University of Southampton

Faculty of Environmental and Life Sciences

School of Psychology

An Exploration of the Neuropsychology and Neuroelectrophysiology of University Students Experiencing Symptoms of ADHD

by

Amy Sophia Boyson

Thesis for the degree of Doctor of Philosophy

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Abstract

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Attention-deficit/hyperactivity disorder (ADHD) is one of the most prevalent neurodevelopmental disorders affecting approximately 5% of school-aged children and 2-5% of adults. Evidence suggests that childhood symptoms of the disorder continue into adulthood for the majority of those affected. University students with ADHD continue to struggle compared to students without the disorder, but never the less they achieve higher academic outcomes than those with ADHD who do not continue on to university and therefore they may represent a 'better-adjusted' subset of the ADHD population. However, little is known about the difficulties faced by this group in UK universities.

Several theoretical models of ADHD pathophysiology/psychopathology have been proposed over the years, initially focused on inhibitory control and executive functions, then reward processing and motivation, and now multiple pathways encompassing a wide range of difficulties. However, current models have not been able to account for all of the variability in the samples tested, suggesting that additional pathways may be needed. One possibility could be the entrainment of ongoing neural oscillations which is implicated in the perception and processing of stimuli, as well as neural communication within and between regions of the brain.

The aims of this research were first to investigate the neuropsychological difficulties faced by university students experiencing symptoms of ADHD, and second to explore the possibility that any such difficulties might be explained by an entrainment deficit. Across two studies, it was found that students who reported a higher level of ADHD symptoms exhibited deficits in working memory and temporal processing, but no difficulties in sustained attention, selective attention, or inhibitory control. There were also no differences between high and low symptom participants in neuro-electrophysiological measures, suggesting no underlying compensatory neural mechanisms

which might explain the equivalent performance in the selective attention and inhibitory control tasks. Understanding the neuropsychological domains in which these students do and do not have difficulties allows the focusing of resources toward support strategies to aid students with ADHD symptoms through their studies.

Two paradigms for eliciting an entrainment response were tested, but neither were successful in eliciting the effect, meaning the question of whether an entrainment deficit might underlie the working memory and temporal processing difficulties remains unanswered. Being unable to elicit the entrainment of ongoing neural oscillations calls into question the ubiquity of this effect, meaning more research and the publication of null results are needed to further our understanding of this phenomenon.

In conclusion, university students with ADHD symptoms show deficits in working memory and temporal processing, but no difficulties with sustained attention, selective attention, or inhibitory control. These findings need to be replicated in larger samples to address the lack of statistical power in these studies and more research is needed to investigate the possibility that the neuropsychological deficits found here could be subserved by an entrainment deficit.

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Research Thesis: Declaration of Authorship

Print name: Amy Sophia Boyson

Title of thesis: An exploration of the neuropsychology and neuroelectrophysiology of university students experiencing symptoms of ADHD

I declare that this thesis and the work presented in it are my own and has been generated by me as the result of my own original research.

I confirm that:

1. This work was done wholly or mainly while in candidature for a research degree at this University;
2. 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;
3. Where I have consulted the published work of others, this is always clearly attributed;
4. 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;
5. I have acknowledged all main sources of help;
6. 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;
7. None of this work has been published before submission

Signature: Date:

Acknowledgements

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Abbreviations

ADHD	Attention-deficit/hyperactivity disorder
ANOVA	Analysis of variance
AWMA	Automated working memory assessment
CEM	Cognitive Energetic Model
CNV	Contingent negative variation
CSS	Current symptoms scale
CTC	Communication through coherence
DSM	Diagnostic and Statistical Manual of Mental Disorders
EEG	Electroencephalogram
ERP	Event related potential
ERSP	Event related spectral perturbation
FA D	False alarm for distractor variables
FA N-T	False alarm for non-target variables
FDR	False discovery rate
FSIQ-II	Estimate Full Scale IQ – 2 sub-scale version
HS	High symptom
ITC	Inter-trial coherence
IQ	Intelligence quotient
LRP	Lateralised readiness potential
LS	Low symptom
M	Mean
MARS	Maudsley Attention and Response Suppression Task battery
RT	Reaction time

Abbreviations

SD	Standard deviation
STFT	Short time Fourier transform
WASI-II	Wechsler Abbreviated Scale of Intelligence second edition
WM	Working memory

Chapter 1 Literature Review

1.1 Background to ADHD

1.1.1 Clinical Features of ADHD

ADHD is a neurodevelopmental disorder characterised by a pattern of behaviour that impacts on functioning in social, educational, and/or work settings. The Diagnostic and Statistical Manual of Mental Disorders: 5th Edition (DSM-V; American Psychiatric Association, 2013) categorises ADHD symptoms into two domains, inattentive and hyperactive/impulsive, with symptoms present in either or both for a diagnosis (Table 1.1). One of the key changes in the DSM-5 compared to the DSM-4 is the adjustment of diagnostic criteria with regards to adults and how presentation changes from childhood into adulthood. The age of onset has also been amended from 7 to 12 years of age and examples provided for how symptoms present in older adolescents and adults (aged 17 years+). The DSM-5 describes three subtypes of ADHD: 1) predominantly inattentive type, 2) predominantly hyperactive type, and 3) combined type.

Table 1.1
Diagnostic criteria for attention deficit/hyperactivity disorder (ADHD)

A. A persistent pattern of inattention and/or hyperactivity-impulsivity that interferes with functioning or development, characterised by (1) and/or (2)

(1) Inattention:
Six (or more) of the following symptoms of inattention for children up to age 16, or five (or more) for adolescents and adults (aged 17 or older), which have persisted for at least 6 months to a degree that is inconsistent with developmental level and negatively impacts on daily activity.
- (a) Often fails to give close attention to details or makes careless mistakes in schoolwork, work, or other activities.
- (b) Often has difficulty sustaining attention in tasks or play activities.
- (c) Often does not seem to listen when spoken to directly.
- (d) Often does not follow through on instructions and fails to finish schoolwork, chores, or duties in the workplace.
- (e) Often has difficulty organising tasks and activities.
- (f) Often avoids, dislikes, or is reluctant to engage in tasks that require sustained mental effort (such as school work or homework, or for adults, preparing lengthy reports or reading papers).
- (g) Often loses things necessary for tasks or activities (e.g. toys, school assignments, wallets, keys, mobile phone, etc.).
- (h) Is often easily distracted by external stimuli (for adults this may include unrelated thoughts)
- (i) Is often forgetful in daily activities (e.g. doing chores or running errands).

(2) Hyperactivity and impulsivity:
Six (or more) of the following symptoms of hyperactivity-impulsivity for children up to age 16, or five (or more) for adolescents 17 or older; symptoms have persisted for at least 6 months to a degree that is inconsistent with developmental level and negatively impacts on daily activity.

Hyperactivity
- (a) Often fidgets, taps hands or feet, or squirms in seat.
- (b) Often leaves seat in situations when remaining seated is expected.
- (c) Often runs about or climbs in situations where it is inappropriate (adolescents or adults may be limited to feeling restless).
- (d) Often unable to play or engage in leisure activities quietly.

(e) Is often 'on the go', acting as if 'driven by a motor'.
(f) Often talks excessively

Impulsivity

(g) Often blurts out answers before questions have been completed.
(h) Often has difficulty waiting his/her turn.
(i) Often interrupts or intrudes on others (e.g. butts into conversations or games, for adults, may intrude into or take over what others are doing).

B. Several inattentive or hyperactive symptoms were first present before age 12 years.
C. Several symptoms are present in two or more settings (e.g. at home, school, or work; with friends or relatives).
D. There is clear evidence that the symptoms interfere with, or reduce the quality of, social, academic, or occupational functioning.
E. The symptoms do not happen only during the course of schizophrenia or another psychotic disorder and are not better explained by another mental disorder (e.g. mood disorder, anxiety disorder, dissociative disorder, personality disorder, or substance abuse).

Note. Adapted from the Diagnostic and Statistical Manual of Mental Disorders: 5th Edition (American Psychiatric Association, 2013).

ADHD is a highly comorbid disorder; one study found that 52% of patients had one comorbid disorder, while 26% had two or more (Jensen & Steinhausen, 2014). The most common comorbidities were conduct disorder (CD)/oppositional defiance disorder (ODD, 16.5%), specific developmental disorders of language, learning and motor skills (15.4%), autism spectrum disorder (ASD, 12.4%), and intellectual disability (7.9%). Consistent with previous findings (Levy, Hay, Bennett, & McStephen, 2005), the study found that the type of comorbid disorder depended on gender, with males more likely to have a neuropsychiatric disorder (e.g. ASD, CD) and females more likely to have internalising disorders (e.g. anxiety, affective disorders). In addition, comorbidity also varied with age as certain groups of disorders manifested either in early childhood (e.g. ASD, attachment disorders), late childhood/early adolescence (e.g. anxiety, CD), or late adolescence (e.g. psychotic disorder, affective disorder). Another study found that 92% of adult patients had a lifetime prevalence of comorbid axis I (clinical) disorder, while current comorbidity was 47% (Edvinsson, Lindström, Bingefors, Lewander, & Ekselius, 2013). Moffitt et al. (2015) found that 70% of adults who self-reported ADHD symptoms, also reported contact with a mental health professional between the ages of 21 and 38, with 48% receiving medication.

Both pharmacological and non-pharmacological therapies are used to treat patients with ADHD. Recent network meta-analyses have shown good efficacy and acceptability of pharmacological interventions (Catalá-López et al., 2017), and specifically advocate for the use of methylphenidate in children and adolescents, and amphetamines in adults, at least in the short term (Cortese et al., 2018). Conversely, the only non-pharmacological treatment to show evidenced based efficacy was behavioural therapy, either in isolation or with stimulant medication (Catalá-López et al., 2017).

1.1.1.1 Epidemiology

ADHD is more common in males with a ratio of approximately 3:1 (Willcutt, 2012), however this ratio is usually higher in clinical settings (e.g. Nøvik et al., 2006; Sayal, Prasad, Daley, Ford, & Coghill, 2018). Males show significantly greater severity of symptoms across all three subtypes of ADHD (Arnett, Pennington, Willcutt, DeFries, & Olson, 2015). However, in adult ADHD this gender divide appears to disappear (Moffitt et al., 2015). The disorder has a worldwide prevalence rate of 3.4-5.3% in children and adolescents, a rate that has remained stable over the last three decades (Polanczyk, de Lima, Horta, Biederman, & Rohde, 2007; Polanczyk, Salum, Sugaya, Caye, & Rohde, 2015; Sayal et al., 2018). It has been noted that there is a lack of studies investigating adult ADHD but prevalence rates have been estimated between 2-5% (Ramos-Quiroga, Nasillo, Fernandez-Aranda, & Casas, 2014). One meta-analysis suggests that 15% of those diagnosed with ADHD maintain this diagnosis into adulthood, while 65% meet DSM-IV criteria for ADHD in partial remission (Faraone, Biederman, & Mick, 2006). One study has found that nearly 70% of adults assessed as having the disorder since childhood, maintained their ADHD diagnosis at a 7 year follow-up (Karam et al., 2015). Caution is required, however, as this study relied upon retrospective reports of childhood symptoms.

1.1.1.2 ADHD in Undergraduate Students

Data from studies conducted in multiple countries (UK, USA, Italy, and New Zealand), suggest that approximately 2-4% of university students report clinically relevant levels of ADHD symptoms (Weyandt et al., 2013). In Ireland, published data show that in the 2016/17 academic year, 5.2% of disabled students reported having ADHD (AHEAD, 2018), this was up from just 2% in the 2010/11 year group (AHEAD, 2011). Students with ADHD appear to have greater emotional distress and psychological difficulties compared to non-ADHD students, and have greater alcohol, tobacco, and drug use (Green & Rabiner, 2012). Those who attend university, while struggling compared to those without the disorder, have achieved a higher level of academic success than their non-university peers with the disorder and may represent a better adjusted group of young people with ADHD, meaning they may not show the same difficulties (Green & Rabiner, 2012).

It has been observed that adult's with ADHD consistently show deficits in executive functions such as attention, inhibition, reasoning, planning, and working memory (Barkley, Murphy, & Fischer, 2010; Boonstra, Oosterlaan, Sergeant, & Buitelaar, 2005; Hervey, Epstein, & Curry, 2004; Willcutt, Doyle, Nigg, Faraone, & Pennington, 2005). However, it has been noted that there is little empirical information available with regards to cognitive and neuropsychological functioning in university students, and what evidence there is, is inconsistent (Weyandt, Oster, Gudmundsdottir, DuPaul, & Anastopoulos, 2017). Despite this, students with ADHD appear to consistently self-

report executive function impairments in daily life (Dehili, Prevatt, & Coffman, 2013; Gray, Fettes, Woltering, Mawjee, & Tannock, 2016; Weyandt et al., 2013).

Conclusions with regard to the difficulties faced by this population are limited. There are inconsistences with how the samples are classified as being in the ADHD group: self-reported as having a diagnosis, self-reported symptom count, symptoms compared to normative data (1.5-2 standard deviations above average), verses clinically sound diagnosis according to DSM criteria. As such, comparing results across studies and to the ADHD population of university students is problematic. However, a recent study has shown that across classification based on self-report, symptom count or normative data, the pattern of results remain similar (Green & Rabiner, 2013). Another cautionary note is that the majority of studies in this area of research are conducted at single sites within North America, limiting their generalizability not only within North America, but also other countries. Sedgwick (2018) notes that there is a distinct lack of research available investigating the difficulties faced by university students with ADHD in the UK and Ireland.

A recent study has made great strides in addressing some of the concerns outlined above. Weyandt et al. (2017) report on the neuropsychological functioning in students both with and without ADHD as part of a longer 4-year multi-site longitudinal study (the Trajectories Related to ADHD in College (TRAC) project). Recruitment for the study employed a four-stage multi-method assessment procedure, which included a review of each case by an expert panel to verify eligibility for the ADHD group according to full DSM-5 criteria. Results showed that the students with ADHD displayed deficits in attention, sustained attention, vigilance, and impulsivity as measured by a continuous performance test. In addition, students self-reported difficulties with organization, planning, inhibition, working memory and metacognition. However, this work is still conducted within North America and needs to be replicated elsewhere as well as with alternative measures of the same domains before conclusions can be firmly drawn.

1.1.2 ADHD in Adults: A Debate

A debate has arisen in the literature regarding the status of adult ADHD, which includes ADHD in university students, as a childhood onset neurodevelopmental disorder, as defined in the DSM-5. One of the key changes in the DSM-5 with regards to ADHD, was the recognition that ADHD does not necessarily stop in childhood but can continue into adulthood for some individuals. This recognition should ensure that for those affected, there is a continuation of care and support into adulthood. However, some authors are now putting forward an argument that adult ADHD is in and of itself a separate disorder, and not a continuation of a childhood onset condition. Moffitt et al. (2015) conducted a longitudinal study using a birth cohort from New

Zealand, born in 1972-73 in which individuals were followed up to 38 years of age. The authors found a childhood prevalence of 6% for ADHD using a DSM-III diagnosis, and 3% for adult ADHD at age 38. However, there was very little overlap of individuals between those with a diagnosis as a child and those with a diagnosis as an adult, with only 5% of those with childhood ADHD maintaining this diagnosis as an adult. As such, the majority of individuals in this cohort with adult ADHD did not have ADHD as a child. The authors also investigated whether any neurocognitive deficits were evident during childhood, a requirement for adult ADHD being a neurodevelopmental disorder, but found none. It is therefore argued that adult ADHD cannot be a childhood onset neurodevelopmental disorder. However, when taking a closer look at the study, there were a number of limitations.

The authors highlight the fact that adults with ADHD lack a childhood diagnosis, but a childhood diagnosis is not a requirement for adult ADHD; one of the reasons for giving an adult diagnosis is due to the disorder *not* being diagnosed during childhood. The study further states that these adults did not show even a borderline level of symptoms in childhood. However, the version of the DSM used at the time was the DSM-III, whereas the version used for adulthood was the DSM-5. As such, it could be that given the current understanding of childhood ADHD, adults who were not diagnosed as a child using DSM-III may have received a diagnosis with DSM-5. Unfortunately, it is not possible to know whether this could be the case, as the study does not report symptom counts. In addition, the DSM-5 simply states that “several” symptoms must be present before the age of 12 years, and that “several” symptoms must be present in two or more settings. It does not state that the symptoms present at childhood must also be present in two or more settings, and the results of this study do show that the adult ADHD participants did have, although modestly, increased symptom levels at school compared to the control group between the ages of 11 and 15. Another key factor not adequately explored by the study, are alternative explanations for the self-reported symptoms. Drug and alcohol dependence was evident in 48% of the sample and tobacco use in 39%. It was also found that 70% of the adult ADHD participants had contact with a mental health professional between the ages of 21 and 38 years, with 48% taking medication for a mental health disorder at some point during this time period. The symptoms being attributed to ADHD by the authors of this study might be better explained by another disorder. The authors state that: “Apart from schizophrenia, adult ADHD was diagnosed regardless of the presence of other disorders” (Supplementary Materials, p.2). As such, it would appear that not enough has been done by the authors to explore other explanations for the symptoms being reported, potentially leading to misdiagnosis of adult ADHD.

Agnew-Blais et al. (2016) reports on a longitudinal twin study looking at ADHD across childhood to young adulthood at age 18. They found that 21.9% of individuals had a persistent

ADHD diagnosis from childhood to adulthood. Of those diagnosed with adult ADHD, 67.5% were late onset with no childhood history of an ADHD diagnosis. Those with persistent ADHD had the most negative outcomes, but those with remitted ADHD by age 18, still had higher levels of self and informant rated symptoms, depression, alcohol dependence, conduct disorder, and lower life satisfaction and job preparedness, compared to controls. Late onset ADHD was associated with higher IQ at age 18 and a higher level of alcohol dependence compared to those with persistent ADHD, but there was no difference in life satisfaction, job preparedness, engaging in formal education, or psychiatric profile. The authors argue that their results show that adult ADHD is "more complex than a straightforward continuation of the childhood disorder" (p. E6).

In this study, unlike Moffitt et al. (2015), the age of onset was taken into consideration when giving an adult ADHD diagnosis, following the DSM-5 criteria for the disorder. However, although informant information was measured, it was not taken into consideration when giving the diagnosis just as was the case for Moffitt et al. (2015). Agnew-Blais et al. (2016), unlike Moffitt et al. (2015), further explored the idea that the self-reported symptoms could be a reflection of another disorder rather than ADHD. After excluding individuals with comorbid anxiety, depression, and drug/alcohol dependence, late onset prevalence dropped to approximately a third of what it was, and even in this third there could still be other comorbid disorders which were not measured that could account for the symptoms. This study highlights the potential overestimation of adult ADHD in the Moffitt et al. (2015) study. In addition, this study talks about "remitted" ADHD, but it does not give mention of the DSM-5 option of "ADHD in partial remission". The findings of continued impairment by this group might suggest that they could fall into this category, and with 78% of the childhood ADHD individuals being listed in remission, that would mean a large proportion still falling with the DSM-5 scope for some form of adult ADHD to a potentially similar or higher degree found by Faraone et al. (2006).

Caye, Rocha, Anselmi, and et al. (2016) is the third paper published being used to argue the case that adult ADHD is not a childhood onset neurodevelopmental disorder. This study is also a longitudinal follow up study, based in Brazil. This study found a 17.2% persistence rate of ADHD from childhood to young adulthood. Of those adults without a comorbidity (i.e. alternative disorders can't explain the ADHD symptoms), 86% did not have a childhood diagnosis of ADHD. Just as with the Moffitt et al. (2015) study, age of onset was not taken into consideration when giving an adult ADHD diagnosis. This means the rate of adult diagnoses given by the researchers could be inflated compared to the level that would be found using the full DSM-5 criteria. There is also no record of the self-reported age of onset of these adults, so although they may not have received a diagnosis, we do not know if they could have been at risk of one. However, the authors do state that all other DSM-5 criteria were met, which would include the requirement of several

symptoms being present during childhood. Another point of note for this study is that childhood diagnosis was based on self and parent report using the Strengths and Difficulties Questionnaire; no measurements were taken from teachers so there is a lack of corroborative evidence that the difficulties reported at childhood were present in at least two settings.

Together these three papers put forward a suggestion that adult ADHD may not be a continuation of a childhood onset disorder, but rather a separate disorder in its own right. This conclusion is based on the finding of an ADHD symptom profile in a number of individuals who do not display ADHD as a child. However, each study has methodological flaws in how the participants have been diagnosed at each time point, which leads one to doubt their conclusions. A key criticism across these studies is that as adults, only self-report measures were used to give the diagnosis of ADHD, no corroborating evidence was used from informants. As a child, diagnosis is based on the reports of others, but this has not been considered necessary at adulthood. However, the gold standard in giving an adult ADHD diagnosis, the Diagnostic Interview for ADHD in Adults 2.0 (DIVA 2.0; Kooij & Francken, 2010) highlights the importance of obtaining corroboration in the diagnostic process, either from an informant or from historic records such as school reports. As such, relying solely on self-report could lead to an overestimation of adult ADHD. At this time, there is not sufficient evidence to overthrow the 20 years of research that lead to adult ADHD being recognised as it is in the DSM-5. Therefore, until more evidence is put forward and the findings from these studies are replicated, adult ADHD should continue to be classified as a childhood onset neurodevelopmental disorder.

1.1.3 Neurophysiological Models of ADHD

There are numerous models outlining how neuro-psychological disturbance may lead to ADHD symptomology. Such models have traditionally focused on executive functions and/or motivation/state regulation as core deficits of the disorder. In the following section, each model of ADHD shall be discussed in terms of its neuropsychological and neurophysiological evidence base.

1.1.3.1 Inhibitory Control Model

In 1997, Barkley argued that at the core of ADHD was dysfunctional behavioural inhibition (also referred to as self-control), which he linked to four executive functions: working memory, self-regulation of emotion, internalised speech, and reconstruction (higher order analysis of behaviour) (Barkley, 1997). With this argument, persistent inattention and other impaired cognitive and social functioning arise as secondary expressions of poor inhibition and cognitive interference control.

1.1.3.1.1 Neuropsychological Test Evidence for the Inhibitory Control Model

Patients with ADHD show evidence of poorer response inhibition (Dimoska, Johnstone, Barry, & Clarke, 2003; Overtoom et al., 2002; Schachar, Mota, Logan, Tannock, & Klim, 2000) and interference (or conflict) inhibition (Hart, Radua, Nakao, Mataix-Cols, & Rubia, 2013). One example of a response inhibition task is the Stop Signal task in which participants are presented with a Go signal but on a percentage of trials (between 10-25%) this is followed by a stop signal indicating that the response must be withheld. This task looks at the timing of the inhibitory response as indexed by the stop signal reaction time (SSRT). SSRT is usually calculated by subtracting the duration of the delay between the Go signal and the Stop signal from the Go reaction time, with longer SSRT representing poorer inhibition. Children with ADHD often show longer SSRTs, slower Go reaction times, and make more errors in such tasks (Dimoska et al., 2003; Overtoom et al., 2002; Rubia, Smith, & Taylor, 2007; Schachar et al., 2000). Another response inhibition task is the Go/No-Go task in which participants must respond to one stimulus, but not to another. This No-Go stimulus is presented on a smaller number of trials such that the prepotent response of the participant is to respond rather than withhold. As with the stop-signal tasks, those with ADHD often make more errors indicating poorer response inhibition (Rubia et al., 2007; Woltering, Liu, Rokeach, & Tannock, 2013).

Interference inhibition can be measured with tasks such as the Stroop. In such tasks participants must respond to either congruent (e.g. the word “blue” written in blue ink) or incongruent stimuli (e.g. the word “blue” written in red ink). When responding to incongruent stimuli, the prepotent response is to give the congruent answer and as such this creates an interference or conflict, which must be inhibited in order for a correct response to be given. Inhibiting the prepotent response leads to longer reaction times in the incongruent condition. The Stroop Effect is the difference in reaction time between the two conditions, with a larger effect reflecting poorer inhibitory control. Lansbergen, Kenemans, and van Engeland (2007) completed a meta-analysis of the colour-word Stroop task and found that those with ADHD have a higher level of interference than controls. Cao et al. (2013) used a hybrid Stroop/Simon task and again found that interference control was impaired in ADHD. Those with ADHD also had lower accuracy, longer mean reaction times, and greater reaction time variability.

1.1.3.1.2 Neural Evidence for the Inhibitory Control Model

Functional magnetic resonance imaging (fMRI) studies with ADHD patients have shown reduced activation of the right inferior frontal cortex extending into the anterior insula, supplementary motor area, anterior cingulate cortex, caudate, and thalamus, all of which are regions associated with inhibition (Hart et al., 2013). Interference control studies suggest that

those with ADHD recruit different neural networks, showing frontal rather than parietal conflict-related event-related potentials (ERPs) (Van Mourik, Sergeant, Heslenfeld, Konig, & Oosterlaan, 2011). In addition, during the 450-550 ms time window, control participants displayed more positive amplitudes in the incongruent condition than the congruent; this effect was absent in the ADHD participants. This time window falls within the range of the P3b, an ERP component reflecting attention and memory processing, and as such the findings here suggest that children with ADHD fail to recruit additional resources in the presence of conflicting information, perhaps supporting Barkley's notion that inhibition (in this case, conflict inhibition) gives rise to the other executive function difficulties. The P3 component is often studied in conjunction with the N2 component; in this context, frontal P3 is associated with response inhibition, while the N2 reflects the processing required to deal with the response conflict (Groom & Cragg, 2015). Woltering et al. (2013) found that both the N2 and P3 amplitudes were reduced in ADHD and were correlated with symptom severity. However, such results are not consistently found (Cao et al., 2013; Dimoska et al., 2003).

During stop-signal tasks, in healthy subjects there is a fronto-central positivity after onset of the stop-signal which is larger when inhibition is successful, and a late positive wave over occipital sites when inhibition fails. In children with ADHD, both of these effects have been found to be smaller compared to healthy controls suggesting not only altered neural processing of motor inhibition, but error detection also (Overtoom et al., 2002). These studies point to an altered neural signature during inhibitory processes in patients with ADHD.

1.1.3.1.3 Evaluation of the Inhibitory Control Model

In Barkley's formulation of ADHD, only the predominantly hyperactive and combined subtypes of ADHD were associated with executive function deficits, and the predominantly inattentive subtype likely represented a distinct diagnostic disorder in its own right, separate from ADHD. A key criticism of this model is that it is not specific to ADHD, that such inhibitory control deficits also apply to children with opposition defiant disorder or conduct disorder (Oosterlaan, Logan, & Sergeant, 1998). As such, it would appear that behavioural inhibition appears to be a more general deficit in children whose behaviour can be classified as "disruptive". In addition, not all studies find behavioural evidence of deficits in inhibitory control in ADHD (Groom et al., 2013; Kakuszi, Tombor, Papp, Bitter, & Czobor, 2016; Van Mourik et al., 2011). An alternative suggestion is that differences in inhibitory control might better be explained by deficits in neural preparation (Kakuszi et al., 2016). Kakuszi et al. (2016) found that patients with ADHD showed an enhanced response-preceding negative potential shift (an indicator of response preparation) during responses on Go trails of a Go/No-Go task which was associated with increased errors in an offline

Stroop task as well as ADHD symptom severity and response variability. The authors argue that this altered neural preparation could represent a "pathway for core symptoms of ADHD" (p.1), including impulsive and inaccurate responding, as well as motor-hyperactivity.

Barkley's model suggests that inhibitory control deficits lead to deficits in other executive functions. Individuals with ADHD have been shown to perform worse on measures of executive function compared to those without the disorder (Gooch, Snowling, & Hulme, 2011; Willcutt et al., 2005). Although the meta-analysis by Willcutt et al. (2005) found that one of the most consistent findings in the literature were differences in SSRT, this was also the case for Continuous Performance Test omission errors, a measure of sustained attention or vigilance. The authors of the meta-analysis conclude that the executive function domains of response inhibition, planning, vigilance, and working memory all play a role in the neuropsychology of ADHD, but executive function deficits are not necessary nor sufficient for the development of ADHD.

1.1.3.2 Cognitive Energetic Model (CEM)

Adopting a different perspective, Sergeant (2000, 2005) and Sergeant and van der Meere (1990) proposed the cognitive-energetic model (CEM) of ADHD suggesting that a mediating factor between the executive functioning and computational mechanisms of attention (encoding, search, decision, and motor organisation) in ADHD is the energetic state of the individual (effort, arousal, and activation), and as such this model encompasses both top-down and bottom-up processes. Effort is defined as the energy necessary to meet task demands (motivation and response to contingencies). It is affected by variables such as cognitive load, and is engaged when the state of the individual does not match that required by the task at hand. The theory posits that effort is located within the hippocampus and controls the other two energetic states. Arousal is defined as temporal responding time locked to stimulus processing and is affected by stimulus characteristics such as intensity and novelty. This energetic state is theorised to be associated with the mesencephalic reticular formation and the amygdala. The final energetic state, activation, relates to readiness to respond and is affected by variables such as preparation and alertness. This state is suggested to be associated with the basal ganglia and striatum. According to the CEM, ADHD arises from an executive function deficit which leads to a failure to moderate the energetic state of activation and to a lesser extent effort, and these deficits are specifically related to motor organisation as evidence suggests that the encoding and search mechanisms of attention are intact in ADHD (Sergeant & van der Meere, 1990).

1.1.3.2.1 Neuropsychological Test Evidence for the Cognitive Energetic Model

One line of evidence to support the idea of the CEM in ADHD is that of event rates. It is argued that event rate alters the energetic state of the individual with fast event rates leading to over activation/arousal resulting in fast yet inaccurate responding, and slow event rates leading to the opposite arousal pattern resulting in slow yet inaccurate responding. Individuals with ADHD show a sensitivity to event rate, performing significantly worse in slow versus fast event presentations (Van der Meere, Vreeling, & Sergeant, 1992; Wiersema, Van der Meere, Antrop, & Roeyers, 2006). In one study comparing ADHD children with and without comorbid tic disorders and controls, event rate had a negative effect on the ADHD-only children with more errors in the fast and slow conditions, but not the medium conditions of a Go/No-Go task (Van der Meere, Stemerdink, & Gunning, 1995). Sergeant (2000) argues that a lack of response inhibition in these tasks is modulated by their inability to adjust their internal state.

Another line of evidence to support the CEM relates to error detection. A phenomenon known as reaction time after error (RTE + 1) has been found in which on a trial following an error, it takes longer to produce the correct response, presumably to ensure a correct response. In ADHD, it has been found that cognitive load, which affects effort in the CEM, affects the RTE + 1, with low load leading to much slower RTE + 1 and a high load leading to much faster RTE + 1, whereas in controls this is a linear relationship (Oosterlaan et al., 1998). RTE + 1 has also been shown to be slowed by the use of methylphenidate (Krusch et al., 1996), and as drugs are considered to influence both energetic and computational factors of the CEM, such findings, Sergeant (2000) argues, indicate the influence of energetic state on executive processing. In addition, the inhibition model proposed by Barkley would have predicted only a faster RTE + 1, yet the finding of both fast and slow responses argues against the inhibition model, and instead supports the idea that it is a failure to adapt to task demands.

1.1.3.2.2 Neural Evidence for the Cognitive Energetic Model

Grünewald-Zuberbier, Grünewald, Rasche, and Netz (1978) compared children with low, medium, and high levels of inattention on a Go/No-Go task. The results showed that alpha-attenuation (reduction) was related to No-Go reactions in children with high levels of inattention, with lower levels of attenuation predicting failures of inhibition. Alpha activity reduces with task engagement (Wang, 2010), therefore, findings of reduced alpha attenuation might be suggestive of a reduction in task engagement by the child, which would support the hypothesis that energetic failures, of activation and/or effort, underlie inhibitory dysfunction (Sergeant, 2000). Further EEG evidence has found that failure to inhibit responses on the Stop Signal task was related to an early N1 (1st negative ERP component, typically associated with attention), but this

component appeared too early in the EEG signal for it to be in response to the stop signal itself. Therefore, the suggestion is made that the "brain state" of the child was not as it should be and could reflect a difference in energetic state between the groups rather than a failure of inhibition per se (Sergeant, 2000).

1.1.3.2.3 Evaluation of the Cognitive Energetic Model

The CEM model of ADHD is specifically related to motor organisation as previous work found that the other two facets of attention (encoding and search) were intact in ADHD. However, specifically relating to motor functions does not adequately account for the inattentive subtype of ADHD. A more pertinent criticism of this model is that it over simplifies the neural representation of the energetic pools. The model suggests that each pool is separate and distinct from the executive function systems in the prefrontal cortex. However, the brain is not so segmented; it is interconnected, with regions sharing reciprocal information transfer. In addition, as supporting evidence for the energetic deficits in ADHD, Sergeant (2000) cites evidence of poor performance to different event rates (slow vs medium vs fast event rates). It is suggested that the negative effects of event rates in ADHD (poorer performance to very fast or very slow events) reflect an inability to adjust their internal state, which in turn modulates an ADHD child's "lack of response inhibition" (p.10). However, it could be argued that in fact the difficulty with event rates simply reflects an underlying temporal processing difficulty, which in turn could lead to an error in the timing of their inhibitory response. Such temporal difficulties could then also be tied to an error in the timing of the required attentional processes for a given task.

1.1.3.3 Motivation and Reinforcement

The effort energetic state proposed by the CEM is partly comprised of motivation. Other models of ADHD suggest that a dysfunction in motivation is a causal factor of the disorder; a move away from focusing on executive functioning, to a reward processing model of ADHD. One such argument posits that a dysfunctional dopamine system gives rise to symptoms described as "executive functions" in previous models (Johansen, Aase, Meyer, & Sagvolden, 2002). Sagvolden, Johansen, Aase, and Russell (2005) explains that in this dopamine based model, reduced functioning of the meso-cortical dopamine branch (connecting the ventral tegmentum to the prefrontal cortex) would lead to attention response deficiencies and poor behavioural planning/executive functions, whereas reduced functioning of the nigro-striatal dopamine branch (connecting the substantia nigra to the dorsal striatum (caudate nucleus and putamen)) would lead to impaired modulation of motor functions and deficient non-declarative habit learning and memory. The key to this model, however, is a dysfunctional meso-limbic dopamine branch (connecting the ventral tegmental area to the nucleus accumbens) leading to altered

reinforcement of behaviour and deficient extinction of previously reinforced behaviours. Altered reinforcement leads to a reduction in the control exerted by future actions and a drop in their perceived "value", behaviours such as impulsivity and hyperactivity arise because they are short term reinforcers, giving an immediate response. A failure of extinction means that such behaviours are not then pruned as ineffective responses. In this way, this model is a dynamic developmental behavioural model of ADHD; it highlights underlying biological deficits, the expression of which depends on the environmental surroundings affecting the degree of behavioural reinforcement and extinction.

1.1.3.3.1 Neuropsychological Test Evidence for the Reward model

Research has found that motivation and incentives can improve performance on executive function tasks. A longitudinal study has recently been published investigating the relationship between attention bias to reward and risk of behavioural problems later in life (Morales et al., 2019). This study recruited 291 children in infancy and followed them at 3 years (n = 218), 4 years (n = 205), 7 years (n = 174), and 9 years (n = 190). At age 7, attention bias to reward was associated with higher levels of externalising and attention problems, and lower levels of parent reported effortful control. The study found that the association with externalising and attention problems was still present at age 9. For males only, an association was found between both exuberance at age 3 and effortful control at age 4, and attention bias at age 9. The findings indicate that males with high exuberance and a large bias to reward exhibited the highest levels of externalising and attention problems later in childhood. Similarly, males who exhibited lower levels of effortful control and a large bias to reward, had the highest level of attention and externalising problems.

Another study manipulated the level of incentive for correct responses or penalty for incorrect responses in No-Go trials of a Go/No-Go task (Groom et al., 2013). Results showed that participants adjusted their performance according to motivational incentives, with lower error rates in the reward and cost conditions compared to baseline. Luman, Oosterlaan, and Sergeant (2005) conducted a review of the literature related to reward and ADHD on neuropsychological test performance, covering 22 studies published between 1986 and 2003. The review found that improved performance was evident for both control and ADHD participants for both reward and response cost, but that this improvement was more pronounced for those with ADHD. In addition, children with ADHD showed a preference for immediate over delayed reward (see Section 1.1.3.4).

A recent meta-analysis looked at the effects of reward on inhibitory control for 484 children and adolescents, 210 with ADHD and 274 controls (Ma, van Duijvenvoorde, & Scheres, 2016). The

analyses found that those with ADHD had poorer response inhibition than control participants, and that reinforcement improved this inhibition in the ADHD participants, normalising it to the baseline levels found in the control participants. It is important to note, however, that this relationship only became clear once the meta-analysis had been completed; the systematic review conducted by the authors using 17 studies rather than the 8 used in the meta-analysis showed a much more mixed pattern of results with no clear conclusions able to be made.

1.1.3.3.2 Neural Evidence for the Reward model

ADHD has long been connected with the neurotransmitter dopamine. The drug methylphenidate, used to treat ADHD, is a dopaminergic agonist, which is to say it increases the level of dopamine in the brain. It does this by blocking dopamine transporters (DAT), which remove the neurotransmitter, meaning there is more available in the synaptic cleft for receptors to use. It has been found that in both adults (Dougherty et al., 1999; Krause, Dresel, Krause, Kung, & Tatsch, 2000) and children (Vles et al., 2003), there is an increase in DAT density in the basal ganglia, which is reduced with methylphenidate. Spencer et al. (2007) used positron emission tomography (PET) with a medication naïve group of ADHD adults, controlling for smoking and alcohol consumption (drugs known to affect the dopamine reward system), and found increased DAT binding in the right caudate. The relationship between reward processing and the dopaminergic system has been shown to affect attenuation of the default mode network (DMN) in children with ADHD (Liddle et al., 2011). When off their methylphenidate medication, children with ADHD were found to have attenuated DMN activation under low incentive conditions, which normalised under high incentive conditions. DMN attenuation was also normalised when children with ADHD were on their methylphenidate medication.

Groom et al. (2013) compared two EEG components related to error monitoring in children with and without ADHD who performed a Go/No-Go task. Along with motivational manipulation outlined above, participants with ADHD also took part both on and off their methylphenidate medication. Error-related negativity (ERN) is a fronto-central ERP which peaks around 100 ms and is thought to relate to automatic detection of conflicting responses. Error positivity (Pe) is a centro-parietal ERP which peaks at approximately 300 ms and is thought to relate to error awareness and the motivational evaluation of an error or the orienting of attention as a precursor to adjusting performance. The study found that methylphenidate normalised both ERN and Pe amplitudes in the ADHD group to match control subjects. Independent of this effect, results also showed a significant effect of motivation on both ERP measures, with greater amplitude evident for both motivation conditions (reward for correct response, or cost for incorrect response) on ERN and of reward but not cost on Pe. This study supports the reward processing model of ADHD

on two fronts; it shows that motivation and reward mediates neural processes, and also further highlights the relationship with the dopamine pathways in ADHD with normalisation of EEG components with methylphenidate.

The ventral striatum forms part of the dopaminergic system within the basal ganglia. Adolescents with ADHD have shown increased reward signalling within both the ventral striatum and the superior frontal gyrus, and hyper-connectivity between the ventral striatum and the motor control regions as a function of reward/cognitive control integration (Ma, van Holstein, et al., 2016). However, unlike control participants, connectivity for those with ADHD was not associated with performance improvements, suggesting an inefficient connectivity between reward processing and motor control regions. The finding in this study of hyper-response in the ventral striatum is in contrast to the frequently reported hypo-response to reward anticipation (Plichta & Scheres, 2014). Ma and colleagues highlight that this could relate to different neural responses to the different stages of reward: anticipation, target or receipt (Tripp & Wickens, 2009).

1.1.3.3.3 Evaluation of the Reward Model

The dopamine reward model of ADHD is another reductionist model arguing for one core deficit of ADHD. However, not all ADHD patients respond to methylphenidate as a treatment for ADHD, which suggests that a model based solely on dopamine is not sufficient to explain all cases of the disorder. In addition, the longitudinal study by Morales et al. (2019) found that the moderating role of bias to reward to the relationship between attention and externalising problems and early life exuberance and effortful control were only significant for males and not females. This suggests that the role of reward bias in later attentional difficulties is different for each gender; meaning models of ADHD based solely on reward processing may not be able to account for all cases of ADHD.

With regards to the neuropsychological evidence of reward based models of ADHD, Luman et al. (2005) notes that the methodologies employed differ between studies; some give the reward for participation, some for accuracy of response, others also punish for incorrect response, and in some cases reward is given on a subset of trials. Such inconsistency in procedure means it is difficult to directly compare the research to come to an overall conclusion. Likewise, the studies in this review evaluated different neuropsychological domains, and while Luman and colleagues made efforts to overcome this by using only absolute changes in performance, the possibility remains that some cognitive functions may be affected more than others by reinforcement, which may call into question whether reward is an underlying core symptom of ADHD.

Five years after the previous review, Luman, Tripp, and Scheres (2010) reviewed 7 neurobiologically valid models of ADHD that include altered reinforcement sensitivity. From these theoretical models, 15 testable predictions were made and the evidence for each of these reviewed. At the time of the review, there was a lack of studies focused on underlying cognitive or neural mechanisms behind altered reinforcement sensitivity in ADHD. The review also noted a lack of studies investigating "what subgroup of children with ADHD shows alterations in reinforcement sensitivity" (p.744), with some evidence suggesting that ADHD subtype, comorbidity, gender, and age may act as moderators. As such, it would appear that while reinforcement sensitivity clearly has a role within ADHD, it cannot account for all cases of the disorder.

1.1.3.4 Motivation and Delay Aversion

The delay aversion hypothesis of ADHD is another motivation/reward-based approach, arguing that deficient reward signalling is compounded by a developmentally acquired motivation to escape or avoid delay (Sonuga-Barke, 2004; Sonuga-Barke, Sergeant, Nigg, & Willcutt, 2008). Sonuga-Barke (2004) suggests that, rather than arising as direct result of deficient reward processing, as is the case in Sagvolden's (2005) model, delay aversion is the result of three developmental phenomena. First, due to deficient reward signalling in the brain, impulsiveness, hyperactivity, and/or attention difficulties manifest at an early age as a coping strategy to deal with delay and give a feeling of time moving faster. Under certain circumstances, this will lead to negative reactions from the social and family environment in response to the child's failure to behave appropriately in a delay-rich environment. Second, this negative social environment, over time, leads to a conditioned motivation to escape or avoid delay; delay settings are associated with negativity, eliciting a negative affective state from which the child wishes to escape. Finally, this shifts to an individual accommodation to the child's predisposition towards impulsiveness, and the child is no longer provided the opportunity to learn an alternative behavioural response. The delay aversion model therefore posits that the inattentive, overactive, and impulsive behaviours of ADHD represent a functional expression of delay aversion.

1.1.3.4.1 Neuropsychological Test Evidence for the Delay Aversion model

Delay aversion can be measured in delay discounting tasks. In such tasks, the participant is asked to choose between a smaller sooner reward and a larger later reward. Individuals with ADHD consistently show a greater preference for the sooner reward, displaying delay aversion (Sonuga-Barke, Taylor, Sembi, & Smith, 1992). It has also been suggested that a delay aversion endophenotype of ADHD underlies not only the preference for immediate rewards, but also slower reaction times to slow event rates, and increased response rate during periods of delay

(suggestive of increased frustration with the delay) (Bitsakou, Psychogiou, Thompson, & Sonuga-Barke, 2009).

1.1.3.4.2 Evaluation of the Delay Aversion Model

Just as with the other models reviewed so far, the delay aversion model does not adequately account for the heterogeneity seen in ADHD; the evidence reviewed suggests that delay aversion is just one facet of the ADHD profile, rather than an explanation for all symptoms of the disorder. For example, as reviewed in Sonuga-Barke et al. (2008), effect sizes for two delay aversion tasks, the Maudsley Index of Delay Aversion (Kuntsi, Oosterlaan, & Stevenson, 2001) at *d* = .57 and The Choice Delay Task (Toplak, Jain, & Tannock, 2005) at *d* = .71, show that delay aversion effects are "too small to be clinically diagnostic of DSM-defined cases but may pertain to a meaningful subgroup" (p. 374). Sonuga-Barke et al. (2008) highlight that the same is also true of executive function tasks reviewed by Willcutt et al. (2005) (*d* = .6 - .8) and Martinussen, Hayden, Hogg-Johnson, and Tannock (2005) (*d* = 1.0). Therefore, a model in which delay aversion and executive functions are combined is likely to be more accurate.

1.1.3.5 Neuropsychological Heterogeneity: Integrating the two views

The two broad classes of approaches to explaining ADHD, the executive dysfunction models (Inhibitory Control Model and CEM) and the dysfunctional motivation/state models (Reward and Delay Aversion Models), have traditionally been in competition with each other (Sonuga-Barke, 2004). Each posits that there is a single underlying cause of ADHD, and each seeks to present a grand unifying theory of the disorder. However, this is at odds with the overwhelming evidence of the heterogeneity of ADHD, with not all patients showing consistent deficits that can be explained by one factor (Nigg, Willcutt, Doyle, & Sonuga-Barke, 2005). Head-to-head studies, directly comparing the executive and motivation models of ADHD, show that both concepts are independent characteristics, while both are strongly associated with ADHD (Solanto et al., 2001; Sonuga-Barke, Dalen, & Remington, 2003). Sonuga-Barke, Bitsakou, and Thompson (2010) proposed the three-pathway model of the disorder to account for the level of heterogeneity in ADHD, which includes executive, motivational, and temporal processing pathways. In this model heterogeneity is determined by the degree to which each pathway is affected within the individual as a result of their environment. The executive and motivation pathways follow a similar structure to that previously described with the executive circuit modulated by meso-cortical dopamine and the motivation/reward circuit by meso-limbic dopamine, leading to executive/inhibition deficits and delay aversion respectively. Temporal processing refers to the ability to process the temporal domain within behaviour. For example, the adjustment of behaviour to specific timeframes (motor timing), the perception and estimation of time intervals

(perceptual timing), the ability to consider future consequences of behaviours (temporal foresight).

1.1.3.5.1 Neuropsychological Test Evidence for the Three-Pathway Model

Evidence in support of the executive and delay aversion pathways has already been discussed, therefore the focus here will be on temporal processing. ADHD is commonly accompanied by such deficits (Noreika, Falter, & Rubia, 2013): In the motor timing domain, those with ADHD show deficits in tapping along to a fixed rhythm (Sonuga-Barke et al., 2010; Toplak & Tannock, 2005) and deficits in reaction times (e.g. Castellanos & Tannock, 2002). As previously discussed, individuals with ADHD also show a sensitivity to event rate. Duration discrimination tasks are thought to be one of the most perceptual measures of perceptual timing due to their relatively small load on working memory and attention (Noreika et al., 2013). Using such tasks it has been shown that those with ADHD are less able to differentiate between durations of both milliseconds and seconds (Smith, Taylor, Warner Rogers, Newman, & Rubia, 2002; Toplak, Rucklidge, Hetherington, John, & Tannock, 2003). Temporal foresight is another facet of temporal processing and can be measured using tasks such as delay discounting (see above RE delay aversion).

1.1.3.5.2 Neural Evidence for the Three-Pathway Model

Another aspect of temporally based processes is the body's internal rhythms, such as the circadian rhythm for the sleep/wake cycle. The suprachiasmatic nucleus (SCN) in the ventral hypothalamus drives the 24-hour fluctuations in the physiological and psychological functioning that give rise to this sleep/wake cycle. This internal rhythm exists even in the absence of external information (e.g. light, social cues), but uses such information to tune this "body clock" to a particular rhythm. Sleep disturbance is a well-documented finding in ADHD, suggestive of a disrupted circadian rhythm in this population (Coogan, Baird, Popa-Wagner, & Thome, 2016; Cortese, Faraone, Konofal, & Lecendreux, 2009; Gruber et al., 2012; Imeraj et al., 2012; Kooij & Bijlenga, 2013). A meta-analysis by Cortese et al. (2009), which controlled for medication use and comorbid anxiety and depression, found that children with ADHD had greater bedtime resistance, more sleep onset difficulties and night time awakenings, difficulty waking up in the morning, sleep disordered breathing, and daytime sleepiness. Physiological measures also found that children with ADHD had a poorer sleep quality across multiple indexes compared to controls. Dim light melatonin onset (DLMO) is a reliable marker of where someone is in their circadian cycle, as melatonin levels are very low during the day, increase at nightfall, and peak in the early hours of the morning (3-4am) (Haus, 2007). Studies in both children (Van der Heijden, Smits, Van Someren, & Gunning, 2005) and adults (Van Veen, Kooij, Boonstra, Gordijn, & Van Someren, 2010) have

shown delayed sleep phase syndrome in individuals with ADHD and sleep onset insomnia (SOI); this includes longer sleep onset, later wake-up time, and delayed DLMO. Research also shows that administering melatonin to patients, to reset the timing function of the SCN, improves SOI in children with ADHD (Imeraj et al., 2012).

1.1.3.5.3 Evaluation of the Three Pathway Model

The reviewed evidence shows that temporal processing is negatively affected in ADHD, supporting the suggestion that a temporal pathway be included in a model of the disorder. The analysis by Sonuga-Barke et al. (2010) identified three independent components in their battery of assessments: inhibition, timing, and delay (positive and negative), with 71% of the variability in their sample displaying a neuropsychology deficit. However, although this model better reflects the heterogeneity seen in ADHD, it was still unable to account for the full sample, which suggests that perhaps more pathways are needed to be able to account for the wide spectrum of neuropsychological deficits. In what has been called a 'landmark' study by some (Coghill, Seth, & Matthews), Fair, Bathula, Nikolas, and Nigg (2012) found that typically developing children could also be classified into distinct neuropsychological subgroups. As such the authors suggest that some of the heterogeneity seen in individuals with ADHD might be 'nested' within this normal variation. Coghill et al. (2014) tested a group of medication naïve boys with ADHD and showed that a 6-pathway model including the domains of working memory, inhibition, delay aversion, decision making, timing, and response variability, accounted for 75% of the variability. This work shows that a multiple pathway model of ADHD is necessary, but that even 6-pathways is not able to fully account for the ADHD population.

The evidence reviewed for each of the proposed models of ADHD highlights the importance of neural evidence, as is required for a disorder to be classified as "neurodevelopmental". In the following section, a review of literature related to neural oscillations, and more specifically neural entrainment, is provided culminating in a suggestion that aspects of the multiple pathway model of ADHD may be subserved by an entrainment deficit (Calderone, Lakatos, Butler, & Castellanos, 2014).

1.2 Neural Oscillations

1.2.1 Functional Oscillatory Activity

Neural oscillations are rhythmic changes in local field potentials (LFPs), generated by transmembrane currents in populations of neurons, which produce a sinusoidal wave pattern. The periodicity, or frequency, of these oscillations ranges from 0.05-600 cycles per second, with each

time point within a cycle defined by its phase (0-360°; Figure 1.1). This cyclic behaviour of oscillations produces a reference frame on to which temporal relations between groups of neurons and between neural elements and the environment can be coded (Thut, Miniussi, & Gross, 2012). Key to the relationship between oscillations and their effect on behaviour, this reference frame is not fixed, but subject to dynamic changes through phase resetting, or the modulation of phase by event-related input (entrainment). Neural oscillations can be seen to represent cyclic changes in local neural excitability, with peaks (positive polarity/amplitude) and troughs (negative polarity/amplitude) depicting high and low excitability respectively.

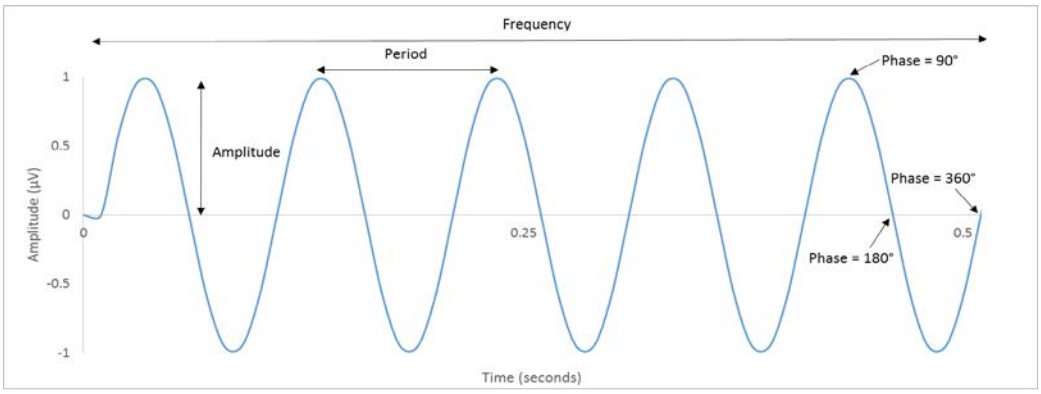


Figure 1.1 Example Oscillation.
An approximation of Alpha frequency at 10 Hz, or 10 cycles per second; 0.5 seconds is depicted and 5 complete cycles can be seen. Amplitude refers to the voltage of the signal and is indicative of the strength or power of a signal. Periodicity is the time taken for the wave to complete one cycle, while frequency is the number of cycles completed per second. Phase represents a specific point on the curve and is measured in degrees or radians (π). The high excitability phase of the oscillation occurs at the wave's peak, while the low excitability phase occurs at the trough; in the above example, at 90° and 270° respectively.

There are numerous oscillatory frequencies in the general neural signal which are assumed to be generated by specific brain regions and associated with specific functions (Wang, 2010). Alpha frequency oscillations (~10 Hz) are evident over the occipital lobe when a subject is in a relaxed state with their eyes closed. When a subject opens their eyes, alpha decreases while beta rhythms (12-30 Hz) increase; a process known as "alpha blockage". Beta is usually associated with thought and mental activity, and is generally seen over parietal and frontal regions. Beta frequency oscillations have been associated with preparation and inhibitory control in the motor system, attenuating with the onset of movement and increasing when responses are withheld. In rats, theta frequencies (4-8 Hz) are seen in the hippocampus and surrounding areas, and are associated with episodic and spatial memory. In humans, theta is associated with working memory, and is prominent in the frontal midline, across areas associated with cognition, including behaviour monitoring and valuation of response outcomes. Gamma frequency oscillations (30-80

Hz) are widespread. They were first noted in the olfactory bulb and have also been shown to be coupled with theta rhythms in the hippocampus. In cats, gamma is also generated in frontal and parietal areas, associated with hypervigilance, and has been suggested to be linked to attention in humans. In occipital areas, gamma has been suggested to play a role in sensory integration. Delta oscillations (0-4 Hz) are present during deep sleep and are characterised by very irregular and slow wave patterns. Memory consolidation has been linked to non-rapid eye movement (REM) sleep and some have suggested that slow wave oscillations (<1 Hz) might be associated with this process.

Schroeder and Lakatos (2009) state that "there is gathering consensus that neuronal oscillations have an important role in brain operations to the extent that understanding neuronal oscillation 'rhythms' now seems to be essential to our understating of brain function" (p.9). One theory put forward as an explanation of the functional importance of oscillations is the "communication-through-coherence" (CTC) hypothesis (Fries, 2005, 2015). Fries (2005) argues that communication through purely anatomical connections is not sufficient for the timely and flexible communication required in tasks such as selective attention, an *effective* communication is also required. Anatomical connections are fixed, with each neuron sending and receiving signals from neurons to which they are physically connected. However, cognition is flexible, meaning brain regions not anatomically connected need to communicate with each other in a timely way. If one were to rely solely on anatomy, communication between regions may not occur with the speed required. The CTC hypothesis states that "only coherently oscillating (or phase-locked) neuronal groups can interact effectively, because their communication windows for input and output are open at the same times" (Fries, 2005, p.474). In other words, communication between neuronal groups is facilitated when their high excitability phases are aligned with each other. This is known as neuronal coherence (or phase-locking), and is achieved via the process of entrainment (or synchronisation) whereby the phase of oscillations is reset.

In line with the CTC hypothesis, research has shown that different properties of the oscillation have modulatory effects on others. The "oscillatory hierarchy" hypothesis states that the amplitude of oscillations at specific frequencies is modulated by the phase of a local lower frequency oscillation (Lakatos et al., 2005). This work showed that the amplitude of theta oscillations was modulated by the phase of delta oscillations, and that gamma amplitudes were modulated by theta phase, such that the upward going phase trajectory aligned with peak amplitudes (see Figure 1.2). As such, the phase properties of spontaneous oscillations was shown to control the excitability (amplitude) of local neuronal ensembles, which in turn influences the processing of incoming stimuli. Such a finding highlights the ability of oscillations to modulate each other to aid information processing, a notion consistent with the CTC hypothesis. Further,

oscillations of different frequencies phase-lock to each other (Palva, Palva, & Kaila, 2005). This cross-frequency coherence is critical to the CTC hypothesis as this shows that the frequencies generated in different brain regions become synchronised with each other spontaneously, allowing them to communicate; in the author's words, "We propose that cross-frequency phase synchrony mediates cross-hierarchical and cross-functional integration essential for unified cognitive operations by enabling the integration of spectrally distributed neuronal processing" (Palva et al., 2005, p.3971).

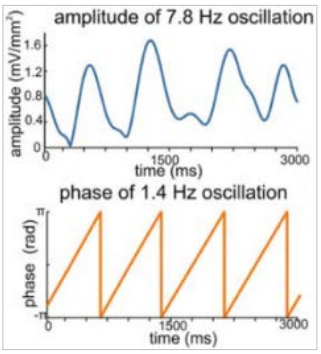


Figure 1.2 Modulation of amplitude by phase.
Top blue trace shows amplitude changes of the spontaneous theta oscillation, bottom orange trace shows phase of the delta oscillation. Taken from Lakatos et al. (2005).

In summary, growing evidence shows that neural oscillations have a specific functional role within the brain, with different frequencies involved in specific functions. Oscillations are able to modulate each other in terms of amplitude and phase coherence, and such modulations are one way by which communication across regions of the brain is organised in a timely and flexible way.

In the next section research relating to the coherence of oscillations in response to external stimulation will be discussed and it will be shown that the brain is able to modulate its internal rhythms to match the rhythms of the environment leading to more efficient and accurate information processing.

1.2.2 Entrainment of Neural Oscillations

The concept of entrainment of neural oscillations was first introduced in the late 19th century. French psychologist Pierre Janet noted that his patients were calmer when exposed to a rhythmic strobing light source (as cited in Huang & Charyton, 2008). In 1934 it was shown that this was due to amplification of alpha frequency oscillations when the light was also presented at alpha rate (Adrian & Mathews, 1934). Figure 1.3 is a stylised depiction of the entrainment process; here it can be seen that there are a number of ongoing oscillations present (each of the

coloured lines in the plot) but out of sync with each other. When a rhythmic stimulus is introduced, the phase of these oscillations resets such that they synchronise and oscillate coherently with each other; it can be seen that the peak of each of the coloured lines occurs at the same time.

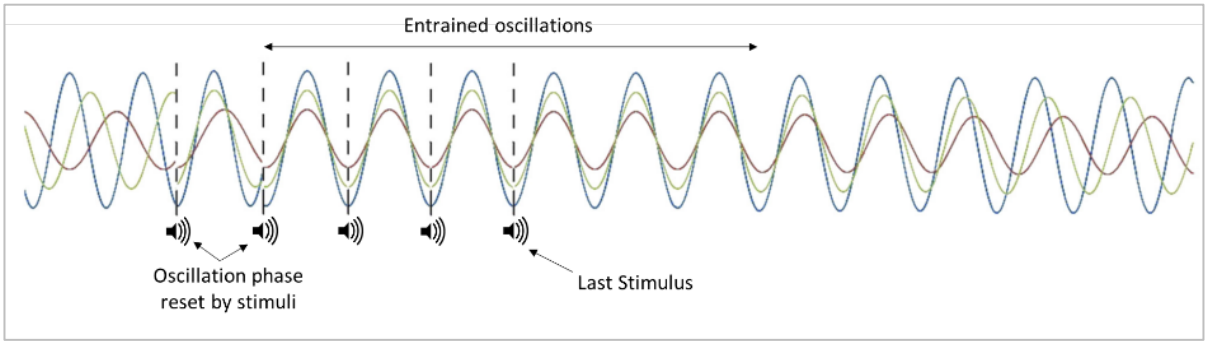


Figure 1.3 Depiction of the entrainment of neural oscillations by phase reset due to an auditory rhythmic stimulus; Taken from Calderone et al. (2014). Each line represents an individual neural oscillation.

Neural entrainment appears to be the means by which the brain organises itself to function most efficiently and effectively in our environment; when neural oscillations are entrained to a rhythmic stream, behavioural performance and perception improves; targets presented in phase with previous entraining stimuli are more readily perceived than those presented out of phase (Mathewson, Fabiani, Gratton, Beck, & Lleras, 2010; Rohenkohl & Nobre, 2011). Improved perceptual discrimination as a result of entrainment gives rise to shorter reaction times and more accurate responding (Cravo, Rohenkohl, Wyart, & Nobre, 2011; de Graaf et al., 2013; Lakatos, Karmos, Mehta, Ulbert, & Schroeder, 2008; Rohenkohl, Cravo, Wyart, & Nobre, 2012). Evidence suggests that this improved perception of temporally expected events could be a result of entrainment of low frequency oscillations leading to enhanced contrast sensitivity of targets (Cravo, Rohenkohl, Wyart, & Nobre, 2013; Rohenkohl et al., 2012).

1.2.3 Entrainment and Attentional Processes

The evidence reviewed above has shown that entrainment has an impact on stimulus processing, as such, there is a possibility that entrainment also has a mediating role for attentional processes, which are impaired in ADHD. In this regard, the oscillatory selection hypothesis outlined by Schroeder and colleagues (Schroeder, Herrero, & Haegens, 2014; Schroeder & Lakatos, 2009) suggests that there are two modes of neural processing, rhythmic and random/continuous, and that these modes are implemented based on task demands, which in turn determine how oscillations are used to process the sensory information. When in rhythmic mode, entrainment gives rise to amplification and suppression of oscillations; low frequency oscillations entrain to the rhythm of attended (Lakatos et al., 2008) or attention-grabbing/salient

stimuli (Lakatos, Chen, O'Connell, Mills, & Schroeder, 2007), shifting the high excitability phase to amplify the attended stimulus, while suppressing input of stimuli out of phase with attended events. The suggestion is that the rhythmic mode is preferred as it is more efficient due to high excitability being tuned to when it is needed rather than being in a continuous state which is metabolically more demanding. Schroeder and Lakatos (2009) highlight converging lines of theory and findings which culminate in the conclusion that entrained oscillations, either in a steady-state (continuous) mode and/or phase resetting trial by trial (rhythmic mode), provide a likely candidate for the physiological underpinnings for the effects of attention.

Lakatos et al. (2008) used macaque monkeys trained to attend to either visual or auditory stimuli in a selective attention task, and found that delta-band oscillations were present, with a period matching the rate of stimulus presentation. Inter-trial coherence values (a measure of phase coherence across trials) were larger for attended vs non-attended stimuli, regardless of modality, suggesting that entrainment is modulated by attention. Further, this entrainment was present in primary visual cortex for both auditory and visual stimuli. The level of entrainment was related to the level of neuronal excitability, as evidenced by increased theta, gamma, and event-related response amplitudes in line with entrained delta-band phase near attended stimulus onset. In addition, decreased amplitude near non-attended stimulus onset was also shown, suggesting a suppression of neuronal excitability to irrelevant stimuli. Thus, this animal model suggests that selective attention modulates neural oscillations to maximise excitability when stimuli are expected and supressing activity when irrelevant stimuli are present, which optimises the processing of predicted stimuli.

Lakatos et al. (2009) extended the above work by taking measurements from both primary visual and auditory cortices of macaques. Results showed that attended stimuli of the preferred modality (i.e. visual stimuli in visual cortex, auditory stimuli in auditory cortex) gave rise to both evoked (amplitude increase) and phase reset (entrained oscillations) responses, whereas attended non-preferred stimuli only resulted in phase reset. In other words, non-preferred visual stimuli in auditory cortex led to entrainment but not to increased amplitude, and vice versa. Such results highlight the role of attention in modulating the phase of neural oscillations in the primary sensory cortices. The fact that only the oscillatory phase was modulated in the non-preferred cortex, highlight the potential importance of this function over overall excitability levels in order to communicate the stimuli to other neural assembles (e.g. the preferred sensory cortex). This indicates that oscillations are likely the preferred method of communication, over anatomical communication achieved via excitability levels; a notion key to the CTC hypothesis.

Lakatos, Musacchia, et al. (2013) looked specifically at auditory selective attention in macaques, noting that a purely temporally-based system for maximising neural excitability to rhythmic streams would not be sufficient if such streams were to have temporal overlap. Based on a proposal by Shamma, Elhilali, and Micheyl (2011) that dominant frequency content in the attended stream guides temporal attention, Lakatos, Musacchia, et al. (2013) proposed a spectro-temporal filter system to enhance sensory representation of attended stimuli. Results showed that the phase of oscillatory entrainment was frequency-dependent and that this continued to be the case when the monkeys performed the selective attention task. This suggests that, when the preferential frequency of a neuronal ensemble matches the frequency of attended stimuli, attention will either have a facilitative or suppressive effect on neuronal activity when attended stimuli are predicted to occur; if stimuli overlap temporally, neuronal activity related to ignored frequency content will be suppressed. On the other hand, if stimuli overlap in frequency, neuronal activity at non-attended time points will be suppressed.

In humans, Besle et al. (2011) investigated entrainment and attention by recording from electrodes placed directly on the surface of the cortex of patients awaiting brain surgery. The results show the same entrainment of oscillations as the stimulus rate in primary sensory cortices, but also entrainment over a large neural network. In addition, they also found that the size of this effect increased with increased stimulus predictability showing that attentional bias has a direct effect on the degree of modulation. Together, this body of work (Besle et al., 2011; Lakatos et al., 2008; Lakatos, Musacchia, et al., 2013; Lakatos et al., 2009) has shown that, oscillations across the brain entrain to the temporal and frequency content of attended stimuli while supressing neural activity to non-attended stimulus streams, and that the degree of entrainment increases with increased predictability of stimuli. However, this may only apply when selective attention tasks are employed. When a single modality attention task is used and compared to passive listening, there is only a slight increase in power for the attention task in auditory sustained neural entrainment of gamma-band frequency (Hamm et al., 2015).

Despite the findings of Hamm et al. (2015), the connection between entrainment and attention clearly goes beyond selective attention paradigms. Lutz et al. (2009) implemented an attention based meditation program and found that those trained to increase their attentional focus had increased phase-locking of oscillatory activity in theta band in response to deviant tones in an attended stimulus stream. Participants who received the attention training also showed a reduction in reaction time variability as well as a reduction in event-related desynchronisation suggestive of lower resources required to complete the task after training. Lutz et al. (2009) have shown that focused attention has a measureable effect on the coherence of theta band oscillations supporting the proposal that entrainment and attention are linked.

In summary, the evidence reviewed has shown that neural oscillations entrain to the rhythm of attended, predictable stimuli in both macaques and humans. This entrainment is triggered by attentional processes and leads to improved perception of and response times to these stimuli. As such, entrainment of ongoing neural oscillations is modulated by selective attention with the entrained oscillations then aiding in the processing of stimuli which occur within the rhythm. The following section will outline evidence in relation to deficient entrainment of neural oscillations in specific disorders and how such deficits could explain some of the symptomology of these disorders.

1.2.4 Dysfunctional Entrainment

In patients with schizophrenia, Lakatos, Schroeder, Leitman, and Javitt (2013) found reduced entrainment to attended stimuli which correlated with deficits in behavioural performance as well as symptom severity. Deficient sustained neural entrainment in the form of an evoked 40 Hz auditory "steady state" response has been suggested as a biomarker for the disorder as there is consistent evidence of reduced entrainment with auditory stimuli of 500 ms duration (Brenner et al., 2009; Hamm et al., 2015). Visual steady state deficits are also found in schizophrenia in early stage visual processing in the alpha and beta frequency bands (Brenner et al., 2009), with additional evidence suggesting a specific deficit in the magnocellular pathway (Butler & Javitt, 2005; Butler et al., 2001), which could explain some of the sensory deficits seen in the disorder. Schizophrenia is accompanied by a range of sensory deficits in both the auditory and visual domain beyond the hallucinatory symptoms; these include motion perception, form perception, low spatial frequency discrimination, tone matching, and temporal and pitch discrimination. Relatedly, MRI studies have consistently found grey matter reductions in the superior temporal gyrus, the location of both primary and secondary auditory cortex, and cellular studies show volume reductions in pyramidal cells of layer 3 of the auditory cortex. In visual cortex, reduction of grey matter thickness in primary visual cortex is seen at first episode of schizophrenia, whereas patients with chronic development show reduced volume in visual association areas. It is likely that the entrainment deficits seen in schizophrenia are a reflection of the alterations in grey matter volume and cellular abnormalities evident in sensory cortices (Brenner et al., 2009).

Entrainment deficits have also been found in dyslexia, a learning disability characterised by reading deficits. Dyslexia has been shown to be accompanied by temporal processing deficits, which have been shown to predict reading ability (Flaugnacco et al., 2014). Goswami and colleagues have studied the relationship between dysfunctional entrainment and dyslexia in both adults and children. In 2011, they put forward the "temporal sampling" hypothesis of dyslexia

which states that temporal sampling of speech by neural oscillations that encode information at different frequencies could be disrupted in dyslexia giving rise to perceptual and phonological difficulties (Goswami, 2011). This hypothesis received empirical support with the finding that phase coherence to slow amplitude modulations (which correspond to syllable and stress pattern-level elements in speech) at 2 Hz (delta) was atypical in dyslexia (Hamalainen, Rupp, Soltesz, Szucs, & Goswami, 2012). Soltész, Szucs, Leong, White, and Goswami (2013) showed that adults with dyslexia displayed weaker oscillatory entrainment to regular rhythmic tones at delta rates (1.5 and 2 Hz), and less anticipatory neural response to the expected stimuli (contingent negative variation; CNV). In addition, these deficits were correlated with symptom severity. Children with dyslexia show differences in the preferred phase of entrainment (i.e. at which point in the oscillation's cycle they entrain to) to delta-band stimuli in both auditory and audio-visual syllable presentation. This suggests an enhanced processing at less informative temporal points of the incoming signal, i.e. not at its peak, leading to impairments of phonological representation (Power, Mead, Barnes, & Goswami, 2013).

Calderone et al. (2014) argue that dysfunctional entrainment may underlie the selective attention and temporal processing deficits seen in ADHD. The evidence reviewed by the authors shows that ADHD is accompanied by deficits in early stage processing of sensory information; at the same stage that entrainment is implicated. Abnormal oscillations have also been found in ADHD, with neurofeedback treatment specifically designed to correct these. However, the current view is that there is no support for neurofeedback as an effective treatment for ADHD (Cortese et al., 2016), in which case more research is needed to investigate the underlying neural oscillation deficits in this disorder to improve or discount this line of treatment. Together, these lines of evidence converge toward a compelling argument for an investigation of entrainment in ADHD.

1.2.4.1 ADHD as a disorder of entrainment

To understand the rational for arguing the case for an entrainment deficit in ADHD, first it needs to be understood that ADHD can be seen as a disorder of low sensory processing. A growing body of evidence suggests that patients with ADHD show deficits in early-stage (low-level) sensory processing. It had been noted that patients with ADHD report problems with selective attention but behavioural experimental studies had not been able to reliably detect this (Stevens et al., 2012). Across two experiments, Stevens et al. (2012) concluded that perceptual interference might explain the difficulties being reported, rather than spatial attention deficits. Their work showed that those with ADHD had poorer performance in crowded versus clean displays, and that this was unaffected by the use of spatial pre-cues to manipulate spatial attention, showing that the deficits lie in the perception of the stimuli itself. Supporting this idea,

those with ADHD have been found to have impaired early-stage orienting to sensory stimuli, the very initial step of perceiving and attending to a stimuli, evident in both the EEG and behavioural data (Johnstone, Barry, & Clarke, 2013). Ortega, López, Carrasco, Aboitiz, and Anllo-Vento (2013) have also shown that external orienting of attention is dysfunctional in ADHD, finding evidence of a larger P2 ERP component (2nd positive peak; associated with automatic processing and inhibition of non-relevant information) and reduced CNV (a negative dip in the ERP signal indicative of cortical arousal during orienting and attention), indicating a lack of preparation for the expected stimuli. A reduced early ERP component of the visual N1 (1st negative peak; associated with selective attention) was also found suggesting reduced allocation of attentional resources. These studies suggest that the initial stages of perception of attended stimuli are disrupted in ADHD, along with a reduced allocation of attentional resources.

Missonnier et al. (2013) used time-frequency analysis to show that adults with ADHD have task-independent reduced amplitude of early frontal theta activity suggesting impaired activation of neural circuits that subserve directed attention, despite equivalent behavioural performance, in working memory, oddball detection, and passive fixation tasks. In addition, those with ADHD also showed significantly reduced alpha power suggesting inefficiency of information transfer across pathways connecting the thalamus (through which all sensory information is transmitted) and cortex, which are required for active cortical processing. This was followed by a power increase, which the authors argue could represent a compensatory neural mechanism in these adult patients, explaining the equivocal behavioural performance. Such compensatory mechanisms have also been suggested in gamma-band responses during processing of stimulus features and integration of sensory input (Lenz et al., 2008). Evoked gamma-band responses are among the first cortical responses to emerge after visual stimulation. It has been shown in patients with ADHD, such gamma responses are equivalent for both known and unknown stimuli, suggesting a deficit in early visual processing and classification of stimuli in ADHD (Lenz et al., 2010).

Deviations have also been found with alpha neural oscillations. During attentional tasks, typically developing children show differentially modulated posterior alpha activity to auditory and visual cues, which was coupled with mid-frontal theta activity. Children with ADHD do not show these oscillatory correlates of top-down attentional control (Mazaheri et al., 2010). The authors suggest that this represents a disconnection between frontal and occipital cortex during preparatory attention. In a more recent study comparing ADHD subtypes, Mazaheri et al. (2014), found that both predominantly inattentive and combined subtypes show weak functional connectivity between frontal theta and posterior alpha, again suggestive of a deficit in top-down control of behaviour. The study also notes differences in the EEG profile of ADHD subtypes.

Predominantly inattentive ADHD participants were found to have less post-cue alpha suppression, suggestive of reduced processing of the cue in visual cortex. Combined type participants showed reduced beta suppression contralateral to the response hand, which suggests a lack of motor preparation to respond. Together, these works suggest that those with ADHD show reduced neural responses during the preparatory stage of each level of cue-stimulus interaction (attending, processing, and responding). This disrupted preparation could reflect a disruption in early stage processing of the stimulus.

Evidence suggests that entrainment of neural oscillations underlies early stage selective attention to sensory stimuli (Lakatos et al., 2008; Lakatos, Musacchia, et al., 2013; Lakatos et al., 2009). These are the very deficits outlined above. As such, the argument being made here is that such deficits seen in ADHD might be underpinned by an entrainment deficit. The reviewed ERP evidence suggests deficits in preparation for expected upcoming stimuli such as the CNV. Schroeder and Lakatos (2009) suggest that the frontal CNV likely reflects a phase reset of frontal low-frequency oscillations, directly connecting this ERP component to entrainment.

Consistent with findings implicating deficient anticipatory preparation for upcoming stimuli (Benikos & Johnstone, 2009; Doehnert, Brandeis, Schneider, Drechsler, & Steinhausen, 2013; Ortega et al., 2013), Sidlauskaite et al. (2014) found that those with ADHD had decreased anticipatory engagement of task-relevant brain regions during rest-to-task state switching, as well as a reduced level of default mode network (DMN) anticipatory upregulation during task-to-rest switching. These results suggest that those with ADHD have a deficit in anticipatory engagement of state-relevant brain regions. It could be the case that such engagement of state-relevant brain regions is triggered by communication through coherent oscillations, which would be tied to entrainment; if there is a deficit in entrainment, the signal required to tell brain regions they need to be ready to respond could be disrupted or delayed.

Sidlauskaite, Sonuga-Barke, Roeyers, and Wiersema (2016) furthered their work on the DMN by investigating the organisation of neural networks in ADHD. This work showed that those with ADHD have increased connectivity between the ventral and dorsal attention networks, within the DMN, and within the ventral attention network, and decreased connectivity between the salience network and the dorsal attention network. The functional significance of this connectivity is yet to be studied but it is suggested that this could show an imbalance between the two attention systems, with the ventral implicated in task engagement, making those with ADHD susceptible to distraction in the presence of salient task-irrelevant stimuli. Such distraction away from the relevant task stimuli means that entrainment itself could be less efficient as a weaker signal would be being transmitted due to interference from the task-irrelevant stimuli.

Less efficient entrainment would then impact on the effective communication to other neural ensembles and compound the poor selective attention to the task-relevant stimuli.

Entrainment deficiencies have been found in other neurodevelopmental disorders such as dyslexia (Soltész et al., 2013) and schizophrenia (Lakatos, Schroeder, et al., 2013), and are thought to underlie some of the difficulties seen in these disorders, such as temporal perception. As has been previously discussed, timing deficits are well documented in ADHD (Noreika et al., 2013), with deficits seen in reaction times (Castellanos & Tannock, 2002), tapping along to a fixed rhythm (Sonuga-Barke et al., 2010; Toplak & Tannock, 2005), and sensitivity to event rate (Wiersema et al., 2006). Attenuation of the DMN in ADHD is also connected to event rate, with both very fast and very slow event rates giving rise to excessive DMN activity, showing dysregulation of the DMN when additional effort is required to complete a task (Metin et al., 2014). In addition, evidence also suggests a dysfunctional internal timing or body clock in at least some patients with ADHD (Imeraj et al., 2012). As entrainment is inherently a process based in timing and rhythm, it is again plausible to suggest that such temporal processing deficits could be related to an underlying entrainment deficit in ADHD.

Further evidence of a possible relationship between deficient entrainment and ADHD comes from studies using entrainment-based intervention methods as a treatment for various symptoms, including those seen in ADHD (for a review see Huang & Charyton, 2008). Patrick (1996) gave rhythmic photic stimulation (light pulses) to 8-14 year old participants with ADHD, with the goal to increase production of beta frequency oscillations at the 12-14Hz range and reduce theta activity. Results showed that after 15 sessions participants had improvements in impulsivity, processing speed, and distractibility. One aim of this study was to train participants to produce the altered neural rhythms on their own without the need for stimulation but EEG data was not able to ascertain whether this had been achieved. Joyce and Siever (2000) used an audio-visual entrainment intervention with school-aged participants with ADHD. Participants received an average of 31 sessions of combined visual and auditory rhythmic stimulation for approximately 20 minutes. Results indicated a reduction in both inattention and impulsivity scores. Furthermore, two students were able to reduce their medication and others who were candidates for pharmacological treatment no longer were after the intervention. Although the results of both studies sound promising for an entrainment-based intervention in ADHD, no direct measure of an entrainment deficit was taken in either study. Therefore, although this work highlights that intervention based on entrainment could be beneficial, an underlying entrainment deficit was not measured so the mechanism of the effects are unknown.

1.3 Summary

ADHD is a neurodevelopmental disorder characterised by age inappropriate and impairing levels of impulsivity, hyperactivity, and/or inattention. Core symptoms manifest prior to the age of 12 and can be predominantly inattentive, predominantly hyperactive/impulsive, or a combination. ADHD is a highly comorbid disorder, with 52% of patients showing one comorbidity and 26% having 2 or more. Treatment for ADHD is available as pharmacological or non-pharmacological (including neurofeedback based on abnormal neural oscillations) interventions, with evidence suggesting that pharmacological are the most effective.

Evidence suggests that 15% of patients maintain their childhood diagnosis into adulthood, with 65% meeting criteria for ADHD in partial remission. For those who do not receive a childhood diagnosis, but for whom symptoms were present and are impairing in adulthood, might receive a diagnosis of adult ADHD. Undergraduate students with ADHD may represent a distinct population, being better adjusted and achieving higher academic success compared to peers with the disorder who do not attend university. However, research in this group has been limited and conclusions difficult as there has been no consensus on how to classify participants for the "ADHD" group, and majority of work is carried out at single sites within the USA. More research is needed to investigate the difficulties faced by this population using criteria which more closely reflects the diagnostic standard (DSM-5), but also that is applicable to students here in the UK.

Various models have been proposed to account for ADHD, taking different perspectives. Broadly speaking there have been two schools of thought; executive function based models and motivation/state regulation models. Each approach attempts to explain ADHD as stemming from one core deficit. However, such an approach cannot adequately account for the heterogeneity seen in the disorder. The currently accepted models of ADHD are ones that include multiple pathways in which heterogeneity is accounted for by a person's environment determining the extent to which they are affected on each pathway. Such multiple pathway models are supported by both neuropsychological and neurological evidence that shows multiple brain regions and networks are involved. The suggestion has been made that a dysfunction in the ability for oscillations in the brain to entrain to each other and the environment might underlie selective attention and temporal processing difficulties seen in ADHD; a suggestion that warrants investigation.

1.4 Research Aims

The aims of this research are twofold: 1) explore the neuropsychological functioning of University students in the UK who experience a clinically significant level of ADHD symptoms, and 2) explore the possibility of an entrainment deficit in these individuals, which may underpin deficits in such neuropsychological functioning.

1.4.1 Neuropsychological functioning in undergraduate ADHD

Evidence suggests that there are multiple pathways involved in ADHD, with individuals affected to a differing degree on each one. University students with the disorder are also affected on these different pathways but the evidence is conflicted in terms of which neuropsychological domains are at play in this, possibly, better-adjusted population of individuals with the disorder. In this research a range of neuropsychological domains were examined, which have each been implicated in the multiple pathway models: working memory, sustained attention, temporal processing, and inhibitory control. In addition, a measure of IQ was also assessed due to the conflicting evidence with regards to what degree IQ is negatively affected in the student ADHD population. It was predicted that those students exhibiting a greater level of ADHD symptoms would show deficits in each of the domains tested and would have a lower IQ than those who show no evidence of ADHD symptoms.

1.4.2 Entrainment and ADHD

To assess the possibility of an entrainment deficit in ADHD, a paradigm was developed based on that of previously published literature. It was predicted that those who displayed a higher level of ADHD symptoms would show less efficient entrainment to rhythmic stimuli; this would be evident by 1) a reduction in the strength of entrained response (lower inter-trial coherence value) and/or 2) a temporal shift such that entrainment occurred at a less informative point of the oscillation cycle.

Chapter 2 Methodology

In this chapter the methodology for each of two studies shall be outlined including a description of the participant sample in each study. In order to minimise burden on participants, such that those exhibiting ADHD symptoms would have the best opportunity to maintain their focus and effort throughout, the neuropsychological testing session was kept to 1 hour. As such, each of the specific tests chosen to measure each of the domains had to be able to be completed within this time. A review of the literature was conducted with search terms including the domain in question and "ADHD", and experimental procedures compared to find a robust measure of the domain with as short an implementation time as possible.

2.1 Study 1

2.1.1 Design

A between-subjects design was used, comparing two ADHD symptom groups (high and low) on three classes of measures: behavioural, electrophysiological, and neural entrainment.

2.1.2 Participants

Fifty-four participants, 24 high symptom (HS; mean age 21.84 years, range 18-29 years, 7 males) and 30 low (LS; mean age 20.46, range 18-27 years, 5 males) were recruited from the University of Southampton via online and poster advertisements and reimbursed for their time with either course credits or money. Six low symptom participants did not complete the EEG recording session either due to incompatible hairstyles or technical difficulties during the session. As a result, there were 24 participants for each group with EEG available (LS: mean age 20.84 years, range 18-27 years, 4 males). EEG pre-processing procedures (see below) left a final sample of 20 HS (mean age 22.03 years, range 18-29 years, 4 males) and 23 LS participants (mean age 20.82 years, range 18-27 years, 4 males) for the inhibitory control EEG analysis and 12 participants per group for the entrainment EEG analysis (HS: mean age 22.09 years, range 18-29 years, 3 males; LS: mean age 20.51 years, range 18-27 years, 1 male).

Inclusion criteria were:

1. HS group: endorsement of 5 or more symptoms in either or both subscales of the Current Symptoms Scale (CSS) Self-Report in accordance with the Diagnostic and Statistical Manual of Mental Disorders 5th Edition (DSM-5). In addition, a "significant other" must report at least 3 symptoms from either subscale as a means of

minimising self-report bias; as not all symptoms would be visible by an outsider a cut-off of 5 to match the DSM-V was deemed too severe.

2. LS group: Endorsement of no more than one symptom across both subscales of the CSS Self-Report in-line with previous work conducted with a similar population of adults (Hsu, Broyd, Helps, Benikos, & Sonuga-Barke, 2013). In addition, a "significant other" must also not report more than one symptom across the subscales.
3. Fluent in the English language; as there is a verbal component of the IQ test, fluent English is required to ensure an accurate result. The experimenter judged language proficiency when administering the tasks.
4. Participants were given written instructions that should they be taking medication for symptoms of hyperactivity/impulsivity or inattention, they were required to be medication free for 24 hours prior to testing. This was to minimise the risk that the medication would affect the results.

ADHD symptoms were assessed using the Current Symptoms Scale (CSS) (Barkley & Murphy, 2006).The CSS has two parts, the first of which is filled out by the participant (see Appendix A.1) and the second by an additional informant known to the participant (see Appendix A.2) in order to reduce self-report bias. The scale is based on DSM-4 criteria for ADHD and measures the number of symptoms experienced in the last 6 months. It includes 18 items where each asks the participant to endorse a symptom via a four-point Likert scale (never or rarely (0), sometimes (1), often (2), and very often (3)). As per the administration guidelines, responses of "often" or "very often" were taken as endorsement of that symptom. The 18 items are separated into 9 statements for the inattentive subscale and 9 for the hyperactive/impulsive subscale. Total scores range from 0-54 (0-27 for each subscale), where increased scores reflect a great degree of symptom severity. Both the self- and other-report, showed excellent reliability, overall and for each subscale (Table 2.1). These results are consistent with published data (Gomez, 2011).

Table 2.1
Reliability (Cronbach's alpha) of Current Symptoms Scale for both Self- and Other-Report Overall and for Each Subscale in Study 1

	Self	Other
Total	.93	.94
Inattentive	.90	.91
Hyperactive/Impulsive	.87	.89

Note. Self N = 585; Other N = 76

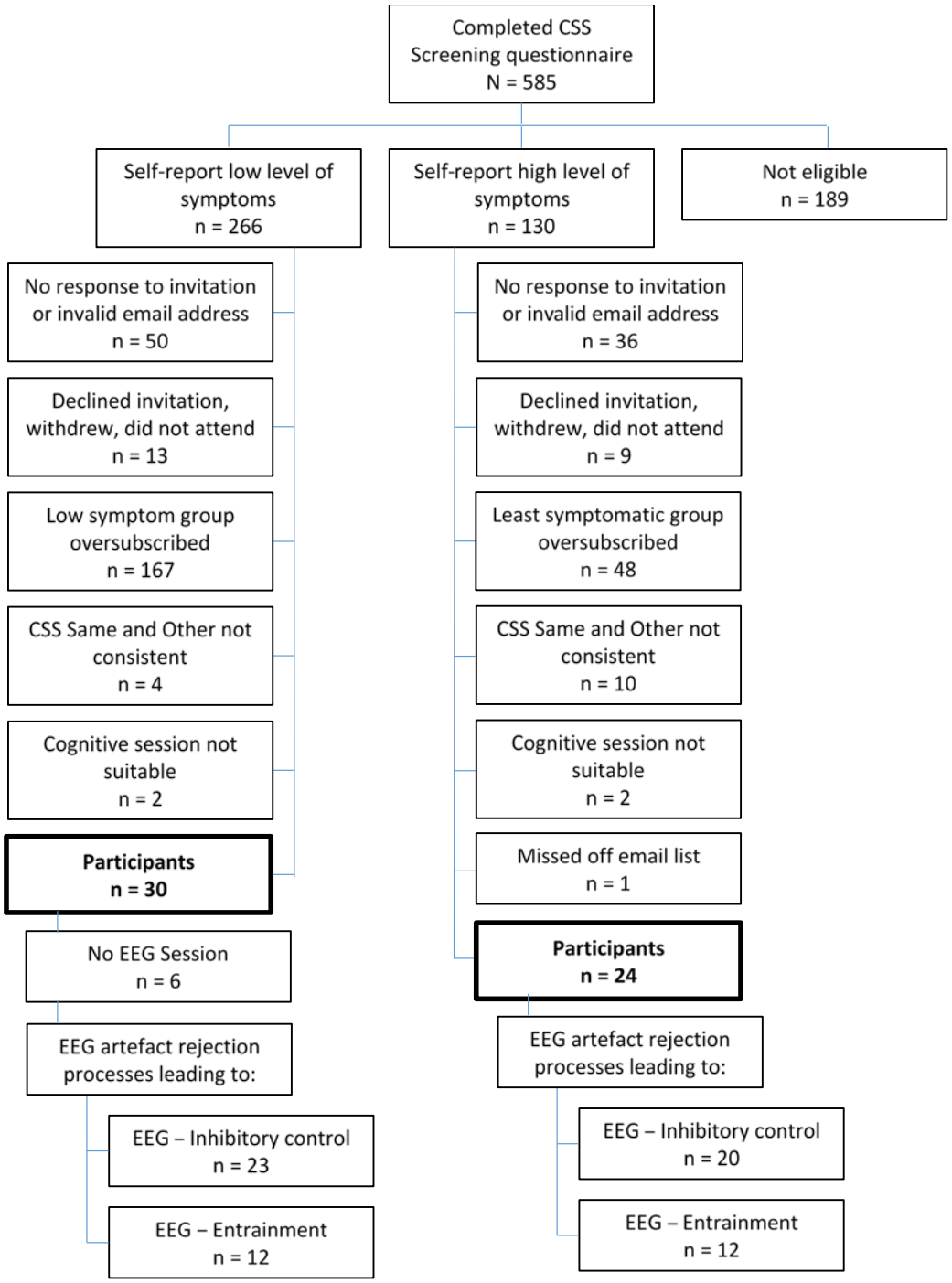


Figure 2.1 Flow chart showing the number of participants at each stage of the recruitment process in Study 1.

585 individuals (mean age 20.31, *SD* = 3.88 years, range 17-49 years, 119 males) completed the online screening questionnaire; 130 showed eligibility for the HS group, 266 for the LS group, and 189 were not eligible for the study. Figure 2.1 gives a flow chart of the participant numbers and how the final sample of 54 was reached; means and standard deviations of these participants CSS results can be found in Table 2.2. Other-reports were not received for 3 HS participants, but these individuals reporting having a current diagnosis of ADHD and as such were included in the

study. Wilcoxon Signed Rank Tests were performed (Bonferroni correction: .05/12 = .004) which show that there were significant differences between self- and other-report for the Total Inattentive score in the LS group (Z = -3.05, p = .002), and for the number of total symptoms reported in the HS group (Z = -3.07, p = .002). In the LS group, the severity of self-reported symptoms of inattention were higher (M = 3.71, SD = 2.16) than other-reported symptoms (M = 1.75, SD = 1.39). In the HS group, the number of total symptoms endorsed in the self-report (M = 11.67, SD = 3.00), was significantly higher than in the other-report (M = 8.78, SD = 3.77). No other differences were found between self- and other-reports for either group.

Correlations between the self- and other-report were also computed for the final 54 participants which, after correction for multiple comparisons (.05/12 = .004), found no significant associations for both the number and severity of symptoms, overall and for each subscale.

Table 2.2
Means, standard deviations, and Spearman's Correlations for the Current Symptom Scale Self- and Other-Report in Study 1 for the high (n = 24) and low symptom (n = 30) groups

	High						Low					
	Self		Other				Self		Other			
	M	*SD*	*M*	*SD*	r_s	*p*	*M*	*SD*	*M*	*SD*	r_s	*p*
Number of symptoms												
Total	9.08	2.41	9.14	3.73	.54	.01	.23	.43	.33	.48	-.06	.77
Inattentive	5.92	1.84	4.86	2.26	.55	.01	.07	.25	.07	.25	-.07	.71
Hyperactive/Impulsive	5.75	2.27	4.29	2.51	.46	.04	.20	.41	.27	.45	.08	.69
Hyperactive	*3.17*	*1.27*	*2.33*	*1.43*			*.17*	*.38*	*.20*	*.41*		
Impulsive	*2.58*	*1.44*	*1.95*	*1.53*			*.03*	*.18*	*.07*	*.25*		
Severity Score												
Total	33.04	7.41	27.62	8.56	.33	.15	7.03	3.16	4.07	2.64	-.14	.46
Inattentive	16.83	3.63	13.95	5.14	.51	.02	3.67	2.32	1.77	1.70	.10	.60
Hyperactive/Impulsive	16.21	5.50	13.67	5.81	.47	.03	3.37	1.63	2.30	1.66	-.13	.48
Hyperactive	*8.95*	*2.88*	*7.29*	*3.30*			*2.30*	*.88*	*1.57*	*1.17*		
Impulsive	*7.25*	*3.18*	*6.38*	*3.12*			*1.07*	*1.11*	*.73*	*.87*		

2.1.3 EEG Acquisition

EEG data were collected using a 64 Quik-Cap Electrode System (Compumedics NeuroScan, Singen, Germany). The Ag/AgCl electrodes were actively amplified, mounted on an elastic cap, and conform to the standard 10/20 montage. Electrodes were referenced to Cz, but re-referenced off-line to an average reference. Eye movements were monitored by electrodes placed above the left eyebrow and below the left eye, as well as on each temple (VEO/HEO). EEG was amplified

using a BrainAmp amplifier (Brain Products), recorded from DC and sampled at 1000 Hz. Curry 7.0 Neuroimaging Suite (Compumedics NeuroScan) was used to record the data.

2.1.4 Materials

2.1.4.1 Behavioural (Neuropsychological tests)

2.1.4.1.1 IQ

IQ was measured using the two subscales version (FSIQ-II) of the Wechsler Abbreviated Scale of Intelligence second edition (WASI-II): non-verbal Matrix Reasoning and verbal Vocabulary subscales (Wechsler, 2011). In the Vocabulary subscale, participants were presented with a list of words, one at a time, both visually and aurally, and asked to give a definition. For the Matrix Reasoning task participants were presented with a grid of images, with one image missing, and asked to indicate which of the additional items below should be placed into the missing square to complete the pattern. In both tasks, 30 seconds were given for the participant to respond, after which a prompt was given such as "do you have an answer". The task was stopped if three consecutive incorrect answers were given. The administration of both subscales took no more than 15 minutes. The two subscale scores were combined to form a FSIQ-II score taken as the participant's IQ.

2.1.4.1.2 Working Memory

Working memory (WM) was assessed using the Automated Working Memory Assessment (AWMA) Screener (Alloway, Gathercole, Kirkwood, & Elliott, 2008). The AWMA is a computerised WM assessment for use with children and young adults between the ages of four and 22. The Screener version of the AWMA was used and comprises of two WM assessments: Listening Recall and Spatial Recall. In the Listening Recall task, participants were presented with sentences one at a time and after each were asked to state whether the statement was true or false, after all sentences had been presented they recalled the last word from each sentence in the order they were presented. In the Spatial Recall task participants viewed shapes on the screen with a red dot above them and were asked to state whether the shape was in the same or opposite orientation to an adjacent sample shape. Once all shapes had been presented, participants then had to point on the screen to the locations of each of the red dots in the order they were presented. For both tasks the participant was first presented with one sentence/shape, then two, three, etc. in successive blocks of 6 trials each. As soon as the participant gave three incorrect answers within a block the task was stopped. The software provided a score for both recall and processing (identifying as true/false or same/opposite) for each task, with higher values indicating better performance. These scores were transformed to z-scores to allow direct comparison between the

two measures. Administration of the AWMA Screener took approximately 10 minutes to complete.

2.1.4.1.3 Sustained Attention

The sustained attention task was a computer-based task used by Szucs, Devine, Soltesz, Nobes, and Gabriel (2013). Participants were required to attend to a stream of letters, presented one at a time, and detect the target sequence (A B C) while withholding responses to "deceiver trials" which contain two target letters (e.g. A B D) and "non-target" trials with only one target letter (e.g. A H F). There were 80 of each of the three different trial types (240 total trials), presented randomly, but as a continuous stream of letters. Each letter was presented for 300 ms with a gap of 300 ms between each letter. The task took 7-8 minutes to complete, including a practice block. The number of hits, missed targets (errors of omission), and false alarms (errors of commission) for both deceiver and non-target trials were recorded, along with reaction times for hits and false alarms of both types. It was anticipated that there would be more false alarms for deceiver compared to non-target trials, as these trials more closely resemble the target. In this task, errors of omission reflect error in sustained attention, while errors of commission reflect impulsive responding.

2.1.4.1.4 Duration Discrimination

The duration discrimination task was based on that of the Maudsley Attention and Response Suppression Task battery (MARS) as used and designed by Rubia et al. (2007). Participants were presented with two circles, one after the other with no pause and in a random order. A red circle appeared on the left side of the screen and a green circle on the right side, separated by a 1 cm gap. One circle was randomly presented for 1000 ms and the other for either 1300, 1400, or 1500 ms. The participant was asked to indicate with a button press whether the left or right circle appeared for the longer time. Sixty pairs of stimuli were presented and the task took no longer than 5 minutes to complete. The total number of errors and reaction time data for each of the three durations (1300, 1400, 1500 ms) was recorded. It was anticipated that discrimination would be most difficult for the 1300 ms condition as this was the duration closest in time to the comparison circle, this would be evident by increased error rate which would improve with increasing duration of the target circle.

2.1.4.1.5 Inhibitory Control

The animal Stroop task used here was the same used by Bryce, Szucs, Soltesz, and Whitebread (2011) and used to index inhibitory control. Stimuli were comprised of coloured pictures of two animals presented on the right and left sides of the screen. Participants were required to respond with a button press, as quickly as possible, to indicate which animal would be

larger in real life, while ignoring the relative size of the images on the screen. In congruent trials, the animal that is larger in real life had a larger on-screen picture, while in the incongruent trials, the animal that is smaller in real life had the larger on-screen image. There were 288 trials, equal congruent and incongruent, requiring a maximum of 26 minutes to complete; however, in practice it took less time than this (average 19.7 minutes, including practice trial) as progression was based on participant response times. Reaction times and error rates for both trial types were recorded. The Stroop effect was taken as the difference in reaction time between the incongruent and congruent trials, where higher scores indicate poorer inhibitory control as more time is needed to overcome the impulse to respond to the larger image on the screen rather than the larger in real life animal. It was expected that more errors would be made in the incongruent trials compared to congruent.

2.1.4.2 Entrainment Task

The design of this task was based on that used by Besle et al. (2011); it includes both auditory and visual rhythmic stimuli (Figure 2.2). The visual stimuli used represent “alien heads” (a solid circle with two rectangular “stalks” protruding from the top left and right sides) and a picture of a teddy bear presented for 100 ms. The auditory stimulus used is a tone of 33 ms duration at 450 Hz. Stimuli were presented in a rhythmic stream of 1 Hz, where target stimuli (a brighter image or higher pitch tone at 580 Hz) comprised 15% of stimulus presentations (see Soltész et al., 2013). Within an experimental block, participants were presented with a single modality stimulus stream of 30 stimuli, followed by a 16 second blank period to allow for the time taken for the brain to fall back into its natural rhythm. Participants were then given a selective attention entrainment task in which they were presented with both modality stimuli, presented alternately, but asked to attend only to the stimulus stream previously presented and to respond to targets within this stream while ignoring the other. Participants completed ten alternating blocks, counterbalanced such that half of participants received an auditory block first, and half a visual block first. There were 164 stimuli in each block, 84 auditory and 84 visual, giving a total of 1640 stimulus presentations. For the purpose of EEG data analysis, target trials and the corresponding response were removed from the dataset and only the raw EEG data for non-target stimuli were used to assess the level of entrainment. Reaction times and accuracy data were also analysed.

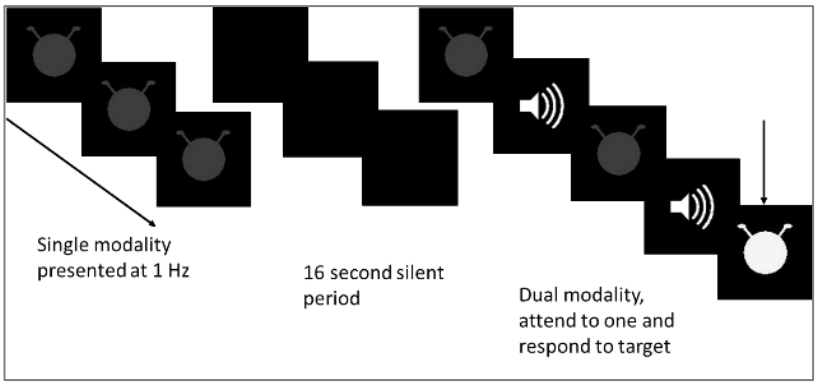


Figure 2.2 Depiction of the entrainment task.
First was the presentation of 30 single modality stimuli at a rate of 1 Hz. This was followed by 16 seconds of silence in which only a black screen is presented to the participants. After this, participants were presented with the dual modality selective attention task in which the two stimulus streams were presented alternately, each at 1 Hz, with target stimuli in 15% of trials in each stream. During this task, participants only attended to the modality presented at the start of the experiment (before the silence) and ignored the other.

2.1.4.3 Electrophysiological Measures

2.1.4.3.1 Lateralised readiness potential (LRP)

Electrophysiological data was recorded during the inhibitory control task in order to investigate motor preparation to respond to the stimuli, giving an indication of response inhibition processes. This data was analysed using the lateralised readiness potential (LRP), calculated using Coles (1989) equation:

$$\frac{[(C4-C3)_{left\ hand\ response}+(C3-C4)_{right\ hand\ response}]}{2}$$

Where C3 and C4 refer to the activity in the C3 and C4 electrode respectively. Initial peak amplitudes and latencies were extracted for analysis. Jack-knifing was implemented to analyse peak onset and duration, as well as the transition from incorrect to correct response preparation, which is the component that represents response inhibition (Miller, Patterson, & Ulrich, 1998; Miller, Ulrich, & Schwarz, 2009; Ulrich & Miller, 2001). Peak onset was determined as the latency at which the amplitude was 75% of the min/max peak amplitude (Bryce et al., 2011), and was calculated for both the initial peaks and the secondary peak in the incongruent condition which reflects the onset of the correct response preparation. Transition from incorrect to correct response (transition factor) in the incongruent condition was taken as the difference between the latency of the cessation of the initial peak and onset of the secondary peak.

Electrophysiological data was high pass filtered at .02 Hz and low pass filtered at 30 Hz offline using a 2nd order Butterworth filter with Hann taper at 10% using Curry 7.0 Neuroimaging Suite (Compumedics NeuroScan). Subsequent analysis was performed with Matlab and the EEGlab toolbox. Epochs from -100 to 1000 ms were extracted for artefact rejection. Epochs with

data points over or below ± 120 μV or with a slope in excess of 50 Hz were marked for rejection. Electrodes showing stationary and non-movement related noise were interpolated. Participants with an excess of 60% rejected trials or more than 5 interpolated channels were removed from analysis resulting in 20 HS and 23 LS participants. This pre-processing procedure was based on that used in previous literature (e.g. Bryce, et al., 2011). There was no significant, difference in the total number of epochs at the start of analysis between the groups (t (46) = -1.32, p = .19) and no difference in the number of rejected epochs through artefact rejection (t (46) = .56, p = .58).

2.1.4.3.2 Event related potential (ERP)

ERP data was obtained during the entrainment task and pre-processed with the following parameters: high pass filtered at .01 Hz and low pass filtered at 45 Hz offline using a 2nd order Butterworth filter with Hann taper at 10% using Curry 7.0 Neuroimaging Suite (Compumedics NeuroScan). Epochs from -100 to 800 ms were extracted and any containing data over or below ± 100 μV were marked for rejection. This epoch window was chosen such that both an attended and non-attended stimulus could be seen within one epoch. Electrodes showing stationary and non-movement related noise were interpolated. Participants with an excess of 60% rejected trials or more than 5 interpolated channels were removed from analysis resulting in 12 HS and 12 LS participants for analysis. Matlab with EEGlab toolbox were used for data analysis. Six electrodes were selected: F1, Fz, F2, FC1, FCz, and FC2. These electrodes were chosen as they showed the strongest inter-trial coherence effect (ITC) over the frontal region where effects were expected based on previous research (Besle et al., 2011; Soltész et al., 2013).

2.1.4.3.3 Entrainment

Data were pre-processed as outlined above for the ERP analysis. Epochs from -800 to 800 ms were extracted for time/frequency decomposition using the *newtimef()* function of the EEGlab toolbox (Delorme & Makeig, 2004). This window was chosen to ensure 3 stimuli were present in the window, one both before and after the chosen stimulus. There was no significant, difference in the total number of epochs at the start of analysis between the groups (t (45.15) = -1.76, p = .09) and no difference in the number of rejected epochs through artefact rejection (t (46) = .50, p = .62). Morlet wavelets were computed with the following parameters: 1 cycle at the lowest frequency, .5 at the highest, window size 1000, 200 time points, with FDR correction for multiple comparisons. This gave 50 linear-spaced frequency from 1-50 Hz from -242.5 to 241.5 ms. The output of the decomposition gives two measures: ITC and event-related spectral perturbation (ERSP). ITC indexes the degree of entrainment across trials, while ERSP is a measure of the power of the signal at any given time/frequency window.

2.1.5 Procedure

Participants completed the screening questionnaire online. Potentially eligible participants were contacted by the experimenter who provided the "Other" version of the CSS for them to give to a significant other to complete and send back to confirm eligibility for the either the HS or LS group. Eligible participants were invited to the lab for two testing sessions. In the first session participants completed measures of IQ, working memory, sustained attention, and duration discrimination. These measures were delivered in the same order to all participants. Order effects can be controlled for in two ways: a fixed order such that any effects are the same for all participants, or randomisation. Here, a fixed order approach was used to simplify administration of the experiment. During a second testing session participants completed the EEG recording in which they were fitted with an electrode cap and their scalp EEG recorded whilst engaging in the entrainment task and then the inhibitory control task.

2.1.6 Statistical analyses

2.1.6.1 Behavioural data

IQ was assessed using an independent t-test to assess group differences. Working memory was assessed using a 2 by 2 by 2 mixed model ANOVA with modality (listening vs spatial) and measure (recall vs processing) as the within- and group (HS vs LS) as the between-subjects factor. For the sustained attention analysis, one participant from the HS group was removed from the dataset as an outlier due to an extremely low hit rate of just 12.5%. Due to non-normally distributed data, sustained attention accuracy data (ratio of hits and false alarms) and reaction times were analysed using the Mann-Whitney U tests to assess group differences. The duration discrimination task was analysed using two 3 by 2 mixed model ANOVAs for the ratio of correct responses made for each condition and reaction times with duration difference (300 vs 400 vs 500 ms) as the within- and group as the between-subjects factor. Inhibitory control reaction times and the number of errors were each analysed using a mixed model 2 by 2 ANOVA, with congruency (congruent vs incongruent) as the within- and group as the between-subjects factor. The presence of ceiling effects was determined by reviewing the skewness of the distribution, with the z-score of skewness used to determine the significance of the skew. In addition, (Roberts, 1978) advises that if the difference between the mean and median of a distribution exceeds $1/5^{th}$ the standard deviation, this also suggests the presence of significant skewing. Based on these two methods, a determination was made as to the presence of ceiling effects.

2.1.6.2 Electrophysiological data

2.1.6.2.1 LRPs

The first step in the analysis of the LRP data was to determine whether a significant LRP was present. To do this point-by-point one sample t-tests were conducted to test whether the waveform deviated significantly from zero at each time point. Deviations were considered to reach significance if the *p*-value was less than .05 for more than 20 consecutive time points (20 ms). Miller (1996) MrFub program for unequal group sizes was used to analyse the jack-knifed data; the software implements a correction to the standard error calculations to correct for the artificial loss of variability due to the jack-knifing procedure.

2.1.6.2.2 ERPs

ERPs were analysed for the Entrainment tasks to investigate attention to a single modality stimulus and the selective attention to either an auditory or visual stimulus stream while ignoring a stimulus stream of the other modality. Between groups analysis was conducted using point-by-point independent *t*-tests for each modality at each latency. *P*-values were FDR corrected using the Benjamini and Hochberg (1995) method, implemented using the *mafdr()* function in Matlab, and considered to be significant if less then .05.

2.1.6.2.3 Entrainment

The first question for the entrainment results was whether there were any baseline deficits in entrainment, which might contribute to the general attention and timing deficits found in ADHD. To analyse this, the data for the single modality task were collapsed across modalities by creating an average of auditory and visual data. Point-by-point *t*-tests were run at each latency of the time window for each frequency band for both ITC and ERSP, comparing the two symptom groups. The next analysis sought to investigate whether there were any differences in the dual modality task that would be specifically related to selective attention. 2 by 2 mixed model point-by-point ANOVAs were run with attendedness (attended vs non-attended) as the within- and group (HS vs LS) as the between-subjects factor for both ITC and ERSP. Finally, any differences between the two tasks were analysed with 2 by 2 mixed model point-by-point ANOVAs with task (single modality vs dual modality task) as the within- and group (HS vs LS) as the between-subjects factor. For the purpose of this analysis, only the attended to stimuli were used in the dual modality task condition. Post-hoc analyses of significant interaction effects in both ANOVA analyses were conducted using independent measures *t*-tests with Bonferroni corrected alpha (.05/4 = .0125).

Reaction times to target stimuli in the dual modality task, were analysed using a 2 by 2 mixed model ANOVA with modality (auditory, visual) as the within- and group as the between-subjects factor. The number of errors made were analysed with a 2 by 2 by 3 mixed model ANOVA with modality (auditory, visual) and error type (missed targets, wrong responses to incorrect stimulus modality, and false alarms) as the within- and Group as the between-subjects factors.

2.2 Study 2

2.2.1 Design

As with Study 1, a between-subjects design was used, comparing two ADHD symptom groups (high and low) on three classes of measures: behavioural, electrophysiological, and neural entrainment.

2.2.2 Participants

Forty-two participants, 21 HS (mean age 22.61 years, range 18-40 years, 5 males) and 21 LS (mean age 24.04, range 18-34 years, 7 males) were recruited from the University of Southampton via online and poster advertisements and reimbursed for their time with either Psychology course credits or money. There was no significant difference in age between the two groups. Three LS and seven HS participants did not complete the EEG recording session due to technical difficulties during the session. As a result, there were 14 HS (mean age 23.88 years, range 18-40 years, 4 males) and 18 LS participants (mean age 24.80 years, range 18-34 years, 7 males) with EEG available. EEG pre-processing procedures (see below) left a final sample of 11 HS (mean age 24.97 years, range 18-40 years, 3 males) and 13 LS participants (mean age 25.13 years, range 18-34 years, 4 males) for the inhibitory control EEG analysis and 6 HS (mean age 24.98 years, range 19-32 years, 2 males) and 9 LS (mean age 24.07 years, range 18-33 years, 4 male) participants for the entrainment EEG analysis.

Inclusion criteria were the same as Study 1 and summarised below:

1. Participants were included in the high symptom (HS) group if they endorsed 5 or more symptoms in either or both subscales of the Current Symptoms Scale (CSS) Self-Report. In addition a “significant other” had to report at least 3 symptoms from either subscale as a means of minimising self-report bias.
2. Participants were included in the low symptom (LS) group if they endorsed less than one symptom across both subscales of the CSS Self-Report. In addition, their “significant other” did not report more than one symptom across the subscales.

3. Participants were fluent in the English language as judged by the experimenter when administering the first of two testing sessions.
4. Participants were given written instructions to refrain from taking medication for symptoms of hyperactivity/impulsivity or inattention for the 24 hours prior to testing. This was to minimise the risk that the medication would affect the results.

Following the same procedure as Study 1, ADHD symptoms were assessed using the Current Symptoms Scale (CSS) (Barkley & Murphy, 2006). As was the case in Study 1 and published data (Gomez, 2011), for Study 2 both the Self- and Other-report, showed excellent reliability overall and for both the inattention and hyperactive/impulsive subscales (Table 2.3).

Table 2.3
Reliability (Cronbach's alpha) of Current Symptoms Scale for both Self- and Other-Report Overall and for Each Subscale in Study 2.

	Self	Other
Total	.94	.96
Inattentive	.92	.94
Hyperactive/Impulsive	.89	.92

Note. Self N = 235; Other N = 81

235 people (53 males) completed the online screening questionnaire; 69 indicated eligibility for the HS group, 101 for the LS group, and 65 were not eligible based on their self-report. Table 2.4 contains descriptive statistics for CSS data for the final 42 participants. Figure 2.3 depicts a flow chart to show how the final number of recruited participants was reached. Wilcoxon Signed Rank Tests were performed (Bonferroni correction: .05/12 = .004) which show that there was a significant difference in the number of total symptoms reported by the self (M = 11.00, SD = 2.72) and other (M = 9.05, SD = 3.26) in the HS group (Z = -3.02, p = .003). No other differences were found between self- and other-reports for either group.

Table 2.4
Means, standard deviations, and Spearman's Correlations for the Current Symptom Scale Self- and Other-Report in Study 2 for high (n = 21) and low symptom (n = 21) participants.

	High						Low					
	Self		Other				Self		Other			
	M	*SD*	*M*	*SD*	r_s	*p*	*M*	*SD*	*M*	*SD*	r_s	*p*
Number of symptoms												
Total	11.00	2.72	9.04	3.26	.67	.001	.24	.44	.24	.44	-.05	.83
Inattentive	5.67	2.29	4.62	2.48	.71	<.001	.10	.30	.10	.30	-.11	.65
Hyperactive/Impulsive	5.33	1.68	4.43	2.18	.78	<.001	.14	.36	.14	.36	-.17	.47
Hyperactive	*3.33*	*.97*	*2.48*	*1.40*			*.14*	*.36*	*.14*	*.36*		
Impulsive	*2.00*	*1.34*	*1.95*	*1.32*			*.00*	*.00*	*.00*	*.00*		
Severity Score												
Total	31.33	5.69	27.95	7.47	.59	.005	5.14	3.14	3.81	2.91	.32	.16
Inattentive	16.48	4.25	14.10	4.80	.69	<.001	2.86	2.22	2.05	2.33	.36	.11
Hyperactive/Impulsive	14.86	4.23	13.86	4.64	.77	<.001	2.29	1.90	1.76	1.38	.19	.40
Hyperactive	*8.95*	*2.11*	*7.86*	*2.73*			*1.67*	*1.28*	*1.29*	*1.10*		
Impulsive	*5.90*	*2.74*	*6.00*	*2.97*			*.62*	*.97*	*.48*	*.60*		

Spearman correlations found that, after correction for multiple comparisons (.05/12 = .004), for those in the HS group, the CSS outcomes were significantly correlated between the self- and other-report ($p < .001$) for all but the overall severity score ($p = .005$). There were no significant correlations between the self- and other-report in the LS group. However, this is perhaps not surprising given the lack of variability in this group by the nature of how the groups are determined.

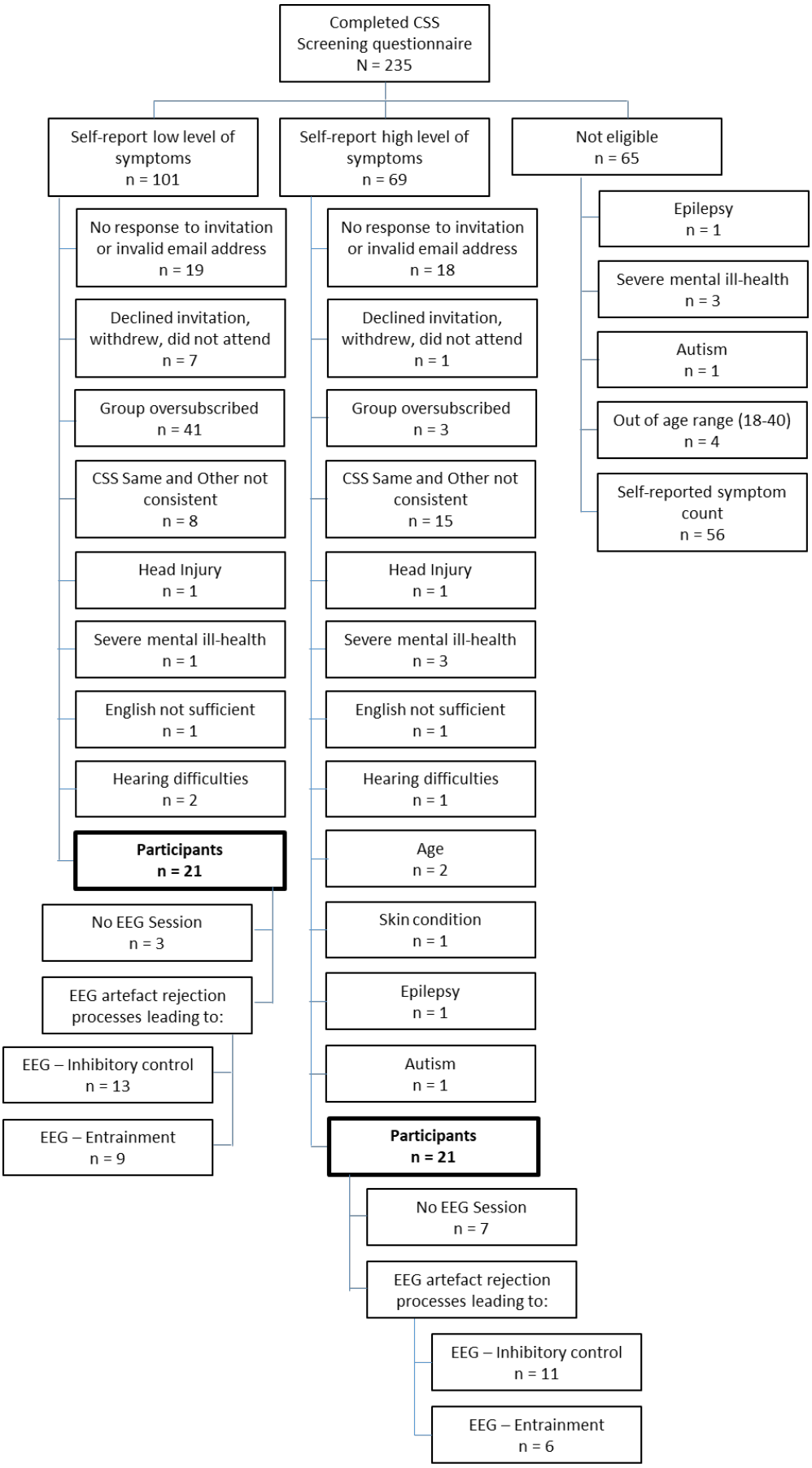


Figure 2.3 Flow chart showing the number of participants at each stage of the recruitment process in Study 2.

2.2.3 EEG Acquisition

EEG data were collected using a 64 Quik-Cap Electrode System (Compumedics NeuroScan, Singen, Germany) using Quik-Cells. The Ag/AgCl electrodes were actively amplified, mounted on an elastic cap, and conform to the standard 10/20 montage. Electrodes were referenced to Cz, but re-referenced off-line to an average reference. Eye movements were monitored by electrodes placed above the left eyebrow and below the left eye, as well as on each temple (VEO/HEO). EEG was amplified using a BrainAmp amplifier (Brain Products), recorded from DC and sampled at 1000 Hz. Curry 7.0 Neuroimaging Suite (Compumedics NeuroScan) was used to record the data.

2.2.4 Materials

2.2.4.1 Behavioural (Neuropsychological Tests)

IQ and working memory were measured using the same materials as Study 1. The parameters of the sustained attention, temporal processing, inhibitory control and entrainment tasks were altered for Study 2, primarily to make the tasks more difficult. These changes are outlined below.

2.2.4.1.1 Sustained Attention

Each letter was presented for 250 ms with an inter-stimulus interval of 250 ms, as opposed to 300 ms for each in Study 1. This was the only change, and all other parameters remained the same. In order to determine the new duration for Study 2, durations of 250 and 200 ms duration were tested alongside the original 300 ms duration. Four individuals independent from the project completed the task and provided feedback with regards to the difficulty, as well as the comfort of being presented stimuli with such frequency. From this feedback it was determined that a new duration of 250 ms increased the difficulty sufficiently without causing discomfort, as was the case for 200 ms durations.

2.2.4.1.2 Temporal Processing

In Study 1 the 1300, 1400, and 1500 ms presentations were only compared to the 1000 ms stimulus. As such, it may have been possible for the participants to learn that one of the stimuli was always presented for 1 second and therefore also learn that they simply need to select the other as it will always be longer, and not need to wait for the second circle to be presented before making their decision. Therefore, for Study 2 the four stimulus durations of Study 1 (1000, 1300, 1400, 1500 ms) were presented randomly such that the participants would not be able to predict which of the circles would be longer in advance of being presented *both* circles. The random

presentation of the four durations produced two additional conditions of only 100 and 200 ms duration differences between the two circles. Sixty pairs of stimuli were presented.

2.2.4.1.3 Inhibitory Control

For Study 2, the task was made more difficult by increasing the size difference between the images such that the large image was four times the size of the small as per Cragg, Keeble, Richardson, Roome, and Gilmore (2017), thus giving a larger size difference to overcome in the incongruent trials to give a correct answer. EEG data were processed in the same way as Study 1. As detailed in Figure 2.3, 14 HS and 18 LS participants completed the EEG recording with 7 of these exhibiting excessively noisy data and removed from the analysis, leaving 11 HS and 14 LS participants. There was no significant, difference in the total number of epochs at the start of analysis between the groups (t (28) = .28, p = .78) and no difference in the number of rejected epochs through artefact rejection (t (28) = 1.11, p = .28).

2.2.4.2 Entrainment

The design of the entrainment task used in Study 2 was the same as Study 1 but with one alteration; instead of participants receiving the same intensity stimuli, they would instead be presented with stimuli just above detection threshold. Visual stimuli were grey circles presented on a black background, and auditory stimuli were identical to those used in Study 1 (440 Hz tones for standard stimuli and 580 Hz tones for target stimuli, both of 33 ms duration). To determine individual perception thresholds a staircase procedure was used. Participants were first presented with an ascending trial in which the image brightness or tone volume would increase with subsequent presentations of the stimulus, given a rate of 1 Hz. Participants were required to press a button when they could first perceive the stimulus. This was followed by a descending trial in which the stimulus was first presented at its brightest/loudest, and gradually decreased in intensity until seeming to disappear, at which point the participant was required to press the button. Individual thresholds for perception were taken as the average intensity at which the button was pressed across both ascending and descending trials. Image brightness was given in 2% brightness increments starting from 6% brightness up to 20%. These values were rated by 3 individuals prior to the study commencing as the most appropriate for the screen and ambient lighting conditions of the lab such that no image was visible on the screen at the lowest setting, while increments were sufficient to yield just perceptible difference between the images. Tone volume was given at 5 dB increments starting at -5 dB up to 30 dB. These values were used in order that participants would perceive silence at the lowest value and a tone no louder than a whisper at its highest value. To determine visual target brightness, a shortened version of the

main task was presented and the brightness of the target adjusted until the participant could detect the target approximately 75% of the time, in line with Besle et al. (2011).

Once detection and discrimination thresholds had been determined, participants proceeded to complete the task depicted in Figure 2.4, in which they first complete a single modality task and then a dual modality (selective-attention) task. The task design is the same as Study 1 and EEG data were processed in the same way. 17 participants exhibited excessively noisy data and were removed from the EEG analysis, leaving 6 HS and 9 LS participants. There was no significant, difference in the total number of epochs at the start of analysis between the groups (t (27) = -.11, p = .92) and no difference in the number of rejected epochs through artefact rejection (t (27) = .52, p = .61).

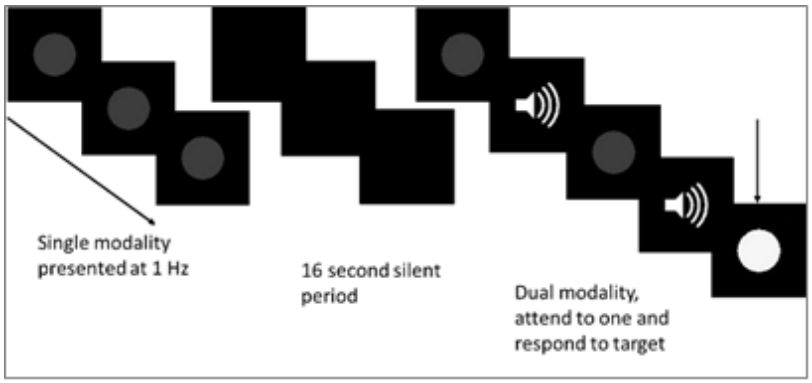


Figure 2.4 Depiction of the entrainment task of Study 2.
First was the presentation of 30 single modality stimuli at a rate of 1 Hz. This was followed by 16 seconds of silence in which only a black screen was presented to the participants. After this, participants were presented with the dual modality selective attention task in which the two stimulus streams were presented alternately, each at 1 Hz, with target stimuli in 15% of trials in each stream. During this task, participants only attend to the modality presented at the start of the experiment (before the silence) and ignored the other.

2.2.5 Procedure

Participants completed the screening questionnaire online. Potentially eligible participants were contacted by the experimenter who provided a link to the "Other" version of the CSS for them to send on to a significant other to complete online to confirm eligibility for the either the high or low symptom group. Eligible participants were invited to the lab for two testing sessions. In the first session participants completed measures of IQ, working memory, sustained attention, and duration discrimination. These measures were delivered in the same order to all participants to control for order effects. During a second testing session participants completed the EEG recording in which they were fitted with an electrode cap and their scalp EEG recorded whilst engaging in first the entrainment task and then the inhibitory control task.

2.2.6 Statistics

2.2.6.1 Behavioural data

Working memory was assessed using a 2 by 2 by 2 mixed model ANOVA with modality (listening vs spatial) and measure (recall vs processing) as the within- and group (HS vs LS) as the between-subjects factor. Normality tests revealed that sustained attention reaction times and error rates were not normally distributed and therefore group differences were analysed using Mann-Whitney U tests with a Bonferroni corrected alpha level (.05/3 = .0125). The duration discrimination task was analysed using two 5 by 2 mixed model ANOVAs for the number of errors made for each condition and reaction times with duration of target (100, 200, 300, 400, 500 ms) as the within- and group as the between-subjects factor. Inhibitory control reaction times and the number of errors made were each analysed using a mixed model 2 by 2 ANOVAs, with congruency (congruent vs incongruent) as the within- and group as the between-subjects factor.

2.2.6.2 Electrophysiological data

2.2.6.2.1 LRPs

As stated for Study 1, the first step in the analysis of the LRP data was to determine whether a significant LRP was present. To do this point-by-point one sample *t*-tests were conducted to test whether the waveform deviated significantly from zero at each time point. Deviations were considered to reach significance if the *p*-value was less than .05 for more than 20 consecutive time points (20 ms). Miller (1996) MrFub program for unequal group sizes was used to analyse the jack-knifed data; the software implements a correction to the standard error calculations to correct for the artificial loss of variability due to the jack-knifing procedure.

2.2.6.2.2 ERPs

ERPs were analysed for the Entrainment tasks to investigate attention to a single modality stimulus and the selective attention to either an auditory or visual stimulus stream while ignoring a stimulus stream of the other modality, which occurred alternately. Between groups analysis was conducted using point-by-point independent *t*-tests for each modality at each latency. *P*-values were FDR corrected using the Benjamini and Hochberg (1995) method, implemented using the *mafdr()* function in Matlab, and considered to be significant if less then .05.

2.2.6.2.3 Entrainment

The first question for the entrainment results is whether there are any baseline deficits in entrainment, which might contribute to the general attention and timing deficits found in ADHD.

To analyse this, the data for the single modality task were collapse across modalities by creating an average of auditory and visual data. Point-by-point *t*-tests were run at each latency of the time window for each frequency band for both ITC and ERSP, comparing the two symptom groups. The next analysis sought to investigate whether there were any differences in the dual modality task that would be specifically related to selective attention. 2 by 2 mixed model point-by-point ANOVAs were run with attendedness (attended vs non-attended) as the within- and group (HS vs LS) as the between-subjects factor for both ITC and ERSP. Finally, any differences between the two tasks were analysed with 2 by 2 mixed model point-by-point ANOVAs with task (single modality vs dual modality task) as the within- and group (HS vs LS) as the between-subject factor. For the purpose of this analysis only the attended to stimuli were used in the dual modality task condition. Post-hoc analyses of significant interaction effects in both ANOVA analyses were conducted using independent measures *t*-tests with Bonferroni corrected alpha (.05/4 = .0125).

Reaction times to target stimuli in the dual modality task, were analysed using a 2 by 2 mixed model ANOVA with modality (auditory, visual) as the within- and group as the between-subjects factor. The number of errors made were analysed with a 2 by 2 by 3 mixed model ANOVA with modality (auditory, visual) and error type (missed targets, wrong responses to incorrect stimulus modality, and false alarms) as the within- and group as the between-subjects factor.

Chapter 3 Behavioural Results

3.1 Introduction

Attention-deficit/hyperactivity disorder (ADHD) is one of the most prevalent neurodevelopmental disorders, affecting approximately 5% of the school-aged population (Polanczyk et al., 2015), with symptoms continuing into adulthood for the majority of individuals (Faraone et al., 2006). However, little is known about the extent of neuropsychological difficulties faced by university students with the disorder (Weyandt et al., 2017). This population of ADHD sufferers could represent a better-adjusted group with ADHD as they achieve higher academic outcomes than peers with the disorder who do not attend university (Green & Rabiner, 2012). Understanding the neuropsychological difficulties faced by university students with symptoms of ADHD would not only mean better interventions could be designed to address these difficulties, but it could also aid in understanding why this group attain greater academic success. If this can be understood, this knowledge could then lead to interventions for younger ADHD individuals so that they too could be "better-adjusted".

3.2 IQ

In Study 1, there was no significant difference in IQ between the High (HS) and Low symptom (LS) groups (t (52) = 1.00, p = .32, d = .27; Table 3.1). However, in Study 2 the LS group exhibited a significantly higher IQ than the HS group (t (40) = -2.19, p = .03, d = .68; Table 3.1). For participants included in the EEG analyses, there was no significant difference in IQ between the HS and LS groups, for those included in the inhibitory control analysis in Study 1 (t (41) = .37, p = .71, d = .12), or in the entrainment analyses for both Study 1 (t (22) = .99, p = .34, d = .40) and Study 2 (t (13) = -.72, p = .48, d = .37). For those included in the inhibitory control EEG analysis in Study 2, a trend toward the HS group having a lower IQ was found (t (22) = -1.83, p = .08, d = .75).

Table 3.1
Descriptive statistics (M, SD) for IQ with p-values and effect sizes for group comparisons, for all participants, those with Inhibitory Control EEG and those with Entrainment EEG.

		High			Low				
		n	*M*	*SD*	*n*	*M*	*SD*	*p*	*d*
Study 1	All Participants	24	108.17	8.08	30	105.87	8.67	.32	.27
	Inhibitory control EEG	20	107.35	7.71	23	106.39	8.94	.71	.12
	Entrainment EEG	12	108.42	8.97	12	104.92	8.40	.34	.40
Study 2	All Participants	21	104.86	6.98	21	109.71	7.36	.03	.68
	Inhibitory control EEG	11	105.27	8.86	13	111.62	8.11	.08	.75
	Entrainment EEG	6	108.17	7.47	9	110.67	5.92	.48	.37

3.3 Working Memory

In both studies a main effect of group was found (Study 1 F (1, 52) = 4.24, p = .04, η_p^2 = .08; Study 2 F (1, 40) = 4.27, p = .05, η_p^2 = .10), with the HS group performing worse overall compared to the LS group (Table 3.2). No other significant effects were found in either study. For those individuals included in the Inhibitory Control EEG analysis, a trend towards a main effect of group was found in Study 1 (F (1, 41) = 4.27, p = .06, η_p^2 = .10), with a suggestion that the HS group performed worse overall compared to the LS group (Table 3.2). However, no effects were found in Study 2. For those individuals included in the Entrainment EEG analyses, in Study 1 a trend towards a main effect of modality was found (F (1, 22) = 3.19, p = .09, η_p^2 = .13), with the listening tasks having a poorer performance overall compared to the spatial tasks (Table 3.2). However, again no significant effects were found for Study 2.

Table 3.2
Descriptive statistics (M, SD) for working memory with p-values and effect sizes for group comparisons, for all participants, those with Inhibitory Control EEG and those with Entrainment EEG.

			High			Low				
			n	*M*	*SD*	*n*	*M*	*SD*	*p*	*d*
Study 1	All Participants	Listening Recall	24	17.04	4.44	30	17.57	3.92	.65	.13
		Spatial Recall		21.46	5.13		25.73	6.51	.01	.73
		Listening Processing		47.08	16.96		50.50	19.25	.50	.19
		Spatial Processing		65.33	24.77		89.63	37.65	.006	.76
	Inhibitory	Listening Recall	20	16.50	4.55	23	18.04	4.12	.25	.35

			High			Low			
			n	*M*	*SD*	*n*	*M*	*SD*	*p*	*d*
	control EEG	Spatial Recall		21.90	5.28		25.22	6.59	.08	.56
		Listening Processing		45.15	17.65		52.83	20.11	.19	.41
		Spatial Processing		67.90	25.73		86.83	37.82	.07	.59
	Entrainment EEG	Listening Recall		15.58	4.54		16.33	3.58	.66	.18
		Spatial Recall	12	21.17	5.77	12	26.17	7.70	.09	.73
		Listening Processing		41.00	16.79		44.58	15.73	.60	.22
		Spatial Processing		66.33	28.28		92.25	42.21	.09	.72
Study 2	All Participants	Listening Recall		15.52	3.97		17.86	4.59	.09	.55
		Spatial Recall	21	22.24	7.19	21	26.29	6.22	.06	.60
		Listening Processing		42.14	17.34		50.33	18.97	.16	.45
		Spatial Processing		70.76	34.58		92.95	36.99	.05	.62
	Inhibitory control EEG	Listening Recall		15.91	3.05		17.38	4.79	.39	.36
		Spatial Recall	11	22.45	8.38	13	25.23	5.81	.63	.39
		Listening Processing		44.73	17.28		48.38	18.99	.35	.20
		Spatial Processing		72.82	41.45		86.15	34.01	.40	.35
	Entrainment EEG	Listening Recall		16.50	3.21		17.67	4.98	.62	.28
		Spatial Recall	6	27.00	8.08	9	27.22	5.89	.80	.03
		Listening Processing		47.00	16.15		49.67	22.05	.95	.14
		Spatial Processing		94.83	42.78		97.33	36.30	.91	.06

3.4 Sustained Attention

Mann Whitney tests were applied to both the RT and accuracy data (with Bonferroni correction: .05/3 = .0125) for each study (Table 3.3). After correction, there were no significant differences between the groups on any measure, in either Study 1 or Study 2. However, there was a trend towards the HS group having a poorer performance in Study 2 (W_s = 362.00, p = .02). Due to the length of time recorded for the false alarm trials (Study 1: 1016.67 – 4031.95 ms, Study 2: 966.89 – 3998.63 ms), it is unlikely that the participants were responding to a designated non-target or deceiver trial, instead responding after the presentation of at least 1 stimulus from the next 3-letter set of stimuli. For this reason, the reaction time results for false alarms have not been analysed. Ceiling effects analysis suggest that the task was too easy in Study 1 and despite

being made more difficult in Study 2 (by reducing the duration and inter-stimulus interval from 300 to 250 ms), ceiling effects remained. Analysis of the data for those included in the EEG analyses found no significant difference between the groups.

Table 3.3
Descriptive statistics (M, SD) for the sustained attention task with p-values and effect sizes for group comparisons, for all participants, those with Inhibitory Control EEG and those with Entrainment EEG.

				High			Low			*p*	*d*
				n	*M*	*SD*	*n*	*M*	*SD*		
Study 1	All Participants	Ratio	Hits	23	.90	.11	30	.95	.05	.15	.59
			FA D	23	.07	.05	30	.06	.07	.31	.16
			FA N-T	23	.02	.02	30	.01	.02	.13	.50
		RT (ms)	Hits	23	311.21	47.92	30	299.78	30.27	.82	.29
	Inhibitory control EEG	Ratio	Hits	19	.89	.12	23	.95	.05	.09	.65
			FA D	19	.07	.05	23	.06	.08	.25	.15
			FA N-T	19	.02	.02	23	.01	.02	.16	.50
		RT (ms)	Hits	19	314.39	47.50	23	301.36	29.91	.73	.33
	Entrainment EEG	Ratio	Hits	11	.96	.03	12	.95	.06	.88	.21
			FA D	11	.06	.05	12	.08	.11	.80	.23
			FA N-T	11	.02	.02	12	.02	.02	.95	.00
		RT (ms)	Hits	11	294.47	30.70	12	293.49	32.61	.90	.03
Study 2	All Participants	Ratio	Hits	21	.87	.11	21	.93	.07	.02	.65
			FA D	21	.06	.04	21	.05	.03	.12	.28
			FA N-T	21	.02	.02	21	.02	.02	.45	.00
		RT (ms)	Hits	21	312.37	42.93	21	302.03	28.08	.53	.29
	Inhibitory control EEG	Ratio	Hits	11	.86	.14	13	.93	.08	.15	.61
			FA D	11	.06	.05	13	.05	.04	.77	.22
			FA N-T	11	.02	.02	13	.02	.02	.79	.00
		RT (ms)	Hits	11	300.20	33.88	13	295.18	28.37	.82	.16
	Entrainment EEG	Ratio	Hits	6	.89	.12	9	.97	.03	.19	.91
			FA D	6	.04	.02	9	.04	.04	.51	.00

		High			Low			*p*	*d*
		n	*M*	*SD*	*n*	*M*	*SD*		
	FA N-T	6	.01	.01	9	.02	.02	.57	.63
RT (ms)	Hits	6	296.33	28.00	9	311.16	30.12	.26	.70

Note. RT = Reaction time; FA D = False alarm deceiver trials; FA N-T = False alarm non-target trials.

3.5 Temporal Processing

3.5.1 Reaction Times

No significant effects were found for RTs in Study 1 (Table 3.4). For Study 2, a main effect of condition was found (F (3.28, 131.01) = 126.06, p < .001, η_p^2 = .76; Greenhouse-Geisser applied), with Sidak post-hoc analyses showing that the 100 and 200 ms conditions were responded to significantly slower (p < .001), but did not differ from each other. The 300, 400, and 500 ms conditions also did not differ from each other. There was no main effect of group, but a significant group by condition interaction was found (F (3.28, 131.01) = 2.81, p = .04, η_p^2 = .07; Greenhouse-Geisser applied). Separate one-way ANOVAs were run for each group, which found a main effect of condition for each group (p's < .001). In each case, the 100 and 200 ms conditions lead to significantly longer RTs than the other 3 conditions. However, for HS participants the 100 and 200 ms RTs were no different, whereas for LS participants, the 100 ms RTs were significantly longer (Figure 3.1).

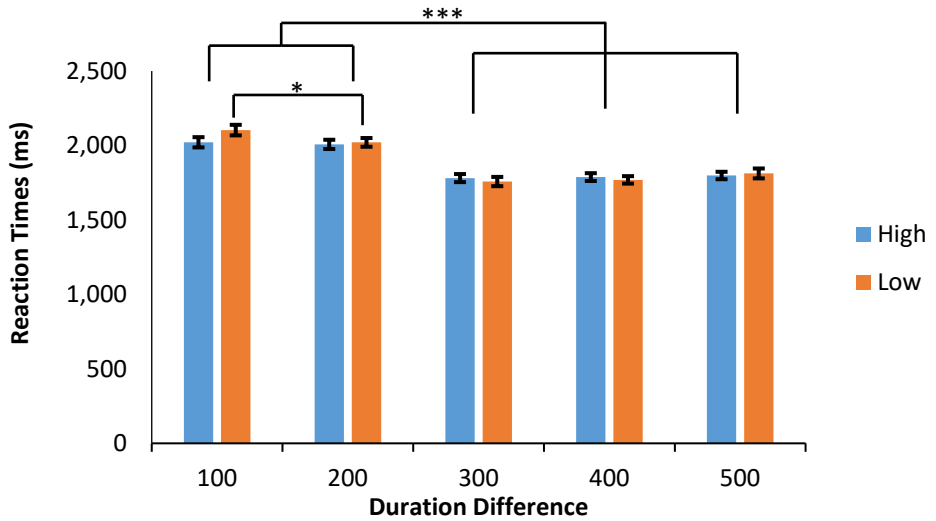


Figure 3.1 Mean reaction times (ms) for Study 2 with SEM error bars for each condition for each group. *** denotes significance at p < .001, * at p < .05

For only those participants of Study 1 included in the EEG analyses, no significant effects were found. In Study 2, however, for individuals included in the Inhibitory Control EEG, a main effect of condition (F (4, 88) = 78.57, p < .001, η_p^2 = .78) and a significant condition by group interaction were found (F (4, 88) = 2.68, p = .04, η_p^2 = .11). Sidak post-hoc analysis showed that, irrespective of group, the 100 and 200 ms conditions gave rise to a significantly longer RT than the 300-500 ms conditions (p < .001). To investigate the interaction, independent t-tests were conducted between the groups at each condition but found no significant differences. When analysing data for only those individuals included in the Entrainment EEG analyses of Study 2, the same main effect of condition was found (F (4, 52) = 61.37, p < .001, η_p^2 = .83), but no main effect of group nor an interaction.

3.5.2 Accuracy

For accuracy in Study 1 (Table 3.4), a main effect of condition (F (2, 104) = 14.97, p < .001, η_p^2 = .22), and a main effect of group (F (1, 52) = 12.33, p = .001, η_p^2 = .19) were found. Sidak post-hoc analysis showed that the 300 ms condition resulted in a significantly poorer performance than both the 400 and 500 ms conditions. Due to significant Levene's test, group differences were reanalysed using independent t-tests for each condition with Bonferroni correction (.05/3 = .0125), using the variances not assumed corrected output. These results show that the HS group performed worse in the 300 (t (35.15) = -3.70, p = .001) and 500 ms conditions (t (27.80) = -3.35, p = .002), but only a trend towards this in the 400 ms condition (t (31.08) = -1.87, p = .07; Table 3.4). A trend towards an interaction between condition and group was also found (F (2, 104) = 2.58, p =.08, η_p^2 = .05). Repeated measures ANOVAs for the HS and LS groups suggest that for the HS group, participants perform significantly worse in the 300 ms condition compared to both other conditions, but LS participants perform equally well in the 300 and 400 ms condition and significantly better in the 500 ms condition. The LS group have a trend towards a linear performance such that the more difficult the task, the worse the performance gets. However, the HS group trend towards a poorer performance which then plateaus (Figure 3.2). Ceiling effects analysis suggest possible ceiling effects for the easier 400 and 500 ms conditions, but not the harder 300 ms condition.

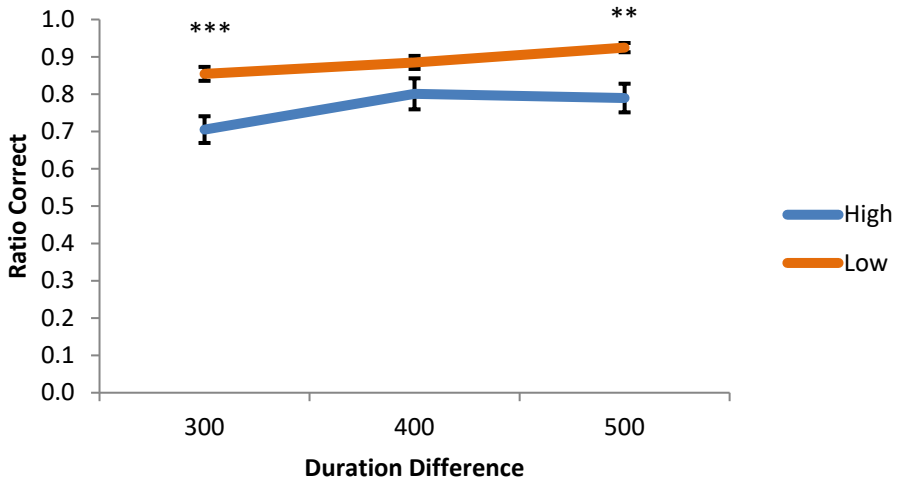


Figure 3.2 Mean ratio correct for the Temporal Processing task of Study 1 with SEM error bars. *** denotes significant group difference at $p = .001$, ** at $p < .01$

For Study 2 accuracy, a main effect of condition (F (3.26, 130.33) = 83.39, $p < .001$, $\eta_p^2 = .68$; Greenhouse-Geisser correction applied), and a main effect of group were evident (F (1, 40) = 11.08, $p = .002$, $\eta_p^2 = .22$). Irrespective of condition, the HS group had a poorer performance than the LS group. Sidak post-hoc analyses found that only the 400 and 500 ms conditions did not differ, confirming that the manipulation worked in the expected direction such that as the duration difference between the two circles decreased, performance accuracy also decreased ($p < .002$). Ceiling effects were found to be present only in the easiest (500 ms) condition, which was not unexpected.

For participants in Study 1 included in the inhibitory control EEG analysis, the exact same pattern of results was found. However, for those included in the entrainment EEG, only a main effect of condition was evident, with significantly poorer performance in the 300 compared to the 500 ms condition ($p = .004$), but not the 400 ms condition. In Study 2, for those individuals included in the Inhibitory Control EEG analysis, the same main effect of condition was found (F (4, 88) = 77.14, $p < .001$, $\eta_p^2 = .78$), but no main effect of group and no interaction. The same results were found when analysing data from only those participants included in the Entrainment EEG analyses (F (2.44, 31.65) = 50.98, $p < .001$, $\eta_p^2 = .80$; Greenhouse-Geisser applied).

Table 3.4
Descriptive statistics (M, SD) for the temporal processing task with p-values and effect sizes for group comparisons, for all participants, those with Inhibitory Control EEG and those with Entrainment EEG.

			Duration Diff (ms)	High			Low				
				n	*M*	*SD*	*n*	*M*	*SD*	*p*	*d*
Study 1	All Participants	Ratio	300		.71	.18		.85	.10	.001	.96
			400		.80	.20		.89	.10	.07	.57
			500		.79	.19		.92	.07	.002	.91
				24			30				
		RT (ms)	300		1777.32	202.07		1736.80	151.19	.40	.23
			400		1775.66	173.88		1723.12	126.76	.21	.35
			500		1735.06	129.37		1728.53	115.65	.85	.05
	Inhibitory control EEG	Ratio	300		.69	.19		.86	.11	.002	.50
			400		.79	.21		.89	.10	.06	.61
			500		.77	.20		.92	.07	.004	1.00
				20			23				
		RT (ms)	300		1796.84	213.47		1732.50	154.97	.26	.34
			400		1782.34	180.05		1717.43	135.78	.19	.41
			500		1736.02	138.95		1736.31	117.30	.99	.00
	Entrainment EEG	Ratio	300		.71	.22		.84	.10	.08	.76
			400		.79	.25		.87	.13	.32	.40
			500		.78	.25		.91	.06	.10	.72
				12			12				
		RT (ms)	300		1758.75	224.09		1719.88	180.70	.64	.19
			400		1754.57	199.82		1735.20	155.43	.79	.11
			500		1713.76	161.22		1745.80	124.71	.59	.22
Study 2	All Participants	Ratio	100		.55	.10		.63	11	.02	.76
			200		.67	.15		.76	.11	.03	.68
			300		.76	.14		.86	.11	.02	.79
			400		.80	.14		.93	.08	.001	1.14
			500		.84	.17		.93	.09	.04	.66
				21			21				
		RT (ms)	100		2021.62	157.80		2103.41	162.76	.11	.51
			200		2007.48	142.67		2020.93	134.01	.75	.10
			300		1781.20	124.18		1758.05	142.72	.58	.17
			400		1788.04	119.90		1769.19	114.47	.61	.16
			500		1798.61	114.14		1812.45	152.45	.74	.10

		Duration Diff (ms)	High			Low				
			n	*M*	*SD*	*n*	*M*	*SD*	*p*	*d*
Inhibitory control EEG	Ratio	100		.56	.11		.60	.10	.35	.38
		200		.67	.16		.78	.09	.04	.85
		300		.79	.13		.88	.12	.11	.72
		400		.85	.15		.93	.08	.11	.67
		500		.91	.12		.93	.11	.65	.17
	RT (ms)	100	11	2009.26	121.43	13	2118.60	182.04	.10	.71
		200		2006.12	142.98		2031.02	141.79	.67	.17
		300		1766.60	103.69		1778.14	116.51	.80	.10
		400		1799.59	131.69		1765.55	91.01	.46	.30
		500		1796.03	100.13		1821.32	164.75	.66	.19
Entrainment EEG	Ratio	100		.57	.15		.66	.12	.25	.66
		200		.70	.13		.81	.03	.09	1.17
		300		.86	.07		.89	.12	.49	.31
		400		.91	.10		.96	.05	.18	.63
		500		.94	.08		.97	.04	.33	.47
	RT (ms)	100	6	2006.94	159.10	9	2146.55	196.66	.17	.78
		200		1988.62	143.99		2044.01	147.59	.49	.38
		300		1717.19	101.84		1752.73	141.07	.61	.29
		400		1773.17	129.89		1767.94	94.62	.93	.05
		500		1778.20	125.02		1817.29	121.80	.56	.32

Note. RT = Reaction time

3.6 Inhibitory Control

3.6.1 Reaction Times

In both Study 1 (F (1, 46) = 169.58, p < .001, η_p^2 = .79) and Study 2 (F (1, 28) = 68.73, p < .001, η_p^2 = .71) a main effect of condition was found with RTs significantly longer in the incongruent condition (Table 3.5), confirming successful elicitation of the Stroop effect in both studies. However, no other significant effects were found. The same pattern of results were found when analysing data for only those participants included the EEG analyses for both studies.

3.6.2 Accuracy

Ceiling effects analysis suggest possible ceiling effects were present in Study 1, and as such task difficulty was increased for Study 2. For both studies, a main effect of congruency was found (Study 1: F (1, 46) = 38.37, $p < .001$, $\eta_p^2 = .46$; Study 2: F (1, 28) = 20.18, $p < .001$, $\eta_p^2 = .42$; Table 3.5). As predicted, irrespective of group, more errors were made in the incongruent condition compared to the congruent. In Study 1, a trend towards a main effect of group was also found (F (1, 46) = 3.24, $p = .08$, $\eta_p^2 = .07$), with the HS group having a marginally poorer performance, irrespective of condition, compared to the LS group (Table 3.5). However, no effects of group were seen in Study 2 (Table 3.5). When analysing data only for participants with clean EEG, the same main effect of condition was found in both studies, but no effect of group and no interactions.

For those individuals included in the entrainment EEG, the same main effect of Congruency was found in both studies. However, in Study 1 a significant Group by Congruency interaction was also found (F (1, 22) = 5.68, $p = .03$, $\eta_p^2 = .21$). Independent t-tests with found no significant difference between the groups within each condition. Paired samples t-tests found no difference between the conditions for the LS group, but for the HS group, performance was significantly worse in the incongruent compared to congruent condition (t (11) = 4.62, $p = .001$, $d = .96$).

Table 3.5
Descriptive statistics (M, SD) for inhibitory control with p-values and effect sizes for group comparisons, for all participants, those with Inhibitory Control EEG and those with Entrainment EEG.

				High			Low				
				n	*M*	*SD*	*n*	*M*	*SD*	*p*	*d*
Study 1	All Participants	Ratio	Congruent	24	.94	.02	24	.94	.02	.24	.00
			Incongruent		.90	.04		.92	.03	.08	.57
		RT (ms)	Congruent		595.39	154.54		605.14	108.32	.80	.07
			Incongruent		657.68	182.68		668.81	117.04	.80	.07
	Inhibitory control EEG	Ratio	Congruent	20	.94	.02	23	.94	.02	.30	.00
			Incongruent		.91	.04		.92	.03	.22	.28
		RT (ms)	Congruent		604.89	165.40		605.28	110.75	.99	.00
			Incongruent		668.56	196.42		669.19	119.66	.99	.00
	Entrainment EEG	Ratio	Congruent	12	.94	.02	12	.94	.02	.70	.00
			Incongruent		.90	.05		.92	.04	.10	.44
		RT (ms)	Congruent		569.35	111.88		615.38	134.94	.37	.37

				High			Low				
				n	*M*	*SD*	*n*	*M*	*SD*	*p*	*d*
			Incongruent		629.08	115.74		685.65	142.95	.30	.43
Study 2	All Participants	Ratio	Congruent		.94	.01		.94	.01	.31	.00
			Incongruent		.92	.02		.92	.03	.78	.00
				14			16				
		RT (ms)	Congruent		556.91	76.96		543.92	95.41	.48	.15
			Incongruent		629.82	98.42		603.76	115.42	.52	.27
	Inhibitory control EEG	Ratio	Congruent		.94	.01		.94	.01	.24	.00
			Incongruent		.92	.03		.92	.03	.55	.00
				11			13				
		RT (ms)	Congruent		570.09	77.30		539.17	92.64	.39	.36
			Incongruent		626.51	105.71		592.51	108.84	.45	.32
	Entrainment EEG	Ratio	Congruent		.94	.01		.94	.02	.88	.00
			Incongruent		.92	.03		.93	.02	.58	.39
				6			7				
		RT (ms)	Congruent		545.08	87.35		558.22	97.41	.81	.14
			Incongruent		595.27	106.35		611.66	121.41	.80	.14

Note. RT = Reaction time

3.7 Discussion

3.7.1 IQ

Each study found the opposite pattern of results; the LS group in Study 1 exhibited a non-significantly lower IQ than HS participants, while Study 2's LS group exhibited a significantly higher IQ. In both studies, the same pool of potential participants were accessed; students of the University of Southampton. Given this demographic, it was predicted that, although individuals with a diagnosis of ADHD have a tendency toward a lower IQ, the two symptom groups would be similar. The lack of group difference found in Study 1 matches Weyandt et al (2017) who also did not find group differences using the same measure of IQ and a rigorous ADHD 'diagnosis' procedure. However, given the opposing patterns found across the two studies, no conclusions can be made at this time.

3.7.2 Working Memory

Across both studies, the HS group consistently had an overall poorer performance than the LS group, across both modalities and type of metric (recall vs processing). With the HS group performing worse in both processing and recall, a suggestion can be made that the poorer recall

could be a result of the poorer processing. Working memory deficits appear to be a consistent feature of ADHD, being found in university students (Gropper & Tannock, 2009; Kim, Liu, Glizer, Tannock, & Woltering, 2014), children and adolescents (Cockcroft, 2011; Dovis, Van der Oord, Wiers, & Prins, 2013; Holmes et al., 2014; Kasper, Alderson, & Hudec, 2012; Lenartowicz et al., 2014; Martinussen et al., 2005), and adults (Woods, Lovejoy, & Ball, 2002).

3.7.3 Sustained Attention

Both studies show a consistent lack of effects for both RTs and accuracy between the HS and LS groups showing that an increase in ADHD symptoms was not associated with sustained attention difficulties in this sample. These findings are in contrast to Weyandt et al. (2017) who did find sustained attention deficits in their sample of university students with ADHD. However, effect sizes for the accuracy data are in the medium range for both Study 1 (d = .59) and Study 2 (d = .65), which may suggest a lack of statistical power to be the reason for the lack of significance. A medium effect size for the difference between the two groups suggests a poorer performance in the task for the high symptom group in both studies, which would bring the results of the present studies in line with those of Weyandt et al. (2017).

Ceiling effects were evident in the studies presented here, with both the easier and more difficult task, which may suggest that the task used was not sufficiently difficult to find group differences. In addition, the excessive reaction times found for the false alarm data, show that participants were not responding as intended to the different false alarm conditions, with responses being made 1-4 seconds after the designated trial. As such, it is not known to which stimuli participants were actually responding. This calls into question the validity of the task to differentiate between deceiver and non-target trials.

3.7.4 Temporal Processing

By randomising the stimulus pairing for Study 2, with the addition of the more difficult 100 and 200 ms conditions, the ceiling effects seen in Study 1 were reduced. As such, clear evidence was found which showed that the HS group had poorer temporal processing than the LS group. This evidence is in line with previous work across all age ranges of ADHD (Noreika et al., 2013), supporting the idea that temporal processing is a core neuropsychological deficit in this disorder.

When looking at the RT results, Study 1 found no significant effects of any kind. However, Study 2 found that for both groups the RTs were significantly longer in the 100 and 200 ms conditions, but for the HS group these were no different from each other, whereas for the LS group the 100 ms condition was significantly longer. These results suggest that in the most

difficult condition, the HS group responded faster showing perhaps a more impulsive response compared to the LS group.

3.7.5 Inhibitory Control

Both studies were successful in eliciting the Stroop effect with longer RTs in the incongruent condition compared to the congruent. The task was made more difficult for the second study by making the larger pictures four times the size of the smaller, opposed to double the size in the first study. This change meant there were no ceiling effects in the second study, but unfortunately this more difficult task was still not able to detect any significant differences in performance between the two symptom groups. However, in Study 1 a medium effect size was evident for the between groups comparison of the incongruent accuracy data (d = .57), with a trend toward significance (p = .08). Such an effect size suggests the high symptom group made more errors, and that a lack of statistical power may account for the lack of significance. Unfortunately, such findings were not present for the more difficult task in Study 2, meaning that at this time no firm conclusions can be made with regards to inhibitory control and ADHD symptoms in these participants. Previous studies have shown that across all age groups, individuals with ADHD show impairments in interference control as measured by the colour-word Stroop test (Lansbergen et al., 2007). One possible explanation for the different findings in these studies is the use of a non-verbal Stroop measure and it may be that those with ADHD are more affected by the verbal nature of the traditional Stroop task. This explanation is partly supported by Kóbor et al. (2015) who, using the same animal Stroop task, found no difference in accuracy in children with ADHD. However, this study also found that children with ADHD responded significantly slower than typically developed peers, a finding not replicated with the university students in the present studies.

3.7.6 Summary

The university students in these experiments show consistent difficulties with working memory and temporal processing, but not in sustained attention and inhibitory control. The finding of deficits in temporal processing is encouraging for an entrainment-based hypothesis of ADHD.

Chapter 4 Electrophysiological Results

4.1 Introduction

In the previous chapter, it was shown that participants who exhibit a higher level of ADHD symptoms did not have any behavioural difficulties in the inhibitory control task, nor the sustained attention task. This lack of difficulty could be evidence that university students with higher levels of ADHD symptoms do not have difficulties in this area, or these students may have developed a coping mechanism which helps them to overcome an underlying difficulty. In this chapter the results of the electrophysiological data from the inhibitory control and entrainment tasks will be outlined to investigate whether there are any underlying neural differences between those with high and low levels of ADHD symptoms.

4.2 Inhibitory Control: Lateralised Readiness Potential (LRP)

Inhibitory control was measured using the Stroop task. The LRP waveforms for Study 1 and Study 2 are shown in Figure 4.1 and Figure 4.2 respectively. These represent the smoothed data before the jack-knifing procedure on which the statistical analysis was run using the Mr Fub program (Miller et al., 1998). Due to the difference in participant numbers across Study 1 (n = 43) and Study 2 (n = 24), a between studies analysis was not deemed appropriate. Table 4.1 shows the number of trials included for each group for each study. There is no significant difference in the number of trials included in the analysis in the HS and LS groups in both studies. Despite the lower number of participants in the second study, there were more usable trials compared to Study 1.

Table 4.1
Mean number of trials (n) included in the ERP analysis of the entrainment task for both Study 1 and Study 2

	High			Low			*p*	*d*
	n	*M*	*SD*	*n*	*M*	*SD*		
Study 1	20	167	35	23	178	35	.34	.31
Study 2	11	171	37	13	182	43	.50	.27

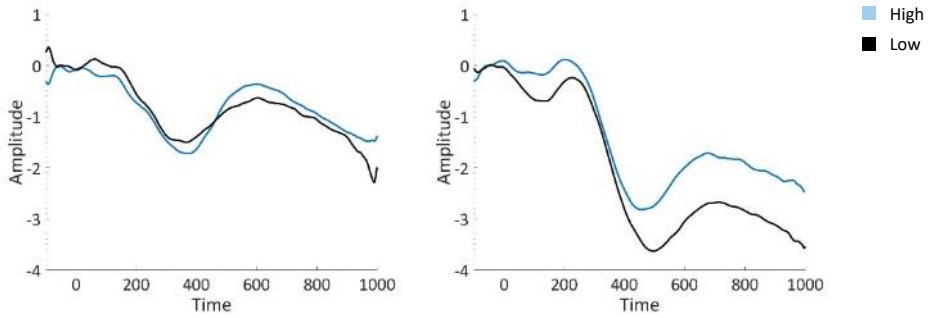


Figure 4.1 Study 1 LRP waveforms for congruent (left) and incongruent (right) trials. Positive up.

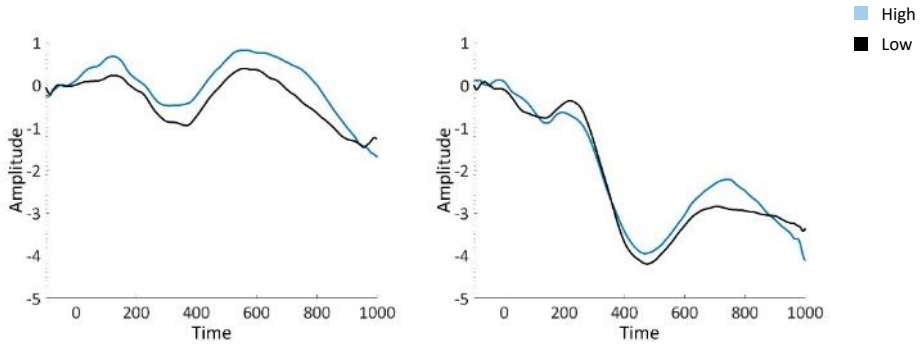


Figure 4.2 Study 2 LRP waveforms for congruent (left) and incongruent (right) trials. Positive up.

Initial peak onset. In Study 1 (Figure 4.1) a significant main effect of congruency was found (F (1, 41) = 72.26, p < .001, η_p^2 = .64); initial LRP onset was earlier for the incongruent condition (M = 187.05 ms, SD = 8.67) compared to the congruent (M = 278.35 ms, SD = 6.29). The same was also true in Study 2 (Figure 4.2) with the more difficult task (F (1, 22) = 25.08, p < .001, η_p^2 = .53; incongruent M = 184.20 ms, SD = 9.69; congruent M = 260.32 ms, SD = 10.96). No significant effect of group and no interaction were found in either study.

LRP duration for the initial peak. In Study 1 a significant main effect of congruency was found (F (1, 41) = 51.01, p < .001, η_p^2 = .57); duration of the initial LRP in the incongruent condition was significantly shorter (M = 60.42 ms, SD = 5.67) than in the congruent (M = 167.84 ms, SD = 16.57). Again, the same was also true in Study 2 (F (1, 22) = 21.91, p < .001, η_p^2 = .50; incongruent M = 51.75 ms, SD = 8.79; congruent M = 147.18 ms, SD = 9.89). No significant effect of group and no interaction were found in either study.

Transition (response inhibition). The transition factor is the point at which the response preparation changes from incorrect to correct, representing the moment of inhibition, in this case the suppression of the interference. In Study 1 a significant main effect of transition factor was found (F (1, 41) = 141.99, p < .001, η_p^2 = .78), showing a significant difference between the time when the first peak ended (M = 247.47 ms, SD = 13.41) and the second began (M = 388.44 ms, SD = 11.96). As with the other measures, the same was also found in Study 2 (F (1, 22) = 70.96, p

< .001, η_p^2 = .76; cessation of first peak *M* = 235.95 ms, SD = 15.76; congruent *M* = 379.12 ms, *SD* = 5.44). Again, there was no significant effect of group and no significant interaction in either study.

4.2.1 Discussion of LRP findings

The LRP waveforms for each study appear consistent with each other, with the peaks occurring around the same latency in each condition. The results of both studies show a significant effect of condition, highlighting the different neural responses to congruent and incongruent stimuli. The nature of this difference represents the expected LRP waveform; a positive potential for a correct response, and an initial negative potential for the initial priming of the incorrect response in the incongruent condition before this is overcome to produce the correct response. No effect of group was found in either study suggesting that individuals with a higher level of ADHD symptoms do not differ in their interference suppression capacity. In a previous study investigating children with ADHD, using the same animal stroop task, the expected/correct LRP waveforms were not evident in the data (Kóbor et al., 2015). Therefore, the studies presented here, to this author's knowledge, represent the first to be able to measure this component using this task in individuals with symptoms of ADHD. When using a Go/No-Go task, the LRP of university students with ADHD has been found to have an earlier onset for No-Go stimuli and the amplitude of the early LRP window was also smaller (Gorman Bozorgpour, Klorman, & Gift, 2013). The contrasting results of this study and the present studies are likely due to the different type of inhibition being measured, and as such it may be the case that response inhibition and interference inhibition are differentially affected in this population.

4.3 Attention during the entrainment task: Event Related Potential (ERP)

Event related potentials (ERPs) were analysed for the Entrainment tasks to investigate attention to a single modality stimulus and the selective attention to either an auditory or visual stimulus stream while ignoring a stimulus stream of the other modality. Between groups analysis was conducted using point-by-point independent *t*-tests at each modality. *P*-values were FDR corrected using the Benjamini and Hochberg (1995) method, implemented using the *mafdr*() function in Matlab, and considered to be significant if less than .05. Due to the difference in participant numbers across Study 1 (n = 21) and Study 2 (n = 15), a between studies analysis was not deemed appropriate. The group comparisons carried out for Study 2 should also be taken with caution due to the low number of participants in each group (HS group n = 6, LS group n = 9). Table 4.2 shows the number of trials included for each group for each study. There was no significant difference in the number of trials included in the analysis between the groups in either study. However, in Study 1 there is a very strong effect size for this comparison suggesting that the difference is meaningful, with the LS group having a larger number of trials than the HS group.

Table 4.2
Mean number of trials (n) included in the ERP analysis of the entrainment task for both Study 1 and Study 2

	High			Low			*p*	*d*
	n	*M*	*SD*	*n*	*M*	*SD*		
Study 1	12	1995	367	12	2244	287	.08	.76
Study 2	6	930	385	9	949	449	.93	.05

4.3.1 Single modality task

Across both studies and modalities an N1 peak occurred at approximately 150 ms post-stimulus (see Figure 4.3-Figure 4.6). However, the amplitude of this N1 peak did not differ between the groups for either modality in either study. The presence of the N1 confirms participant attention to the stimuli presented, for both modalities. The amplitude of response in Study 1 was greater than Study 2 (~2 μV compared to ~1.5 μV), which was likely due to the reduced stimulus intensity in Study 2, with stimuli being just above detection threshold.

In Study 1, for the auditory stimuli a P200 peak was also visible (Figure 4.3) showing the presence of the N1-P2 complex. An N300 was also evident. However, there is no clear evidence of these latter peaks in Study 2.

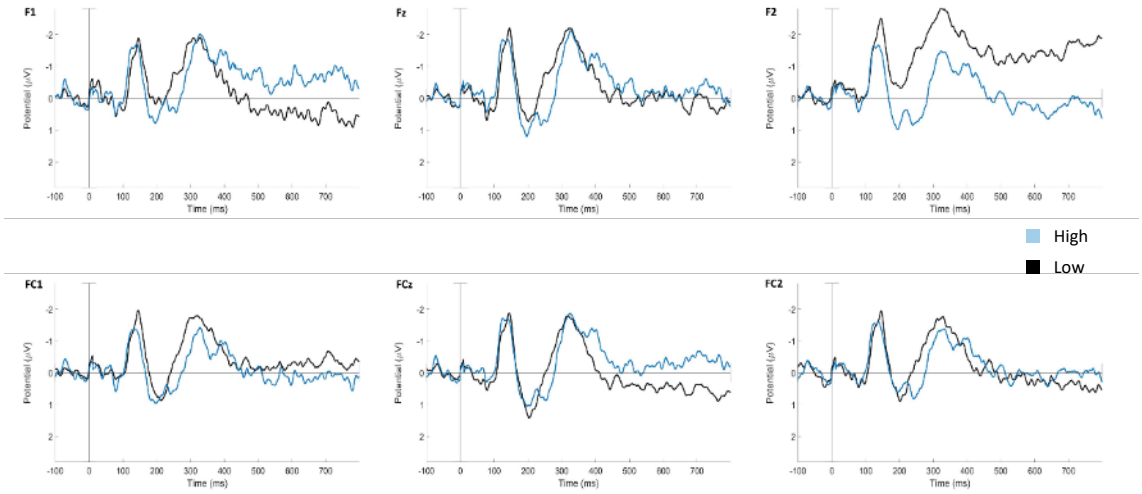


Figure 4.3 Study 1 ERPs for the auditory single modality task for fronto-central electrodes. Positive down.

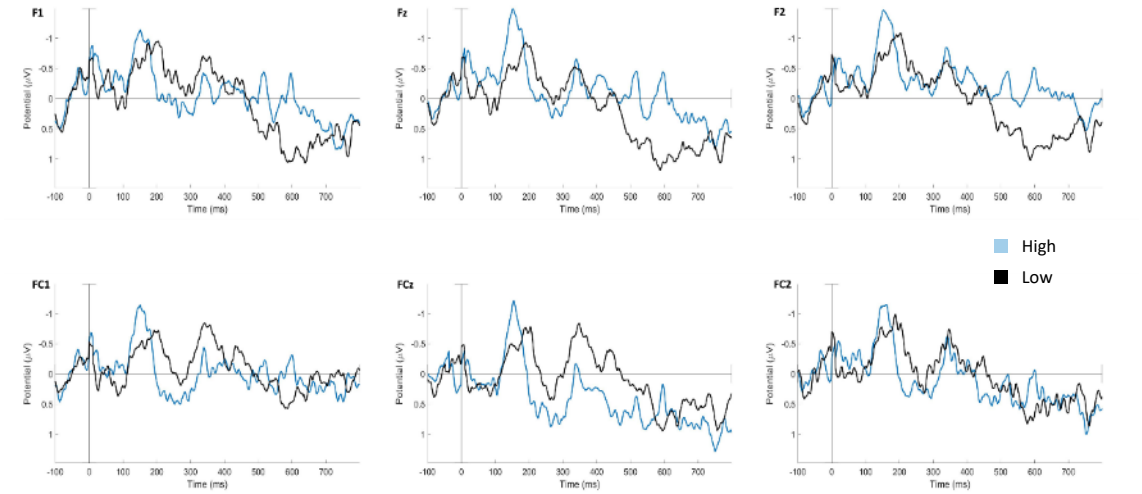


Figure 4.4 Study 2 ERPs for the auditory single modality task for fronto-central electrodes. Positive down.

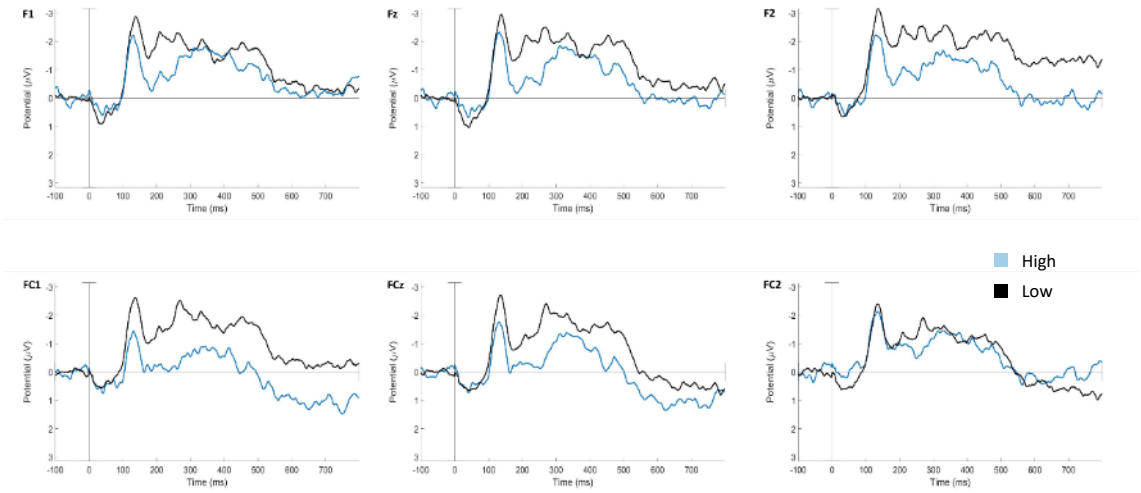


Figure 4.5 Study 1 ERPs for the visual single modality task for fronto-central electrodes. Positive down.

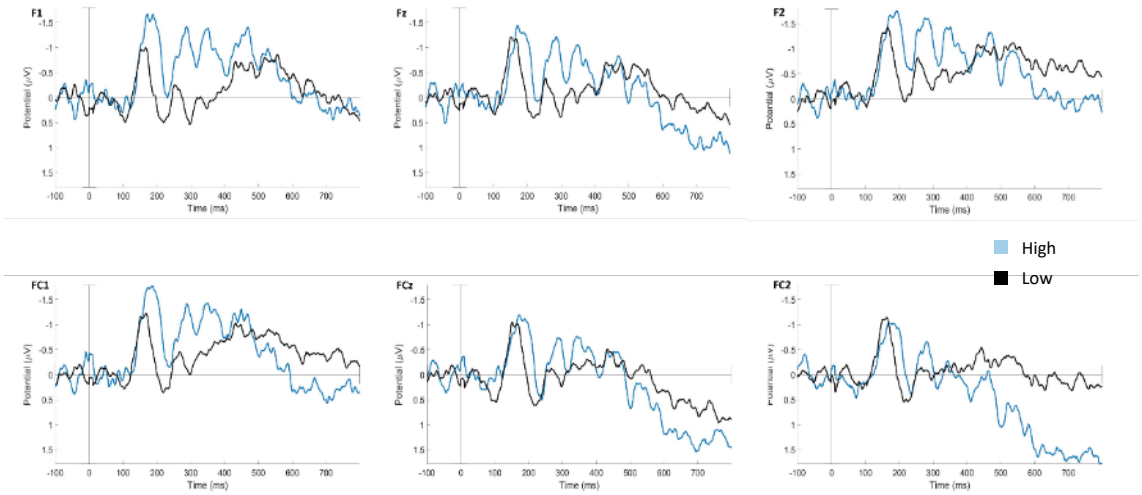


Figure 4.6 Study 2 ERPs for the visual single modality task for fronto-central electrodes. Positive down.

4.3.2 Selective attention

Figure 4.7-Figure *4.14* show the ERPs for the attended auditory (Figure 4.7 & Figure 4.8), attended visual (Figure 4.9 & Figure 4.10), non-attended auditory (Figure 4.11 & Figure 4.12), and non-attended visual (Figure 4.13 & Figure 4.14) stimuli for each study. The results show no effect of group for any stimuli except the attended visual stimuli in Study 1 for Fz at approximately 675 ms, which is approximately 175 ms after the presentation of the non-attended auditory stimuli. However, no significant effects were found when analysing the non-attended auditory stimuli independently.

An N1 peak was found for all stimuli, attended and non-attended, in both studies, except for the non-attended auditory stimuli in Study 2. The amplitude of this peak appears to be smaller

in Study 2 compared to Study 1, suggesting that reducing the intensity of the stimuli presented was successful in reducing the size of this evoked neural response.

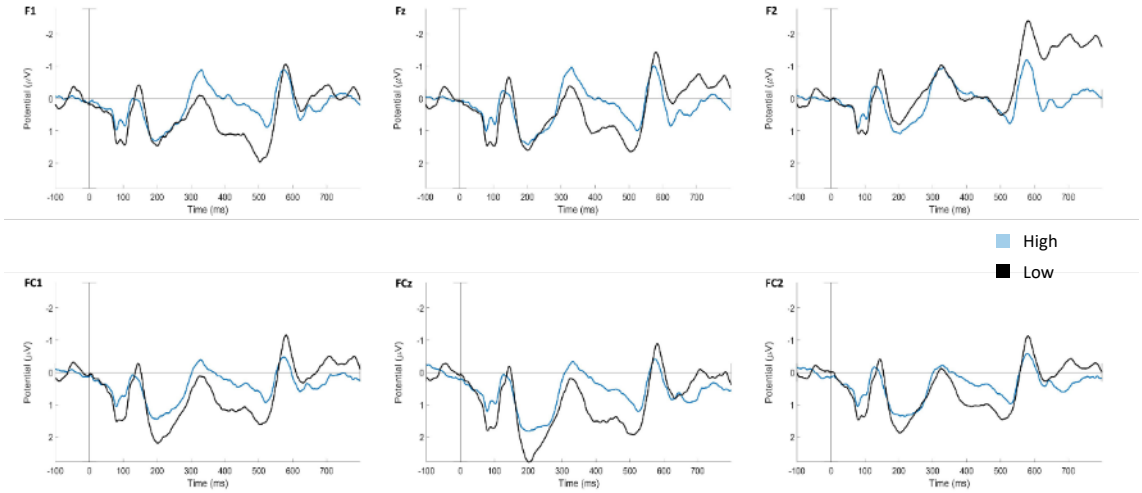


Figure 4.7 Study 1 ERPs for the attended auditory stimuli in the dual modality task for fronto-central electrodes. Positive down.

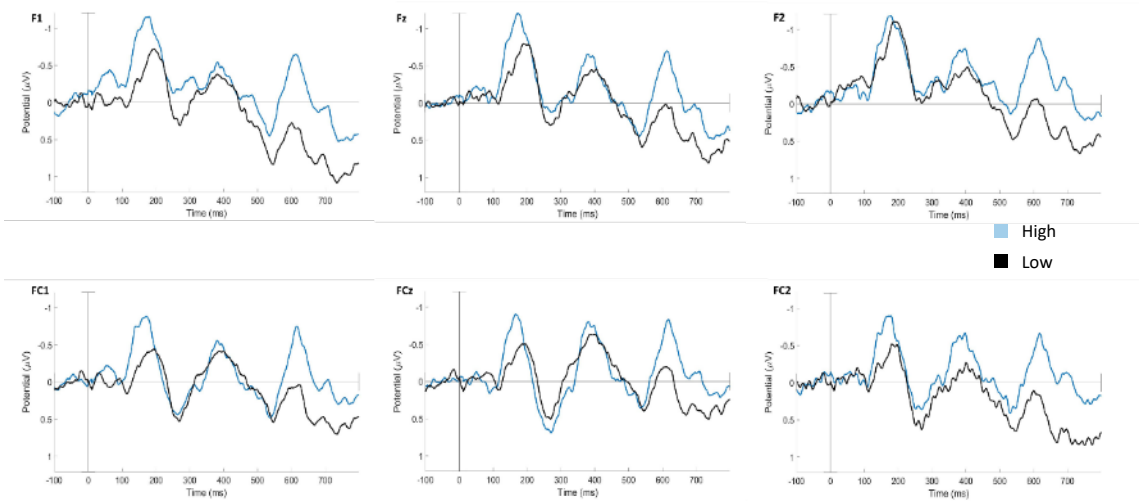


Figure 4.8 Study 2 ERPs for the attended auditory stimuli in the dual modality task for fronto-central electrodes. Positive down.

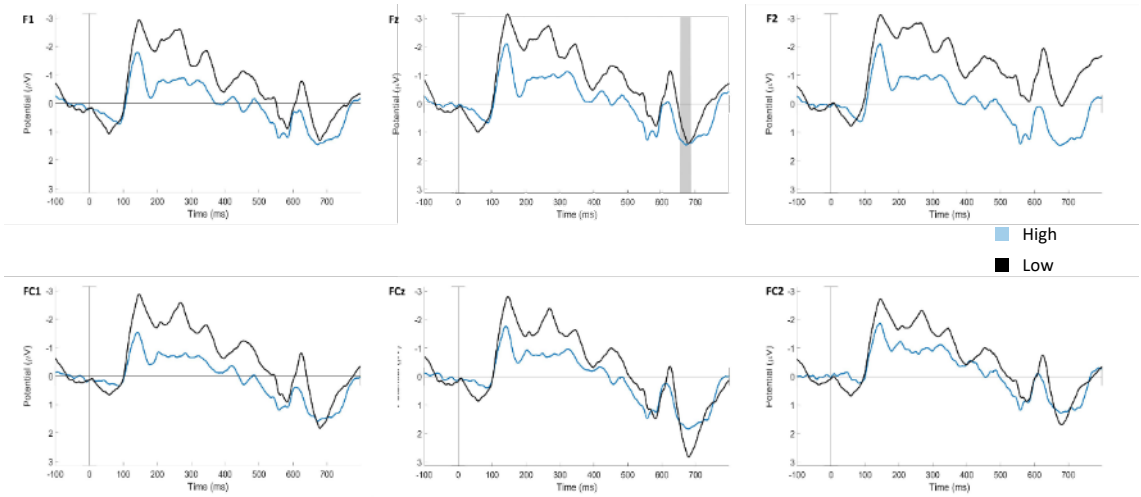


Figure 4.9 Study 1 ERPs for the attended visual stimuli in the dual modality task for fronto-central electrodes. Positive down.
The shaded area on electrode Fz shows a region of significant difference between the groups with FDR corrected *p*-value < .05.

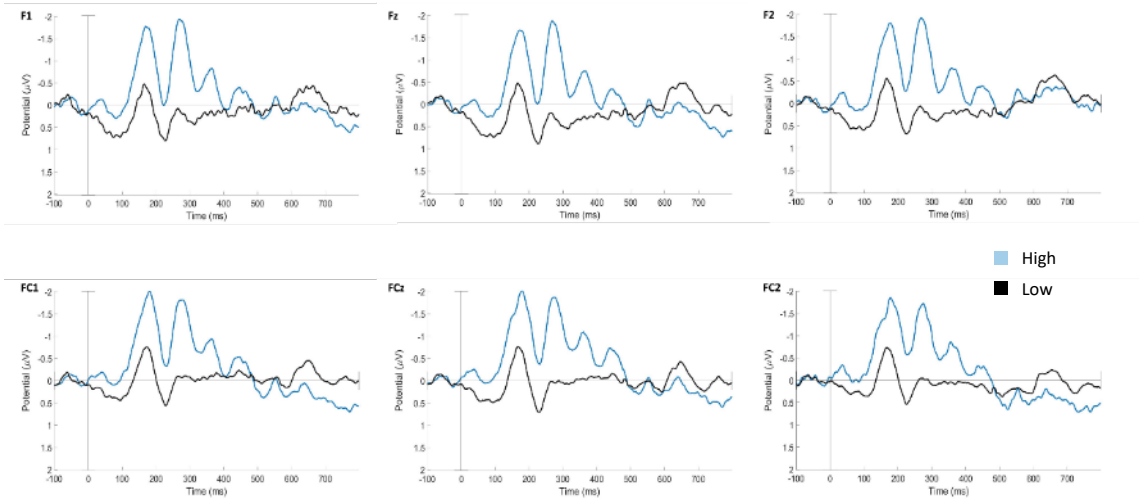


Figure 4.10 Study 2 ERPs for the attended visual stimuli in the dual modality task for fronto-central electrodes. Positive down.

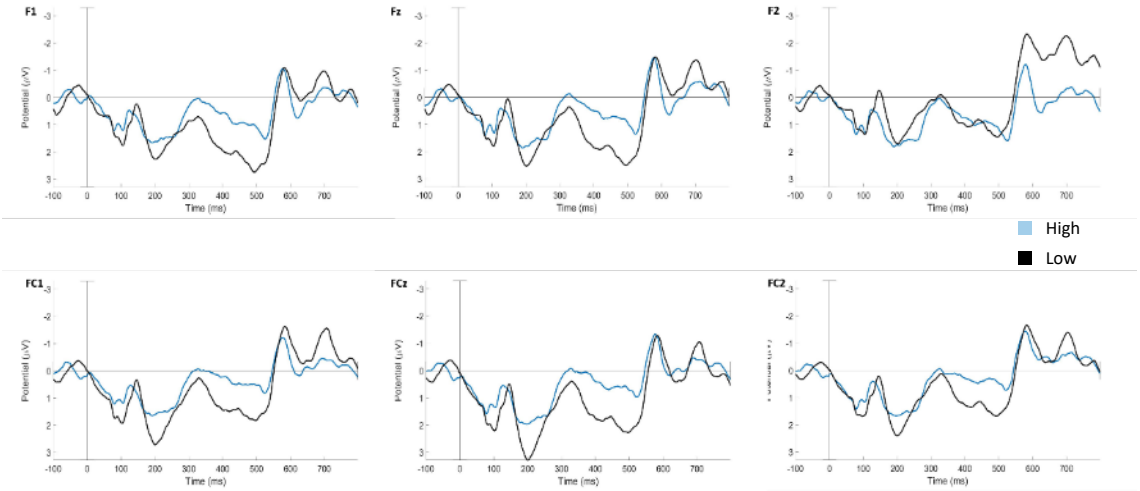


Figure 4.11 Study 1 ERPs for the non-attended auditory stimuli in the dual modality task for fronto-central electrodes. Positive down.

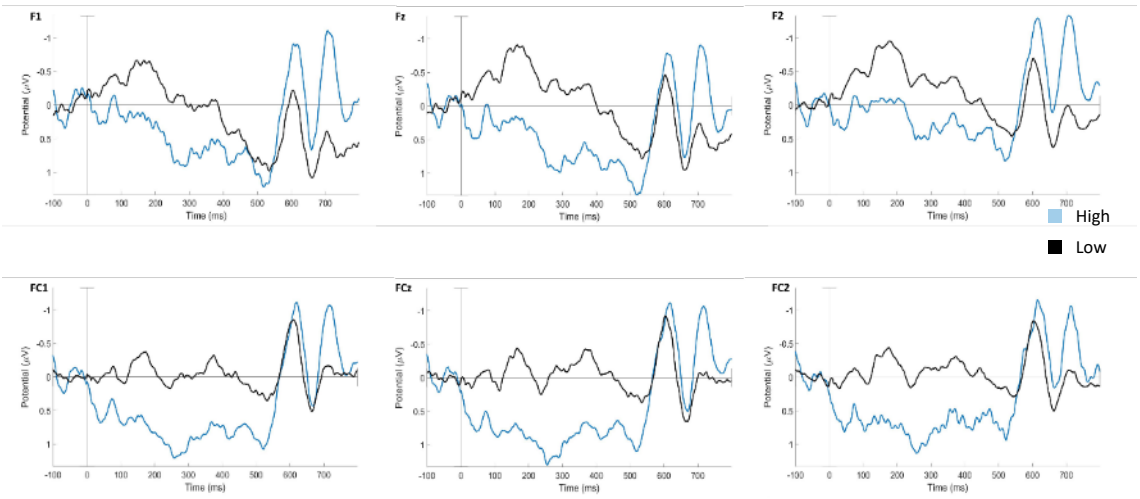


Figure 4.12 Study 2 ERPs for the non-attended auditory stimuli in the dual modality task for fronto-central electrodes. Positive down.

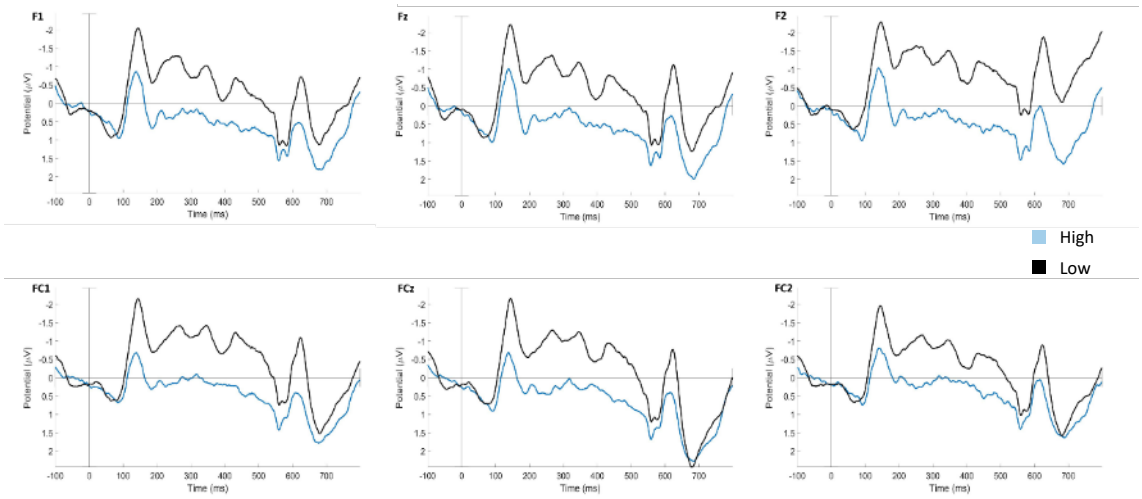


Figure 4.13 Study 1 ERPs for the non-attended visual stimuli in the dual modality task for fronto-central electrodes. Positive down.

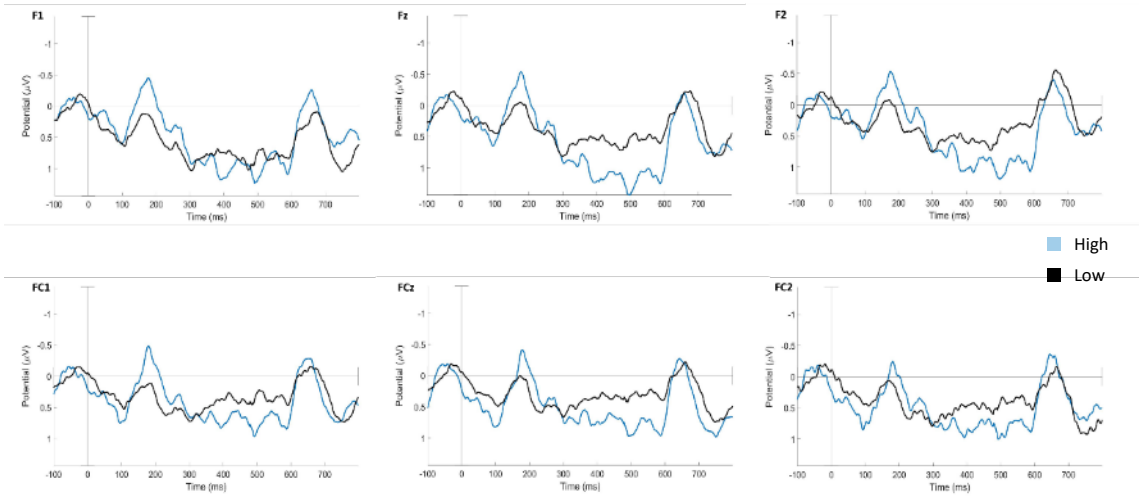


Figure 4.14 Study 2 ERPs for the non-attended visual stimuli in the dual modality task for fronto-central electrodes. Positive down.

4.3.3 Discussion of Attention related ERP findings

The presence of the N1 peak in nearly all conditions in both studies is evidence that participants attended to the stimuli presented to them. However, the N1 is also evident for the "non-attended" visual stimuli in both studies, and the auditory in Study 1, showing that these stimuli were too salient for the participants to ignore. The non-attended auditory stimuli of Study 2 show no clear ERP components before 600 ms, suggesting participants were able to ignore this

stimulus. The “non-attended” visual N1 in Study 2 has a smaller amplitude than Study 1 suggesting that the individualised thresholds were successful in reducing this saliency.

In the single modality tasks the N1-P2 complex was evident for the auditory stimuli in Study 1. This complex is a well-established objective measure of hearing threshold in adults and older children (Lightfoot, 2016). The lack of a clear N1-P2 complex in Study 2 may therefore suggest that the individualised thresholds for auditory volume were successful in achieving a stimulus that was only just detectable. This notion is supported by evidence that arousal, alertness, and attention can affect the amplitude, variability, and latency of the N1-P2 complex (reviewed by Lightfoot, 2016).

The ERPs in Study 2 appear much noisier than those in Study 1 and this is due to the limited data available in the second study compared to the first, with less than half the number of trials available for analysis. In Study 2 there were only 6 HS and 9 LS participants with usable EEG data, compared to 12 in each group in Study 1. In order to maximise the signal to noise ratio, the more data points that can be included in the grand average ERPs, the less noisy the data would be. To that end, the lack of available data has led to more noise in Study 2.

Chapter 5 Entrainment Results

5.1 Introduction

Entrainment of neural oscillations appears to underlie early stage selective attention to sensory stimuli (Besle et al., 2011; Lakatos et al., 2008; Lakatos, Musacchia, et al., 2013; Lakatos et al., 2009). Such early stage processing deficits are seen in ADHD (Johnstone et al., 2013; Ortega et al., 2013). Therefore, it is plausible that atypical entrainment could underlie these deficits. Neural oscillations entrain to rhythms in the environment such that perception and processing of stimuli is optimised, likely due to effective communication between regions in line with the communication through coherence hypothesis (CTC). If this process does not work as it should, then processing deficits are likely to be seen. The evidence suggests that an entrainment deficit hypothesis of ADHD is plausible and could mediate some of the attentional, temporal and neural deficits seen in the disorder. The data presented in this chapter represent an initial investigation into the potential for an entrainment-based hypothesis of the disorder of ADHD, initially just in the student population.

5.2 Behavioural Results

Descriptive statistics for error rates and reaction times for both Study 1 and Study 2 are shown in Table 5.1. Error rates were subject to 2 by 3 by 2 mixed-model ANOVAs to assess the effects of modality (auditory vs visual stimuli), error type (missing response, response to wrong modality, false alarm), and group (high vs low symptoms). No effects of group were found in either study. In Study 1, results showed a main effect of error type (F (1.36, 62.63) = 74.87, $p < .001$, $\eta_p^2 = .62$) with Sidak post-hoc analysis indicating significantly more missing responses than both responses to the wrong modality and false alarms ($p < .001$). Trends towards a main effect of modality (F (1, 46) = 3.27, p =.08, $\eta_p^2 = .07$) and a modality by error type interaction (F (1.72, 79.18) = 2.71, p = .08, $\eta_p^2 = .06$) were also found. These trends suggest that more errors could have been made in the auditory condition, and that this was more so with wrong responses than missing responses or false alarms. However, as this was only a trend, further studies with larger samples would need to be conducted before conclusions can be drawn.

Table 5.1
Descriptive statistics (M, SD) for the entrainment task, for all participants, and those with usable EEG for this task

				High					Low				
					Auditory		Visual			Auditory		Visual	
				n	*M*	*SD*	*M*	*SD*	n	*M*	*SD*	*M*	*SD*
Study 1	All Participants	Errors	Missing	24	5.00	3.02	4.46	3.84	24	4.83	2.60	3.50	2.80
			Wrong		1.46	1.38	.58	1.38		.83	1.05	.63	1.66
			False alarm		.63	1.13	.88	1.70		.46	1.06	.63	1.86
		RT (ms)	Hits		492.38	67.92	452.65	64.99		472.38	48.64	434.94	34.14
	Entrainment EEG	Errors	Missing	12	4.75	2.67	5.42	4.48	12	6.33	2.57	3.92	2.97
			Wrong		1.33	1.50	.58	1.73		.75	.87	.33	.49
			False alarm		.25	.45	1.17	2.25		.67	1.37	.92	2.57
		RT (ms)	Hits		475.88	40.89	436.56	46.30		475.34	43.83	433.73	32.53
Study 2	All Participants	Errors	Missing	14	7.15	4.67	19.23	10.08	18	9.38	9.98	18.69	10.49
			Wrong		.15	.38	.54	1.13		.19	.40	.56	1.15
			False alarm		.62	1.26	2.23	3.09		.75	.93	3.44	4.15
		RT (ms)	Hits		495.85	56.43	517.76	46.44		504.23	70.49	561.42	50.63
Study 2	Entrainment	Errors	Missing	6	4.67	2.25	15.33	9.16	9	11.33	12.38	15.44	6.25

			High				Low			
			Auditory		Visual		Auditory		Visual	
			n	*M*	*SD*	*M*	*SD*	n	*M*	*SD*	*M*	*SD*
EEG												
		Wrong		.33	.52	.83	1.60		.11	.33	.56	.88
		False alarm		.67	1.63	3.17	3.87		.56	.88	4.33	5.20
	RT (ms)	Hits		470.22	40.57	495.05	47.52		511.15	80.40	562.16	38.96

In study 2, a main effect of modality was found (F (1, 27) = 31.55, p < .001, η_p^2 = .54) with significantly more errors made in the visual condition. A main effect of error type was also found (F (1.09, 29.47) = 79.51, p < .001, η_p^2 = .75); Sidak post-hoc analysis showed that significantly more missing response errors than both responses to the wrong modality and false alarms (p < .001), and more wrong responses than false alarms (p = .001). A significant modality by error type interaction was found (F (1.14, 30.81) = 23.17, p < .001, η_p^2 = .46). Paired sample t-tests to compare the modalities for each error type showed that there was no difference in the number of wrong responses made in each modality, but significantly more missing response errors and false alarms were made in the visual condition compared to the auditory.

Reaction times were subject to a 2 by 2 mixed-model ANOVA to assess the effects of modality and group. Again, no effects of group were found for either study. For Study 1, results show a main effect of modality (F (1, 46) = 55.96, p < .001, η_p^2 = .55) with the visual stimuli being responded to significantly faster than the auditory. For Study 2, a main effect of modality was again evident (F (1, 27) = 11.98, p = .002, η_p^2 = .31), however, with the just perceptible stimuli of this study, visual stimuli were reacted to significantly slower than auditory.

The above analyses were also computed including only those participants with usable EEG for this task. For error rates in Study 1, the main effect of error type remained and all trends from the main analysis disappeared. However, trends were found for the modality by group and modality by group by error type interactions. There were no differences between the groups for any of the conditions. Paired sample t-tests computed for each group between the modalities for each error type found that for the HS group significantly more wrong responses were made in the auditory condition, while for the LS group significantly more no responses occurred in the auditory condition. However, as these interactions were only a trend caution is required. For error rates in Study 2, the same pattern of results as the main analysis was found, except one; the difference between wrong responses and false alarm errors became a trend (p = .06).

For RTs in Study 1, the same pattern of results was found. For RTs in Study 2, the previous main effect of modality became a trend (F (1, 13) = 4.29, p = .06, η_p^2 = .25) and a main effect of group was found (F (1, 13) = 5.25, p = .04, η_p^2 = .29). This main effect of group suggests that the HS group had significantly faster RTs than the LS, perhaps indicating they were more impulsive or less considered in their responses.

5.3 Electrophysiological Results

To analyse the entrainment data, the auditory and visual modality trials were combined in order that the effect of attention could be analysed directly. Inter-trial coherence (ITC) values are plotted in Figure 5.1 and Figure 5.2 for the single modality and dual modality tasks respectively. It is clear from these images that neither Study 1 nor Study 2 were successful in eliciting the expected entrainment of neural oscillations to the rhythmic stimuli presented. An entrained neural response would result in an increase in ITC around time zero at the stimulation frequency. The images below for Study 1 show a decrease in ITC at this time and for Study 2 ITC values remain constant or decrease. The increased ITC seen at approximately 100-200 ms reflects the N1 peak seen in the ERP analysis reported in Chapter 4. It is due to the strength of this peak and its effect on ITC that the paradigm was changed for Study 2 to minimise the impact of this evoked potential. The ITC images for Study 2 confirm that the strength of the effect on ITC was reduced. However, in this second paradigm there was still no entrained response.

As outlined in Chapter 2, statistical analyses comprised of point-by-point independent *t*-tests and 2 by 2 ANOVAs at each latency for the single and dual modality tasks respectively. For Study 1, no effect of group was found for baseline attention in the single modality task. In the selective attention task, group differences were found at higher delta and theta frequencies between 0-100 ms post stimulus ($p < .05$), with a higher ITC for LS participants, but none at stimulation rate at time zero where an entrainment effect would be expected. Given these group effects for ITC during the dual but not the single modality task, a comparison of the two tasks was carried out with 2 by 2 point-by-point ANOVAs. Results show that ITC was stronger in the single modality task compared to the dual modality ($p < .05$; Figure 5.3a). For Study 2, no significant effects were found for either task (Figure 5.1b and Figure 5.2b) and there was no difference between the two tasks (Figure 5.3b). No differences in event related spectral perturbation (ERSP) were found in either study for either task.

a)

b)

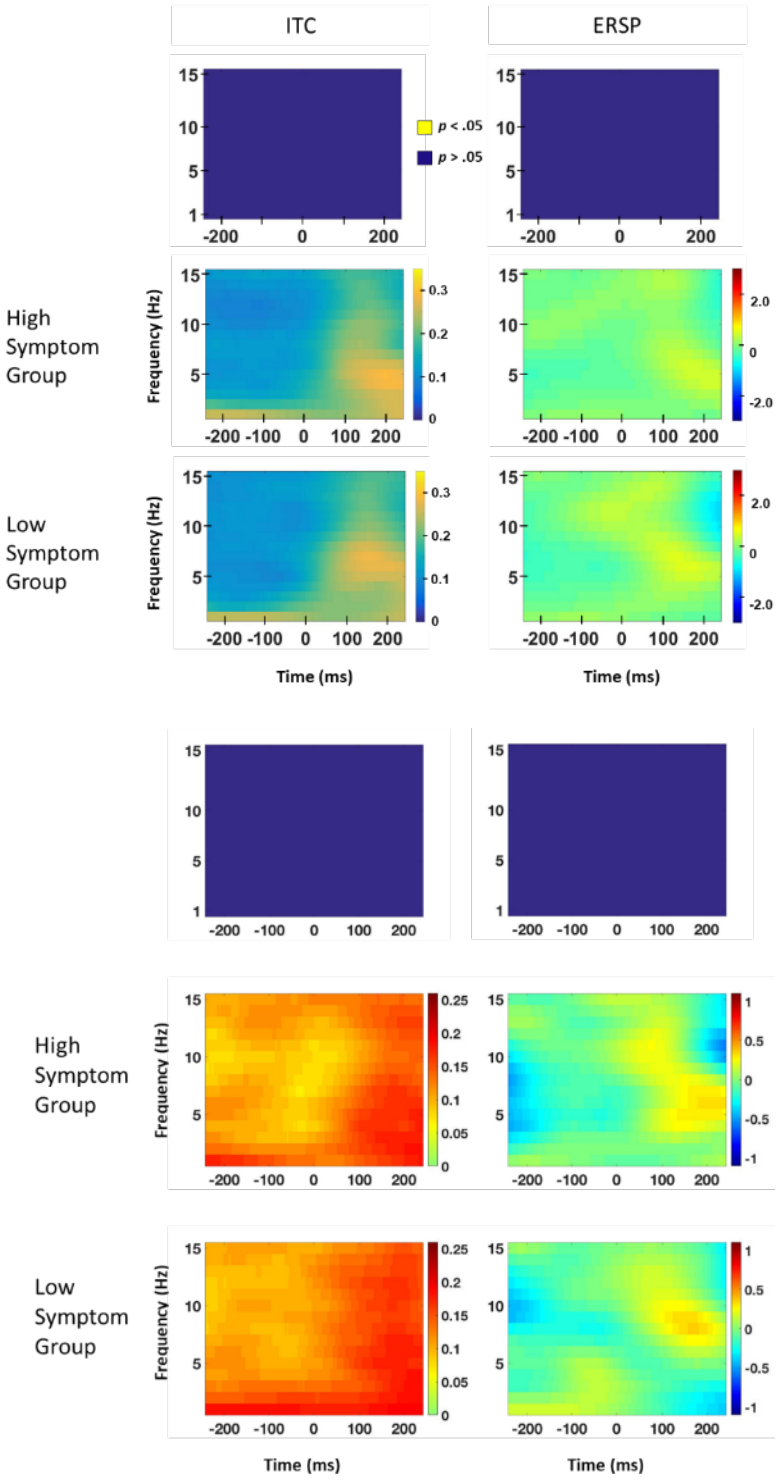


Figure 5.1 Time-frequency plots for ITC and ERSP data for a) Study 1and b) Study 2 for the single modality task.

ITC values lie between 0 and 1, with higher values representing a higher level of phase coherence from trial to trial. ERSP images show the degree of change in the power of signal at any given frequency, and can be positive or negative showing an increase or decrease in power respectively. The top row of images depicts regions of the time/frequency plots that show a significant difference between the groups by the point-by-point ANOVAs, which were run on FDR corrected data. Blue indicates no significant difference ($p > .05$); yellow regions are areas where a significant difference was found ($p < .05$). The middle and bottom row of images show averaged data for the respective condition/group.

a)

b)

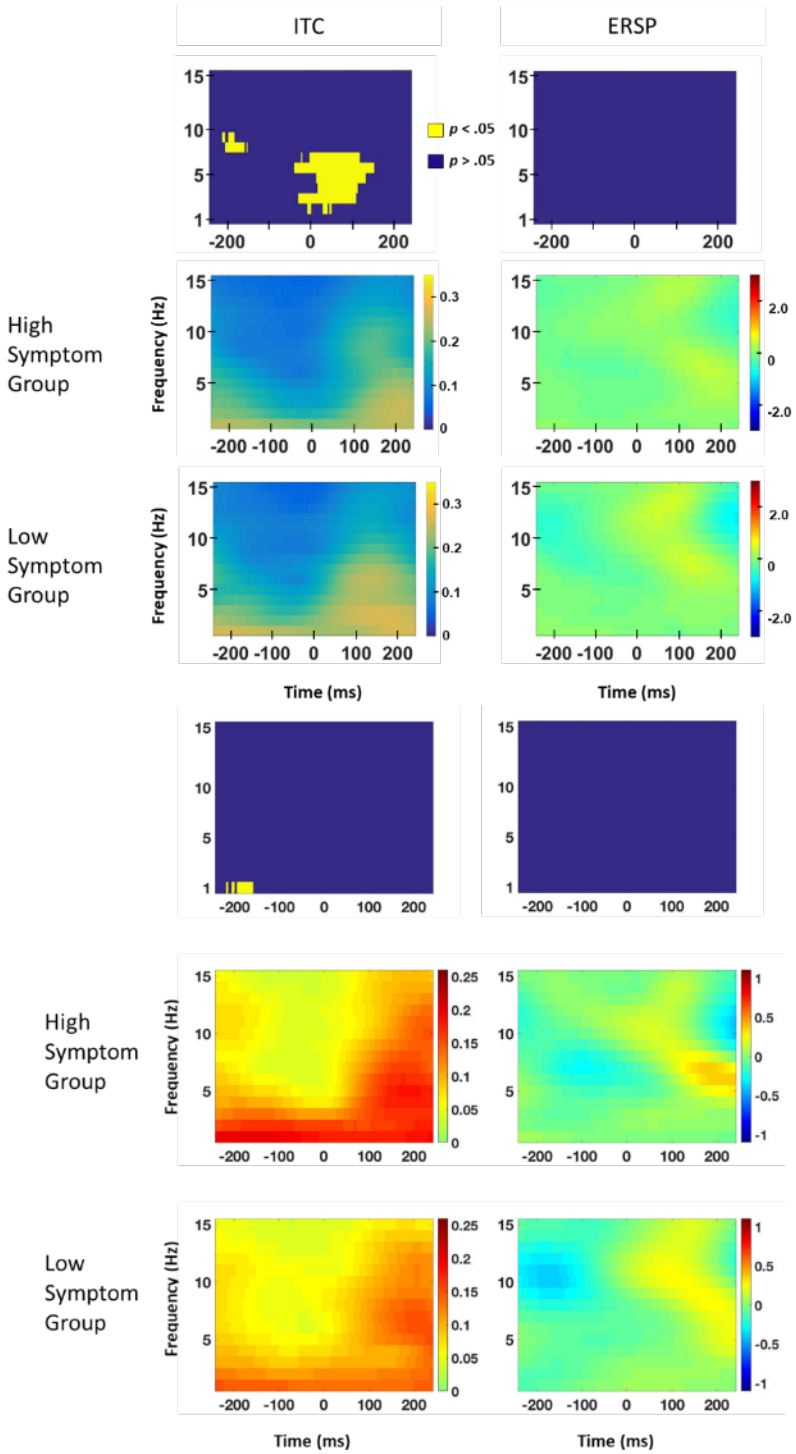


Figure 5.2 Time-frequency plots for ITC and ERSP data for a) Study 1and b) Study 2 for the dual modality task for the main effect of Group.
Top row of images are p-value plots showing regions of the time/frequency plots that show a significant difference. Blue indicates no significant difference; yellow regions are areas where a significant difference was found at $p < .05$ by the point-by-point ANOVAs. The middle and bottom row of images show averaged data for the respective condition/group.

a)

b)

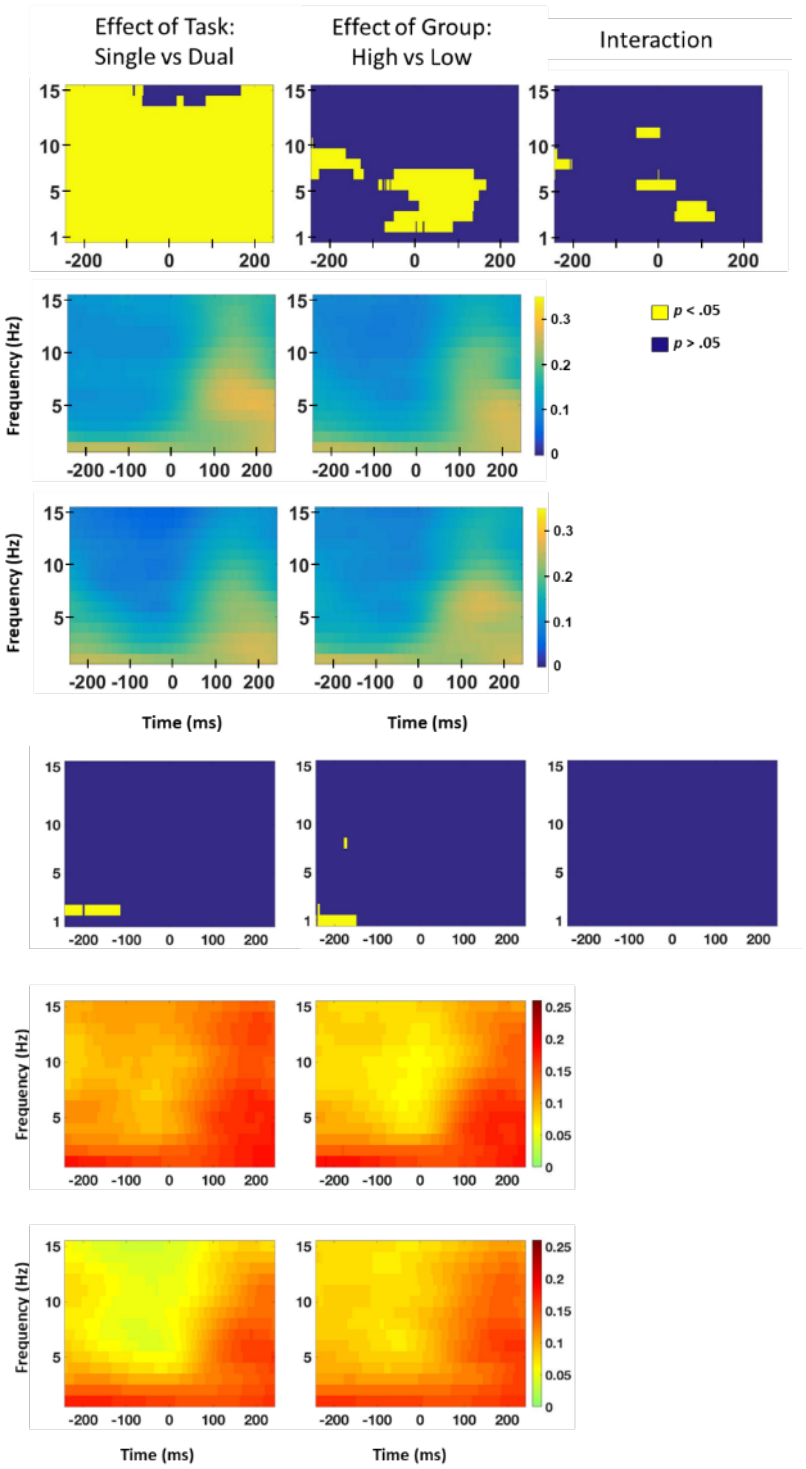


Figure 5.3 Time-frequency plots comparing the ITC values for the single and dual modality tasks of a) Study 1 and b) Study 2.

The first column shows the main effect of Task and second column the main effect of Group, with the third showing the p values for the interaction. The top row of images are p-value plots showing regions of the time/frequency that show a significant difference. Blue indicates no significant difference; yellow regions are areas where a significant difference was found at $p < .05$. The middle and bottom row of images show averaged data for the respective condition/group. Minimal interaction effects were evident and subsequent analyses did not provide more information than was already determined from previous analyses.

5.4 Discussion

The aim of these experiments was to examine the potential for an entrainment deficit in ADHD that may underlie some of the symptoms of the disorder, namely selective attention and temporal processing, but also deficits more widely through the communication through coherence hypothesis.

Neither study was successful in eliciting the expected entrained neural response to the rhythmic stimuli presented. This would have been evident by an increase in ITC at stimulation frequency (1 Hz) just before stimulus onset. As discussed in Chapter 4, the paradigm in Study 1 evoked a large potential around 100 ms, which may have masked the lower level entrainment effect. As such, for Study 2 the paradigm was changed such that the stimuli presented were only just detectable by the participant with individualised stimulus intensities. Unfortunately, this adjustment was not sufficient to elicit the entrainment effect. As the procedures used in these studies follow that of previously published work, the question then remains of why the effect was not seen. A highly likely reason for this was lack of participant numbers. In Study 1, there were 12 participants in each group, and in Study 2 there were only 9 in the low symptom group and 6 in the high. In addition, in both studies, the data collected was quite noisy. Noisy EEG data makes it more difficult to see the true neural response amongst the noise. In combination, these two factors mean these studies were not given the best opportunity to find the expected effects.

Error rates and reaction times (RTs) were recorded during the selective attention entrainment task. In both studies, for both error rates and RTs, no group differences were found suggesting that the level of ADHD symptoms experienced by an individual does not negatively impact selective attention. Analysis of the errors committed during the task confirmed that participants found the Study 2 paradigm harder to complete, suggesting that the individualised thresholds for stimulus intensity meant that the stimuli were more difficult to perceive. However, this was more evident for the visual than the auditory stimuli, suggesting that the auditory stimuli may still be too salient in the Study 2 paradigm. The individualised thresholds for the auditory stimuli were based only on volume, these results may suggest that a 2-factor threshold may be required based on frequency of the tone also such that the two tones are not only barely audible, but are also only just distinguishable from each other in pitch.

Chapter 6 General Discussion

Over the years several theoretical models of ADHD pathophysiology/psychopathology have been proposed. The first of these was Barkley's inhibitory control model which posited that the core deficit of ADHD was inhibitory control (Barkley, 1997). Barkley linked inhibitory control to other executive functions and suggested that inattention and other cognitive and social functioning deficits arise as secondary expressions of poor inhibitory control. While there is evidence to support an inhibitory control deficit in ADHD, it is clear that such deficits are not unique to ADHD and apply to other disorders of 'disruptive' behaviour such as opposition defiant disorder and conduct disorder (Oosterlaan et al., 1998). In addition, meta-analytic evidence shows that executive function deficits, while they play a role in the neuropsychology of ADHD, are not necessary, nor sufficient for the development of the disorder (Willcutt et al., 2005).

Sergeant and colleagues proposed the cognitive energetic model (CEM) in which the energetic state of the individual (effort, arousal, and activation) acts as a mediating factor between executive functioning and computational mechanisms of attention (encoding, search, decision, and motor organisation) (Sergeant, 2000, 2005; Sergeant & van der Meere, 1990). However, Sergeant links the CEM only to the motor organisation arm of attention, arguing that the others are intact in ADHD. A key criticism of this model is that is oversimplifies the neural representation of the "energetic pools" (effort, arousal, activation), suggesting that each are separate and distinct from the executive function systems of the prefrontal cortex. However, the brain is not so segmented, regions are interconnected, reciprocally sharing information. Sergeant also argues that the sensitivity to event rate found in ADHD reflects an inability of the individual to adjust their internal state, which then modulates the lack of response inhibition. However, sensitivity to event rate could be explained by an underlying temporal processing deficit, which may then affect the timing of an inhibitory response.

Reward processing models of ADHD have also been proposed by Sagvolden and by Sonuga-Barke. Sagvolden and colleagues propose a model based solely on the dopaminergic pathways in the brain (Sagvolden et al., 2005). The meso-cortical branch is linked to attention, behaviour planning, and executive functions, the nigro-striatal branch is linked to motor functions, non-declarative habit learning, and memory, and the meso-limbic branch is associated with the reinforcement of behaviour and the extinction of previously learnt behaviour. Dysfunction in any of these branches will lead to poorer outcomes. Sonuga-Barke (2004) suggested that reward signalling is compounded by developmentally acquired motivation to avoid/escape delay. There is clear evidence that dopamine is implicated in ADHD as one of the key medications used in its treatment (methylphenidate) is a dopaminergic agonist, meaning the level of dopamine in the

brain is increased. However, methylphenidate does not work for everybody, suggesting that a model based solely on dopamine cannot account for all cases of the disorder.

None of the models outlined above can adequately account for the heterogeneity seen in ADHD, yet aspects of all of them are supported by both neurological and neuropsychological evidence. As such, it is clear that the type of model best suited to explain the heterogeneity of ADHD is a multiple pathway model. Sonuga-Barke et al. (2010) proposed the three-pathway model combining executive function, motivation/reward, and temporal processing. Temporal processing deficits are commonly seen in ADHD (Noreika et al., 2013), including circadian rhythm deficits (Cortese et al., 2009). Coghill et al. (2014) proposed a six-pathway model including the domains of working memory, inhibition, delay aversion, decision-making, timing, and response variability.

As children with the disorder age, the presentation of symptoms can also change. Evidence shows that while ADHD may be more prevalent and severe in males during childhood and adolescence (Arnett et al., 2015; Willcutt, 2012), this gender divide does not appear in adulthood (Moffitt et al., 2015). Research suggests that the overall severity of symptoms reduces with age such that approximately 65% of those diagnosed as children qualify for a diagnosis of ADHD in partial remission as adults, and 15% retain their full diagnosis (Faraone et al., 2006). With this changing pattern of symptoms and impairments over time, one group of individuals who we know little about is university students with the disorder. This group attain higher academic outcomes than their non-university peers, and although they continue to struggle compared to non-ADHD university students, they may represent a 'better-adjusted' sub-group of those with ADHD (Green & Rabiner, 2012). Understanding what makes this group different could lead to interventions aimed at improving academic outcomes for all individuals with ADHD, but having a better knowledge of the difficulties faced by this population could also mean more tailored support can be given to assist them in completing their university studies. The majority of research with this group has been carried out at single sites within Northern America, with varying methods employed to classify individuals as being in the ADHD group. As such, there is a lack of research applicable to the UK university student population.

The first aim of this research was to explore the symptom and neuropsychological profiles of university students who self-report clinically relevant levels of ADHD symptoms. In-line with DSM-5 criteria for the diagnosis of ADHD in older adolescence and adulthood, participants for the high symptom (HS) group were required to endorse at least 5 symptoms from either or both the inattentive and hyperactive/impulsive subscales of the current symptoms scale (CSS). However, unlike previous studies (Broyd, Helps, & Sonuga-Barke, 2011; Hsu et al., 2013) a significant other

was also required to corroborate the presence of symptoms, a crucial step in the gold standard of adult ADHD diagnosis (DIVA), but one that is often not taken into account for the inclusion criteria of participants. The neuropsychological domains of working memory, sustained attention, selective attention, temporal processing, and inhibitory control were assessed, along with IQ. It was expected that HS participants would show deficits in each of these domains, as each of them has been implicated in the models of ADHD outlined above. In the first study there was evidence of ceiling effects in the sustained attention, temporal processing and inhibitory control tasks. Therefore, a second study was conducted in which the tasks were amended to be more difficult. This lead to no ceiling effects in the temporal processing (except for the easiest condition, as would be expected) and inhibitory control tasks, but was not successful in eliminating them from the sustained attention task.

The second aim of this research was to explore the possibility of an entrainment deficit in ADHD that might underlie some of the symptoms of the disorder. The multiple pathway models of ADHD are a great step forward in the attempt to account for the heterogeneity seen in the disorder. However, the three-pathway model could only account for 71% of the variation in the sample tested (Sonuga-Barke et al., 2010), and the six-pathway model was only able to account for 75% of the variation . It would therefore appear that other factors are needed in order for these models to be able to accurately account for all cases of ADHD. One possibility could be a deficit in entrainment, which may be able to account for multiple symptoms of the disorder. Entrainment is a critical component of the communication through coherence hypothesis (Fries, 2005, 2015), which argues that communication within and between regions of the brain is facilitated by oscillations that are phased locked to each other. This phase locking is achieved by the process of entrainment and as such if this process doesn't work as it should, communication within the brain could be compromised leading to poorer processing of information with consequences for behavioural outcomes.

The oscillatory selection hypothesis suggests two modes of neural processing, rhythmic and random/continuous (Schroeder et al., 2014; Schroeder & Lakatos, 2009) . When in rhythmic mode, low frequency oscillations entrain to the rhythm of attended (Lakatos et al., 2008) or attention-grabbing/salient stimuli (Lakatos et al., 2007), shifting the high excitability phase to amplify the attended stimulus, while suppressing input of stimuli out of phase with attended events. The hypothesis suggests that the rhythmic mode is preferred as it uses high excitability only when it is needed rather than being in a continuous state, which is metabolically more demanding. As such, entrained oscillations, either in a steady-state (continuous) mode and/or rhythmic (entrained) mode, provide a likely candidate for the physiological underpinnings for the effects of attention (Schroeder & Lakatos, 2009).

Key to the suggestion that ADHD could be a disorder of entrainment (Calderone et al., 2014), is evidence that ADHD is also a disorder of early stage sensory processing. Several lines of evidence point to deficits in the perception of sensory stimuli (Johnstone et al., 2013; Ortega et al., 2013; Stevens et al., 2012), including a reduced contingent negative variation, a component that Schroeder and Lakatos (2009) suggests could reflect the phase reset of low-frequency oscillations when found in frontal regions. As such, it is plausible that entrainment could underlie the early stage sensory processing deficits in ADHD.

To address the possibility of an entrainment deficit in ADHD, a paradigm was developed in line with previously published literature (Besle et al., 2011; Lakatos et al., 2008; Lakatos et al., 2009; Lakatos, Schroeder, et al., 2013). In this task participants first attended to a single modality stimulus to assess entrainment to a single modality 1 Hz rhythmic stream. Second, participants were presented with both visual and auditory stimuli presented alternately, each with a rhythm of 1 Hz, and were asked to attend to only one modality. It was anticipated that participants exhibiting a higher level of ADHD symptoms would show evidence of an altered entrainment process such as a reduced inter-trial coherence, and/or a shift in the timing of entrainment such that oscillations were entrained to a less informative part of the wave (i.e. not at its peak). In the first study every participant received the same intensity of stimuli, while in the second study stimulus intensities were individualised such that stimuli were only just perceptible.

6.1 Main findings

In both studies, participants in the HS group self-reported significantly more symptoms than their significant others. This is in part due to the lower level of required symptoms from the significant other, three compared to five. Participants also reported a higher degree of severity of symptoms but this was not significantly different to the report of their significant other. This might suggest that participants self-reported more symptoms at a lower severity, while their significant other reported fewer symptoms but at a higher degree severity. Previous work has also found a higher level of severity in the self-report compared to informants, but this difference was not tested statistically (Broyd et al., 2011; Hsu et al., 2013). After correction for multiple comparisons, no significant correlations were found between the self and other reports for either the low or the high symptom groups in Study 1. In Study 2, significant correlations were found for the high symptom group only. Previous work has reported significant relationships between the self- and other-reports (Broyd et al., 2011; Hsu et al., 2013), but they do not specify whether multiple comparisons were made or whether the correlations were run for the two groups separately. Due to the degree of separation in symptom counts between the two groups, it is

highly likely that positive relationships would be found just as an artefact of having the two groups as one sample.

Hsu et al. (2013), Broyd et al. (2011), and Weyandt et al. (2017) all used the same 18-item, 4-point scale to measure ADHD symptoms in their sample. Unfortunately, Weyandt et al. (2017) did not report the symptom counts or severity of their sample on this scale, and Hsu et al. (2013) and Broyd et al. (2011) only report severity. Comparing the two studies presented here with these severity scores, for the low symptom group Broyd et al. (2011) reports the highest level of symptom severity (Supplementary Table 6.1, see Appendix B), Hsu et al. (2013) report very similar levels to those reported in Study 1 here, and Study 2 has the lowest severity of symptoms for the low symptom group. For the high symptom groups, the studies presented here have the highest level of reported symptom severity compared to Hsu et al. (2013) and Broyd et al. (2011). One possible explanation for this was the requirement of the corroboration of symptoms from a significant other as part of the inclusion criteria in the present studies, rather than just relying on the self-report of the participants. This meant that the participants recruited here were more severely impaired such that the presence of symptoms was more evident to those around them.

Evidence suggests that symptoms of hyperactivity lessen with age (Biederman, Mick, & Faraone, 2000; Cherkasova, Sulla, Dalena, Pondé, & Hechtman, 2013). However, in both studies, HS participants reported very similar levels of hyperactive/impulsive symptoms as they did inattentive, with a higher average severity for hyperactive over impulsive symptoms. Broyd et al. (2011) found a very similar degree of severity of inattention and hyperactivity/impulsivity symptoms in their university sample and Gray et al. (2016) also found a higher than expected degree of hyperactivity in their study. Together with the present findings, it might suggest one way in which the university population of individuals with ADHD may differ from their non-university peers. However, Hsu et al. (2013) found higher severity of inattention compared to hyperactivity, as did Study 2 (despite a very similar number of reported symptoms), meaning more work is needed to ascertain if this truly is the case. Unfortunately, it was not possible to investigate the subtypes of ADHD in the present studies due to the lack of representation in each subtype (Supplementary Table 6.2, see Appendix B).

ADHD is typically thought of as a male dominant disorder, with the gender divide lessening in adulthood. In the two studies presented here there was a higher number of females than males in the HS group. However, this gender ratio might be a reflection of the ratio present within the Psychology department from which the majority of the participants were recruited, rather than a true representation of the gender ratio in university students with ADHD. Broyd et al. (2011) and Hsu et al. (2013) conducted their research within the same department, accessing the same

demographic of students. Broyd et al. (2011) had 10% males in their low symptom group and 30% males in their high symptom group. Hsu et al. (2013) had 25% males in each group. Across both studies conducted here, there were 27% males in the high symptom groups and 24% in the low symptom. All three studies show a higher proportion of females across both groups, suggesting that this is the norm within this demographic and therefore the gender ratio found in the current studies is simply a reflection of this rather than the presence of any relationship between gender and ADHD symptoms.

The neuropsychological assessments carried out in Study 1 revealed no significant differences between the two groups in IQ, sustained attention, or inhibitory control, suggesting that the level of ADHD symptoms experienced by university students does not affect these domains. Working memory and temporal processing on the other hand were found to be significantly worse for those in the high symptom group. In Study 2, the sustained attention, inhibitory control, and temporal processing task were all made more difficult in an effort to remove the ceiling effects seen in these tasks in the first study. The results of these more difficult tasks still show no significant group differences in sustained attention or inhibitory control, further suggesting that the level of ADHD symptoms experienced does affect these domains. However, a medium effect size with marginal significance was found for the sustained attention task in Study 2, suggesting a possible group effect with the high symptom group showing poorer performance. Significant group differences were again found in the working memory and temporal processing task with the high symptom group showing poorer performance. In addition, reaction times recorded during the temporal processing task suggest a different tactic between the groups. The low symptom group had significantly longer RTs in the 100 ms condition compared to the 200 ms condition, whereas the high symptom group did not. The results suggest that during the most difficult condition, the high symptom group had a more impulsive reaction whereas the low symptom group took longer to consider their answer. Another difference found in Study 2 was that the high symptom group were found to have a significantly lower IQ than the low symptom group.

Given the multiple pathway models of ADHD and evidence of widespread neuro-psychological deficits in the disorder, it was anticipated that the high symptom group would show deficits in all of the domains tested. In the study by Weyandt et al. (2017), it was found that students with ADHD showed no differences in IQ, just as with Study 1 here, but did show deficits in sustained attention, where no significant differences were found in the present studies but medium effect sizes were. A possible explanation for the lack of differences found in the studies presented here were low statistical power and the presence of ceiling effects, even after making the task more difficult in Study 2. The medium effect sizes suggest the presence of sustained

attention deficits, but that with the present numbers of participants and the specific task used, these differences did not reach significance. The use of a continuous performance task, such as that used by Weyandt et al. (2017), might be a suitable alternative to the task used here.

The students in Weyandt et al. (2017)'s study also showed difficulties with vigilance and impulsivity, and while not the same, no inhibitory control deficits were found in the present studies, despite a higher than expected level of hyperactivity/impulsivity symptoms. Response inhibition deficits have been found in the student ADHD population (Woltering et al., 2013) and a meta-analysis across all ages show interference inhibition (Lansbergen et al., 2007). However, interference and response inhibition are not the same, and it is not known whether the participants in the present studies may have actual difficulties with response inhibition as measured by the type of Go/NoGo task used by Woltering et al. (2013). With regards to the interference inhibition deficits shown by the Lansbergen et al. (2007) meta-analysis, these deficits were specifically found with the colour-word version of the Stroop task, which is confounded by its use of language, something intentionally avoided in the present studies.

In both studies presented here a significant Stroop effect was found and the ceiling effects were eliminated in Study 2. Given this, it would appear that the task used might not be able to account for the lack of group differences. While it is tempting to suggest that lack of interference inhibition difficulties could represent one of the ways in which the student population of ADHD differ from the non-university ADHD young adult population, there are other tasks that measure interference inhibition and it would be important to replicate these findings with such tasks before making such a conclusion. For example, the Flanker (Eriksen & Schultz, 1979) and the Simon tasks (Simon & Wolf, 1963) are other non-verbal interference inhibition tasks, in which participants again have to overcome the influence of conflicting stimuli to produce the correct response. Deficits using both of these tasks have been found in children with ADHD (Mullane, Corkum, Klein, & McLaughlin, 2009) and it would be recommended to test the student ADHD population using these tasks to provide convergent evidence. In addition, interference inhibition is only one aspect of inhibitory control. As outlined previously, response inhibition difficulties have also been found within the ADHD population using tasks such as the Go/NoGo (Woltering et al., 2013) and the Stop Signal (Rubia et al., 2007). In order to understand the extent of inhibitory control difficulties faced by the student ADHD population it would also be important to assess response inhibition with such tasks.

Another possible explanation for equivalent behavioural performance between the high and low symptom groups in the interference inhibition task could be an underlying neural compensatory mechanism. To test this, electroencephalogram (EEG) was also recorded during

this task to investigate the lateralised readiness potential (LRP). This potential represents the motor preparation for a response, capturing the moment of inhibition in the transition from an incorrect to correct motor response. In both Study 1 and Study 2, no group differences were found in any of the LRP metrics suggesting that there was no underlying compensatory mechanism that could explain the equivalent performance. In a Go/NoGo task, university students with ADHD symptoms have been found to have poorer LRP responses than control subjects suggesting weaker preparation to respond (Gorman Bozorgpour et al., 2013). However, the Go/NoGo task is a measure of response inhibition, whereas the Stroop task used in the present studies is a measure of interference inhibition. As such it may be that response preparation is unaffected in this type of task for this population. Alternatively, together with the equivalent behavioural performance, interference inhibition may simply be unaffected in university students with ADHD.

Working memory deficits have been well documented in ADHD (Coghill et al., 2014; Willcutt et al., 2005), including in university students (Gropper & Tannock, 2009; Kim et al., 2014). The findings presented here reinforce the conclusion that working memory difficulties appear to be a core deficit in ADHD. Likewise, timing difficulties are also consistently found in this disorder (Coghill et al., 2014; Noreika et al., 2013; Sonuga-Barke et al., 2010) and across both studies presented here, perceptual temporal processing deficits were found. However, there was limited evidence of reaction time differences between the two groups across all tasks. This was surprising as in both children and adults, reaction times have been found to affected either with a higher degree of reaction time variability, or too fast/slow responses (Castellanos & Tannock, 2002; Noreika et al., 2013). Woltering et al. (2013) did not find reaction time differences in a Go/NoGo task with university students, whereas Weyandt et al. (2017) found poorer reaction times using the continuous performance task. In Study 2 reaction time differences were found for the hardest levels of the temporal processing task only. It may be the case that reaction time responses are not universally affected in university students with ADHD, but more research is needed to replicate and expand on existing findings.

Selective attention was measured in both studies through the entrainment task. In both Study 1 and Study 2 there were no significant differences in error rates or reaction times between the two symptom level groups. It has been previously noted that people with ADHD report difficulties with selective attention, among other neuropsychological domains, but these are not reliably detected by behavioural studies (Stevens et al., 2012). As discussed above with regards to inhibitory control, equivalent behavioural performance may stem from a compensatory neural response. However, just as with the LRP analysis, no differences were found between the high and low symptom groups, again suggesting no compensatory neural mechanism to account for

the equal behavioural performance. It has been suggested that the presence of a CNV response in frontal electrodes likely reflects phase resetting of low-frequency oscillations (Schroeder & Lakatos, 2009), a suggestion that directly connects this ERP component to entrainment; an important notion for the second aim of the present research. However, there was no evidence of a CNV response in the frontal electrodes in either study, perhaps indicating the lack of an entrained response.

Entrainment was measured using a wavelet time/frequency decomposition of the EEG data during the entrainment tasks to obtain inter-trial coherence (ITC) values. In Study 1 there was no evidence of entrainment in either the single or dual modality task for either group. If entrainment had occurred, this would have resulted in an increase in ITC around 0 ms to coincide with stimulus onset. However, there was no such increase. One possible reason for this could have been that the amplitude of the N1 peak, evidencing attention to the stimuli, could have masked the lower level entrainment effects. For Study 2, the intensity of the stimuli was individualised such that the visual stimuli were only just visible and the auditory stimuli could only just be heard. The aim was to reduce the saliency of these stimuli and therefore to reduce the size and dominance of the N1 evoked potential. However, results show that although the N1 amplitude was lower in Study 2, there was still no evidence of an entrained response, in either task, for either of the symptom groups. That being said, this analysis was only conducted with 6 high symptom and 9 low symptom participants meaning the study was underpowered. Besle et al. (2011) used a very similar paradigm with individualised stimulus thresholds to successfully study entrainment in patients about to undergo epilepsy surgery. As such, the methods used here have been shown to be effective in previously published work, which suggests it is not the paradigm that is at fault. The current study needs to be replicated with larger participant numbers before the effectiveness of this paradigm can be ascertained.

6.2 Limitations

Lack of statistical power was an issue for both studies conducted as part of this research, as evidenced by 67% of the group comparisons shown in Table 3.1 - Table 3.5 of Chapter 3 falling within the low to low/medium effect size range for Cohen's d (i.e. less than .5). Recruitment of participants proved to be more difficult than expected with the addition of the significant other report as part of the inclusion criteria for the high symptom group. However, given the importance of corroboration in ADHD diagnosis, this is not a criterion that could be relaxed. In addition to difficulties recruiting sufficient numbers of participants, more participants were lost to the EEG analysis as a result of excessively noisy data and technical difficulties during EEG data collection. One reason for the difficulties with the EEG was that it was a new system to the

University, utilising Quik-Cells rather than traditional electrolyte gel and, as with any new technology, there were teething problems. That being said, as this new system does not use gel, it is a far more attractive system for participants due to the lack of clean up required. Another potential source of noise could have been external interference, which may have been mitigated by the use of a Faraday cage and a soundproof environment so as not to distract participants.

The end goal for this research was to be able to test the entrainment hypothesis in a clinical sample of adolescents with ADHD (see Appendix C). To this end, the studies were designed in such a way that the tasks would be appropriate for secondary school children as well as the university students, such that a direction comparison could be made if desired. However, in Study 1 ceiling effects were found in several of the tasks, as well as in the sustained attention task in Study 2. This meant that the tasks used might not have been able to detect underlying deficits in the domains tested within this age group.

The studies presented here included typically developed individuals who exhibited a clinically relevant level of ADHD symptoms. Such a sample, while informative, cannot fully represent a true clinical sample of individuals with a confirmed diagnosis of ADHD. However, given the difficulties faced in recruiting the current samples, recruitment of a sufficiently large clinical sample was beyond the scope of the present research. Given the small effect sizes in this dimensional based study, future research related to ADHD should recruit participants based on ADHD as a dimensional disorder. Coghill and Sonuga-Barke (2012) highlight that taxonomic evidence does not support the idea that ADHD is a categorical disorder; if it were one would expect to see a homogenous presentation of the disorder but this is not the case. Instead, ADHD shows clear evidence of being a heterogeneous, dimensional disorder. With this definition of ADHD, it would advantageous to recruit participants across the spectrum of levels of ADHD symptoms, not classifying participants into groups of “high” or “low” symptoms. In this way it would be possible to ascertain whether there are linear relationships between neuropsychological and other deficits and the severity of the symptom presentation, which one would expect if such difficulties are the result of the disorder.

The inability of the entrainment task to be able to elicit entrainment was another limitation of these studies. Without a reliable paradigm to test the entrainment hypothesis, it was not possible to conduct the planned study with clinically diagnosed adolescents with ADHD. Another possible reason for not detecting entrainment could be the type of time/frequency decomposition employed. The results reported here were obtained using a wavelet decomposition, which is the method widely accepted to be the most appropriate. However, for due diligence, a short time Fourier transform (STFT) decomposition was also completed on the

data in both studies (see Appendix D). The results of this analysis again found no evidence of an entrained effect. It is possible, however, that alternative pre-processing filters could have produced a different outcome. Besle et al. (2011) applied a much narrower bandpass filter of 1.2 – 2 Hz in order to isolate neural signals around the stimulation frequency of 1.5 Hz. Based on the work of Soltész et al. (2013), such a narrow filter band was not deemed necessary here, but given the lack of entrainment, the possibility remains that such an approach may have led to a different outcome. That being said, it is important to remember that the method of data acquisition in the Besle et al. (2011) study used intracranial electrodes on the surface of the brains of pre-surgery epileptic patients. As such, the processing of that data necessitates a different approach. Likewise, intracranial recordings have a higher signal to noise ratio than surface EEG recording, thus it is a much more sensitive tool, perhaps better able to detect entrainment than the equipment used in the present research.

6.3 Implications and Future directions

There is a limited amount of published work available investigating the neuropsychological difficulties experienced by university students with ADHD, especially in the UK and Ireland. Such knowledge is crucial to be able to tailor the support these students are offered by their university's support services. The research conducted here suggests that university students who exhibit clinically relevant levels of ADHD symptoms suffer from working memory and temporal processing difficulties. This might have a significant impact on their performance at university, as these are proficiencies that are required in a competitive learning environment. Therefore, these are areas that should be considered targets for support services to focus on when giving support to university students with ADHD in order to help them find suitable ways to cope with or even overcome the impact of these difficulties.

The current research suggests that there are no deficits in sustained attention, selective attention, or inhibitory control in university students with ADHD symptoms. However, due to the lack of statistical power, the present studies need to be replicated with a larger sample, preferably across multiple sites.

Another implication of this work is that entrainment does not appear to be the ubiquitous automatic process that the literature would suggest it to be. Everything known about this process suggests that exposure to a rhythm will always elicit an entrained response. Based on this understanding, there would be no reason for the paradigms used here not to lead to an entrained response. However, it could also be the case that the picture presented by the published literature is skewed, with only positive results being published. There is a large replication crisis

not only within Psychology, but the wider scientific community, such that studies with negative or null findings are not published as readily as those with a significant result. Therefore, it could be the case that there are numerous other studies that have used the same basic paradigms and also not found the effect. However, until any such null and negative findings are more widely accepted by journal publishers (see Matosin, Frank, Engel, Lum, & Newell, 2014), the true answer to the question of ubiquity of the entrained response may never be known.

It is clear that more research is needed investigating the process of entrainment. Future studies may wish to first run behavioural studies of the entrainment paradigm, comparing the rhythmic stimulus streams to a non-rhythmic or jittered stream. In such a paradigm it would be anticipated that the behavioural responses to the rhythmic stream would benefit from entrainment leading to improved perception of and therefore responses to the stimuli presented within the same rhythm. Once such behavioural responses have been confirmed with the paradigm, EEG recordings could then be taken. With regards to the paradigm itself, it may be that different frequencies respond differently. As such, it may be beneficial to test multiple frequencies to ascertain which has the strongest response.

6.4 Conclusion

Working memory and temporal processing deficits appear to be robust neuropsychological deficits in individuals with ADHD symptoms. More research is need to confirm that lack of deficits in sustained and selective attention, as well as inhibitory control and entrainment.

Appendix A Materials

A.1 Current Symptoms Scale – Self-Report

Copyright permissions were granted for the use of this questionnaire in the online screening survey, but not for further distribution. The questionnaire is available from the following reference:

Barkley, R. A., & Murphy, K. R. (2006). *Attention-deficit hyperactivity disorder: A clinical workbook* (3rd ed.). New York, NY: Guilford Press.

The copyright is held with Guildford Publications: permissions@guilford.com

A.2 Current Symptoms Scale – Other-Report

Copyright permissions were granted for the use of this questionnaire in the online screening survey, but not for further distribution. The questionnaire is available from the following reference:

Barkley, R. A., & Murphy, K. R. (2006). *Attention-deficit hyperactivity disorder: A clinical workbook* (3rd ed.). New York, NY: Guilford Press.

A.3 Study 1

A.3.1 Information Sheet – Online Screening Questionnaire

Participant Information for Online Questionnaire

Study Title: The relationship between ADHD symptoms and entrainment of neural oscillations as measured by EEG

Researcher: Amy Boyson **Ethics number**: 15467

Please read this information carefully before deciding to take part in this research. If you are happy to participate you will be asked to consent by ticking the box below.

What is the research about?

I am a first year PhD candidate and the present study represents the pilot study for my work investigating the possible relationship between attention deficit/ hyperactivity disorder (ADHD) and entrainment. Entrainment refers to the process of intrinsic neural oscillations becoming synchronous with rhythmic external stimuli. It has been found that the process is negatively affected in developmental disorders such as schizophrenia and dyslexia, and it has also been linked to selective attention. It has therefore been suggested that there could be a possible connection with ADHD. This is what my PhD work aims to test.

Why have I been chosen?

Participants are being recruited for this pilot from the University of Southampton. In order to take part in the study, you must first complete an online screening questionnaire. Only participants who meet specific score requirements will be invited to take part in the 2 part study.

What will happen to me if I take part?

If you consent to take part the next screen will ask you a series of questions to which you must indicate the frequency with which you perform certain behaviours. This questionnaire is called the Current Symptoms Scale (Barkley & Murphy, 2006) and is a screening measure for the symptoms of ADHD. It is important to note that this measure is not being used as a diagnostic tool and if you have any concerns about possible ADHD symptoms you should contact your GP. The experimenter will then get in touch to advise of your eligibility to take part in the study and provide you with the information sheet.

Are there any benefits in my taking part?

This work has implications for understanding the neuroscience of ADHD which could, with time, aid in both treatment and diagnosis of the disorder.

Are there any risks involved?

There are no risks to your completing the screening questionnaire. However, if you are concerned about any of the issues raised by the questions or about ADHD, you can contact your GP, consult the NHS choices website for ADHD, or contact the University's counselling service at the following links:

http://www.nhs.uk/conditions/Attention-deficit-hyperactivity-disorder/Pages/Introduction.aspx

http://www.southampton.ac.uk/edusupport/mental_health_and_wellbeing/index.page

There are minimal risks in partaking in the EEG procedure. There may be some mild discomfort associated with fitting the cap due to having to make sure the scalp and the gel are well seated with the electrodes. Should you experience any discomfort at any time, you need only to inform the experimenter who will make you more comfortable. The EEG equipment is passive; it only receives signals and does not act as a transmitter of signals, so again there is minimal risk involved.

Will my participation be confidential?

In compliance with the Data Protection Act and University policy your data and information remain confidential. Data will be coded with participant numbers and be kept on a password-protected computer. All paperwork will also be kept secure in a locked office and only made available to those directly related to the research.

What happens if I change my mind?

You have the right to withdrawer from this study at any time with no penalty. If you have already completed the questionnaire but wish to withdrawer, please contact the experimenter on the below details.

What happens if something goes wrong?

If you have questions about your rights as a participant in this research, or if you feel that you have been placed at risk, you may contact the Chair of the Ethics Committee, Psychology, University of Southampton, Southampton, SO17 1BJ. Phone: +44 (0)23 8059 3856, email fshs-rso@soton.ac.uk. Or alternatively you can also contact the Research Governance Manager. Phone: 02380 595058, email: rgoinfo@soton.ac.uk.

Where can I get more information?

If you have any further questions about this research please contact me, Amy Boyson, before signing up for the study at asb1e14@soton.ac.uk

My supervisory team are as follows: Dr Fruzsina Soltesz at F.Soltesz@soton.ac.uk and Prof Edmund Sonuga-Barke at ejb3@soton.ac.uk.

A.3.2 Information Sheet – Laboratory Sessions

Participant Information Sheet

Study Title: The relationship between ADHD symptoms and entrainment of neural oscillations as measured by EEG

Researcher: Amy Boyson **Ethics number**: 15467

Please read this information carefully before deciding to take part in this research. If you are happy to participate you will be asked to sign a consent form.

What is the research about?

I am a first year PhD candidate and the present study represents the pilot study for my work investigating the possible relationship between attention deficit/ hyperactivity disorder (ADHD) and entrainment. Entrainment refers to the process of intrinsic neural oscillations becoming synchronous with rhythmic external stimuli. It has been found that the process is negatively affected in developmental disorders such as schizophrenia and dyslexia, and it has also been linked to selective attention. It has therefore been suggested that there could be a possible connection with ADHD. This is what my PhD work aims to test.

Why have I been chosen?

Participants are being recruited for this pilot from the University of Southampton. In order to take part in the study, you must first complete an online screening questionnaire. Only participants who meet specific score requirements will be invited to take part in the 2 part study.

What will happen to me if I take part?

The first session will involve the completion of tests related to cognitive performance and anxiety. These will be practical, computerised, and pen and paper tasks, and should last an hour.

The second session will involve fitting you with an electrode cap in which electrodes will be placed, with the addition of a saline solution which aids conduction of electrical signals. The electrodes receive signals only; there is no transmission of signals of any kind to you. Once fitted with the cap, you will be seated in front of a computer screen and handed a response box. In the first task you will be required to attend to stimuli and respond to a target. The stimuli will be both auditory and visual in nature; visual stimuli are filled circles and auditory stimuli are tones. Target stimuli are hollow circles and white noise. Your task will be to press the button when you detect one of these target stimuli. There are two parts to this test. The second task will require you to respond with a left or right button press to indicate which animal on the screen is bigger in real life. It is expected that the whole procedure, including set up and both tasks, should take 2 hours but no more than 2.5 hours. You are in control of the pace of the experiment. There are plenty of opportunities to take a break if you wish to, however we won't be able to disconnect the equipment during this time.

Are there any benefits in my taking part?

This work has implications for understanding the neuroscience of ADHD which could, with time, aid in both treatment and diagnosis of the disorder.

Are there any risks involved?

There are minimal risks in partaking in the EEG procedure. There may be some mild discomfort associated with fitting the cap due to having to make sure the electrodes are well seated. Should you experience any discomfort at any time, you need only to inform the experimenter who will make you more comfortable. The EEG equipment is passive; it only receives signals and does not act as a transmitter of signals, so again there is minimal risk involved. You will be required to view stimuli on a computer screen for a lengthy period so every effort will be made to ensure you are comfortable. If you require glasses for viewing display screens, such as computers, then please bring these with you.

Will my participation be confidential?

In compliance with the Data Protection Act and University policy your data and information remain confidential. Data will be coded with participant numbers and be kept on a password-protected computer. All paperwork will also be kept secure in a locked office and only made available to those directly related to the research.

What happens if I change my mind?

You have the right to withdrawer from this experiment at any time with no penalty. Should you wish to do so, please inform the experimenter who will stop the experiment and disconnect the equipment.

What happens if something goes wrong?

If you have questions about your rights as a participant in this research, or if you feel that you have been placed at risk, you may contact the Chair of the Ethics Committee, Psychology, University of Southampton, Southampton, SO17 1BJ. Phone: +44 (0)23 8059 3856, email fshs-rso@soton.ac.uk. Or alternatively you can also contact the Research Governance Manager. Phone: 02380 595058, email: rgoinfo@soton.ac.uk.

Where can I get more information?

If you have any further questions please contact me, Amy Boyson, at asb1e14@soton.ac.uk or one of my supervisory team; Dr Fruzsina Soltesz at F.Soltesz@soton.ac.uk or Prof Edmund Sonuga-Barke at ejb3@soton.ac.uk.

A.3.3 Consent Form – Online Screening Questionnaire

Participant Consent for Online Questionnaire

Study Title: The relationship between ADHD symptoms and entrainment of neural oscillations as measured by EEG

Researcher: Amy Boyson **Ethics number**: 15467

Please tick the box below if you agree with the following statements:

I. I have read and understood the information and have had the opportunity to ask questions about the study

II. I agree to take part in this research project and agree for my data to be used for the purpose of this study

III. I understand my participation is voluntary and I may withdraw at any time without my legal rights being affected

IV. I am happy to give a significant other, who knows me well, a copy of the questionnaire (to be given in a later session) and am happy for them to share this information with the research team

☐ I consent to take part and agree with the above statements.

A.3.4 Consent Form – Laboratory Sessions

UNIVERSITY OF Southampton

CONSENT FORM (V4, 1/6/2015)

Study title: The relationship between ADHD symptoms and entrainment of neural oscillations as measured by EEG

Researcher name: Amy Boyson
ERGO Study ID number: 15467

Please initial the box(es) if you agree with the statement(s):

I have read and understood the information sheet (V4, 1/6/2015) and have had the opportunity to ask questions about the study ☐

I agree to take part in this research project and agree for my data to be used for the purpose of this study ☐

I understand my participation is voluntary and I may withdraw at any time without my legal rights being affected ☐

(Optional) I consent to my details being held by the Developmental Brain Behaviour Lab (DBBL) and that I am happy to be contacted by other researchers in the department with regards to other research. ☐

Name of participant (print name)……

Signature of participant……..

Date……

A.3.5 Debrief Statement – Following Unsuccessful Screening Questionnaire

UNIVERSITY OF Southampton

The relationship between ADHD symptoms and entrainment of neural oscillations as measured by EEG

Debriefing Statement (v2, 02/02/2015)

The aim of this research was to ascertain the relationship between ADHD symptoms and the process of entrainment. Entrainment is the process by which intrinsic neural oscillation become synchronous with external rhythmic stimuli. It has been found that this process is negatively affected in developmental disorders such as schizophrenia and dyslexia. Entrainment has also been linked to selective attention. It is expected that those participants with increased ADHD symptoms will have a less efficient entrainment process; the nature of this deficiency is what we hope to study.

You have completed the screening questionnaire for this research. Unfortunately, your results mean you were not eligible to take part in the EEG recording for this study. This screening questionnaire is not a means to a diagnosis and if you are concerned about possible symptoms of ADHD you should consult your GP. The University also offer a counselling service for students who are concerned about any mental health issues; please see the below link for information on their services. You may also wish to refer to the NHS Choices website which contains more information if you wish to find out more about ADHD:

http://www.southampton.ac.uk/edusupport/mental_health_and_wellbeing/index.page

http://www.nhs.uk/conditions/attention-deficit-hyperactivity-disorder/pages/introduction.aspx

Once again results of this study will not include your name or any other identifying characteristics and will not be made available to anyone other than research staff directly involved in this research. The experiment did not use deception. You may have a copy of this summary if you wish and you may also have a summary of the results when they are ready. Please see the below reference if you wish to find out more about the possible relationship between ADHD and entrainment:

Calderone, D. J., Lakatos, P., Butler, P. D., & Castellanos, F. X. (2014). Entrainment of neural oscillations as a modifiable substrate of attention. Trends in Cognitive Sciences, 18(6), 300-309.

If you have any further questions please contact me, Amy Boyson, at asb1e14@soton.ac.uk or one of my supervisory team; Dr Fruzsina Soltesz at F.Soltesz@soton.ac.uk or Prof Edmund Sonuga-Barke at ejb3@soton.ac.uk.

Thank you for your participation in this research.

If you have questions about your rights as a participant in this research, or if you feel that you have been placed at risk, you may contact the Chair of the Ethics Committee, Psychology,

Appendix A

University of Southampton, Southampton, SO17 1BJ. Phone: +44 (0)23 8059 3856, email: fshs-rso@soton.ac.uk

A.3.6 Debrief Statement – Following Laboratory Sessions

UNIVERSITY OF Southampton

The relationship between ADHD symptoms and entrainment of neural oscillations as measured by EEG

Debriefing Statement (v3, 15/02/2015)

The aim of this research was to ascertain the relationship between ADHD symptoms and the process of entrainment. Entrainment is the process by which intrinsic neural oscillations become synchronous with external rhythmic stimuli. It has been found that this process is negatively affected in developmental disorders such as schizophrenia and dyslexia. Entrainment has also been linked to selective attention. It is expected that those participants with increased ADHD symptoms will have a less efficient entrainment process; the nature of this deficiency is what we hope to study.

Your data will help our understanding of this effect as there is currently no published research on the topic. The screening questionnaire was designed to ascertain your level of ADHD type symptoms. These results allow us to separate those with a higher level of symptoms from those with lower symptom levels. The EEG recordings of these two groups will then be compared to ascertain if there are any differences between them and where these differences lie. The tests taken in the first session were designed to measure IQ, working memory, sustained attention, and fear of uncertainty. These measures were taken to ascertain whether any differences seen in the EEG could be explained by other factors.

The screening questionnaire is not a means to a diagnosis and if you are concerned about possible symptoms of ADHD you should consult your GP. The University also offer a counselling service for students who are concerned about any mental health issues; please see the below link for information on their services. You may also wish to refer to the NHS Choices website which contains more information if you wish to find out more about ADHD:

http://www.southampton.ac.uk/edusupport/mental_health_and_wellbeing/index.page

http://www.nhs.uk/conditions/attention-deficit-hyperactivity-disorder/pages/introduction.aspx

Once again results of this study will not include your name or any other identifying characteristics. The experiment did not use deception. You may have a copy of this summary if you wish and you may also have a summary of the results when they are ready. Please see the below reference if you wish to find out more about the possible relationship between ADHD and entrainment:

Calderone, D. J., Lakatos, P., Butler, P. D., & Castellanos, F. X. (2014). Entrainment of neural oscillations as a modifiable substrate of attention. Trends in Cognitive Sciences, 18(6), 300-9.

If you have any further questions please contact me, Amy Boyson, at asb1e14@soton.ac.uk or one of my supervisory team; Dr Fruzsina Soltesz at F.Soltesz@soton.ac.uk or Prof Edmund Sonuga-Barke at ejb3@soton.ac.uk.

Thank you for your participation in this research.

Appendix A

If you have questions about your rights as a participant in this research, or if you feel that you have been placed at risk, you may contact the Chair of the Ethics Committee, Psychology, University of Southampton, Southampton, SO17 1BJ. Phone: +44 (0)23 8059 3856, email: fshs-rso@soton.ac.uk

A.4 Study 2

A.4.1 Information Sheet

UNIVERSITY OF Southampton

Participant Information Sheet

Study Title: The relationship between entrainment and ADHD in adults II

Researcher: Amy Boyson

ERGO number: 27598

Please read this information carefully before deciding to take part in this research. It is up to you to decide whether or not to take part. If you are happy to participate you will be asked to sign a consent form.

What is the research about?

This research forms part of my PhD in Psychology. I am investigating the possible relationship between attention deficit hyperactivity disorder (ADHD) and entrainment. Entrainment refers to the process by which neural oscillations become synchronised with each other in response to a rhythm and has been associated with selective attention. In addition, deficits in entrainment have been found in other neurodevelopmental disorders such as schizophrenia and dyslexia, and correlated with the symptoms of these disorders. The suggestion has been made that deficits in entrainment might account for some of symptoms seen in ADHD. This is what my work aims to test.

Why have I been asked to participate?

Participants are being recruited for this study from the Southampton area. In order to take part, you must first take some screening questionnaires to ensure you are eligible; only participants who meet specific score requirements will be invited to take part. For the purposes of this research we are seeking participants who report both a high and low level of ADHD symptoms.

What will happen to me if I take part?

The first part of the study is the screening process. You will be asked to fill out an online questionnaire which asks about the level of ADHD symptoms you experience. You will also be

provided with an Initial Screening Form which will ask questions to ensure you are suitable for the study. For example, individuals who have epilepsy would not be suitable due to the nature of the stimulus presentation. You will also be provided with a copy of the online questionnaire for you to give to someone who knows you very well and can answer questions about your behaviour accurately. The responses provided to all 3 of these questionnaires will determine whether you are eligible to take part in the main study.

The second part of the study involves two visits to the University of Southampton. The first session will last an hour and you will complete some pen and paper and some computer based tasks to look at how you process information. The second session is the EEG recording session which will last between 2 and 2.5 hours. During this session you will be fitted with an electrode cap and your EEG recorded while you participate in 2 computerised tasks. The first of these will present you with a rhythmic stream of stimuli and ask you to respond to target stimuli. The second will ask you to make judgements about pictures on the screen. You will be offered plenty of opportunity to take breaks during the sessions. However, during the EEG recording it will not be possible to disconnect the equipment during a break.

Are there any benefits in my taking part?

This work has implications for understanding the neuroscience of ADHD which could, with time, aid in both diagnosis and treatment of the disorder.

As compensation for you volunteering your time to participate in this study we are able to offer up to 44 research credits for psychology students at the University, or a sum of £20 for others payable on completion of the EEG recording session.

Are there any risks involved?

There are minimal risks in partaking in the EEG procedure. There may be some mild discomfort associated with fitting the cap due to having to make sure the electrodes are well seated. Should you experience any discomfort at any time, you need only to inform the experimenter who will make you more comfortable. The EEG equipment is passive; it only receives signals and does not act as a transmitter of signals, so again there is minimal risk involved. You will be required to view stimuli on a computer screen for a lengthy period so every effort will be made to ensure you are comfortable. If you require glasses for viewing display screens, such as computers, then please bring these with you.

Will my participation be confidential?

In compliance with the Data Protection Act and University policy your data and information will remain confidential. Data will be coded with participant numbers and be kept on a password-protected computer such that no personally identifiable information is directly linked to the data. All paperwork will also be kept secure in a locked office. All data will only made available to those directly related to the research such as the researcher and her supervisor(s), as well as the research assistant(s).

What should I do if I want to take part?

If you wish to take part in this study please contact the researcher on the below email address and either she or a research assistant will be in touch to organise access to the screening materials.

What happens if I change my mind?

You have the right to withdraw from this research with no penalty. Should you wish to withdraw during a testing session, you need only to inform the experimenter that you wish to stop and this will be done immediately and the data provided to that point will not be included in research. It will not be possible to withdraw your data one it has been analysed as part of the full data-set. Therefore, if you wish to withdraw your data after your participation, this must be done before the 15th of December 2017 when data collection is scheduled to finish.

What will happen to the results of the research?

The data in this study will be used as part of my PhD thesis with the additional aim of writing it up for journal publication. If you would like to receive a summary of the results when these are available, this can be provided and you will be given the opportunity at the end of the study to indicate this preference.

As per University policy, all data collected will be kept by the University for a minimum of 10 years.

Where can I get more information?

If you have any further questions, please contact Amy Boyson via the following email address: asb1e14@soton.ac.uk

What happens if something goes wrong?

If you have questions about your rights as a participant in this research, or if you feel that you have been placed at risk, you may contact the Chair of the Ethics Committee, Psychology,

University of Southampton, Southampton, SO17 1BJ. Phone: +44 (0)23 8059 3856, email fshs-rso@soton.ac.uk. Or alternatively you can also contact the Research Governance Manager. Phone: 02380 595058, email: rgoinfo@soton.ac.uk.

Thank you for taking the time to read the information sheet and considering taking part in the research.

A.4.2 Consent Form

UNIVERSITY OF Southampton

CONSENT FORM

Study title: The relationship between entrainment and ADHD symptoms in adults II

Researcher name: Amy Boyson

ERGO number: 27598

Please initial the box(es) if you agree with the statement(s):

I have read and understood the information sheet Version 1 20th June 2017 and have had the opportunity to ask questions about the study.	
I agree to take part in this research project and agree for my data to be used for the purpose of this study.	
I understand my participation is voluntary and I may withdraw at any time for any reason without my rights being affected.	

Name of participant (print name)……

Signature of participant……

Date……

Name of researcher (print name)……

Signature of researcher ……

Date……

A.4.3 Health Screening Questionnaire

Initial Screening Form

Study Title: The relationship between entrainment and ADHD in adults II
Researcher: Amy Boyson
ERGO Ethics number: 27598

In order for you to take part in this research you must meet certain inclusion and exclusion criteria. This form allows us to collect some initial information about you to help us ascertain your suitability for the study. All information provided will remain confidential and stored in accordance with the Data Protection Act and University of Southampton policy.

Date of Birth: .....

Do you speak English as your main language?	Yes	No
Have you ever had a serious head injury?	Yes	No
Do you suffer with epilepsy?	Yes	No
Have you been diagnosed with a mental health disorder?	Yes	No
Are you taking any psychoactive medication?	Yes	No
Do you have any vision or hearing problems?	Yes	No
Do you have a skin condition?	Yes	No
Do you have a paediatric condition which could lead to major neurological disorders and/or a severe learning delay?	Yes	No

If you have answered "Yes" to any of the above, please use this space to give further details and/or to provide any further information relating your health, learning, and development which you think could be relevant to your taking part in the study. (Continue overleaf if necessary).

.....
.....
.....
.....
.....

For Office Use Only

Participant ID: .....

Eligible to Participate: Yes No

A.4.4 Debrief Statement

UNIVERSITY OF Southampton

The relationship between entrainment and ADHD symptoms in adults II

Debriefing Statement (Version 1, 07/06/2017)

The aim of this research was to investigate the relationship between entrainment (the synchronisation of neural oscillations) and ADHD symptoms. It is expected that individuals who report a higher level of ADHD symptoms will have a less efficient entrainment process. Your data will help our understanding of this relationship and its association with the symptoms of ADHD. Once again results of this study will not include your name or any other identifying characteristics. The research did not use deception. You may have a copy of this summary if you wish. Please indicate below if you would like to receive a summary of the results of the research once it has been completed.

If you have any further questions please contact me Amy Boyson at *asb1e14@soton.ac.uk*.

Thank you for your participation in this research.

Signature _____ Date _____

Name _____

I would like to receive a written summary of the results of the study when these are available	

If you have questions about your rights as a participant in this research, or if you feel that you have been placed at risk, you may contact the Chair of the Ethics Committee, Psychology, University of Southampton, Southampton, SO17 1BJ. Phone: +44 (0)23 8059 3856, email fshs-rso@soton.ac.uk

Please see the below reference if you wish to find out more about the possible relationship between ADHD and entrainment: Calderone, D. J., Lakatos, P., Butler, P. D., & Castellanos, F. X. (2014). Entrainment of neural oscillations as a modifiable substrate of attention. Trends in Cognitive Sciences, 18(6), 300-9.

Appendix A

The screening questionnaire you completed before the start of the study was designed to ascertain your level of ADHD type symptoms. These results allow us to separate those with a higher level of symptoms from those with lower symptom levels. This screening questionnaire is NOT a diagnosis and if you are concerned about possible symptoms of ADHD you should consult your GP. The University also offer a counselling service for students who are concerned about any mental health issues. Please see the below links for further information.

http://www.southampton.ac.uk/edusupport/mental_health_and_wellbeing/index.page

http://www.nhs.uk/conditions/attention-deficit-hyperactivity-disorder/pages/introduction.aspx

Appendix B Supplementary Tables

Supplementary Table 6.1
A comparison of the severity of ADHD symptoms between Study 1, Study 2, Broyd et al. (2011) and Hsu et al. (2013).

		High			Low			*d*
		n	*M*	*SD*	*n*	*M*	*SD*	
Study 1	Total	24	33.04	7.41	30	7.03	3.16	4.57
	Inattentive		16.83	3.63		3.67	2.32	4.32
	Hyperactive/Impulsive		16.21	5.50		3.37	1.63	3.17
Study 2	Total	21	31.33	5.69	21	5.14	3.14	5.70
	Inattentive		16.48	4.25		2.86	2.22	4.02
	Hyperactive/Impulsive		14.86	4.23		2.29	1.90	3.83
Broyd et al (2011)	Total	20	28.10	3.96	20	10.95	3.14	4.80
	Inattentive		14.05	2.40		5.65	2.21	3.64
	Hyperactive/Impulsive		14.05	3.00		5.30	2.03	3.42
Hsu et al (2013)	Total	16	28.13	6.26	16	7.75	3.09	4.13
	Inattentive		15.63	3.61		4.25	1.92	3.94
	Hyperactive/Impulsive		12.50	3.33		3.50	1.83	3.35

Supplementary Table 6.2
Number of high symptom participants in each ADHD subtype for each study.

		Inattentive	Hyperactive / Impulsive	Combined
Study 1	N	8	4	12
Study 2	N	5	8	8

Appendix C Adolescent Study NHS Ethical Approval

NHS
Health Research Authority
South Central - Hampshire A Research Ethics Committee
Level 3, Block B
Whitefriars
Lewins Mead
Bristol
BS1 2NT

Telephone: 0117 3421328

10 March 2016

Miss Amy S Boyson
Postgraduate Researcher
University of Southampton
University of Southampton B44/3099
Highfield Campus
Southampton
SO17 1BJ

Dear Miss Boyson

Study title:	**The relationship between ADHD and entrainment of neural oscillations in adolescents as measured with EEG**
REC reference:	**16/SC/0072**
Protocol number:	**n/a**
IRAS project ID:	**184564**

Thank you for your submission of 01 March 2016, responding to the Committee's request for further information on the above research and submitting revised documentation.

The further information has been considered on behalf of the Committee by the Vice Chair.

We plan to publish your research summary wording for the above study on the HRA website, together with your contact details. Publication will be no earlier than three months from the date of this opinion letter. Should you wish to provide a substitute contact point, require further information, or wish to make a request to postpone publication, please contact the REC Manager, Mrs Maxine Knight, nrescommittee.southcentral-hampshirea@nhs.net.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

Conditions of the favourable opinion

The REC favourable opinion is subject to the following conditions being met prior to the start of
the study.

Management permission must be obtained from each host organisation prior to the start of the study at the site concerned.

Management permission should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements. Each NHS organisation must confirm through the signing of agreements and/or other documents that it has given permission for the research to proceed (except where explicitly specified otherwise).

Guidance on applying for NHS permission for research is available in the Integrated Research Application System, www.hra.nhs.uk or at http://www.rdforum.nhs.uk.

Where a NHS organisation's role in the study is limited to identifying and referring potential participants to research sites ("participant identification centre"), guidance should be sought from the R&D office on the information it requires to give permission for this activity.

For non-NHS sites, site management permission should be obtained in accordance with the procedures of the relevant host organisation.

Sponsors are not required to notify the Committee of management permissions from host organisations

Registration of Clinical Trials

All clinical trials (defined as the first four categories on the IRAS filter page) must be registered on a publically accessible database within 6 weeks of recruitment of the first participant (for medical device studies, within the timeline determined by the current registration and publication trees).

There is no requirement to separately notify the REC but you should do so at the earliest opportunity e.g. when submitting an amendment. We will audit the registration details as part of the annual progress reporting process.

To ensure transparency in research, we strongly recommend that all research is registered but for non-clinical trials this is not currently mandatory.

If a sponsor wishes to contest the need for registration they should contact Catherine Blewett (catherineblewett@nhs.net), the HRA does not, however, expect exceptions to be made. Guidance on where to register is provided within IRAS.

It is the responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

Ethical review of research sites

NHS sites

The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" below).

Non-NHS sites

The Committee has not yet completed any site-specific assessment (SSA) for the non-NHS research site(s) taking part in this study. The favourable opinion does not therefore apply to any non-NHS site at present. We will write to you again as soon as an SSA application(s) has been reviewed. In the meantime no study procedures should be initiated at non-NHS sites.

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document	*Version*	*Date*
Copies of advertisement materials for research participants [Advert]	3	23 February 2016
Evidence of Sponsor insurance or indemnity (non NHS Sponsors only) [Southampton Insurance]	1	13 October 2015
IRAS Checklist XML [Checklist_01032016]		01 March 2016
Letters of invitation to participant [Letter to Parents]	2	23 February 2016
Letters of invitation to participant [Letter to SHARe Parents]	2	23 February 2016
Non-validated questionnaire [Initial Screening Form]	3	23 February 2016
Other [Letter to Schools]	1	31 July 2015
Other [Intolerance to Uncertainty - Child]		
Other [Intolerance to Uncertainty - Parent]		
Other [SHARe Steering Committee Approval]	1	27 October 2015
Other [Fruzsina Soltesz CV]	1	29 July 2015
Other [Debrief]	2	19 August 2015
Other [Reply Slip]	1	30 July 2015
Other [Supervisor CV - Julie Hadwin]	1	11 January 2016
Other [Duration Discrimination Task]	1	22 February 2016
Other [Sustained Attention Task]	1	22 February 2016
Other [Entrainment Task]	1	23 February 2016
Other [Stroop Task]	1	23 February 2016
Participant consent form [Adolescent Assent Form]	3	23 February 2016
Participant consent form [Parent Consent Form]	3	23 February 2016
Participant information sheet (PIS) [Adolescent Information Sheet]	4	23 February 2016
Participant information sheet (PIS) [Parent Information Sheet]	4	23 February 2016
REC Application Form [REC_Form_26012016]		26 January 2016
Research protocol or project proposal [Research Protocol]	3	23 February 2016
Summary CV for Chief Investigator (CI) [CI CV - Amy Boyson]	1	10 November 2015
Summary CV for supervisor (student research) [Supervisor CV - Edmund Sonuga-Barke]	1	10 November 2015

Validated questionnaire [SNAP-IV]		
Validated questionnaire [DISC-IV ADHD]		
Validated questionnaire [DISC-IV Oppositional Defiance Disorder]		
Validated questionnaire [DISC-IV Conduct Disorder]		
Validated questionnaire [Intolerance to Uncertainty - Child]		
Validated questionnaire [Intolerance to Uncertainty - Parent]		
Validated questionnaire [WASI-II Vocabulary Task]		
Validated questionnaire [WASI-II Matrix Reasoning Task]		
Validated questionnaire [AWMA - Screener]		

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

Reporting requirements

The attached document *"After ethical review – guidance for researchers"* gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Notification of serious breaches of the protocol
- Progress and safety reports
- Notifying the end of the study

The HRA website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

User Feedback

The Health Research Authority is continually striving to provide a high quality service to all applicants and sponsors. You are invited to give your view of the service you have received and the application procedure. If you wish to make your views known please use the feedback form available on the HRA website:
http://www.hra.nhs.uk/about-the-hra/governance/quality-assurance/

HRA Training

We are pleased to welcome researchers and R&D staff at our training days – see details at
http://www.hra.nhs.uk/hra-training/

16/SC/0072	**Please quote this number on all correspondence**

With the Committee's best wishes for the success of this project.

Yours sincerely

Dr Ronja Bahadori Vice Chair

Email:nrescommittee.southcentral-hampshirea@nhs.net

Enclosures: "After ethical review – guidance for researchers"

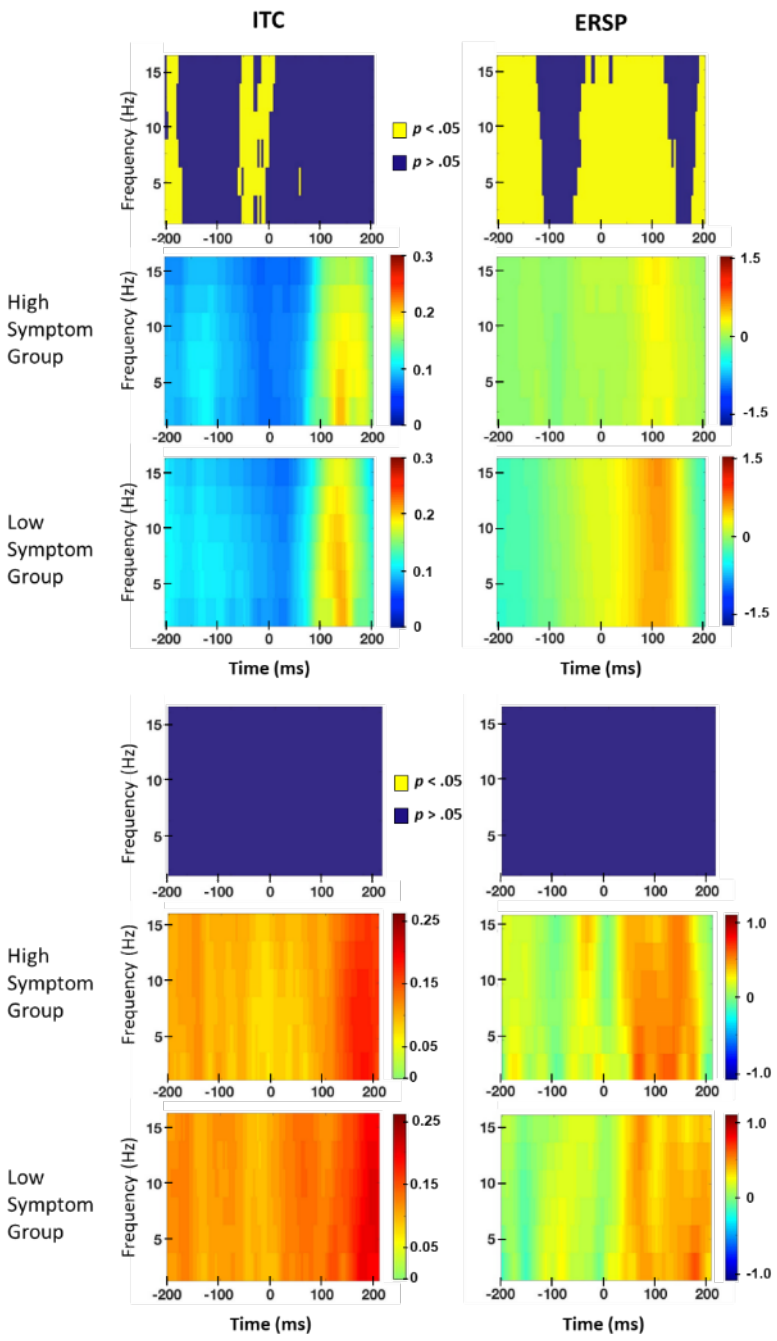
Copy to: *Diana Galpin*
Dr Sarah Williams, Solent NHS Trust Research Department

Appendix D Short Time Fourier Transform Output

D.1 Single Modality Task

a)

b)



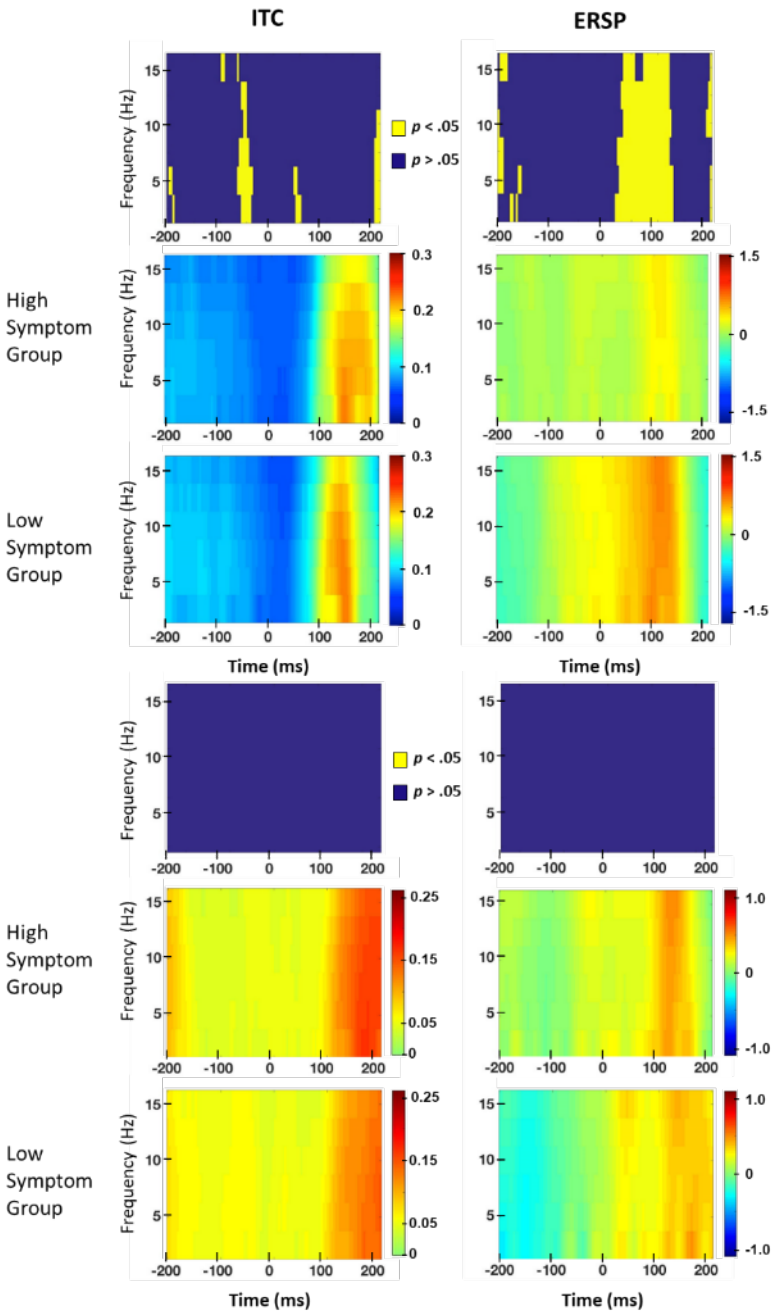
Supplementary Figure 6.1 Time-frequency plots for ITC and ERSP data for a) Study 1and b) Study 2 for the single modality task, derived from short time Fourier transform (STFT).

ITC values lie between 0 and 1, with higher values representing a higher level of phase coherence from trial to trial. ERSP images show the degree of change in the power of signal at any given frequency, and can be positive or negative showing an increase or decrease in power respectively. The top row of images depicts regions of the time/frequency plots that show a significant difference between the groups by the point-by-point ANOVAs, which were run on FDR corrected data. Blue indicates no significant difference ($p > .05$); yellow regions are areas where a significant difference was found ($p < .05$). The middle and bottom row of images show averaged data for the respective condition/group.

D.2 Selective Attention Task

a)

b)



Supplementary Figure 6.2 Time-frequency plots for ITC and ERSP data for a) Study 1and b) Study 2 for the dual modality task, derived from short time Fourier transform (STFT).

ITC values lie between 0 and 1, with higher values representing a higher level of phase coherence from trial to trial. ERSP images show the degree of change in the power of signal at any given frequency, and can be positive or negative showing an increase or decrease in power respectively. The top row of images depicts regions of the time/frequency plots that show a significant difference between the groups by the point-by-point ANOVAs, which were run on FDR corrected data. Blue indicates no significant difference ($p > .05$); yellow regions are areas where a significant difference was found ($p < .05$). The middle and bottom row of images show averaged data for the respective condition/group.

Glossary of Terms

Amplitude – The degree of excitability in a given electrical signal given in micro-volts (μV)

Entrainment – The process by which neural oscillations become synchronised/phase-locked/ coherent with each other or with rhythmic inputs

Event related potential (ERP) – The averaged electrophysiological response to a given event/stimulus input

False discovery rate (FDR) – The expected proportion of Type I errors. Can be controlled for the FDR-correction procedures such as the Benjamini-Hochberg method

Frequency – The number of cycles completed within 1 second of a neuro-electric oscillation

Jack-knifing – A resampling technique in which each participant's data is removed from the dataset and then the data is averaged. This is repeated such that each participant's data has been removed once, leaving the same number of jack-knifed samples as there were original data points. It is a method specifically recommended for the study of the lateralised readiness potential.

Lateralised readiness potential (LRP) – An event related potential specifically related to the motor preparation of a response. In conflict/interference inhibition tasks, the LRP can be used to estimate the point of inhibition from the transition factor; the point at which an incorrect response is changed to a correct one.

Neural oscillation – Rhythmic pattern of neural electrical activity

Neuronal coherence – When neuronal ensembles become phase-locked/entrained such that they oscillate in synchronicity with each other.

Phase – A point in time on a waveform, given in degrees or radians. A wave starts at zero and cycles through 360°

Phase-locking – The process by which oscillations become coherent/synchronous/entrained with each other such that the peak of the waves occur at the same point in time.

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