, for many of the analyses in this thesis, a number of different approaches were trialled before the final analysis was decided upon. For example, when identifying a resting network of S3 activity, we used ICA to identify independent components in the data, we then back-projected all artifact-free components and selected electrodes with greater than the mean S3 power as comprising the S3 network. However we also attempted to delimit the S3 network by identifying the single component extracted by ICA which showed the greatest S3 power for each participant. Both methods showed a very similar pattern of S3 activation; however we decided to use the first method for a number of reasons. Firstly, this method allowed easier comparison across frequency bands: the components extracted by ICA are maximally statistically independent and thus are likely to be independent of other frequencies, which - if we had selected only a single component - would make comparison between different frequencies and locations difficult. Secondly, when ICA was performed, multiple different components were extracted with a low frequency time signature, selecting only a single component for each participant may lose important information. Furthermore, as described in Chapter 4, ICA operates using a termed complete method, and will recover the same number of components as the number of input channels, this can result in some

components being separated by ICA into more than one sub-component. If in some cases (depending on the number of sources in the data), the predominant S3 component was separated into sub-components, but in other cases it was not, and we selected only a single component, we would be unable to fairly compare between participants. Therefore, we have, wherever possible, considered the impact that our processing methods will have on our data and selected the method that we believe will be the most transparent and will least bias the data. However, replication of these findings will be important before they can be accepted with any certainty.

8.3.6 Does RT data have a low frequency structure?

In order to determine whether RT has a low frequency structure, some research has attempted to determine 'peaks' in the FFT of RT data, for example Castellanos et al. (2005) identified a peak in RT FFT at about .05 Hz and Johnson et al.(2007; 2008) identified a similar low frequency RT peak at about .08 Hz using a different task. In this thesis we have also identified low frequency peaks in the FFT, at approximately .04Hz and .08Hz. However, it is important to note that the method of analysis used to examine the periodic structure, in addition to task design, will influence where the peak is observed for specific frequency bands (Geurts, et al., 2008). A clear description of the method of analysis is absolutely crucial for valid comparison. Furthermore, as briefly described in Chapter 7, the sampling rate - which is equivalent to the ISI in RT studies - directly impacts on the frequencies that are able to be examined in the RT data and only frequencies up to half of the ISI can be observed in the data. Therefore, in investigations of frequency domain variability in RT data, in order to allow for participant responses, stimuli cannot be presented at very fast rates, and so only low frequencies will be able to be examined in the data. Thus, when analysing RT data in the frequency domain, no fast frequencies are available for analysis and so it is not clear whether peaks are only evident in the low frequency portion of the spectrum or whether other, possibly larger, peaks also exist in the higher frequencies. Therefore, based on our findings, asserting that RT data has a low frequency structure would be premature. As we reported in Chapter 7, we have tried to combat this problem (and also the problem of aliasing in the data) by developing a task that is capable of a very fast sampling rate so that higher frequencies would be able to be examined in the data. Only when this, or similar, data is available and analysed will we be able to determine whether behavioural data does in fact have a low frequency structure. Furthermore as we described in Chapter 7, it is difficult to directly assess the relative impact of the different frequency bands in other samples as there has been little consistency regarding the frequencies used to delimit the low frequency bands. Much of the previous research into frequency domain measures of variability has adopted frequency bands which cross the S4 and S3 frequencies that we have employed in these studies. For example, in the research by Johnson et al., (2007; 2008) they divided their FFT spectra into fast (> .077 Hz) and slow frequencies (< .077 Hz), our S3 frequency band (.06 -.2 Hz) falls across both of these bands; and in the research by DiMartino et al., (2008) the bands which

they describe as S4 and S3 have different limits to the bands which we have described as S4 and S3. Adopting a consistent approach to low frequency limits would be beneficial for comparison across studies, and this would help to clarify whether a particular frequency band contributes further beyond the global measures of variability than other frequency bands.

8.3.7 Did decomposition of RT data into its frequency domain add anything beyond the global measures of variability?

In both Chapter 5 and Chapter 7 we showed that power in individual RT frequency bands was able to improve the classification of group membership beyond the global measures of variability. This does suggest that power in individual frequency bands is able to contribute something beyond the global measures of variability and that the periodic structure of RT contains information which is not expressed in the global variability statistics. This is consistent with the findings of Di Martino et al. (2008) who also showed that that power in the .03 - .07 Hz frequency band was able to predict the diagnosis of ADHD above and beyond SD of RT. Therefore, decomposition of RT data into its frequency domain might well be a useful addition to analyses of variability in ADHD.

However, as discussed in Chapter 7, we did not find a consistent pattern as to which frequency band made the greatest improvement to each model (in which group membership was classified). In Chapter 7 we suggest that this may be because the frequency bands are not functionally distinct. The limits of the S3 frequency band have been theoretically determined and thus, the low frequency RT bands that we have investigated in this thesis may not represent functionally distinct RT frequencies. It will be important for future research into the periodic structure of RT data (which typically investigates the very low frequency components of the spectrum) to determine functionally distinct frequency bands.

8.3.8 Was there synchrony between EEG and performance?

In both Chapter 5 and Chapter 7 we showed that there was synchrony between S3 EEG and S3 RT data. In both cases the synchrony was small but significantly different from zero. In Chapter 5 we suggest that we would expect the synchrony between these two signals to be low, as the EEG signal is inherently complex and is influenced by numerous cortical sources, and the RT signal, again is complex and is also a much less than perfect measure of attention. We would not expect the correlation between two complex, imperfect signals to be high. However, it is also possible that the synchrony between these two signals is itself periodic and participants experience periods of high- and periods of low-synchrony between EEG and RT data. As we assessed only the mean synchrony between these two signals across the entire 10 minute testing session, this measure was not sensitive to changes in the synchrony between the two signals over time, therefore if during the session there were some periods of high- but other periods of no- or anti-correlations between the two signals this would have reduced the size of the mean synchrony measure. Analyses that measure the changes in the synchrony over time between the two signals will help to clarify the association between low frequency EEG and variations in RT data.

Also, as mentioned earlier, it is not clear whether the S3 frequency band represents a discrete physiological boundary. If the S3 frequency band that we have used to assess synchrony between the EEG and RT signals did not represent a discrete boundary, this may have artificially reduced the synchrony between the two signals. However, as we mentioned earlier, we chose to focus on the S3 frequency band based on previous fMRI research and because this band contained an oscillatory peak in our data. Replicating these analyses on multiple different frequency bands would not only be a very lengthy and computationally demanding process (for each participant, synchrony in each frequency band would need to be assessed between data from each of 27 electrodes and their RT data), but would also considerably increase the number of comparisons necessary, which would make type I errors more likely. Therefore, although it is possible that focussing on a specific frequency band for synchrony analyses may have reduced the synchrony between these signals, we ran these analyses on a frequency band that we believed was most justified theoretically and empirically. Future research could investigate whether the synchrony is specific to this frequency band or whether synchrony is also evident in other frequency bands.

8.3.9 Do the results support the default-mode interference hypothesis?

In this thesis we directly tested a number of predictions made by the default-mode interference hypothesis. Specifically, we tested whether there was attenuation of low frequency EEG from rest to task and whether inattentive or ADHD participants exhibited less attenuation than controls. We also assessed whether there was synchrony between the fluctuations in low frequency EEG and lapses in attention. Generally we did find support for these predictions. In both Chapter 4 and Chapter 6 we showed that there was attenuation from rest to task and that neither participants with high self-reported ratings of inattention (Chapter 4) nor participants with ADHD (Chapter 6) exhibited the same rest-task attenuation of S3 power compared to controls. Similarly, in both Chapter 5 and Chapter 7 we showed that participants who did not effectively attenuate their S3 EEG signal when they transitioned from rest to the RT task, showed greater synchrony between their S3 EEG and their S3 RT signals during the goal-directed task than participants who did attenuate this S3 EEG signal. In both chapters we also showed that attenuation was associated with task performance, so that participants who exhibited less rest-task attenuation performed more poorly on the task, they made more errors and were more variable than those who exhibited greater rest-task attenuation. These findings are consistent with the assertions of the default-mode interference hypothesis, that, if low frequency EEG is not properly attenuated when one engages in a goal-directed task, this low frequency EEG may interfere with goal-directed brain activity, causing poorer task performance, and furthermore that fluctuations in performance should be synchronised with low frequency EEG.

The default-mode interference hypothesis is offered as an account of ADHD. We did find that participants who rated themselves as inattentive and participants with ADHD experienced less attenuation of their resting S3 EEG oscillations: therefore, it is possible that

inefficient attenuation may be a characteristic of ADHD. However we also found that inattentive participants and participants with ADHD also exhibited reduced power in the S3 network at rest when compared to controls, this is not predicted by the default-mode interference hypothesis. In Chapter 4 we offer a number of possible explanations for this, however it is most likely that the association between ADHD and resting brain activity is more complex than is depicted in the default-mode interference hypothesis. The default-mode interference hypothesis suggests that resting state brain activity would be unimpaired in ADHD but that patients with ADHD would differ from controls in either their ability to attenuate this low frequency activity from rest to task, or in the limits for a threshold of impairment. Either of these would increase interference by low frequency brain activity when a participant with ADHD engages in a goal-directed task and should result in impaired attention. However, resting brain activity of the default mode network has been shown to be impaired in ADHD and specifically, in ADHD reduced resting-state functional connectivity has been reported, particularly between the anterior and posterior components of the DMN and those involving the precuneus (Castellanos et al. 2008; Uddin et al., 2008). Therefore, although we have not assessed resting-state functional connectivity in our studies, it is unsurprising that we also identified alterations in the resting state EEG of children with ADHD. As an altered pattern of resting brain activity has been identified in ADHD in both fMRI and EEG research, the default-mode interference hypothesis may need to be adapted to reconcile these findings.

8.3.10 Could VLFOs be explained by physiological signals other than brain activity?

EEG recordings are not only generated by cerebral sources but also contain physiological and non-physiological artifacts. Therefore, it is possible that the VLFOs identified in the present study do not represent oscillatory brain activity but are markers of periodic artifacts. We stated earlier that we felt that it was unlikely that the VLFOs would be created by technical artifacts as the two studies had been conducted in different labs, and using different equipment: however it is possible that these VLFOs may be the result of physiological artifacts. Numerous biological systems are also found to exhibit periodic fluctuations, for example, respiration, cardiac and pulse rate signals are low frequency, periodic signals that can impact on EEG. However, respiration is typically faster than the VLFO peak that we identified in our research, and the average respiratory rate is typically thought to be about 12 breaths per minute (.2 Hz). Similarly, cardiac and pulse rate signals are not only faster than the VLFOs of our research –typically 60-100 beats per minute (1-2Hz) – but these signals are also markedly different in their morphology. Therefore, it seems unlikely that the VLFOs in our studies are the result of other physiological signals.

However, there is a component of heart rate variability which oscillates at a very similar frequency to the oscillatory peak which we identified in our data. Heart rate variability (HRV) refers to the beat-to-beat variations in heart rate patterns and has been shown to be a more sensitive measure of changes of state than mean heart rate is (Althaus, Lambertus, Mulder, Van Roon, & Minderra, 1998). Spectral decomposition of cardiac data identifies

several distinguishable periodic components of HRV, each defined within a specific frequency band. Oscillations in HRV can occur at low frequencies and include a component known as the Mayer wave which oscillates at 0.1Hz. This is very similar in frequency to the oscillatory peak identified in our EEG data. This component of HRV is thought to be related to the regulation of arterial pressure and to be controlled by both the sympathetic and the parasympathetic (vagal nerve) nervous systems, which interact in complex ways. For example, sympathetically mediated changes in arterial pressure are able to trigger changes in vagal-cardiac nerve responses and so produce changes in the parasympathetic signals (Althaus et al., 1998).

The relationship between this Mayer wave in HRV and EEG data is unclear, as the Mayer wave, unlike the .1Hz EEG peak, is not apparent in the raw heart rate data but only in the processed data, which investigates the differences in the peak to peak intervals in heart rate. Therefore it seems unlikely that this component of HRV is able to artifactually induce the .1Hz peak in the EEG data. Instead it is possible that these oscillations may all have a common underlying basis. Data by Tierney, Bergstrom & Walters (unpublished observations in Castellanos et al., 2005) support this and indicate that the .1Hz EEG and the .1 Hz HRV oscillations may both be affected by dopamine systems. They demonstrated that the administration of dopamine agonists induced correlated LFOs (approx 0.1Hz) in the rat globus pallidus (GPe) and subthalamic neurons (STN) and HRV, and that the administration of dopamine antagonists eliminated this periodic activity (see Figure 8.1)

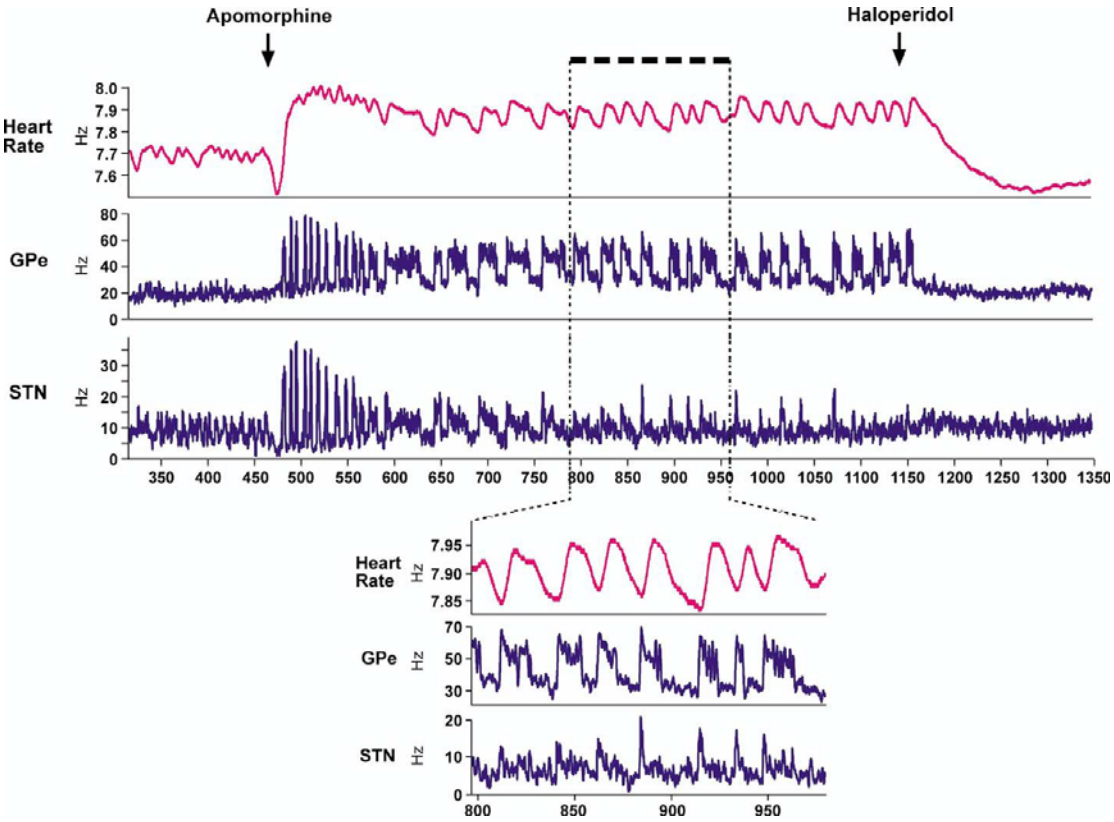


Figure 8.1: Correlated VLFOs in heart rate variability and in EEG.

Note. VLFOs in heart rate variability correlate with VLFOs in the firing rate of rodent globus pallidus (GPe) and subthalamic neurons (STN). Administration of a dopamine agonist (Apomorphine) induces .1 Hz correlated oscillations in these systems. Administration of a dopamine antagonist (Haloperidol) eliminates this periodic activity (from Castellanos et al., 2005).

In both of our studies, we have collected heart rate data, however we have not yet analysed this. In future research it would be interesting to investigate whether the .1Hz component of HRV was correlated with the VLFOs that we identified on EEG. It would also be interesting to investigate the association between these VLFOs and dopamine by assessing whether the administration of a dopamine agonist or antagonist induces or eliminates this low frequency activity.

8.3.11 Is the default-mode interference hypothesis relevant to ADHD per se or just inattention?

Although the default-mode interference hypothesis is offered as an account of ADHD, it particularly focuses on the inattentive symptoms of ADHD. In Chapter 4 we showed that self-reported inattention rather than hyperactivity was associated with altered patterns of low frequency EEG. More specifically we showed that participants with high self-report ratings of inattention exhibited differences in the power in a resting network of S3 activity and in the degree of rest-task attenuation compared to all other participants. In Chapter 6 however, we showed similar altered patterns of low frequency EEG in a group of adolescents with ADHD-combined type, who experienced both inattention and hyperactivity. Therefore, it is unclear whether default-mode interference (intrusions of low frequency resting EEG) may occur in all participants with ADHD, or whether this is specific to patients who experience inattentive symptoms. As our study only included combined-type ADHD patients, we were unable to assess whether hyperactive subtype patients differed from inattentive- or combined-subtype patients in their degree of attenuation. Future, larger studies will be important to elucidate this.

Furthermore, our studies have specifically investigated the association between low-frequency EEG and inattention. The tests that we employed (simple 2-choice response RT tasks) assessed trial-by-trail variation in attention. It is possible that DMN intrusion also leads to periods of hyperactive behaviour, and that inattention and hyperactivity could occur concurrently. Thus, during periods of DMN intrusion, participants not only experience a lapse in attention and a decline in performance but also experience a period of hyperactivity, in which they start to fidget or to squirm in their seat. Future studies could investigate this further either by video-recording participants and coding the participants' movements to determine whether there is any periodicity in the timing of these movements, or by employing an actigraphy measure and investigating these data for periodicity.

8.3.12 How do these findings link to other theories of ADHD

In Table 2.1 we described a number of different theories of ADHD and their predictions about the presentation of response variability in ADHD. The theory of ADHD as a disorder of executive function predicts that response variability in ADHD will present as random variability. From our data is it not clear whether this occurs in ADHD. In Chapter 7 we showed that the patients with ADHD exhibited greater RT power across the whole frequency spectrum than controls, this could reflect global dysregulation of behaviour and executive dysfunction. However there also seemed to be some peaks in the RT data which suggests that response variability is not random but periodic in nature. Furthermore, power in particular RT frequency bands contributed in different ways to the prediction of group membership beyond global measures of variability, which suggests that this periodicity in behavioural data is likely to be important in distinguishing between groups. Therefore, the pattern of response variability appears to be more complex than is accounted for by an executive dysfunction model of ADHD.

The theory of ADHD as delay aversion predicts that response variability in ADHD will occur when patients with ADHD are exposed to delay. Although we did not explicitly test this model and did not include conditions which involved delay, we found that adolescents with ADHD (Chapter 7) were more variable than controls in a fast event-rate condition of a 2-CR RT task, as this task condition did not include a delay it seems unlikely that delay aversion could have contributed to this increased variability. The theory of ADHD as a disorder of astrocyte function, predicts that response variability in ADHD will occur specifically in fast event rate conditions, similarly the theory of ADHD as a disorder of state regulation (the CEM) predicts that response variability in ADHD will occur in fast event rate- or slow event rate conditions. Although we did not include a slow event rate condition of the task, we were able to test these theories' predictions about increased variability in fast event rate conditions. However, we did not find support for this, although we did find that adolescents with ADHD were more variable than controls on a fast event-rate condition of a simple RT task, we also found that adolescents with ADHD were more variable on a moderate event-rate condition of the same task. Although we did find that participants were generally less variable in the moderate compared to the fast event rate of the task, when we controlled for IQ, we found that this was only true for the control cases and in fact the patients with ADHD were found to be more variable in the moderate event rate condition compared to the fast event rate condition. Therefore, our results do not support the predictions of either of these theories.

8.3.13 What are the implications for heterogeneity in ADHD?

As we described in Chapter 1, ADHD is a heterogeneous disorder and therefore, single cause models of ADHD are likely to be inappropriate. The default-mode interference hypothesis is therefore only offered as an account of ADHD in some patients. Consistent with the default-mode interference hypothesis, in Chapter 6, we showed that the ADHD group exhibited less rest-task attenuation of low frequency EEG than controls. However not all

patients with ADHD failed to attenuate this low-frequency EEG, therefore this process cannot be associated with the aetiology of ADHD in all cases. In future, larger studies it would be informative to investigate the clinical and neuropsychological differences between those who do not exhibit rest-task attenuation and those who do.

8.3.14 Are we sure this is specific to ADHD and not just low intelligence or other comorbidities?

As described in the introduction, patients with ADHD often present with other comorbid disorders (see section *1.1.2 Associated Disorders*). Our sample of adolescents with ADHD was found to have lower IQ, more conduct problems and more emotional problems than the controls. Therefore it is possible that any group differences that we identified are not specific to ADHD but are a function of these other differences between the two groups. However, we ran all group comparisons with and without controlling for IQ. The majority of group effects remained statistically significant after IQ was controlled, and the few that did not remain statistically significant remained as non-significant trends ($p < .1$) (with the exception of the group differences in the number of errors made which was reduced to statistical insignificance when IQ was controlled). Therefore, it seems unlikely that the group differences observed are an artifact of IQ.

As we did not exclude participants with either conduct disorder (CD) or oppositional defiant disorder (ODD) from the ADHD group, and both CD and ODD are highly comorbid with ADHD, it is unsurprising that our sample of adolescents with ADHD were found to exhibit a greater number of conduct problems than the controls. In fact, all but 2 of ADHD cases were reported to experience conduct problems (> 4 on SDQ conduct subscale, which is described by Goodman, 1997, as the cut off for 'abnormal' conduct behaviour) but none of the controls cases reached this cut off. As we described in section *1.1.2 Associated Disorders,* the comorbidity of ADHD and ODD/CD appears to be determined by shared genetic factors (Nadder et al. 2002) and that ADHD and ODD/CD may be different behavioural manifestations of the same underlying syndrome. Therefore it may not be appropriate to statistically control for CD or ODD in group comparisons as ODD/CD is likely to be a component of the ADHD phenotype. Consequently, in our study we did not statistically control for ODD/CD and our sample was too small to compare between 'pure ADHD' and ADHD+ODD/CD groups. However, Banaschewski et al. (2003) suggest that the ADHD+ODD/CD phenotype may be functionally distinct from a 'pure ADHD' phenotype, therefore, in future, larger studies this may be an important comparison to make.

ADHD can also be associated with Autistic Spectrum Disorder (ASD). This is important for the present study as Geurts et al. (2008) claim that ASD is highly correlated with variability and that when they stringently tested for ASD and excluded any comorbid cases from a group of children with ADHD, they did not find any differences in variability between children with ADHD and controls, although they did find differences in variability between children with ASD and controls. In our study we only included children with ADHD if they had

not been diagnosed with any other disorder, so we had no clinical cases of ASD in our sample. However, it is possible that undiagnosed ASD may be present in some of these cases; therefore, although we have excluded participants with comorbid ASD, we have not been able to determine whether undiagnosed ASD is present in the sample. Future studies into response variability in ADHD would benefit from more careful assessment of ASD symptoms.

8.4 Limitations

As mentioned in the previous sections, although we have tried to conduct a valid study, a number of limitations and methodological issues remain. Limitations of the sample characteristics and study design, and issues of analysis will be summarised and a number of future directions in research will be suggested.

The main limitations of the sample characteristics study design are:

1) *The sample sizes employed in our studies were small.* Both of our samples were small, our first sample contained 13 high-ADHD and 11 low-ADHD participants, and our second sample contained 16 boys with ADHD and 16 controls. Although these sample sizes gave us sufficient power to detect group differences in the main effects that we were investigating, e.g. group differences in rest-task attenuation, we did not have sufficient power to explore differences in comorbidity of ODD/CD or differences between ADHD subtypes. Future, larger studies will be able to examine comorbid ODD/CD effects and also to determine whether the effects that we have identified are associated with ADHD per se or more specifically with inattention.

2) *Our clinical sample of ADHD cases may be difficult to generalise from.* All of our sample of clinical cases with ADHD were clinic-referred adolescent boys aged 13-16 with no diagnosed comorbidities (except ODD/CD). Although this within-group homogeneity increased our statistical power to identify group differences, it may have reduced the generalisability of our findings. For example, as we did not include girls in our sample, is it not clear whether these differences would also be found in females with ADHD. In fact, some research has suggested that ADHD may present differently in girls than in boys, and for example, in Chapter 1 we reported that females are more likely than males to meet the criteria for ADHD-inattentive subtype (Willcutt & Carlson, 2005). Therefore, it is crucial to replicate these findings in a female sample of cases with ADHD before any generalisations can be made. Similarly, all of the ADHD cases were recruited from a clinic referred sample, and this sample may differ from hyperactive children in the community. Woodward, Dowdney, & Taylor (1997) report that clinic referred samples of children with ADHD are more likely to experience a comorbid disorder or poorer parenting practices than non-referred hyperactive children. Therefore, it will be important to replicate these findings in other samples before the results should be generalised. However it is important to note that

we identified many of these effects in two different samples. Our first sample were recruited from students at the University of Southampton, it contained both males and females and was not clinic referred. Given that many of our main effects were identified in these two different samples, we may be more confident that the effects are likely to also be identified in other samples.

3) *We did not take a measure of comorbid disorders.* In both of our studies we asked participants to report whether they were diagnosed with any clinical disorder (and in the case of clinical ADHD cases, case notes were also checked). Any participants who reported a disorder (other than ODD/CD in the ADHD cases) were excluded from the study. However, we did not take a measure to assess for undiagnosed disorders in our participants. As mentioned previously, this may have been particularly important for assessing undiagnosed ASD in the sample, which may impact on response variability. Future studies should take such measures to ensure that any group differences are in fact specific to ADHD.

The main limitations of the analytical methods employed in our research are:

1) Identification of artifactual components extracted by ICA is somewhat subjective. In our research we used ICA for artifact removal: the independent components extracted by ICA were inspected and artifacts were identified and removed from the original signal. Although we attempted to be objective in our choice of which components were artifactual (the criteria we used to identify artifactual components are outlined in section *4.2.6 Artifact removal*), there still remained an element of individual choice. More importantly, for our research, it appeared that when we used PCA prior to ICA, and fewer components were extracted, any decisions that we made about removing individual components had a greater impact on the data than when more components were extracted (i.e. PCA was not first performed on the data). When we used PCA prior to ICA, the difference in power outside of compared to within the S3 network was greater than when we did not use PCA first. It is normally possible to include a temporal of spatial constraint to ICA to remove some of the subjectivity of component choice, however given that our research is very exploratory (for example no spatial pattern of low frequency EEG has previously been identified) and such a constraint would require a priori hypotheses of the spatial distribution of the S3 network, this would not have been possible in our work. Such constraints are likely to be possible in future research, after the spatial distribution of low frequency EEG is better established.

2) We have not investigated the connectivity within the S3 'network'.
As we mentioned previously in this chapter, despite referring to the pattern of activation that we identified in this thesis as a S3 'network' we have not shown that

there is any functional connectivity between the different network locations. This will be important for determining whether this low frequency EEG is a coherent network similar to the DMN, and also whether the 'network' that we identified contains anti-correlated components, which might reflect the task positive and task negative components. Furthermore, as fMRI research has identified abnormalities in the functional connectivity of DMN in ADHD (as well as numerous other disorders, see Broyd et al., 2009 for a review), it would be very useful to determine whether similar alterations in functional connectivity in this EEG resting network are identified between patients with ADHD and controls.

3) *Our investigations have been limited to a particular frequency band – S3.* As described previously in this chapter, our focus on the S3 frequency band was due to the oscillatory peak evident in our data and also because this frequency was similar to the frequencies of the DMN. However these frequencies may not represent a functionally distinct band - and in fact our data suggest that this is unlikely. Investigating a larger number of frequency bands and bands with different frequency limits may determine the most accurate physiological limits to these low frequency EEG bands and this is likely to enhance power and reliability when assessing differences in RT-EEG synchrony and rest-task EEG attenuation.

8.5 Future Directions

The studies in this thesis have been exploratory in nature, as prior to this thesis very little research had been conducted into very low frequency EEG and no direct tests of the default-mode interference hypothesis had been performed. Therefore, it is essential for our findings to be replicated in larger samples before any sound conclusions can be made. It will also be important to replicate these findings in different samples, for example samples that include female ADHD cases and non-clinic referred hyperactive cases, so that the extent to which these findings can be generalised can be established. It will also be important to more stringently test for undiagnosed comorbidities so that we can be more confident of the relationship between rest-task attenuation and EEG-RT synchrony and ADHD.

There are also a number of questions that we have not been able to answer within this thesis, for example, we have not been able to establish whether the S3 network that we identified is a functionally coherent network or whether it contains anti-correlated components, and we have not been able to determine whether there are differences in the functional connectivity within this network between patients ADHD and controls. Although ascertaining the best methods to assess coherence in our data was beyond the scope of this thesis, this is an important area for future study.

8.6 Concluding Remark

The aim of the present thesis was to test the predictions of the default-mode interference hypothesis and to investigate the possible role of very low frequency,

spontaneous brain activity in response variability in ADHD. We found that periodicity was evident in RT data, and that there was synchrony between low frequency fluctuations in RT data and low frequency EEG. We also showed that low frequency EEG was generally attenuated from rest to task, but the degree of this attenuation was lower in ADHD or inattentive participants compared to controls. These findings provide some initial support for the default mode interference hypothesis, which suggests that if low frequency EEG is not properly attenuated when one engages in a goal-directed task, this low frequency EEG may interfere with goal-directed brain activity, causing poorer task performance, and that fluctuations in performance should have a low frequency structure and be synchronised with low frequency EEG.

Appendices

Appendix A1

Investigation of methods of short-circuiting the transdermal epithelial potential in DC-EEG recordings

Aim

This study aimed to compare two methods of short-circuiting the transdermal epithelial potential (TEP), skin scratching and abrasion.

Sample

One member of our lab participated in the study.

Measures

The participant was fitted with an electrode cap with 15 sintered silver/silver chloride electrodes and seated on a comfortable chair. These 15 electrodes were distributed in groups of 3 across the cap, i.e. 3 leads were located frontally, 3 were located centrally, 3 were located posteriorally, 3 were located above the right temporal lobe and 3 were located above the left temporal lobe. The electrodes were filled with a high abrasive chloride gel, and in each group of 3 electrodes one of three skin manoeuvre methods were used. i) the skin was left intact ii) the skin was scratched by needle to produce a 3mm scratch (see Tallgren, 2004), and iii) the skin was rubbed with abrasive electrode gel using a cotton bud. The participant was then asked to rest quietly for 5 minutes, throughout which the data were recorded (see Chapter 4, section *4.2.5 Electrophysiological Acquisition* for information about measurement parameters)

Results

Results are shown in Figure A1.1, as is evident from this figure, the intact skin has a high skin potential (+3 to -20 mV). However both methods of skin manoeuvring reduced this skin potential closer to 0. The skin abrasion and the scratched skin techniques were largely comparable in terms of the DC value obtained after the skin manoeuvre method and the drift evident in this.

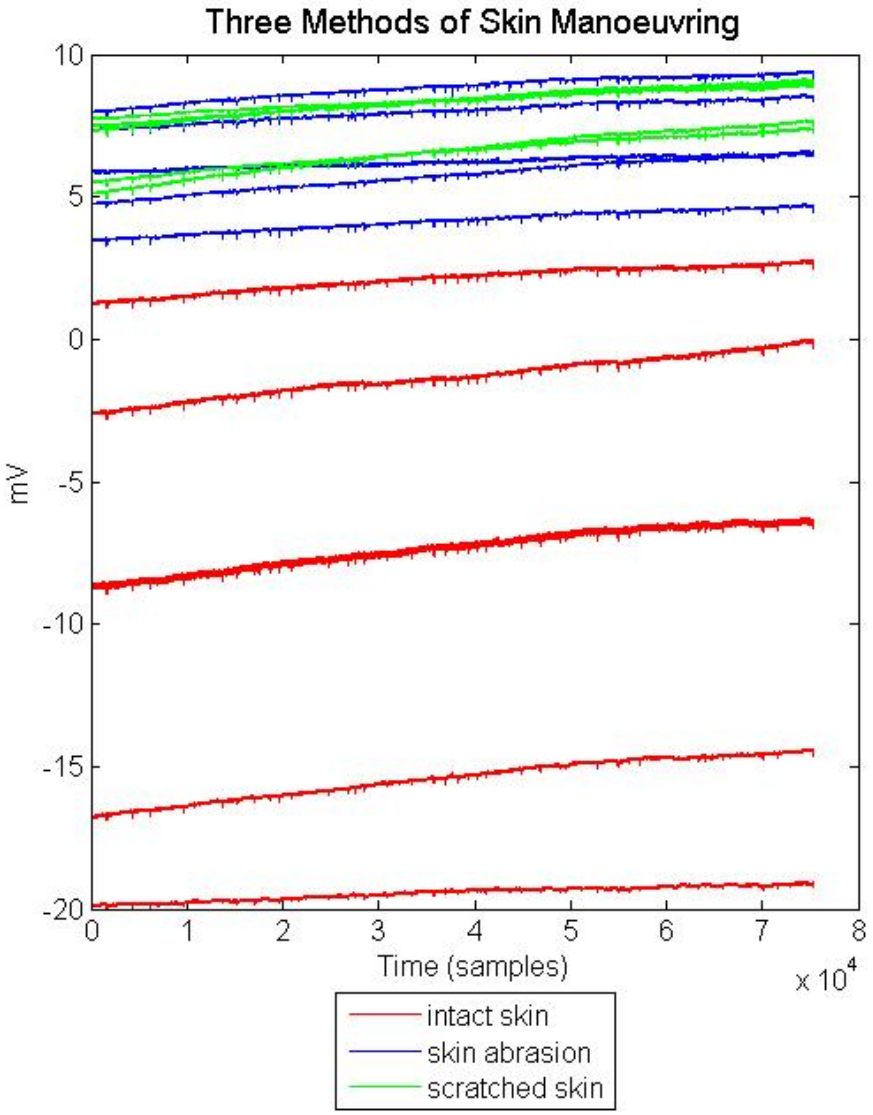


Figure A1.1: The DC response to three different skin manoeuvre methods, across a 5 minute resting session

The participant reported greater pain and discomfort from the scratched skin than the skin abrasion; and visible marks remained on the sites of scratched skin for a number of days after the testing session but not on the skin abrasion sites.

Conclusions

Scratching and abrasion both appeared to 'short-circuit' the TEP; however abrasion caused less pain to the participant. Abrasion may be a more appropriate method for vulnerable participant groups, such as children.

Appendix A2

Barkley ADHD Rating Scale –Self Report

Circle the response which best describes your behaviour over the past six months:

Frequency Code: **0=never**
1=occasionally
2=often
3=very often

1. Fail to give close attention to details or make careless mistakes at work	0 1 2 3
2. Fidget with hands or feet or squirm in seat	0 1 2 3
3. Have difficulty sustaining attention in tasks or fun activities	0 1 2 3
4. Leave seat in situations where seating is expected	0 1 2 3
5. Don't listen when spoken to directly	0 1 2 3
6. Feel restless	0 1 2 3
7. Don't follow through on instructions and fail to finish work	0 1 2 3
8. Have difficulty engaging in leisure activities quietly	0 1 2 3
9. Have difficulty organizing tasks and activities	0 1 2 3
10. Feel "on the go" or "driven by a motor"	0 1 2 3
11. Avoid, dislike, or are reluctant to engage in work that requires sustained mental effort	0 1 2 3
12. Talk excessively	0 1 2 3
13. Lose things necessary for tasks and activities	0 1 2 3
14. Blurt out answers before questions have been completed	0 1 2 3
15. Easily distracted	0 1 2 3
16. Have difficulty awaiting turn	0 1 2 3
17. Forgetful in daily duties	0 1 2 3
18. Interrupt or intrude on others	0 1 2 3

Appendix A3

Barkley ADHD Rating Scale – Other Report

Relationship to participant……

Circle the response which best describes your friend or relative's behaviour over the past six months:

Frequency Code: **0=never**
1=occasionally
2=often
3=very often

1. Fails to give close attention to details or makes careless mistakes at work	0 1 2 3
2. Fidgets with hands or feet or squirms in seat	0 1 2 3
3. Has difficulty sustaining attention in tasks or fun activities	0 1 2 3
4. Leaves seat in situations where seating is expected	0 1 2 3
5. Doesn't listen when spoken to directly	0 1 2 3
6. Feels restless	0 1 2 3
7. Doesn't follow through on instructions and fail to finish work	0 1 2 3
8. Has difficulty engaging in leisure activities quietly	0 1 2 3
9. Has difficulty organizing tasks and activities	0 1 2 3
10. Feels "on the go" or "driven by a motor"	0 1 2 3
11. Avoids, dislikes, or is reluctant to engage in work that requires sustained mental effort	0 1 2 3
12. Talks excessively	0 1 2 3
13. Loses things necessary for tasks and activities	0 1 2 3
14. Blurts out answers before questions have been completed	0 1 2 3
15. Is easily distracted	0 1 2 3
16. Has difficulty awaiting turn	0 1 2 3
17. Is forgetful in daily duties	0 1 2 3
18. Interrupts or intrudes on others	0 1 2 3

Appendix A4

Information Sheet and Consent Form for Research Participants

Information sheet

I am Suzannah Helps, a PhD student at the University of Southampton. I am requesting your participation in a study regarding comparing EEG (brain waves) and heart rate activity when people are resting and when they are performing a task.

This will involve attending two sessions (approximately 1 week apart) in which we will measure your EEG activity and heart rate;

1) When you are resting (5 minutes)
2) When you are performing a computer attention task (10 minutes). In this task, you will be asked to 'drive' along a track that you see on a screen, keeping as close to the road as possible.
3) When you are performing an attention task that measures your reaction time to arrows presented on the computer screen (10 minutes)
4) When you are resting again (5 minutes).

In the first session you will also be asked to fill in a few very brief questionnaires about your behaviour (approx 5 mins). You will also be asked to take a copy of one questionnaire to a friend, partner or relative to fill in about your behaviour (this will take them less than 5 mins to complete).

These tasks will be explained in more detail before you are asked to perform them and you will have a chance to ask any questions.

Personal information will not be released to or viewed by anyone other than researchers involved in this project. Results of this study will not include your name or any other identifying characteristics.

Your participation is voluntary and you may withdraw your participation at any time. If you choose not to participate there will be no consequences to your grade or to your treatment as a student in the psychology department. If you have any questions please ask them now, or contact me; Suzannah Helps at skh204@soton.ac.uk

Signature Date

Name Suzannah Helps

Statement of Consent

I _____ have read the above informed consent form.

[participants name]

I understand that I may withdraw my consent and discontinue participation at any time without penalty or loss of benefit to myself. I understand that data collected as part of this research project will be treated confidentially, and that published results of this research project will maintain my confidentially. In signing this consent letter, I am not waiving my legal claims, rights, or remedies. A copy of this consent letter will be offered to me.

(Circle Yes or No)

I give consent to participate in the above study. Yes No

Signature Date

Name *[participants name]*

I understand that if I have questions about my rights as a participant in this research, or if I feel that I have been placed at risk, I can contact the Chair of the Ethics Committee, Department of Psychology, University of Southampton, Southampton, SO17 1BJ.
Phone: (023) 8059 3995.

Appendix A5

Outline of Pilot study: preliminary investigation of DC-EEG recordings

Aim

This study aimed to investigate 1) whether DC-EEG was able to identify low-frequency oscillations and 2) to establish an appropriate time period to reliably record such oscillations.

Sample

4 postgraduate students from the University of Southampton participated in the study.

Measures

All participants completed four tasks which were identical to those in study 1 except that both resting sessions were of 10 minutes rather than 5 minutes duration.

Results

Low-frequency oscillations were identified in both the raw DC-EEG data and after drift in the data had been removed. FFTs were performed on EEG data segments of varying lengths between 1 and 10 minutes from each task. An example of this is shown in Figure A5.1. This figure illustrates that although the FFT distribution initially changed as the length of data segment increased, after 5 minutes (300 seconds), any further increase in the length of the data segment made little difference to the FFT distribution. Therefore, 5 minutes was deemed to be an appropriate length for each EEG data recording.

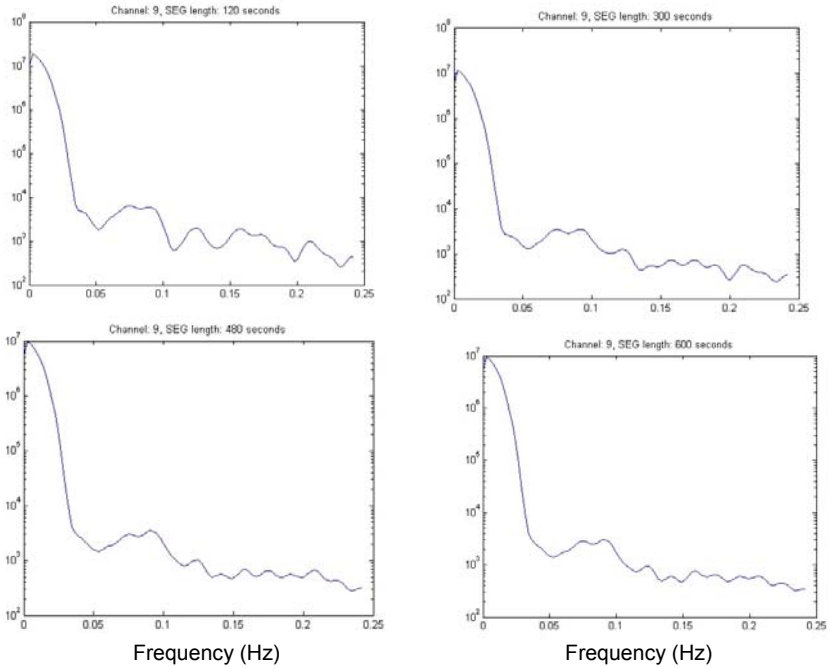


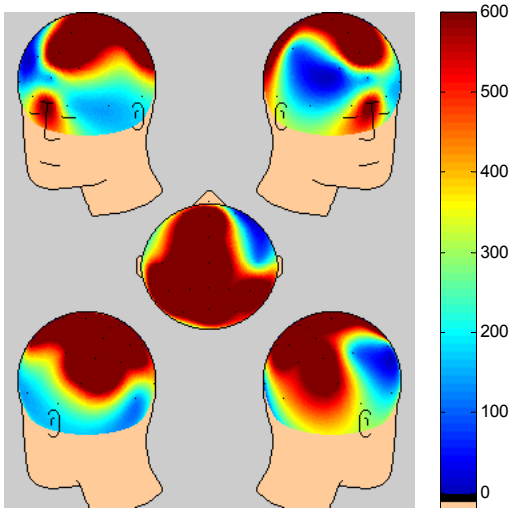
Figure A5.1: FFTs on varying lengths of the same data segment

However, because the sampling rate in the behavioural data was much lower than that of the EEG data, for example, the reaction time task sampled only once per second but the EEG data sampled 250 times each second, reducing the behavioural tasks to 5 minutes would

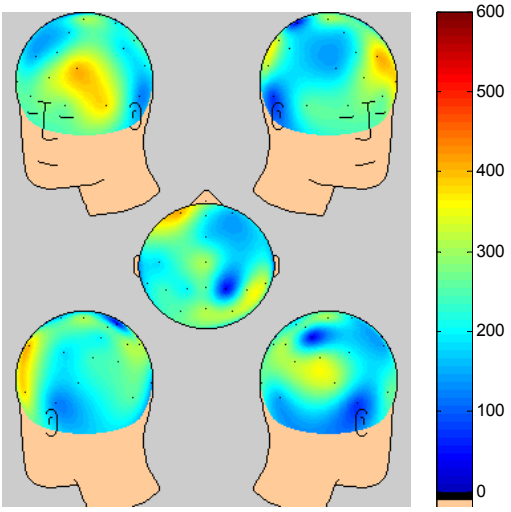
reduce the total number of samples to only 300. Therefore it was decided that the two behavioural tasks, and consequently the EEG recordings of these, should last 10 minutes. This also allows comparisons to be made within the EEG recordings throughout the time course of such goal-directed activity of the EEG profile when boredom or fatigue is likely to occur, that is, it allows the exploration of whether the characteristics of these low-frequency oscillations (e.g. power) change over time.

Appendix A6

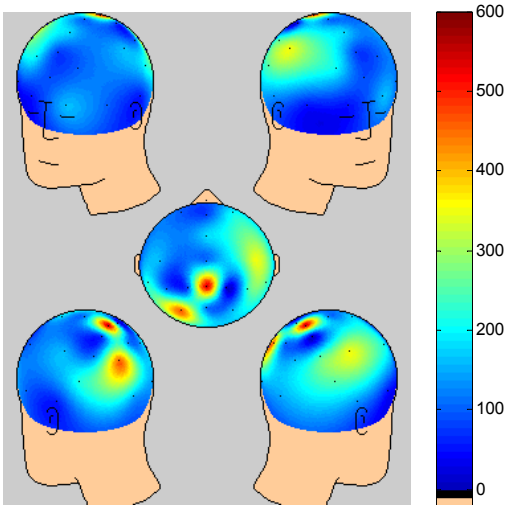
Topographical maps for each *low-ADHD* symptom participant while resting with eyes open (all maps are shown on the same scale)



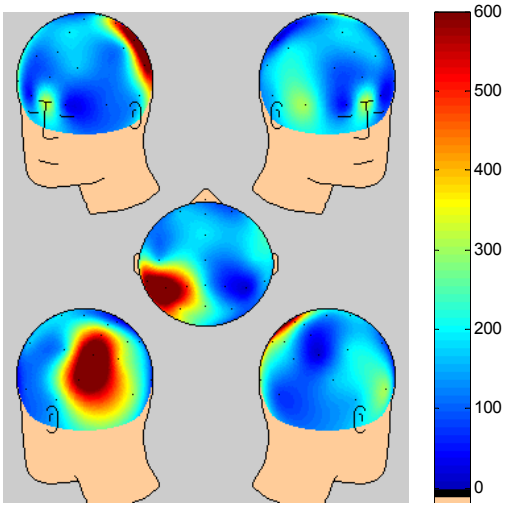
Participant 1 test 1



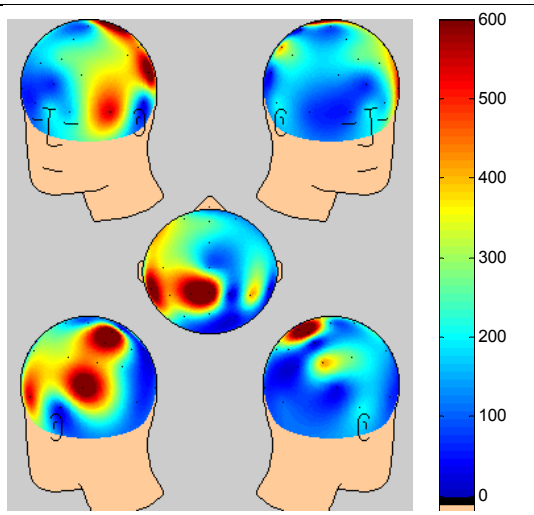
Participant 2 test 1



Participant 3 test 1



Participant 5 test 1



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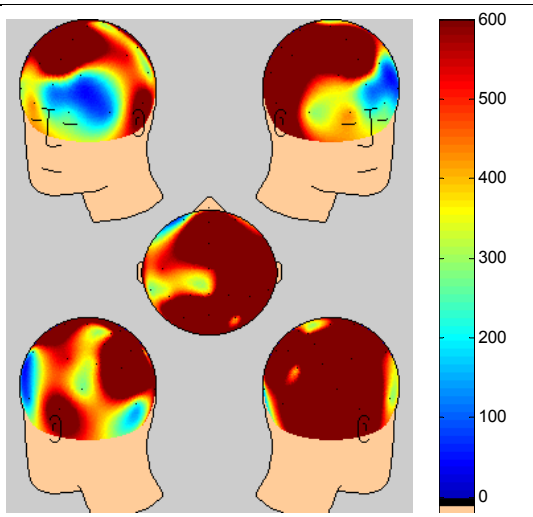
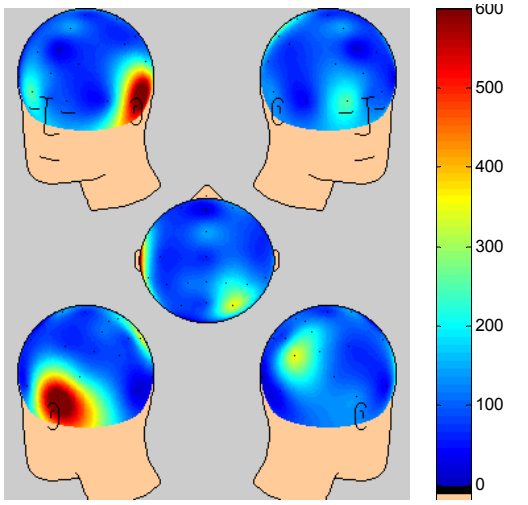
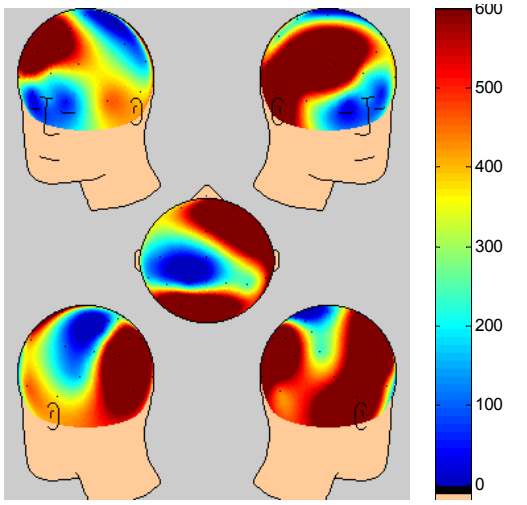


Participant 9 test 1



Participant 13 test 1



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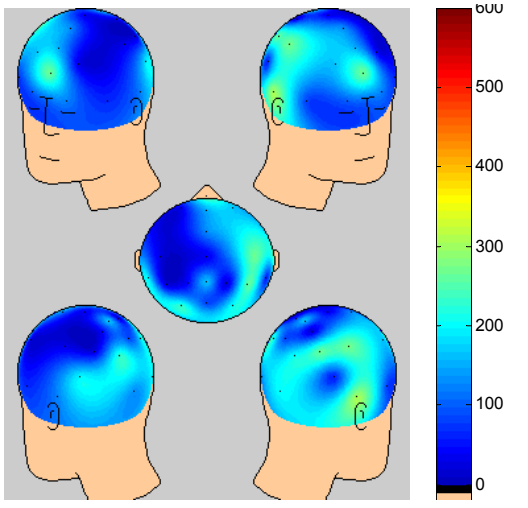

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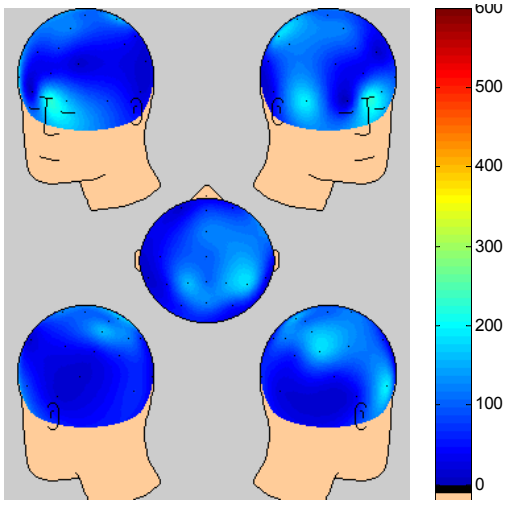

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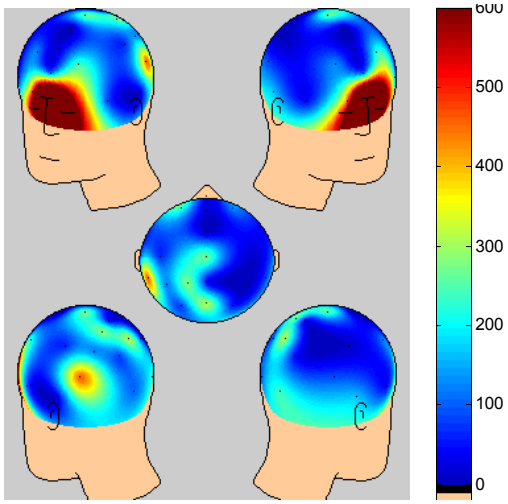
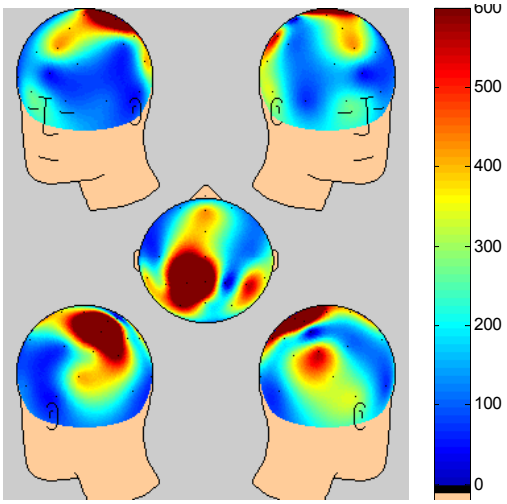
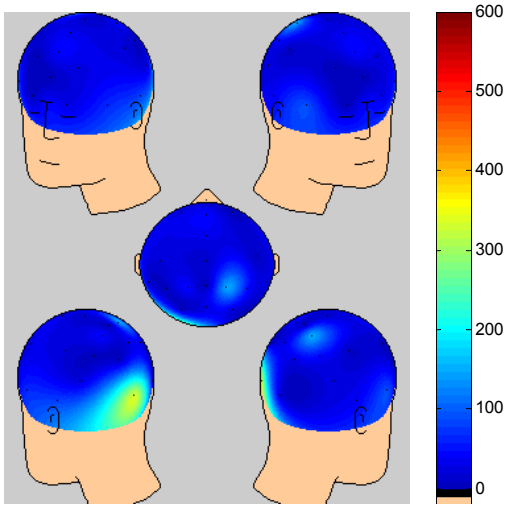


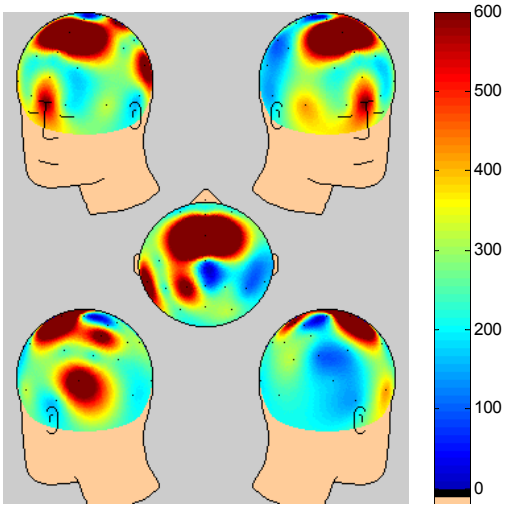
Participant 23 test 1



Participant 1 test 2



Participant 3 test 2



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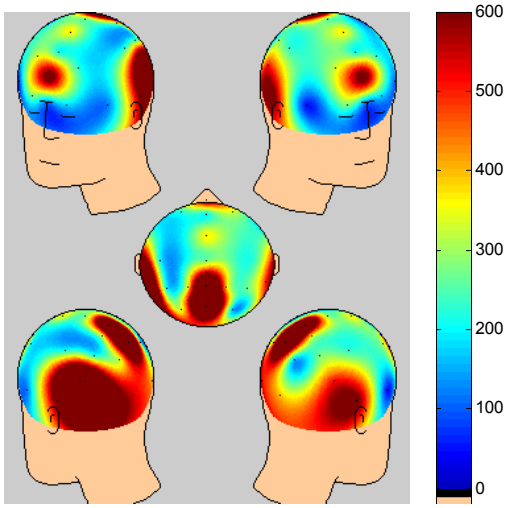
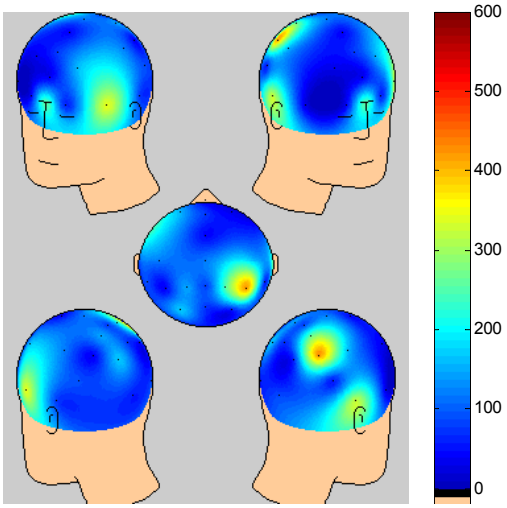


Participant 9 test 2

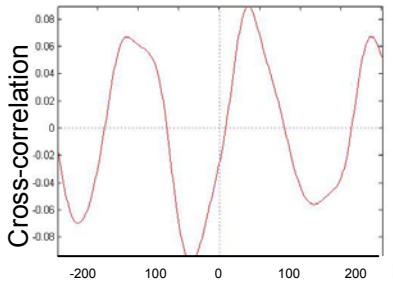
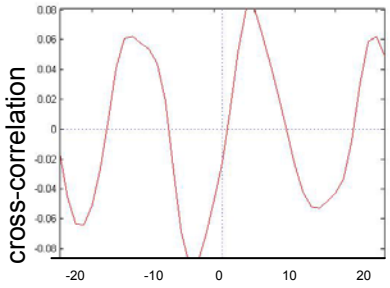
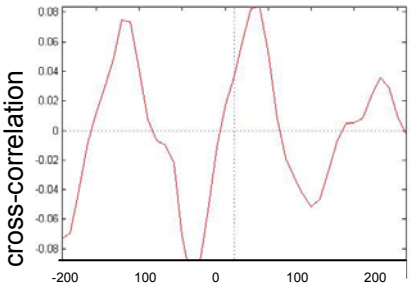
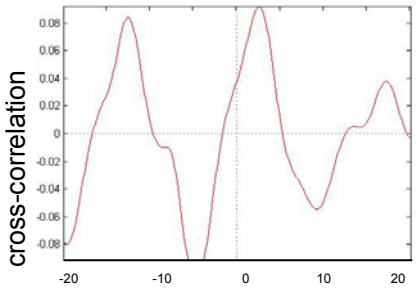
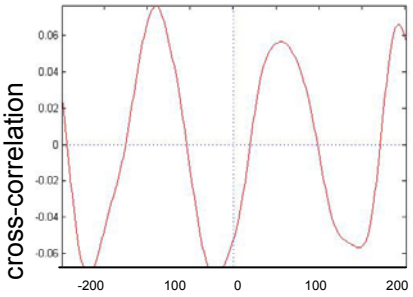
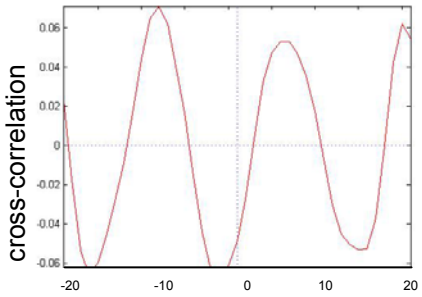
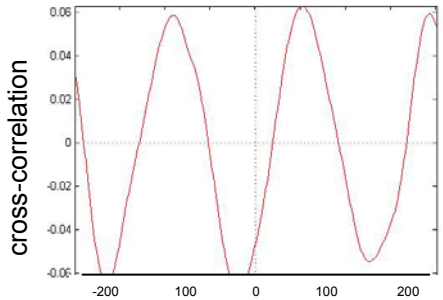
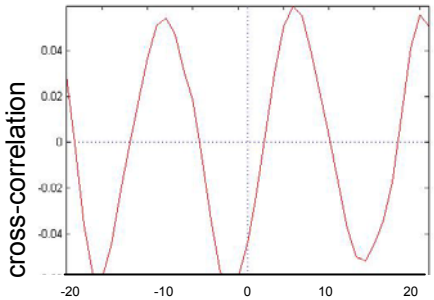


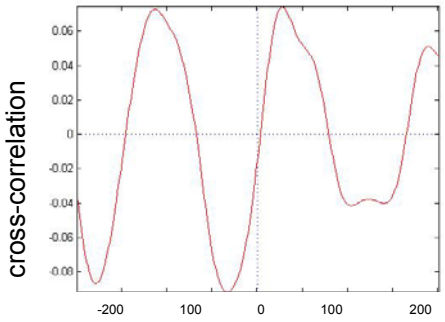
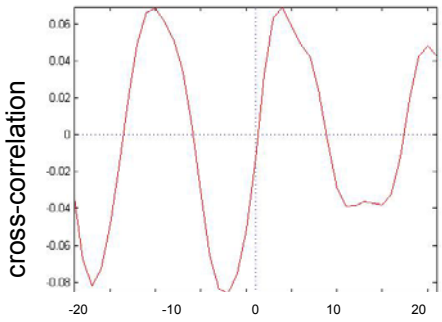
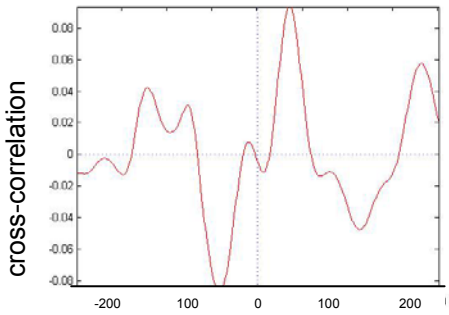
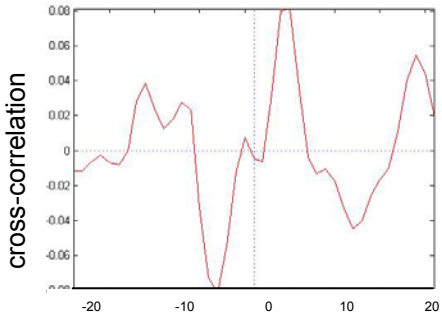
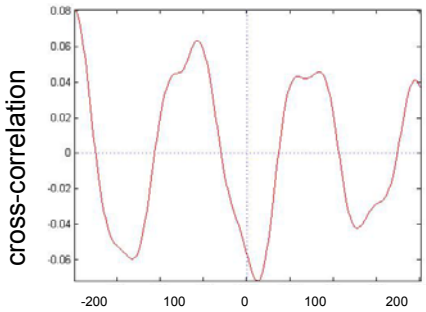
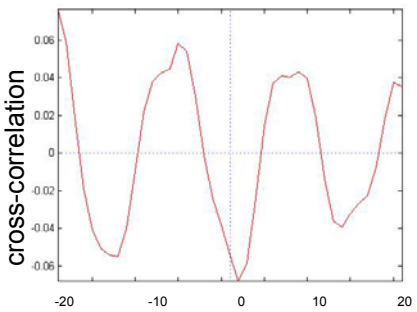
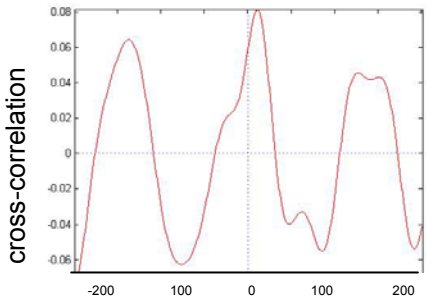
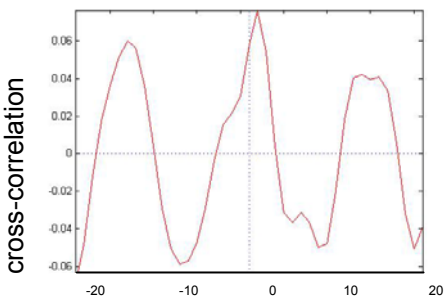
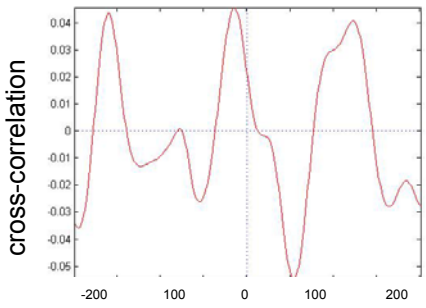
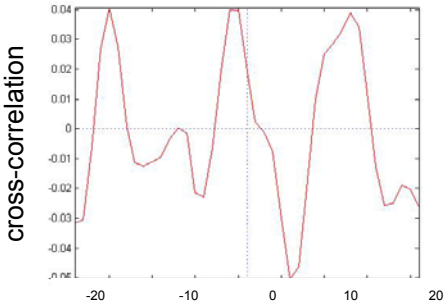
Participant 13 test 2

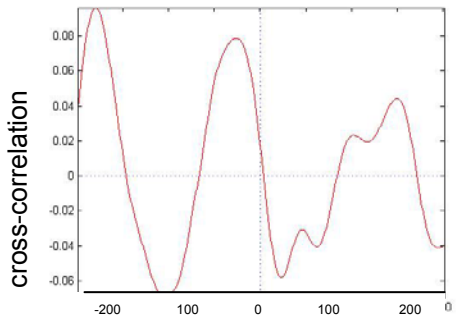
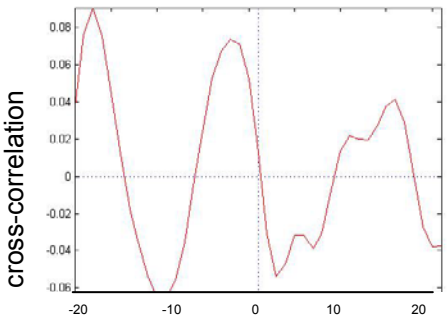
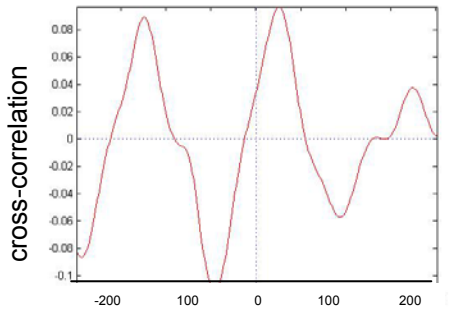
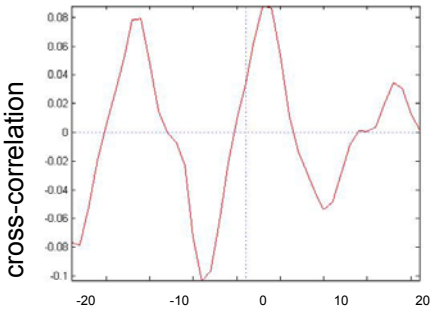
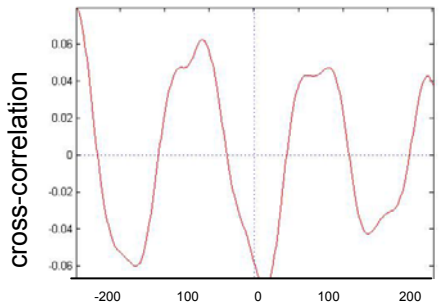
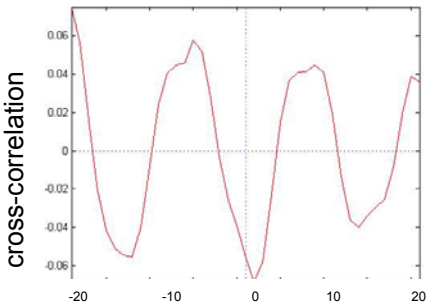
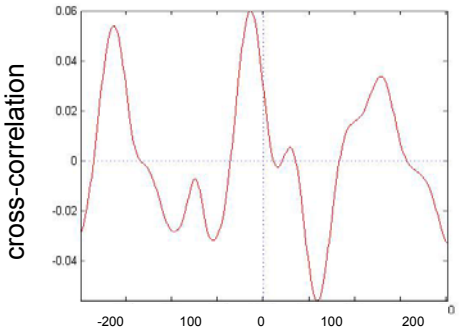
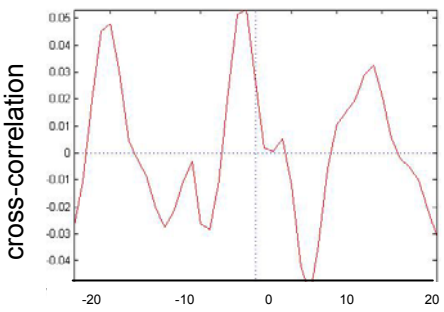
Appendix A7

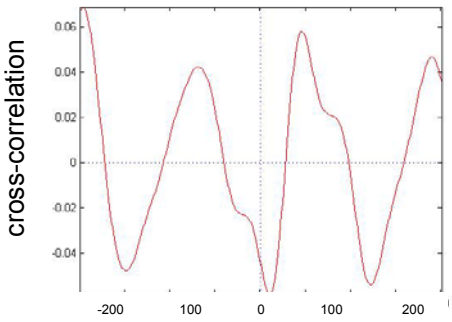
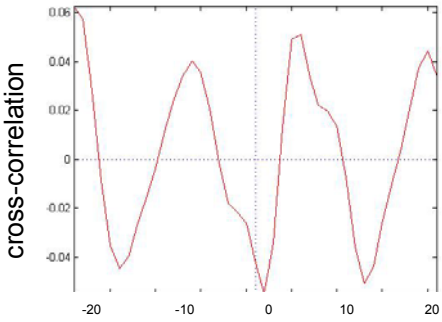
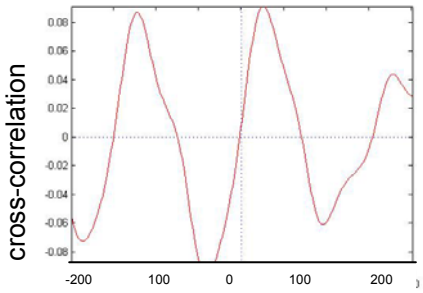
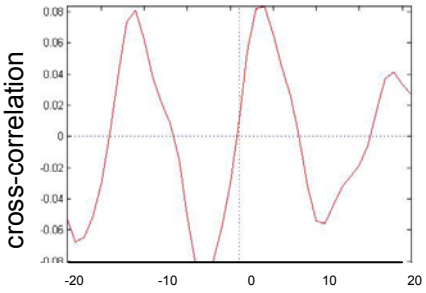
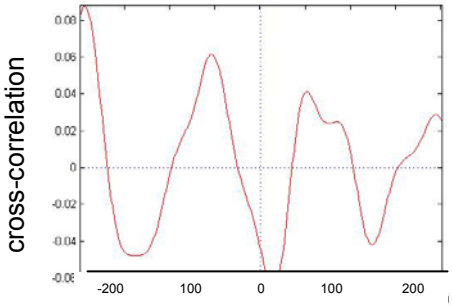
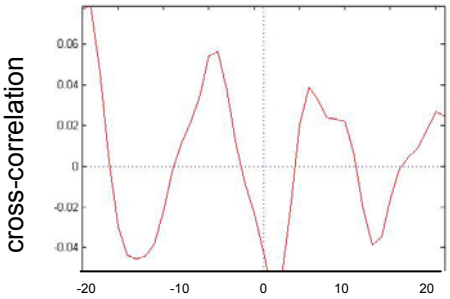
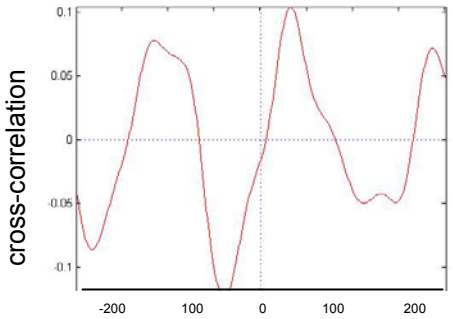
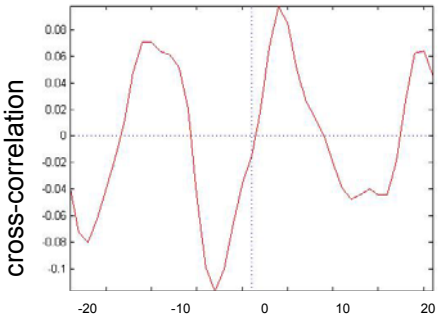
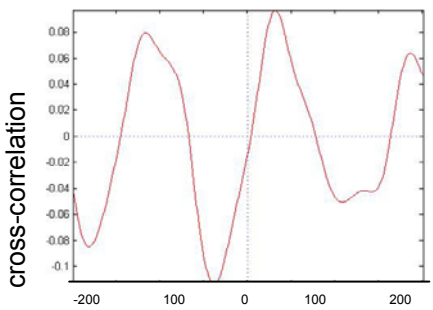
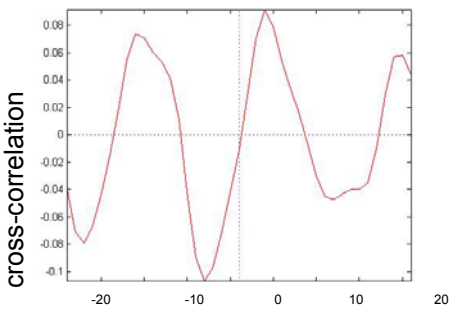
Cross-correlations from two methods of adjusting the sampling rate of the EEG and RT signals – up-sampling the RT time series and down-sampling the EEG – for a single participant, shown for each channel of EEG data (1-27). The two methods of adjusting the sample rate result in very similar patterns of cross-correlation.

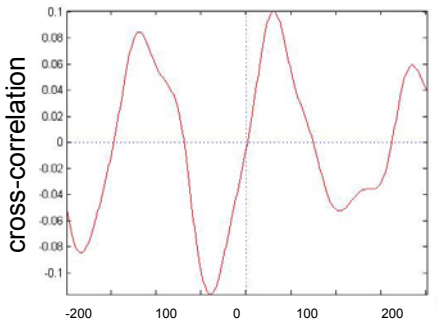
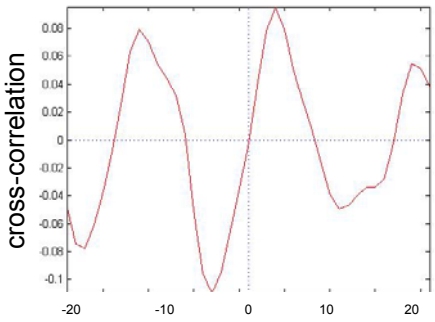
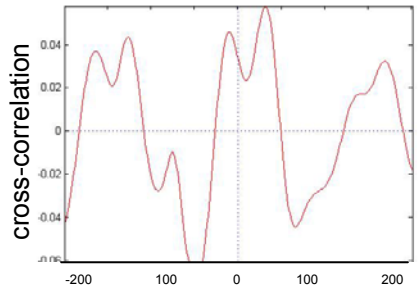
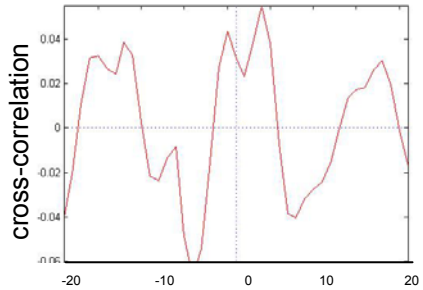
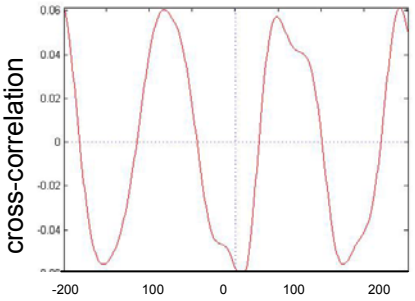
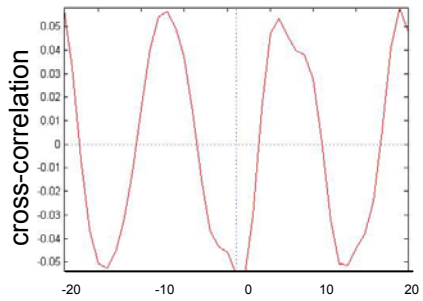
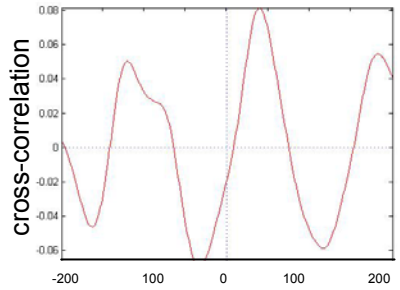
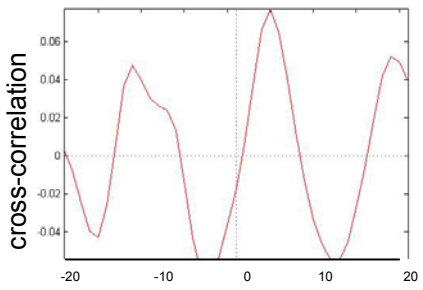
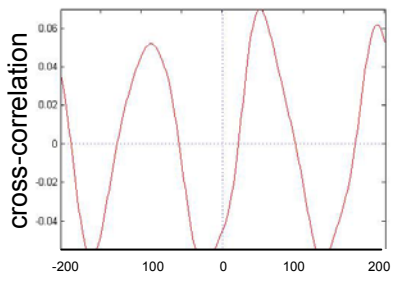
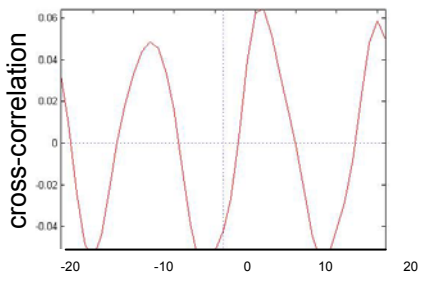
Note. The x-axis shows the lag between the two signals in samples.

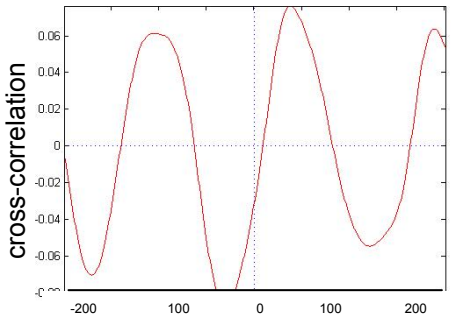
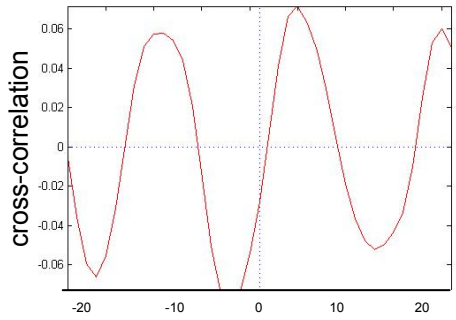
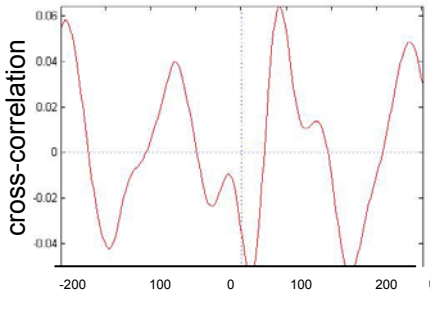
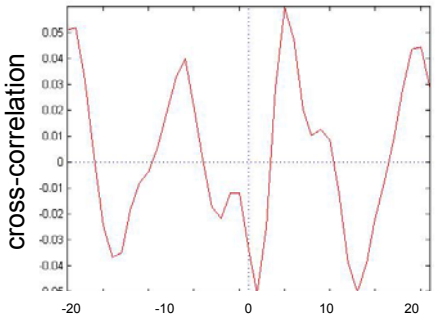
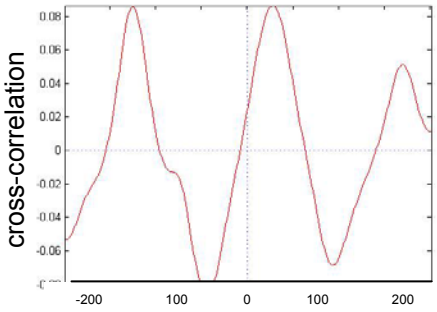
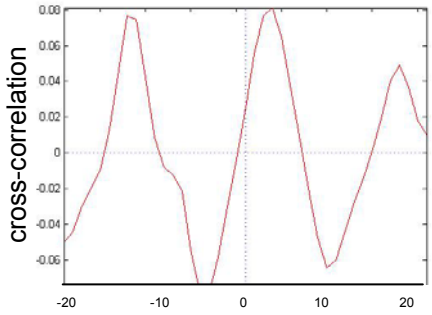
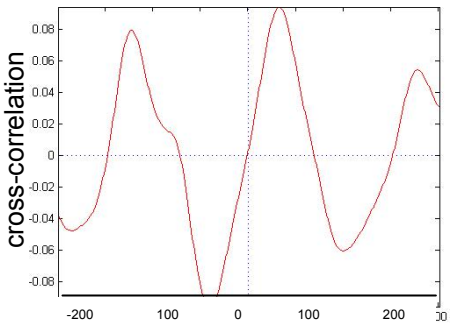
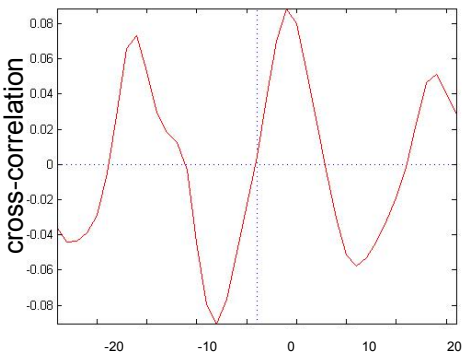
Channel	RT data up-sampled to 10 Hz	EEG data down sampled to 1 Hz
1		
2		
3		
4		

Channel	RT data up-sampled to 10 Hz	EEG data down sampled to 1 Hz
5		
6		
7		
8		
9		

Channel	RT data up-sampled to 10 Hz	EEG data down sampled to 1 Hz
10		
11		
12		
13		

Channel	RT data up-sampled to 10 Hz	EEG data down sampled to 1 Hz
14		
15		
16		
17		
18		

Channel	RT data up-sampled to 10 Hz	EEG data down sampled to 1 Hz
19		
20		
21		
22		
23		

Channel	RT data up-sampled to 10 Hz	EEG data down sampled to 1 Hz
24		
25		
26		
27		

Appendix A8

Assessing whether S3 synchrony might be artifactually induced by our methods of analysis.

Background and aim

In Chapters 5 and 7 we report that although the mean S3 RT-EEG synchrony was small overall, it did differ significantly from zero. However it is possible that the nature of our analysis, i.e. filtering both signals to leave only the narrow S3 frequency band may have artifactually induced some degree of synchrony between the two signals. So that, if any two signals were filtered to leave the same frequency component, they would inevitably exhibit some degree of synchrony. In order to determine whether this degree of synchrony might be artifactually induced by our analyses, we aimed to assess whether two uncorrelated simulated signals would show some degree of synchrony after both signals were filtered to leave only the S3 component.

Analysis

Forty white noise signals (1000 samples long) were generated using the 'rand' command in Matlab. These signals were then bandpass filtered to leave only the S3 frequency component (.06 - .2 Hz). Cross-correlations were then performed on random pairs of these data (i.e. 20 cross correlation trials were performed).

Results

The cross correlation for each trial is shown in Figure A8.1. It is clear from this figure that not all cross-correlations are positive. A one-sampled t-test showed that these cross-correlations did not differ from zero (*t(19)* = .125, *p* = .902, 95% CI -.0307 to .0346).

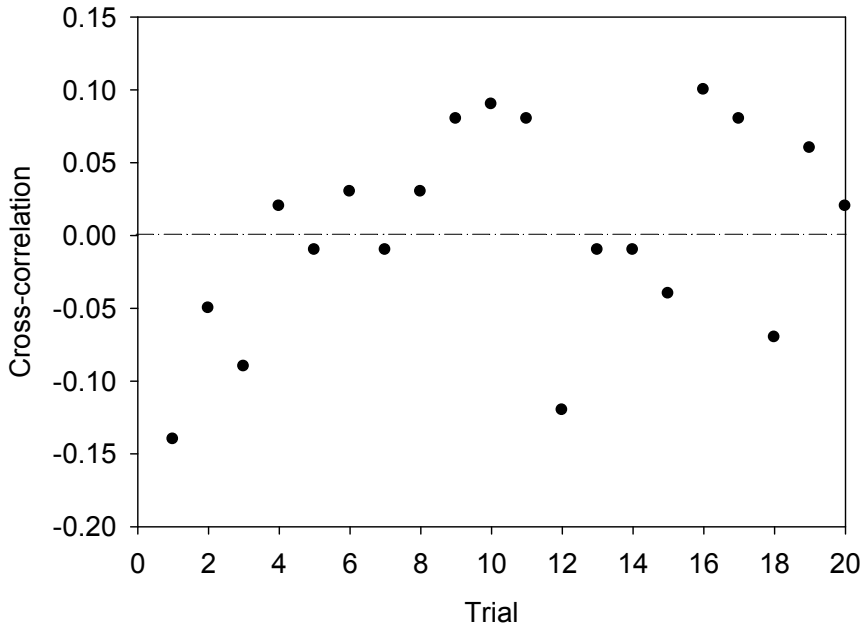


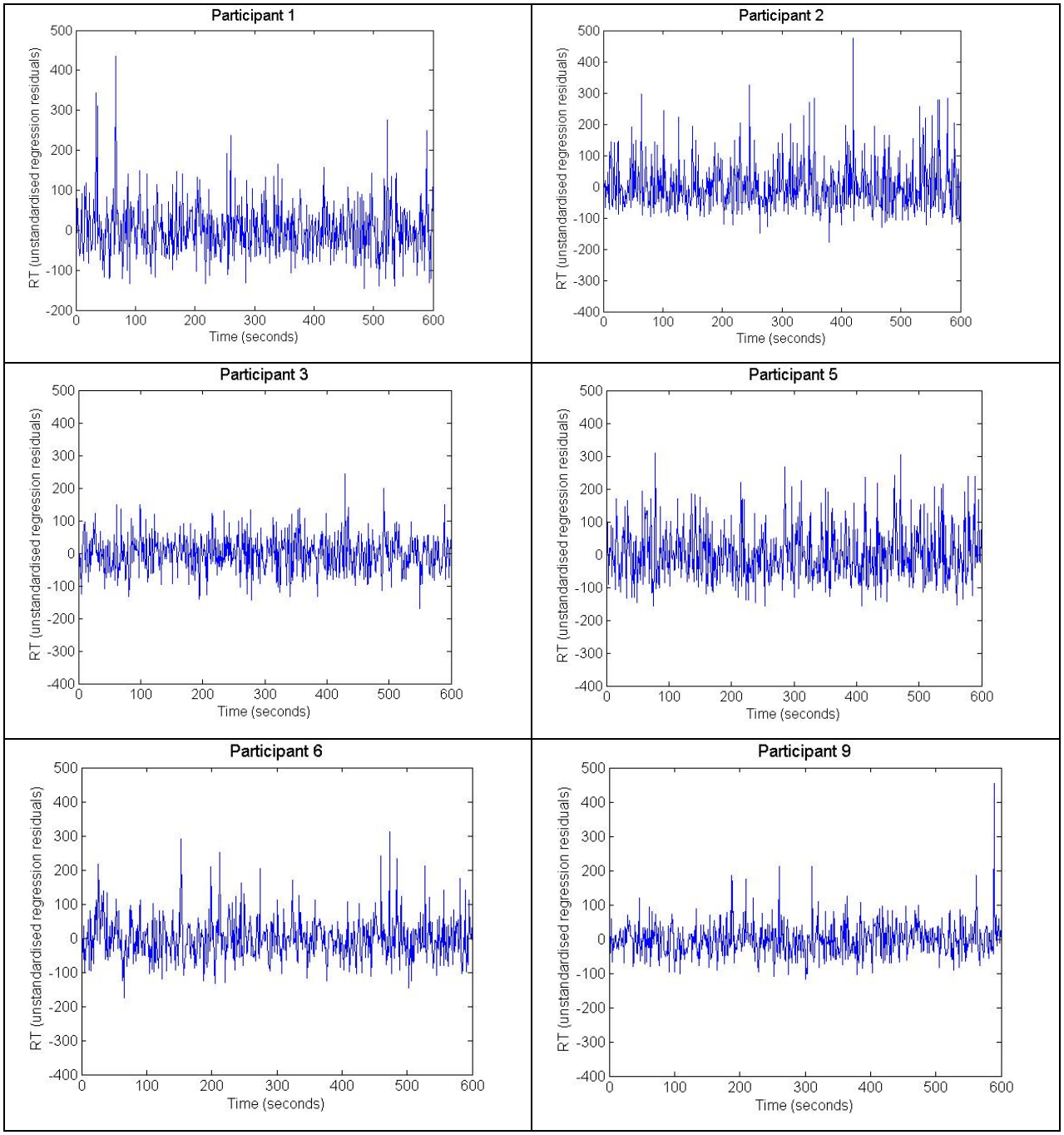
Figure A8.1: Cross-correlation between two filtered white noise signals, for each of 20 trials.

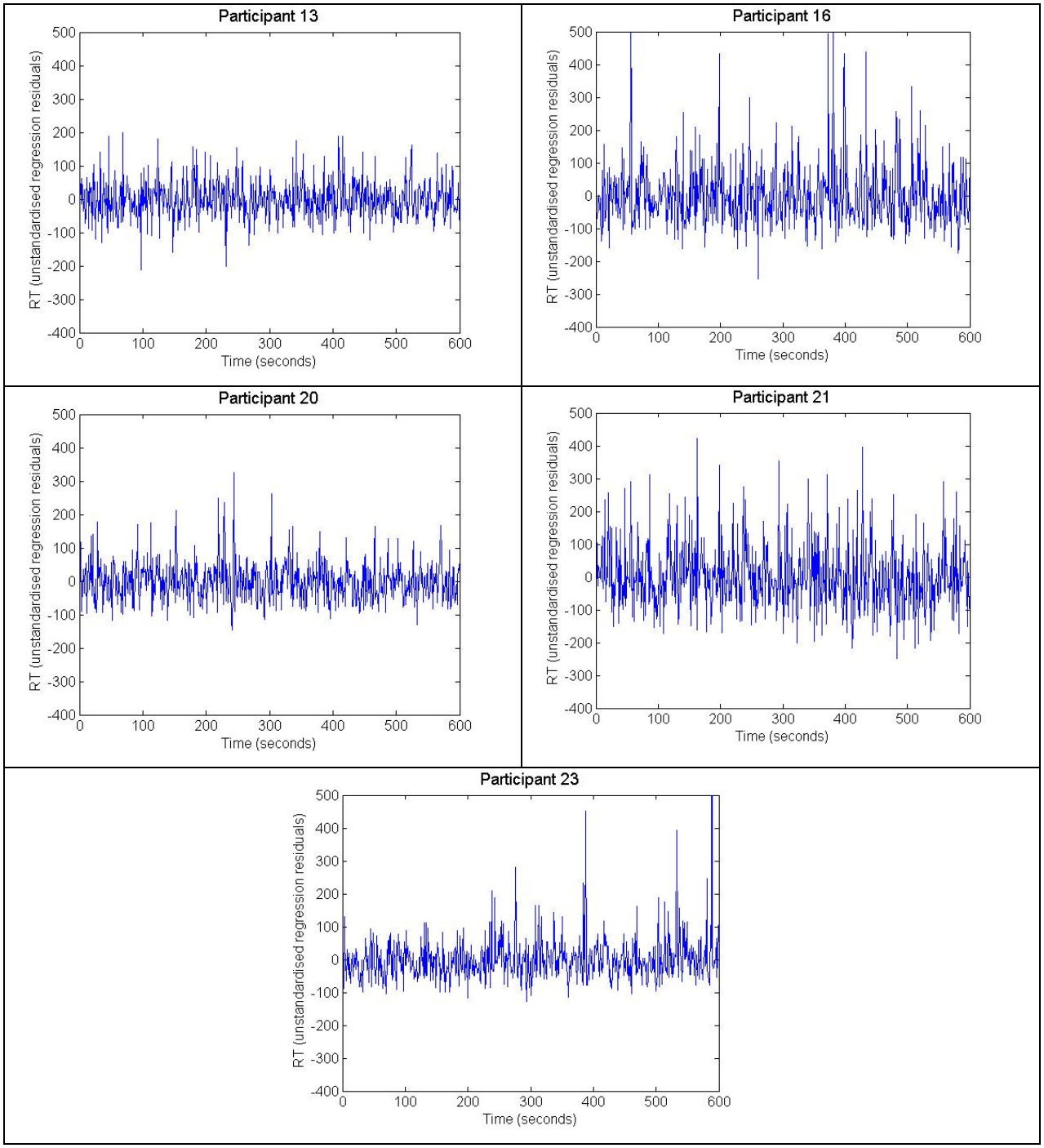
Implications

The cross-correlations between two filtered simulated white noise signals were not inevitably positive, many of the cross correlations between these synchronised signals were negatively- or anti-correlated, and overall the cross-correlations between these simulated signals did not significantly differ from zero. This is in contrast with our measure of S3 EEG-RT synchrony, which was found to be positive and significantly differ from zero. Therefore it seems unlikely that the synchrony which we identified between the S3 EEG and the S3 RT signals would be an artifact of our analysis.

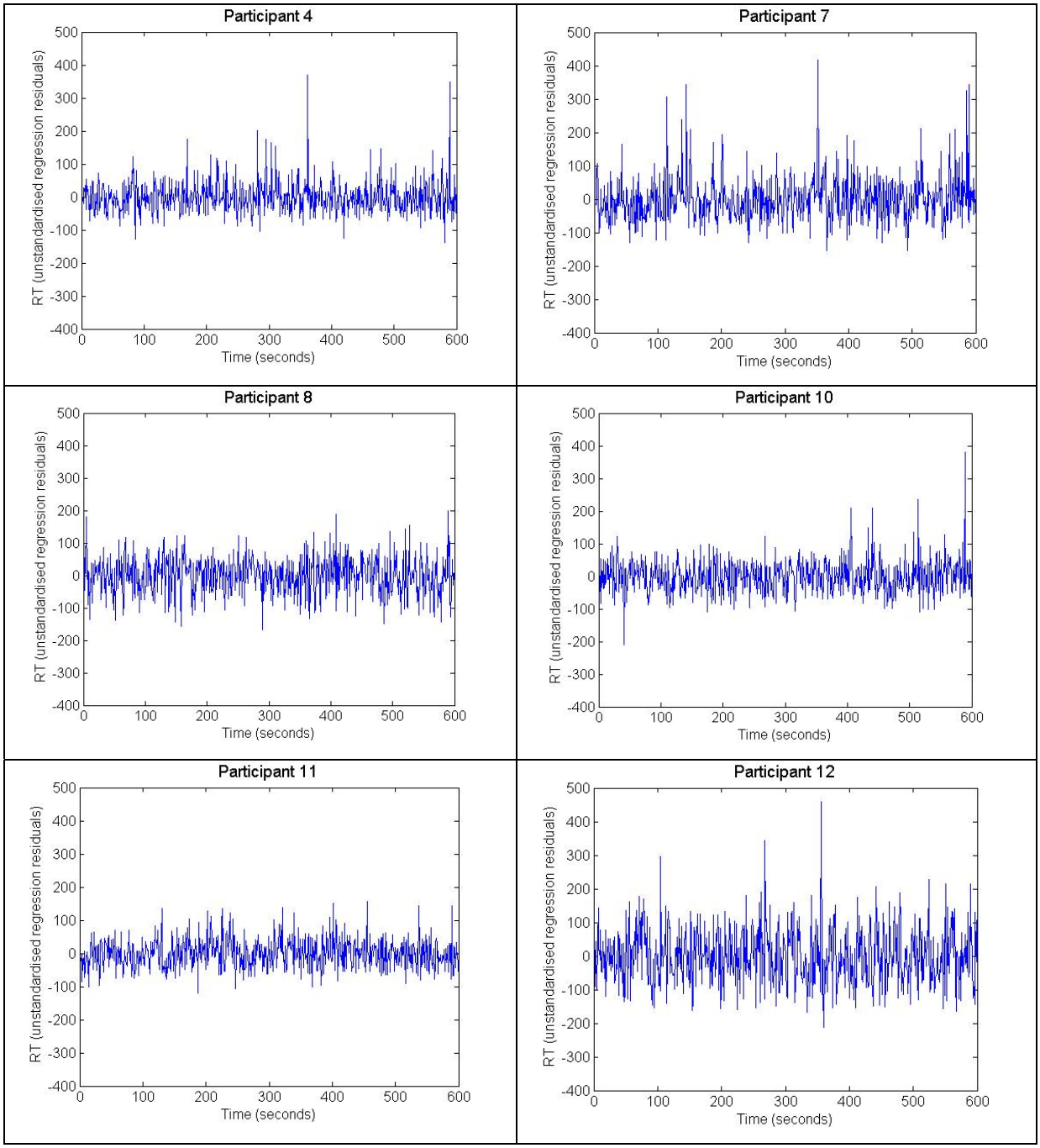
Appendix A9

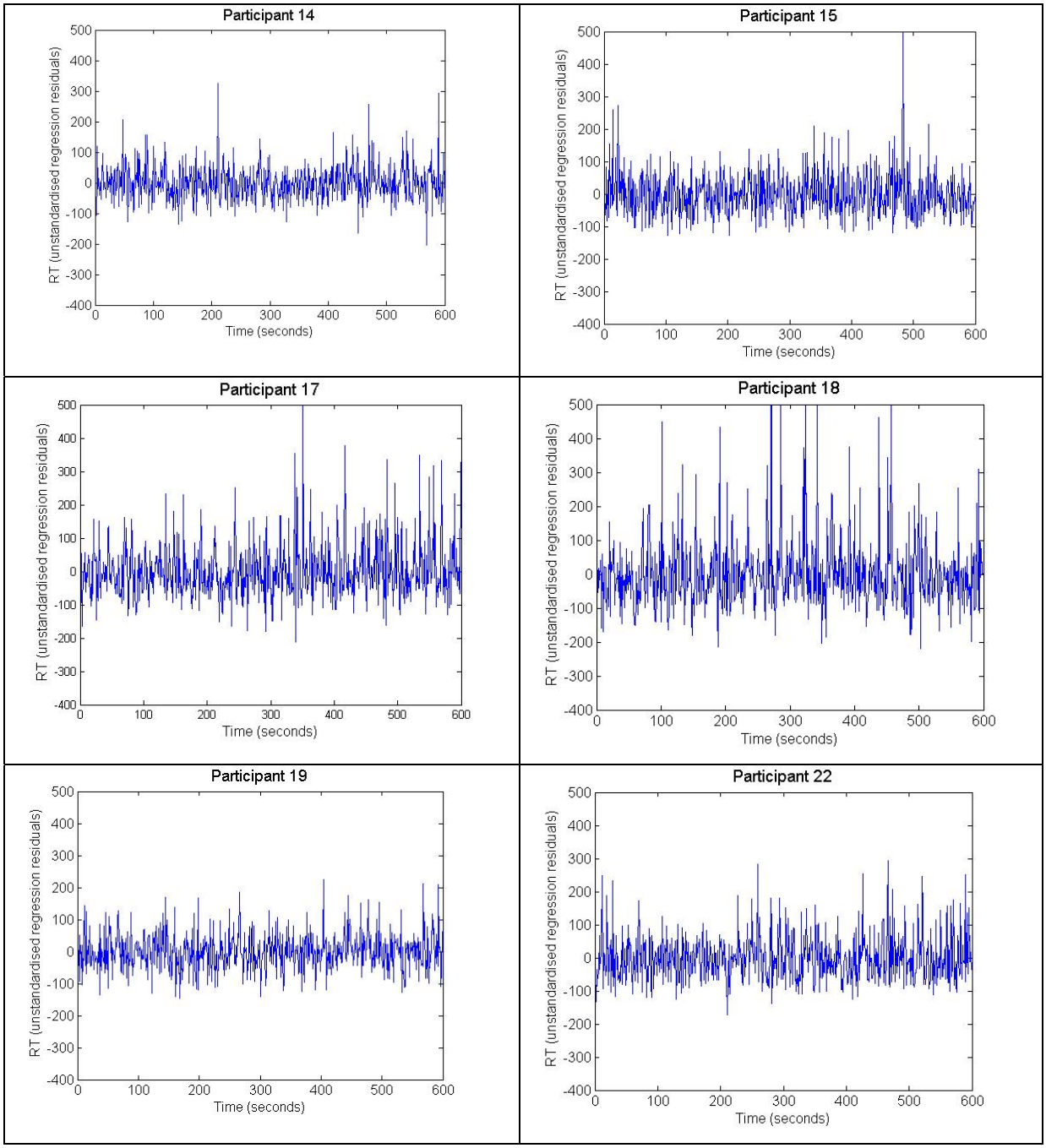
RT time series for all low-ADHD participants across the entire task at T1




Participant 13
RT (unstandardised regression residuals)
Time (seconds)
Participant 16
RT (unstandardised regression residuals)
Time (seconds)
Participant 20
RT (unstandardised regression residuals)
Time (seconds)
Participant 21
RT (unstandardised regression residuals)
Time (seconds)
Participant 23
RT (unstandardised regression residuals)
Time (seconds)

RT time series for all high-ADHD symptom participants across the entire task at T1




Participant 14
RT (unstandardised regression residuals)
Time (seconds)
Participant 15
RT (unstandardised regression residuals)
Time (seconds)
Participant 17
RT (unstandardised regression residuals)
Time (seconds)
Participant 18
RT (unstandardised regression residuals)
Time (seconds)
Participant 19
RT (unstandardised regression residuals)
Time (seconds)
Participant 22
RT (unstandardised regression residuals)
Time (seconds)

Southampton & South West Hampshire LREC (B)

LIST OF SITES WITH A FAVOURABLE ETHICAL OPINION

For all studies requiring site-specific assessment, this form is issued by the main REC to the Chief Investigator and sponsor with the favourable opinion letter and following subsequent notifications from site assessors. For issue 2 onwards, all sites with a favourable opinion are listed, adding the new sites approved.

REC reference number:	08/H0504/16	**Issue number:**	0	**Date of issue:**	12 June 2008
Chief Investigator:	Miss Suzannah Helps				
Full title of study:	Very low frequency EEG activity and the resting brain in ADHD				

This study was given a favourable ethical opinion by Southampton & South West Hampshire LREC (B) on 12 June 2008. The favourable opinion is extended to each of the sites listed below. The research may commence at each NHS site when management approval from the relevant NHS care organisation has been confirmed.

Principal Investigator	*Post*	*Research site*	*Site assessor*	*Date of favourable opinion for this site*	*Notes [1]*
Dr Wai Chen	**Consultant Child and Adolescent Psychiatry**	**Child and Adolescent Mental Health Service New forest**	**Southampton & South West Hampshire LREC (B)**	**12/06/2008**	

Approved by the Chair on behalf of the REC:

..... (Signature of Chair/Co-ordinator)
(delete as applicable)

Mrs Sharon Atwill

Appendix A11

Cover letter for young people with ADHD and their parents

Dear young person; Dear parent,

I am Suzannah Helps, a researcher at the University of Southampton, and I am working with Dr Chen, Consultant Child and Adolescent Psychiatrist at New Forest Child and Adult Mental Health Service. We are writing to let you know about some research that we are running that is trying to find out what happens in peoples' brains when they are resting and when they are paying attention. The purpose of the study is to compare those with ADHD with those without, while resting and paying attention.

We are inviting young people aged 13-16 who have been diagnosed with attention-deficit/hyperactivity disorder (ADHD), and are coming off their ADHD medication for a drug holiday, to take part in this research. However the parent/guardian of the young person must also say that it's OK for them to take part.

Before you decide if you want to join in, it's important to understand why the research is being done and what it will involve for you. So please consider the information sheet that we've included in this pack carefully. If you think that you might be interested in the study please fill in the reply slip at the back of the pack and return it to me in the freepost envelope and I can phone you to let you know more information about the research.

Please contact Suzannah Helps by email s.helps@soton.ac.uk or phone 02380 594586 if you have further questions regarding this research or if you would like more information.

Yours truly,

Suzannah Helps and Dr Wai C

Appendix A12

Cover letter for young people and their parents

Dear young person; Dear parent,

I am a research student at the University of Southampton and I am writing to let you know about some research that we are running that is trying to find out what happens in peoples' brains when they are resting and when they are paying attention. The purpose of the study is to compare those with ADHD with those without, while resting and paying attention.

We are inviting males *without ADHD* aged 13-16 to take part in this research; however their parent/guardian must also say that it's OK for them to take part.

Before you decide if you want to join in, it's important to understand why the research is being done and what it will involve for you. To make this clear we have included separate information sheets for the young person and their parent/guardian. Please consider the information on these sheets carefully. If you think that you might be interested in the study please fill in the reply slip at the back of the pack and return it to me in the freepost envelope and I can phone you to let you know more information about the research.

Please contact me, Suzannah Helps by email s.helps@soton.ac.uk or phone 02380 594586 if there is anything that isn't clear or if you would like more information.

Yours truly,

Suzannah Helps

Appendix A13

Information sheet for parents of young people with ADHD

We would like to invite your child to take part in a research study. Before you and they decide, you need to understand why the research is being done and what it would involve for both of you. Please take time to read the following information carefully. Talk to others about the study if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether you wish to take part.

What is the purpose of the study?

We are trying to find out more about brain activity when people are resting and how this might be important in attention -deficit/hyperactivity disorder (ADHD). We want to compare resting brain activity and brain activity when people are performing tasks between young people who have ADHD and young people who do not have ADHD. This is pain free and harmless for the young person.

Why has my child been invited?

Your child has been invited to join the study so that we can compare the brainwaves of children without ADHD to those with ADHD, and because they are between 13 and 16 years old and have ADHD. We need to recruit 20 young people with ADHD and 20 young people without ADHD.

Does my child have to take part?

No, it's up to you to decide together. If you are interested in the study please send back the reply slip at the end of the booklet and a researcher will phone you to go through this information sheet, which you will be able to keep. We will then ask you to sign a consent form to show that you have agreed for your child to take part. You and your child are free to withdraw at any time, without giving a reason. This will not affect the standard of care that you or your child receives.

What will happen to my child if they take part?

If your child takes part in the research, a researcher will contact you to arrange a time for them to come to the University of Southampton. They will need to come for a single session that will last about an hour and a half. If your child normally takes stimulant medication for their ADHD (e.g. Ritalin) we will arrange this session to occur at a time when they will be taking a 'drug holiday ', this can be discussed with the researcher when they phone.

Will I get my expenses paid?

Yes, £30 will be reimbursed for your travel expenses.

What will I have to do?

You will need to fill in two short questionnaires about your child's behaviour. This will take about 10 minutes. We will also (with your permission) contact your child's teacher and ask them to fill in one of these questionnaires about your child's behaviour.

What will my child have to do?

Your child will spend about 20 minutes doing some tasks so that we get a measure of their general level of intelligence. Then they will be fitted with a number of leads that are mounted on a special cap that allows us to measure the electrical activity of their brains and two leads that measure your child's heart rate – these will be on their chest and their shoulder. This is completely pain free and harmless. All leads will be filled with a gel to improve the quality of the signal. The leads transmit the electrical activity to the computer where it is recorded. Your child will place the heart rate lead onto their own chest, it is simple to place and they will not have to remove any of their clothes for this.

There is no risk involved; the leads do not pass electrical activity back to the brain. The leads can be removed in less than a minute if your child decides that they want to stop. Once the leads have been placed, they will be asked to complete two simple tasks on the computer and also to rest (these tasks will be explained in full before your child is asked to complete them). We will try to remove as much of the gel as possible at the end of the visit, and we have a sink and shower at the university if they would like to wash their hair here.

What are the possible disadvantages and risks of taking part?

There are no significant disadvantages or risks involved in taking part in this study. Many people find the tasks fun, if a little tiring. The gel that we use on the leads is normally harmless. However, to be certain, we will conduct a skin test to check that your child does not react to it. This involves putting a tiny amount of gel on their hand to look for redness or itching before we attach the cap.

What are the possible benefits of taking part?

There are no direct benefits to you or your child, however the information that we get from this study may help to learn more about ADHD and improve the treatment of people who have ADHD.

What will happen to the results of the research study?

The results from the study will provide us with data that we intend to present within the School of Psychology, University of Southampton and an article will be submitted for publication. Your child will not be identified in any presentation of the data. A copy of the study findings will be provided by Suzannah Helps at the end of the study.

What if there is a problem?

It is very unlikely that any part of this study will cause you or your child harm. The study is entirely non invasive. However, if any aspect of the way you have been approached or treated in the course of the study causes you concern, please write to the project supervisor Professor Edmund Sonuga-Barke (ejb3@soton.ac.uk) or the chief investigator Suzannah Helps (s.helps@soton.ac.uk) at the School of Psychology, University of Southampton, Highfield, Southampton SO17 1BJ. If you remain unhappy and wish to complain formally, you

can do this through the Chair of the Ethics Committee, Department of Psychology, University of Southampton, Southampton, SO17 1BJ. Phone: (023) 8059 3995. Alternatively, if you wish to complain through the NHS complaints procedure, details of this can be obtained from the Ashurst Centre, Lyndhurst Road, Ashurst, Southampton, SO40 7AR.

Will my child's taking part in this study be kept confidential?

Yes. We will follow best ethical and legal practice. All information collected about your child during the course of the research will be kept strictly confidential. Personal information will not be released to or viewed by anyone other than researchers involved in this project. All of the data collected will be coded so that it is anonymous and will be stored securely for 15 years and then destroyed. Results of this study will not include your child's name or any other identifying characteristics.

What will happen if I or my child does not want to carry on with the study?

If you no longer wish to participate you are free to leave the study at anytime and this will not affect any aspect of your child's treatment. You will still be reimbursed for your travel.

Who is organising and funding the research?

The study is organised by the University of Southampton and funded by a doctoral studentship to Suzannah Helps.

Who has reviewed the study?

The study has been reviewed and approved by the University of Southampton, School of Psychology Ethics Committee and by the Southampton & South West Hampshire Research Ethics Committee B.

Further Information and contact details

Suzannah Helps
School of Psychology,
University of Southampton,
Highfield, Southampton SO17 1BJ
Office number: 023 8059 4586
Email: s.helps@soton.ac.uk

Information sheet for young people with ADHD

We are asking if you would like to take part in a research project to find out what happens in peoples' brains in two situations: when they are resting and when they are paying attention. Before you decide if you want to join in, it's important to understand why the research is being done and what it will involve for you. So please consider this leaflet carefully. Talk about it with your family, friends, doctor or nurse if you want to.

Why are we doing this research?

We are trying to find out what happens in people's brains when they are resting and when they are paying attention. This will tell us more about how the brain works and how we are able to pay attention. We particularly want to look at young people who have been diagnosed with Attention- Deficit/ Hyperactivity Disorder (ADHD) because they often find it harder to pay attention. If we can understand what happens when young people find it hard to pay attention then we may be able to develop ways of improving attention and concentration.

Why have I been invited to take part?

You have been invited to join our study so that we can compare your brainwaves with those of children who do not have ADHD, and because you have ADHD and are registered at the Southampton City Child and Family Health Centre and you are between 13 and 16 years old. We need to find 20 young people with ADHD and 20 people without ADHD.

Do I have to take part?

No, it's up to you. But if you think you might want to take part, send back the reply slip at the back of this booklet and the researcher will phone you to answer any questions that you might have. If you do decide that you want to take part, you and your parent/guardian will need to sign the consent form at the back of this booklet to show that you have agreed to take part. You will be given a copy of this information sheet and your signed form to keep. But you can stop taking part at any time, without giving a reason. If you decide to stop, this will not affect the care you receive.

What will happen to me if I take part?

If you decide to take part, a researcher will phone you and your parents to arrange a time for you to come to the University of Southampton. One of your parents will need to fill in a couple of questionnaires. You will need to come to the University once for about an hour and a half. We will arrange this session to be at a time when you are having a 'drug holiday' - not taking any medicine that you would normally take for your ADHD.

What will I be asked to do?

When you get here, we'll ask you to do a few puzzles, this will take about 20mins and you will need to copy some shapes using blocks and tell us what you think some words mean. Then we'll fit the cap on your head for measuring your brain activity. When the cap is on your head you will be asked to do three things. You will be asked to rest and to play two different games on the computer. One game asks you to press a button on the computer mouse when you see arrows on the screen and the other game asks you to follow a track keeping as close to the marker as possible. I will tell you more about these games before you play them and there will be time for you to ask any questions. While you are doing these things, sensors on your head will measure activity in your brain. We will also measure your heart rate using a sensor on your chest and your shoulder – this will help us to know how hard you find the task. You will put the sensor on your own chest, and do not need to take off any clothes to do this.

We will also ask one of your teachers to fill in a questionnaire about your behaviour.

Will measuring my brain activity hurt me?

No, the way we measure your brain activity doesn't hurt at all. We put a cap on your head – a bit like a swimming cap. This cap has lots of special sensors that can measure the electrical signals from your brain. We put special gel on these sensors so that we get a clear reading, this doesn't hurt but can make your hair look a bit messy - but it washes off very easily.

Will anybody know my scores?

Nobody will know how you did on each game or the measurements from your brain except for me and other people who are helping me. I won't write your name down next to your scores so if anybody working with me looks at them, they won't know that it was you who scored that.

What are the benefits of taking part?

Taking part in a study like this will help us to understand more about ADHD and the problems that children with ADHD have. It won't benefit you directly. You and your parents will be given a payment of £30 to reimburse any travel costs.

What happens when the study is finished?

When the study is finished we will look at all the scores given by all the people who take part in this study and we will publish this so other researchers can find out more about these things. But we will never publish your name or any other information that will let people know who you are. We will also send you a short booklet to tell you what we have found out and how this might be useful.

What if there's a problem or something goes wrong?

There are very few risks involved in taking part in this study and it's unlikely that there will be a problem. The equipment that we use to measure your brain activity is completely safe. We also think that it is safe for you to stop taking your ADHD medication before the study, but if you are worried about this please talk to your doctor before you agree to take part.

What if I want to stop?

If you decide you want to stop that's OK. No one will be angry with you, all you have to say is that you want to stop and we'll stop straight away.

Will anyone else know that I'm doing this?

We will keep all your information in confidence. This means that we will only tell those who have a need or a right to know. Wherever possible we will only send out information that has your name and address removed.

Who is organising and funding the research?

The research is organised through the School of Psychology in the University of Southampton and is funded by a government body (The Economic and Social Research Council). It will be part of the researcher's PhD project.

Who has reviewed this study?

The study has been reviewed by other people who work at the University of Southampton, this means that they think the project is good and valid. It has also been reviewed by the ethics committee at the University of Southampton and the South West Hampshire Ethics Committee, B they make sure that the research is fair - they are happy that this research is ethical and safe to do.

What happens I want to find out more?

You can ask me any questions that you have or you can contact me on Suzannah Helps, School of Psychology, University of Southampton skh204@soton.ac.uk

Appendix A15

Information sheet for parents of young people without ADHD

We would like to invite your child to take part in a research study. Before you and they decide, you need to understand why the research is being done and what it would involve for both of you. Please take time to read the following information carefully. Talk to others about the study if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether you wish to take part.

What is the purpose of the study?

We are trying to find out more about brain activity when people are resting and how this might be important in attention -deficit/hyperactivity disorder (ADHD). We want to compare resting brain activity and brain activity when people are performing tasks between young people who have ADHD and young people who do not have ADHD (controls). This is pain free and harmless for the young person.

Why has my child been invited?

Your child has been invited to join the study so that we can compare the brainwaves of children without ADHD to those with ADHD, and because they are between 13 and 16 years old and do not have ADHD. We need to recruit 20 young people with ADHD and 20 young people without ADHD.

Does my child have to take part?

No, it's up to you to decide together. If you are interested in the study please send back the reply slip at the end of the booklet. When they receive the reply slip, a researcher will phone you to go through this information sheet, which you will be able to keep. We will then ask you to sign a consent form to show that you have agreed for your child to take part. You and your child are free to withdraw at any time, without giving a reason. This will not affect the standard of care that you or your child receives.

What will happen to my child if they take part?

If your child takes part in the research, a researcher will contact you to arrange a time for them to come to the University of Southampton. They will need to come for a single session that will last about an hour and a half.

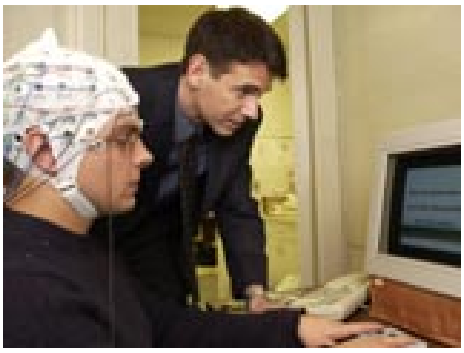
Will I get my expenses paid?

Yes, £30 will be reimbursed for your travel expenses.

What will I have to do?

You will need to fill in two short questionnaires about your child's behaviour. This will take about 10 minutes. We will also (with your permission) contact your child's teacher and ask them to fill one of these questionnaires about your child's behaviour.

What will my child have to do?



Your child will spend about 20 minutes doing some tasks so that we get a measure of their general level of intelligence. Then they will be fitted with a number of leads that are mounted on a special cap that allows us to measure the electrical activity of their brains and two leads that measure your child's heart rate – these will be on their chest and their shoulder. This is completely pain free and harmless. All leads will be filled with a gel to improve the quality of the signal. The leads transmit the electrical activity to the computer where it is recorded. Your child will place the heart rate lead onto their own chest, it is simple to place and they will not have to remove any of their clothes for this.

There is no risk involved; the leads do not pass electrical activity back to the brain. The leads can be removed in less than a minute if your child decides that they want to stop. Once the leads have been placed, they will be asked to complete two simple tasks on the computer and also to rest (these tasks will be explained in full before your child is asked to complete them). We will try to remove as much of the gel as possible at the end of the visit, and we have a sink and shower at the university if they would like to wash their hair here.

What are the possible disadvantages and risks of taking part?

There are no significant disadvantages or risks involved in taking part in this study. Many people find the tasks fun, if a little tiring. The gel that we use on the leads is normally harmless. However, to be certain, we will conduct a skin test to check that your child does not react to it. This involves putting a tiny amount of gel on their hand to look for redness or itching before we attach the cap.

What are the possible benefits of taking part?

There are no direct benefits to you or your child; however the information that we get from this study may help to learn more about ADHD and improve their treatment.

What will happen to the results of the research study?

The results from the study will provide us with data that we intend to present within the School of Psychology, University of Southampton and an article will be submitted for publication.

Your child will not be identified in any presentation of the data. A copy of the study findings will be provided by Suzannah Helps at the end of the study.

What if there is a problem?

It is very unlikely that any part of this study will cause you or your child harm. The study is entirely non invasive. However, if any aspect of the way you have been approached or treated in the course of the study causes you concern, please write to the project supervisor Professor Edmund Sonuga-Barke (ejb3@soton.ac.uk) or the chief investigator Suzannah Helps (s.helps@soton.ac.uk) at the School of Psychology, University of Southampton, Highfield, Southampton SO17 1BJ. If you remain unhappy and wish to complain formally, you can do this through the Chair of the Ethics Committee, Department of Psychology, University of Southampton, Southampton, SO17 1BJ. Phone: (023) 8059 3995.

Will my child's taking part in this study be kept confidential?

Yes. We will follow best ethical and legal practice. All information collected about your child during the course of the research will be kept strictly confidential. Personal information will not be released to or viewed by anyone other than researchers involved in this project. All of the data collected will be coded so that it is anonymous and will be stored securely for 15 years and then destroyed. Results of this study will not include your child's name or any other identifying characteristics.

What will happen if I or my child does not want to carry on with the study?

If you no longer wish to participate you are free to leave the study at anytime and this will not affect any aspect of your child's treatment. You will still be reimbursed for your travel.

Who is organising and funding the research?

The study is organised by the University of Southampton and funded by a doctoral studentship to Suzannah Helps.

Who has reviewed the study?

The study has been reviewed and approved by the University of Southampton, School of Psychology Ethics Committee and by the Southampton & South West Hampshire Research Ethics Committee B.

Further Information and contact details

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Information sheet for young people without ADHD

We are asking if you would like to take part in a research project to find out what happens in peoples' brains in two situations: when they are resting and when they are paying attention. Before you decide if you want to join in, it's important to understand why the research is being done and what it will involve for you. So please consider this leaflet carefully. Talk about it with your family, friends, doctor or nurse if you want to.

Why are we doing this research?

We are trying to find out what happens in people's brains when they are resting and when they are paying attention. This will tell us more about how the brain works and how we are able to pay attention. We are looking at young people who have been diagnosed with Attention- Deficit/ Hyperactivity Disorder (ADHD) because they often find it harder to pay attention. If we can understand what happens when young people find it hard to pay attention then we may be able to develop ways of improving attention and concentration.

Why have I been invited to take part?

You have been invited to join our study so that we can compare your brainwaves with those of children who have ADHD, because you are between 13 and 16 years old and do not have ADHD. We need to find 20 young people with ADHD and 20 young people without ADHD.

Do I have to take part?

No, it's up to you. But if you think you might want to take part, send back the reply slip at the back of this booklet and the researcher will phone you to answer any questions that you might have. If you do decide that you want to take part, you and your parent/guardian will need to sign the consent form at the back of this booklet to show that you have agreed to take part. You will be given a copy of this information sheet and your signed form to keep. But you can stop taking part at any time, without giving a reason. If you decide to stop, this will not affect the care you receive.

What will happen to me if I take part?

If you decide to take part, a researcher will phone you and your parents to arrange a time for you to come to the University of Southampton. Your parent will need to complete a couple of questionnaires. You will need to come to the University once for about

an hour and a half.

What will I be asked to do?

When you get here we'll ask you to do a few puzzles, this will take about 20mins and you will need to copy some shapes using blocks and tell us what you think some words mean. Then we'll fit the cap on your head for measuring your brain activity. When the cap is on your head you will be asked to do three things. You will be asked to rest and to play two different games on the computer. One game asks you to press a button on the computer mouse when you see arrows on the screen and the other game asks you to follow a track keeping as close to the marker as possible. I will tell you more about these games before you play them and there will be time for you to ask any questions. While you are doing these things, sensors on your head will measure activity in your brain. We will also measure your heart rate using a sensor on your chest and your shoulder – this will help us to know how hard you find the tasks. You will put the sensor on your own chest, and do not need to take off any clothes to do this.

We will also ask one of your teachers to fill in a questionnaire about your behaviour.

Will measuring my brain activity hurt me?

No, the way we measure your brain activity doesn't hurt at all. We put a cap on your head – a bit like a swimming cap. This cap has lots of special sensors that can measure the electrical signals from your brain. We put special gel on these sensors so that we get a clear reading, this doesn't hurt but can make your hair look a bit messy - but it washes off very easily.

Will anybody know my scores?

Nobody will know how you did on each game or the measurements from your brain except for me and other people who are helping me. I won't write your name down next to your scores so if anybody working with me looks at them, they won't know that it was you who scored that.

What are the benefits of taking part?

Taking part in a study like this will help us to understand more about ADHD and the problems that children with ADHD have. It won't benefit you directly. You and your parents will be given a payment of £30 to reimburse any travel costs.

What happens when the study is finished?

When the study is finished we will look at all the scores given by all the people who take part in this study and we will publish this so other researchers can find out more about these things. But we will never publish your name or any other information that will let people know who you are. We will also send you a short booklet to tell you what we have found out and how this might be useful.

What if there's a problem or something goes wrong?

There are very few risks involved in taking part in this study and it's unlikely that there will be a problem. But if you decide you want to stop that's OK. No one will be angry with you, all you have to say is that you want to stop and we'll stop straight away.

Will anyone else know that I'm doing this?

We will keep all your information in confidence. This means that we will only tell those who have a need or a right to know. Wherever possible we will only send out information that has your name and address removed.

Who is organising and funding the research?

The research is organised through the School of Psychology in the University of Southampton and is funded by a government body (The Economic and Social Research Council). It will be part of the researcher's PhD project.

Who has reviewed this study?

The study has been reviewed by other people who work at the University of Southampton, this means that they think the project is good and valid. It has also been reviewed by the ethics committee at the University of Southampton and the Southampton & South West Hampshire Research Ethics Committee B, they make sure that the research is fair - they are happy that this research is ethical and safe to do.

What happens I want to find out more?

You can ask me any questions that you have or you can contact me on Suzannah Helps, School of Psychology, University of Southampton skh204@soton.ac.uk

Reply Slip

Title of Project: Resting Brain Activity and ADHD

Name of Researcher: Suzannah Helps

Young person: Please circle if you agree:

I have read the information sheet and would like a researcher to contact me and give me more information about the research Yes

Parent/guardian: Please circle if you agree:

I have read the information sheet and would like a researcher to contact me and give me more information about the research Yes

Your name _____

Date _____

Parent Sign _____

Date _____

Thank you for your help

Telephone Number (s)_____

Best time to contact_____

Any other notes/questions _____

_____

_____

_____

_____

Child ADHD Rating Scales

We are interested in what ADHD symptoms the child experiences. Please complete the following questions. Each rating should be considered in the context of what is appropriate for the age of the child. If the child normally takes medication for ADHD (e.g. Ritalin) please rate their behaviour at a time that they were ***not*** taking this medication.

Frequency Code: 0=never
1=occasionally
2=often
3=very often

1. Fails to give attention to details or makes careless mistakes in schoolwork	0	1	2	3
2. Has difficulty sustaining attention to tasks or activities	0	1	2	3
3. Does not seem to listen when spoken to directly	0	1	2	3
4. Does not follow through when given directions and fails to to finish activities (not due to refusal or failure to understand)	0	1	2	3
5. Has difficulty organizing tasks and activities	0	1	2	3
6. Avoids, dislikes, or is reluctant to engage in tasks that require sustained mental effort	0	1	2	3
7. Loses things necessary for tasks or activities (school assignments, pencils, or books)	0	1	2	3
8. Is easily distracted by extraneous stimuli	0	1	2	3
9. Is forgetful in daily activities	0	1	2	3
10. Fidgets with hands or feet or squirms in seat	0	1	2	3
11. Leaves seat in classroom or in other situations in which remaining seated is expected	0	1	2	3
12. Runs about or climbs excessively in situations in which remaining seated is expected	0	1	2	3
13. Has difficulty playing or engaging in leisure activities quietly	0	1	2	3
14. Is “on the go” or often acts as if “driven by a motor”	0	1	2	3
15. Talks excessively	0	1	2	3
16. Blurts out answers before questions have been completed	0	1	2	3
17. Has difficulty waiting in line	0	1	2	3
18. Interrupts or intrudes on others (e.g., butts into conversations/games)	0	1	2	3

Strengths and Difficulties Questionnaire P 4-16

For each item, please mark the box for Not True, Somewhat True or Certainly True. It would help us if you answered all items as best you can even if you are not absolutely certain or the item seems daft! Please give your answers on the basis of the child's behaviour over the last six months.

Child's Name ..... Male/Female

Date of Birth.....

	Not True	Somewhat True	Certainly True
Considerate of other people's feelings	☐	☐	☐
Restless, overactive, cannot stay still for long	☐	☐	☐
Often complains of headaches, stomach-aches or sickness	☐	☐	☐
Shares readily with other children (treats, toys, pencils etc.)	☐	☐	☐
Often has temper tantrums or hot tempers	☐	☐	☐
Rather solitary, tends to play alone	☐	☐	☐
Generally obedient, usually does what adults request	☐	☐	☐
Many worries, often seems worried	☐	☐	☐
Helpful if someone is hurt, upset or feeling ill	☐	☐	☐
Constantly fidgeting or squirming	☐	☐	☐
Has at least one good friend	☐	☐	☐
Often fights with other children or bullies them	☐	☐	☐
Often unhappy, down-hearted or tearful	☐	☐	☐
Generally liked by other children	☐	☐	☐
Easily distracted, concentration wanders	☐	☐	☐
Nervous or clingy in new situations, easily loses confidence	☐	☐	☐
Kind to younger children	☐	☐	☐
Often lies or cheats	☐	☐	☐
Picked on or bullied by other children	☐	☐	☐
Often volunteers to help others (parents, teachers, other children)	☐	☐	☐
Thinks things out before acting	☐	☐	☐
Steals from home, school or elsewhere	☐	☐	☐
Gets on better with adults than with other children	☐	☐	☐
Many fears, easily scared	☐	☐	☐
Sees tasks through to the end, good attention span	☐	☐	☐

Do you have any other comments or concerns?

Please turn over - there are a few more questions on the other side

Overall, do you think that your child has difficulties in one or more of the following areas: emotions, concentration, behaviour or being able to get on with other people?

No	Yes-minor difficulties	Yes-definite difficulties	Yes-severe difficulties
☐	☐	☐	☐

If you have answered "Yes", please answer the following questions about these difficulties:

- How long have these difficulties been present?

Less than a month	1-5 months	6-12 months	Over a year
☐	☐	☐	☐

- Do the difficulties upset or distress your child?

Not at all	Only a little	Quite a lot	A great deal
☐	☐	☐	☐

- Do the difficulties interfere with your child's everyday life in the following areas?

	Not at all	Only a little	Quite a lot	A great deal
HOME LIFE	☐	☐	☐	☐
FRIENDSHIPS	☐	☐	☐	☐
CLASSROOM LEARNING	☐	☐	☐	☐
LEISURE ACTIVITIES	☐	☐	☐	☐

- Do the difficulties put a burden on you or the family as a whole?

Not at all	Only a little	Quite a lot	A great deal
☐	☐	☐	☐

Signature ..... Date .....

Mother/Father/Other (please specify:)

Thank you very much for your help

Appendix A20

Comparison of data cleaning methods between the two samples

Background and aim

In the first sample (chapters 4 and 5), data were cleaned by first using PCA and then ICA. This method was selected for dimension reduction to prevent components being separated by ICA into more than one sub-component, and to increase data processing speed (e.g. Onton et. al., 2006). However in the second sample (chapters 6 and 7) many more movement artifacts were present in the data and performing PCA for dimension reduction prior to ICA was thought to be inappropriate as a greater number of sources were present in the data. Therefore, ICA was performed on the raw EEG data and not on data that had been transformed by PCA. We found differences in the magnitude of EEG power within compared to outside of the S3 network at rest between these two samples, and although in both samples, reduced S3 power was identified outside of compared to within the S3 network, the difference between locations was much less strongly pronounced in the second sample. In order to examine whether this difference was created by differences in data cleaning methods, data from a small subset of participants from the first study were re-examined using the same methodology as in the present study.

Sample

Resting-condition data from 4 low-ADHD participants from the first sample (see Chapter 4) were reanalysed. These participants were randomly selected from the low-ADHD group.

Analysis

These resting-condition data had previously been analysed as described in Chapter 4 i.e. the data were detrended and down-sampled to 10 Hz, PCA was then performed to reduce the dimensions to 15 and ICA was then performed using the PCA inputs. Artifactual components were identified and removed by back-projection of all but these components. These same data were then reanalysed using the same methods as described in Chapter 6, i.e. the data were detrended and down-sampled to 10 Hz, however PCA was not performed and instead, ICA was performed on the detrended and down-sampled data. Again artifactual components were identified and removed by back projection of all but these components. The mean S3 power within and outside of the S3 network was calculated across these four participants for each type of data analysis.

Results

The power within and outside of the S3 network across these four participants, when the data are analysed first using PCA and when they are analyses without using PCA are shown in Table A20.1. It is evident from this table that when the data are analysed using PCA

there is a marked reduction in mean S3 power outside of the S3 network compared to when the data are analysed without using PCA.

Table A20.1

Power within and outside of the S3 network when each of the data cleaning methods is used

	Inside S3 network Mean (SD)	Outside S3 network Mean (SD)
Data analysis with PCA	5.91 (.595)	2.11 (.041)
Data analysis without PCA	5.35 (.474)	5.06 (.256)

Discussion

Pre-processing data cleaning methods do appear to impact on the S3 power within and outside of the S3 network. Specifically, when PCA is used prior to ICA, low frequency power outside of the S3 network is reduced compared to when ICA is used on data without PCA. PCA may impact on the data in this way for a number of reasons, firstly, PCA operates by identifying dimensions in the data that are able to successively explain as much of the outstanding data variance as possible. Truncating this singular spectrum is likely to eliminate the highest frequency activity (e.g. Onton et. al., 2006). In the present study, data were downsampled prior to PCA and so EEG frequency bands may be comparatively high, compared to the low frequency, high power movement artifacts. It is possible that this method of truncating the PCA spectrum may have eliminated some of the S3 power. However, inspection of a scree plot shows that the majority of the variance is explained in the first 15 components and that very little variance is evident in subsequent components (see Figure A20.1). Therefore, this method of analysis seems unlikely to have removed large portions of the data.

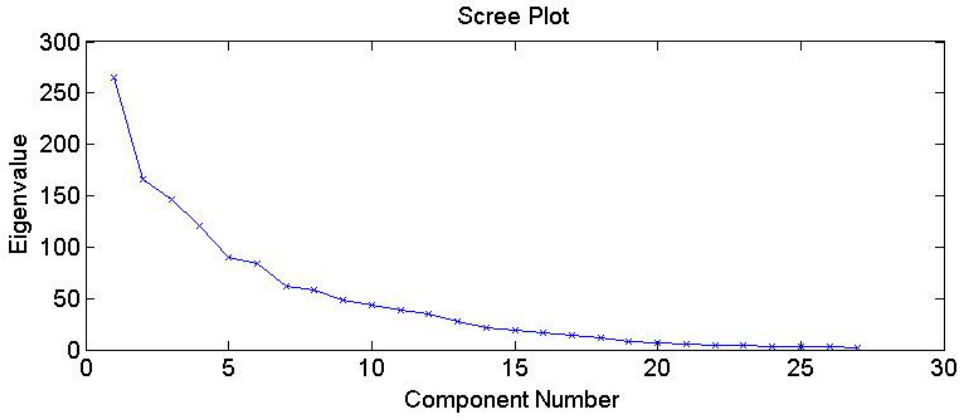

Figure A20.1: Scree plot for a single participant, the majority of the variance is explained in fewer than 15 components

Alternatively, as the dimensional reduction of PCA reduced the number of components that are recovered by ICA, this method of data analysis would reduce ICA's

capacity to split source activities, this may result in some ICs containing both artifact and brain activity. When PCA is not first performed, and a greater number of ICs can be extracted by ICA, the clustering can be more 'fine tuned' and brain activity is less likely to be removed along with artifacts.

Implications

In our studies, adopting PCA prior to ICA did appear to reduce S3 power outside of the S3 network. However, in both samples very similar effects were identified: the S3 network was located in similar regions, reduced S3 power was observed outside compared to within this network, and similar patterns of rest-task attenuation and RT-EEG synchrony were observed between groups. Therefore, this data cleaning method appeared to have a very specific impact on the data and the only apparent difference between the two studies was an effect of magnitude in the difference in S3 power within and outside of the S3 network, however, the direction of this effect remained the same and highly significant ($p < .001$) in both samples. Nonetheless, in future it might be preferable to avoid PCA for data reduction and if dimensional reduction is necessary, the number of channels in the dataset could be reduced rather than employing PCA.

Appendix A21

Extra Analyses: Predicting group membership without including IQ into the model

Table A21.1

Contributions of S4, S3 and S2 RT power to classification of group (ADHD or Control) above SD of RT and normalised variance on the fast event-rate condition

Model	Added variable	% correctly classified	χ^2 model	*p*	χ^2 step	*p*
SD of RT		76.7	11.7	.001**		
SD of RT +	S4 RT power	76.7	12.5	.002**	.787	.375
SD of RT +	S3 RT power	76.7	13.0	.001**	1.32	.250
SD of RT +	S2 RT power	86.7	19.1	<.001**	7.35	.007**
Normalised variance		73.3	7.85	.005**		
Normalised variance +	S4 RT power	73.3	7.89	.019*	.036	.850
Normalised variance +	S3 RT power	76.7	8.56	.014*	.714	.398
Normalised variance +	S2 RT power	86.7	21.3	<.001	13.5	<.001**

**p <.01,*p <.05, $^{\dagger}p$<.1

Table A21.2

Contributions of S4 and S3 RT power to classification of group (ADHD or Control) above SD of RT and normalised variance on the moderate event rate condition

Model	Added variable	% correctly classified	χ^2 model	*p*	χ^2 step	*p*
SD of RT +		90.3	30.4	<.001**		
SD of RT +	S4 RT power	90.3	31.0	<.001**	.586	.444
SD of RT +	S3 RT power	90.3	30.4	<.001**	.068	.794
Normalised variance		90.3	29.9	<.001**		
Normalised variance +	S4 RT power	90.3	32.8	<.001**	2.97	.085†
Normalised variance +	S3 RT power	90.3	31.1	<.001**	1.26	.263

**p <.01,*p <.05, $^{\dagger}p$<.1

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