Does ADHD derive from dysfunction of Gray’s Behavioural Inhibition System?

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Abstract

ADHD is a common childhood disorder that has been classified into three subtypes (ADHD-I, ADHD-H and ADHD-C) but may involve a spectrum of symptoms. Deficits in executive functions have been considered to be a major source of the disability associated with ADHD. Impairments in behavioural inhibition fundamental to executive functions have been hypothesized as the core of ADHD symptoms (Barkley, 1997b; Quay, 1997). This thesis tests whether ADHD deficits derive from dysfunction of Gray’s Behavioural Inhibition System (BIS). It does so by assessing the differences between ADHD-I, ADHD-C and control groups in their Goal Conflict Specific Rhythmicity (GCSR), a biomarker of BIS function (McNaughton, 2014; McNaughton, Swart, Neo, Bates, & Glue, 2013).

Two studies were undertaken, one in New Zealand (initial study) and one in Iran (main study). They demonstrated that ADHD-C showed GCSR activity, at the right frontal site F8, similar to that in control groups. However, ADHD-I showed less GCSR activity than controls – consistent with BIS dysfunction. ADHD-I symptoms such as low levels of attention and arousal could be due to BIS under activity. However, hyperactivity and impulsivity symptoms in ADHD-C cannot be explained by BIS dysfunction as there was no evidence of abnormal BIS activity for ADHD-C in any of the studies. Behavioural Approach System (BAS) over-activity may better explain ADHD-C symptoms by producing a stronger tendency to approach and act. Given that ADHD-I differs from ADHD-C it follows that ADHD as a whole cannot be seen as a single homogenous entity, although both ADHD-I and ADHD-C may share a common factor. The distribution of GCSR, and other measures for the three diagnostic groups overlapped fairly strongly – supporting the concept of a multidimensional spectrum for ADHD symptoms rather than categorical divisions.

ADHD-I and ADHD-C varied from the control to some extent in terms of the accuracy of responses and SSRTs. However, there was no difference between ADHD-I and ADHD-C regarding their behavioural outputs in the SST. Longer SSRTs for ADHD participants have been interpreted as action stopping problems that involve a different, anxiolytic insensitive, neural system from behavioural inhibition. This finding supports the idea of a common factor in ADHD-I and ADHD-C.

Overall, both ADHD-I and ADHD-C share action stopping problems reflected by SSRTs. BAS abnormality might produce some ADHD-C symptoms. BIS abnormality might produce some ADHD-I symptoms. This thesis shows that BIS deficiencies are not sufficient to account for all cases of ADHD as hypothesized by Quay (1997).
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<th>Description</th>
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<td>ADHD</td>
<td>Attention Deficit Hyperactivity Disorder</td>
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<tr>
<td>ADHD-I</td>
<td>Inattentive subtypes of ADHD</td>
</tr>
<tr>
<td>ADHD-C</td>
<td>Combined subtype of ADHD</td>
</tr>
<tr>
<td>ADHD-HI</td>
<td>Hyperactive-Impulsive subtype of ADHD</td>
</tr>
<tr>
<td>ANOVA</td>
<td>Analysis of variance</td>
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<tr>
<td>BAS</td>
<td>Behavioural Approach System</td>
</tr>
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<td>BIS</td>
<td>Behavioural Inhibition System</td>
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<tr>
<td>DSM</td>
<td>Diagnostic and Statistical Manual of Mental Disorders</td>
</tr>
<tr>
<td>EEG</td>
<td>Electroencephalogram</td>
</tr>
<tr>
<td>ERP</td>
<td>Event Related Potentials</td>
</tr>
<tr>
<td>FFFS</td>
<td>Fight, freeze and flight system</td>
</tr>
<tr>
<td>GCSR</td>
<td>Goal conflict specific rhythmicity</td>
</tr>
<tr>
<td>IFG</td>
<td>Inferior Frontal Gyrus</td>
</tr>
<tr>
<td>IR</td>
<td>Iran</td>
</tr>
<tr>
<td>MRT</td>
<td>Median Reaction Time</td>
</tr>
<tr>
<td>NZ</td>
<td>New Zealand</td>
</tr>
<tr>
<td>$P_{\text{inhibit}}$</td>
<td>Probability of inhibition in the stop signal task</td>
</tr>
<tr>
<td>Pre-SMA</td>
<td>Pre-supplementary motor area</td>
</tr>
<tr>
<td>RSA</td>
<td>Rhythmical slow activity</td>
</tr>
<tr>
<td>SSD</td>
<td>Stop-Signal Delay</td>
</tr>
<tr>
<td>SSRT</td>
<td>Stop-Signal Reaction Time</td>
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<td>SST</td>
<td>Stop-Signal Task</td>
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1 Introduction

1.1 What is ADHD?

Attention Deficit Hyperactivity Disorder (ADHD), with an overall incidence of 6%, is one of the most common childhood disorders worldwide (Polanczyk, Silva de Lima, Horta, Biederman, & Rohde, 2007). ADHD can continue through adolescence and adulthood. It has been associated with not only a broad range of negative outcomes for affected individuals but also with a serious financial cost to families and societies (Kupfer et al., 2000). According to the latest (5th) edition (APA, 2013) of the Diagnostic and Statistical Manual of Mental Disorders (DSM), ADHD is a chronic condition and characterised by impairing symptoms of difficulty paying attention, difficulty controlling behaviour and hyperactivity. However ADHD and its diagnosis have been controversial since the disorder was first presented in the second edition of the DSM (APA, 1968). Attempts to provide an inclusive definition of the disorder, which could cover all essential features of ADHD, have caused several changes in successive editions of DSM. According to the DSM-5 (APA, 2013), ADHD can occur as three presentations: predominantly inattentive (ADHD-I); predominantly hyperactive-impulsive (ADHD-HI); and combined (ADHD-C). The presentations (essentially subtypes) are defined according to which symptoms stand out most.

1.2 ADHD: subtypes versus spectrum

The DSM subtype classification system for Attention Deficit Hyperactivity Disorder (ADHD) is widely utilized by both clinicians and researchers, although the validity of the usual division into three subtypes (inattentive, hyperactive-impulsive and combined) has been repeatedly disputed (Milich, Balentine, & Lynam, 2001).

The concept of the disorder was first introduced in the second edition of the Diagnostic and Statistical Manual of Mental Disorders, DSM-II (APA, 1968) with the term “hyper-kinetic reaction of childhood”. It was mostly defined as a type of hyperactivity and restlessness accompanied by a short attention span. The next edition, DSM-III emphasized the problem with attention and changed the name to “attention-deficit disorder” (ADD). Along with its name change, the diagnostic criteria defined two subtypes of ADD: ADD/WO (without hyperactivity) and ADD/H (with hyperactivity). This classification confirmed the presence of attention problems in the absence of impulsivity and hyperactivity (APA, 1980).
Both inattention and hyperactivity were emphasized again in the revised version of the DSM-III, DSM-III-R (APA, 1987) and the disorder was named “attention-deficit hyperactivity disorder”. However the DSM-III-R criteria did not allow for the possibility of the presence of attentional problems without hyperactivity. In this version of the DSM, the symptoms of the disorder were a one-dimensional group of 14 symptoms and the majority of them described hyperactive or impulsive symptoms. The concept of ADHD having three approximately independent subtypes formed in the next editions of the DSM (DSM-IV and DSM-IV-TR): inattentive (ADHD-I), hyperactive-impulsive (ADHD-HI) and combined (ADHD-C) (APA, 1994). Subtype delineation is based on the presence of six or more symptoms of hyperactivity, inattention or both. ADHD-I is diagnosed when six or more of the inattentive symptoms and fewer than six of the hyperactivity/impulsivity symptoms are present; ADHD-HI is diagnosed when six or more symptoms of hyperactivity/impulsivity are present and fewer than six of the inattentive symptoms; and ADHD-C is diagnosed when six or more from both lists are present (APA, 2000). The most recent edition of the DSM (DSM-IV) has maintained the three subtypes and added a fourth “inattentive presentation (restrictive)”, which is diagnosed when six or more of the inattentive symptoms and fewer than three of the hyperactivity/impulsivity symptoms are present (APA, 2013). DSM-IV delineates three presentations of ADHD, which are designed to be distinct from the previous nomenclature (subtypes) to highlight their lack of stability.

The overall DSM disease model is based on categorical classification. This perspective assumes that each category (in this case a subtype of ADHD) involves a list of symptoms that are discontinuous from each other. Categorical classification is best when: (1) all the members of a subtype are homogeneous; (2) there are clear borders between subtypes; and (3) the different subtypes are reciprocally exclusive (APA, 2000). The appropriateness of the use of a categorical system for ADHD has been doubted (Hyman, 2010) and the need for developing a more dynamic model that can cover the complexity of ADHD has been emphasized (Toplak et al., 2009).

Although ADHD subtypes are distinguishable because of the presence of varying symptomatology, the question of fundamental differences in core and aetiological characters has remained unresolved. There has been extensive research concerning this question in the past decades, which has led to a large, but somewhat inconsistent, literature.
Some studies have supported the validity of the three separate subtypes (Glutting, Youngstrom, & Watkins, 2005; Proctor & Prevatt, 2009). Some researchers have gone one step further and conceptualised ADHD-I as a distinct disorder (Barkley, 2001; Diamond, 2005; Hinshaw, 2001). Indeed, the symptoms of ADHD-C and ADHD-I have been found to fall at opposite ends of a spectrum in many ways such as overactive versus hypoactive, externalizing versus internalizing and energetic versus sluggish (Milich et al., 2001). These results are consistent with a large scale study of validation of DSM-IV ADHD subtypes in a nationally representative sample of Australian youths (Graetz, Sawyer, Hazell, Arney, & Baghurst, 2001).

According to a factor analysis carried out by Martel et al. (2010) a bifactor model with a general factor (labelled ‘g’) and two specific symptom domain factors of inattention and hyperactivity/impulsivity fits best with ADHD symptoms (Martel et al., 2010). This model allows for one- and two-factor conceptualizations to exist simultaneously. It suggests that there is one general factor that is shared between two subtypes and captures common variance in inattentive and hyperactive-impulsive symptom domains. At the same time, there are also two additional factors that capture unique variance in inattentive and hyperactive-impulsive symptom domains separately. Based on this view, to provide the maximal information about the symptom profile of ADHD for each individual, general risk of ADHD, specific risk for inattention, and specific risk of hyperactivity-impulsivity should be separately assessed. According to the bifactor model, there are potential implications for distinct etiological inputs that may emphasize different treatment approaches to individual symptom profiles. Martel’s study is consistent with Toplak’s finding of an important unitary component to ADHD symptoms and separable dimensional traits of inattention and hyperactivity/impulsivity (Toplak et al., 2009). Ghanizadeh (2012) also, in a more recent analysis of DSM5 symptoms, supported the two factor model including inattentiveness and hyperactivity/impulsivity. However, the four new items added to the DSM-5 diagnostic criteria can be considered as a third factor (Ghanizadeh, 2012).

In contrast to the bulk of studies, which provide fairly robust evidence for the validity of the distinctiveness of the two subtypes of ADHD (Martel, Nigg, & Eye, 2009; Wahlstedt, Thorell, & Bohlin, 2009), some of the findings are inconsistent and equivocal. For instance, ADHD-I did not differ from ADHD-C in terms of aspects of every day attention relating to selective and sustained attention (Lemiere et al., 2010). Impulsivity itself, as a core symptom
of the impulsivity/hyperactivity subtype in ADHD, could not define a reliable criterion for the accurate classification of subtypes. This means we cannot consider ADHD-I as “not impulsive” compared to ADHD-C as “impulsive”. In fact, both subtypes include some impulsive traits that do not differ significantly (Miller, Derefinko, Lynam, Milich, & Fillmore, 2010).

Despite the large volume of papers since the publication of DSM-IV and its introduction of ADHD-I as a subtype of ADHD, there are only a few studies supporting this diagnosis as a distinct entity. Diagnosis of ADHD-C is more consistent than the other two, although there are no specific data on the reliability of ADHD-I and ADHD-HI (Woo & Rey, 2005).

Baeyens (2006), has reviewed the literature across different measurement levels and concluded that overall similarities between the subtypes are more than dissimilarities and in fact “the more fundamental the measurement level is, the less obvious it becomes that the ADHD subtypes are clearly distinguishable disorders” (Baeyens et al., 2006). Neuropsychological methods for instance could not identify critical neurological substrates for the subtype differences (Solanto, Gilbert, Raj, Zhu, & Pope-Boyd, 2007).

The inconsistent results obtained from different methodological studies might be explained by the fact that the diagnostic criteria of the DSM for each of the ADHD subtypes are based on observations of experts. Each revision of the DSM has generated a list of behavioural criteria to diagnose each subtype of ADHD, which should be observed at least in two different areas (e.g. school and home). So, unsurprisingly, there is little evidence of the diagnostic validity of three separate ADHD subtypes when cognitive and neuropsychological assessments are used. Bernfeld (2012) explained that these two measurement levels (behavioural vs. neuropsychological) are about two totally different facets that are as dissimilar as oranges and apples. Thus we should not expect behavioural outputs to correlate with neuropsychological data. Looking at the more fundamental measurement level of genetic studies also did not provide support for the DSM classification of three subtypes. The high level of heritability of ADHD (70-90%) strongly suggests the importance of genetic factors (Levy, Hay, McStephen, Wood, & Waldman, 1997). The genes for the dopamine receptor DRD4 and DRD5 and the dopamine transporter DAT1 have an influence on the development of ADHD (Yeh, Morley, & Hall, 2004). However when subtypes are taken into
account, the 7-repeat allele of the DRD4 gene is equally linked to both ADHD-I and ADHD-C subtypes (Baeyens et al., 2006). In the next section, we elaborate on the neuropsychological aspects of ADHD and the subtypes in more detail.

1.3 The Neuropsychology of ADHD

The neuropsychology of ADHD is a field that can illuminate the intermediate constructs that bridge between genetic factors and clinical symptoms. Neurological studies show abnormalities on both the neuroanatomical and the neurochemical level that can explain disorders in some processes that underlie different symptoms of ADHD. Reduced volume or functionality of the prefrontal cortex (PFC), caudate and cerebellum in ADHD groups are generally found (Sharma & Couture, 2014). The network activity between these areas which regulate attention, behaviour and emotion is highly neurochemically sensitive (Arnsten & Pliszka, 2011).

This prefrontal/caudate/cerebellum network is maintained by the neurotransmitters, dopamine and norepinephrine, both of which have a powerful, inverted-U shaped influence on PFC cognitive functioning (Arnsten, 2007). The inverted-U occurs because both insufficient and excessive release of catecholamines causes cognitive dysfunctions. Neurochemical research strongly indicates a dopamine/norepinephrine deficit in ADHD (Sharma & Couture, 2014). Specifically, there are deficits in the dopamine transporter (DAT1) that regulates the dopamine in the synaptic cleft. A SPECT study showed that in adults with ADHD, DAT1 levels are almost 70% higher than in controls (Biederman & Spencer, 1999).

Stimulant medications, which facilitate dopaminergic and noradrenergic neurotransmission, are the first line treatment for children and adults with ADHD. These drugs modulate dopamine function in two ways: first, by releasing dopamine from vesicular stores and second, by blockage of the DAT and increasing dopamine within the synaptic cleft (Solanto, 2002).

Serotonergic as well as noradrenergic systems have been suggested to be involved in ADHD. There is evidence that dysfunction in central serotonin (5HT) has a role in aggressive, impulsive, violent and criminal behaviour. Retz et al (2004) examined the association of the 5HTTLPR (5-HT Transporter gene-linked polymorphic region) with
violent behaviour in a sample of 153 males referred for a forensic psychiatric examination and found an association between a history of ADHD related symptoms in childhood and involvement in illegal behaviour. However, 5-HT has been far more extensively linked with aggression and violent behaviour than ADHD.

Cognitive functions have been examined by neuropsychological and cognitive assessments. The results can mostly differentiate between ADHD and control groups (Barkley, 1997a; Nigg, 2001). Deficits in executive functions have been considered a major source of the disability associated with ADHD. Executive functions are defined as higher order cognitive functions that enable self-control of action, thought and emotion (Pennington & Ozonoff, 1996). Pennington and Ozonoff (1996) defined five major domains of executive functions including response inhibition, visual working memory, planning, cognitive flexibility, and verbal fluency. The Stop Signal Task, Go/No-Go and Stroop Color-Word tests were used to measure Executive functions.

Barkley conceptualized behavioural inhibition as the highest order factor of executive functions (Barkley, 1997). Consistent with his theory is the result of a study where deficits in response inhibition were the core problem that caused secondary problems in other executive functions (Cheung, Mitsis, & Halperin, 2004). The key thing is that disinhibited behaviour is among the most consistent deficits found in children with ADHD. That is the reason why in the present thesis, we focus on the concept of a behavioural inhibition system to understand ADHD better.

When subtypes are taken into account, there are few distinctions that have been made between ADHD-I and ADHD-C in terms of neuropsychological features. Likewise, there is little evidence for neuroanatomical differences between the ADHD subtypes. Furthermore, a higher level of dopamine transporter (DAT1) density is a character of ADHD compared to control groups but is involved not only in ADHD-C, but also in ADHD-I (Krause, Dresel, Krause, la Fougere, & Ackenheil, 2003). Although ADHD-related deficits in executive functions have been replicated in many studies (Barkley, 1997a; Nigg, 2001), a recent study suggests that there were only a few executive function measures that can discriminate between ADHD subtypes (Skogli, Egeland, Andersen, Hovik, & Oie, 2014). We will discuss behavioural inhibition in more detail in later sections.
1.4 Electroencephalogram (EEG) and Event Related Potentials (ERPs) in ADHD

Electroencephalogram (EEG) studies in ADHD groups revealed abnormalities on the neurophysiological level compared to control children. There is also some evidence of ADHD-I showing intermediate measures between those of control and ADHD-C (Clarke, Barry, McCarthy, & Selikowitz, 2001b). We will first review studies investigating ERPs and then explain EEG features of ADHD subtypes in more detail below.

1.4.1 Review of Past ADHD-ERP Findings

ERP waveforms are made up of a series of positive and negative voltage deflections in the ongoing EEG that are time-locked to the onset of a sensory, motor, or cognitive event. A positive wave occurring ~200ms after the stimulus is called P2 (or P200), and a negative wave ~200ms after the stimulus is called N2 (or N200). The most common ERP components reported are: N1, N2, P2, P3, event related negativity (ERN), event related desynchronisation, error positivity and contingent negative variation.

During recent years ERPs have been used more frequently to identify underlying deficits in brain processing that appear in patients with mental or psychological disorders, such as ADHD (Johnstone, Barry, & Clarke, 2013). Each of the ERP components is assumed to reflect a specific stage in neural processing, i.e. P3 is thought to reflect processes involved in successfully inhibiting a response (Dimoska, Johnstone, Barry, & Clarke, 2003). Therefore alterations in ERP components such as N2 or P3, which are observed in children with ADHD, may underlie impairments in functions including inhibitory control (Albrecht, Banaschewski, Brandeis, Heinrich, & Rothenberger, 2005; Dimoska et al., 2003; Johnstone, Barry, & Clarke, 2007; Liotti et al., 2007; Carin C. E. Overtoom et al., 2002; S. R. Pliszka, M. Liotti, & M. G. Woldorff, 2000b; Senderecka, Grabowska, Szewczyk, Gerc, & Chmylak, 2012).

This following summarizes a review of the previous ADHD-ERP literature by Thakkar et al. (2014). It concentrated on studies that used tasks associated with response inhibition, including: stop signal tasks (SSTs); continuous performance tasks (CPTs) and oddball paradigms. SST is a neurocognitive task designed to provide a sensitive measure of the time taken by the brain to inhibit or suppress inappropriate motor responses (Morein-
Zamir, 2010). CPTs are a kind of neuropsychological test that measures a person’s sustained and selective attention. Sustained attention is the ability to maintain a consistent focus on some continuous activity or stimuli, and is associated with impulsivity. Selective attention is the ability to focus on relevant stimuli and ignore competing stimuli. This skill is associated with distractibility (Conners & Staff, 2000). The oddball paradigm is an experimental design used within event-related potential research, where presentations of sequences of repetitive audio/visual stimuli are infrequently interrupted by a deviant stimulus. The subject is asked to react either by counting or by button pressing incidents of target stimuli that are hidden as rare occurrences amongst a series of more common stimuli that often require no response. Examination of ERPs in children with ADHD during such tasks may reveal ERP differences linked to deficits in response inhibition. Table 1.1 notes the direction of amplitude and/or latency differences observed in two ERP components (N2 and P3) in ADHD participants, across a number of different scalp regions. Most of these studies focused on ERPs during stop trials (in SSTs) and NoGo trials (in Go/NoGo’s or CPTs) as the goal of these trials is to successfully inhibit responding to a stimulus.

Thakkar et al. (2014) concluded from their review that reduced N2 and/or P3 amplitude during response inhibition tasks is the most common ERP finding in children with ADHD compared to neurotypical children. They, therefore, proposed that reduced N2 and P3 amplitudes may underlie impairments in response inhibition previously reported in children with ADHD (Albrecht et al., 2005; Dimoska et al., 2003; Johnstone, Barry, et al., 2007; Liotti et al., 2007; C. C. E. Overtoom et al., 2002; Pliszka et al., 2000b; Senderecka, Grabowska, Szewczyk, et al., 2012).
Table 1.1. Results of an exhaustive search for reports of ERP components in tasks assessing inhibitory control such as SSTs, CPTs and oddball paradigms in the previous ADHD literature. Papers are grouped together by task type. ADHD participants had reduced (-), unchanged (0) or increased (+) amplitudes or latencies (as indicated) compared to neurotypical controls in two ERP components: N2 and P3. Table and caption taken from Van Bohemen (2014) with permission.

<table>
<thead>
<tr>
<th>Task</th>
<th>Trial Type</th>
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<td>P3-Cz</td>
<td>(-) Amplitude</td>
<td>ADHD</td>
<td>(Fallgatter et al., 2004)</td>
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<td>CPT (Visual)</td>
<td>NoGo</td>
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<td>(0) Amplitude</td>
<td>ADHD</td>
<td>(Fallgatter et al., 2004)</td>
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<td>N2</td>
<td>(-) Amplitude</td>
<td>ADHD-C</td>
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</tr>
<tr>
<td>Flanker (Visual)</td>
<td>Incongruent Trials</td>
<td>N2</td>
<td>(-) Amplitude</td>
<td>ADHD-C</td>
<td>(Johnstone et al., 2009)</td>
</tr>
<tr>
<td>Flanker (Visual)</td>
<td>Neutral Trials</td>
<td>N2</td>
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</tr>
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<td>Incongruent Trials</td>
<td>P3</td>
<td>(+) Amplitude</td>
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<td>(Johnstone et al., 2009)</td>
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<td>(+) Amplitude</td>
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<td>N2</td>
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<td>Flanker-NoGo Hybrid</td>
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<td>N2</td>
<td>(-) Amplitude</td>
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<tr>
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<td>P3-(frontal)</td>
<td>(-) Amplitude</td>
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<td>N2-(central)</td>
<td>(-) Amplitude</td>
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<td>(Johnstone et al., 2009)</td>
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<td>P3</td>
<td>(-) Amplitude</td>
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<td>(Wiersema et al., 2009)</td>
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<td>(Groom et al., 2010)</td>
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<td>(Lazzaro et al., 2001)</td>
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<td>(Lazzaro et al., 2001)</td>
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<td>(Lazzaro et al., 2001)</td>
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<td>(Lazzaro et al., 2001)</td>
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<td>Condition 2</td>
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<td>(Johnstone et al., 2003)</td>
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<td>(-) Amplitude</td>
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<td>(Johnstone et al., 2003)</td>
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<td>(-) Amplitude</td>
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<td>P3b-(Cz)</td>
<td>(-) Amplitude</td>
<td>ADHD-C</td>
<td>(Johnstone et al., 2003)</td>
<td></td>
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<td>(Dimoska et al., 2003)</td>
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<td>(Johnstone et al., 2007)</td>
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<td>Stop Trial</td>
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<td>(+) Amplitude</td>
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<td>P3-(P3, Pz, P4)</td>
<td>(+) Amplitude</td>
<td>ADHD-I</td>
<td>(Johnstone et al., 2007)</td>
</tr>
<tr>
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<td>Correct Stop Trials</td>
<td>N2-(fronto-central)</td>
<td>(+) Amplitude</td>
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<td>(Senderecka, Grabowska, Szewczyk, et al., 2012)</td>
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<td>Correct Stop Trials</td>
<td>N2-(fronto-central)</td>
<td>(+) Latency</td>
<td>ADHD-C</td>
<td>(Senderecka, Grabowska, Szewczyk, et al., 2012)</td>
</tr>
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<td>(-) Amplitude</td>
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<td>(Senderecka, Grabowska, Szewczyk, et al., 2012)</td>
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<td>P3-(fronto-central)</td>
<td>(-) Amplitude</td>
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<td>(Senderecka, Grabowska, Szewczyk, et al., 2012)</td>
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<td>(-) Amplitude</td>
<td>ADHD</td>
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<td>(-) Amplitude</td>
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<td>(-) Amplitude</td>
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<td>Stop Trial</td>
<td>N2-(right frontal)</td>
<td>(-) Amplitude</td>
<td>ADHD-C</td>
<td>(Liotti et al., 2010)</td>
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<td>SST-Visual</td>
<td>Incorrect Stop Trials</td>
<td>P3-(fronto-central)</td>
<td>(-) Amplitude</td>
<td>ADHD-C</td>
<td>(Liotti et al., 2010)</td>
</tr>
<tr>
<td>Stroop-Auditory</td>
<td>Cued Stimuli</td>
<td>P3</td>
<td>(-) Amplitude</td>
<td>ADHD-I</td>
<td>(Kratz et al., 2011)</td>
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<td>(-) Amplitude</td>
<td>ADHD-C</td>
<td>(Kratz et al., 2011)</td>
</tr>
<tr>
<td>Stroop-Auditory</td>
<td>Target Stimuli</td>
<td>P3</td>
<td>(-) Amplitude</td>
<td>ADHD-I</td>
<td>(Kratz et al., 2011)</td>
</tr>
</tbody>
</table>
1.4.2 EEG features of ADHD subtypes

Analyses of EEG rhythmicity have been used to provide information about abnormalities in children with ADHD since 1938 (Jasper, Solomon, & Bradley, 1938). Consistent group differences between children with and without ADHD have been found. Elevated levels of slow wave activity in ADHD groups in comparison to typically developing children are repeatedly reported (Barry, Clarke, & Johnstone, 2003), however with differences between studies. Comparison of studies is complicated by the fact that studies vary in terms of the diagnostic categories for their clinical groups, different diagnostic methods and different methods to quantify the EEG. However, there are reliable dissimilarities between children with ADHD compared to typically developing children, which include increased theta activity, specifically in the frontal regions, increased posterior delta, decreased alpha and beta activity mostly in posterior regions and also increases in theta/alpha and theta/beta ratios (Clarke, Barry, McCarthy, & Selikowitz, 2001a). In the resting EEG, increased slow wave activity (theta, 4–8 Hz, and alpha, 8–13 Hz) and reduced beta (13–30 Hz) activity, especially in central and frontal regions probably reflect under-arousal of the central nervous system (Barry et al., 2003).

However group means may obscure individual differences within the diagnostic groups. In order to better characterise EEG features of individuals with ADHD in each subtype, Clarke et al. (2001a) carried out a cluster analysis of EEG information within a large sample (n = 184) of boys with the combined type of ADHD and identified 3 distinct EEG-defined subtypes. One cluster had greater total power, greater relative theta and a higher theta/beta ratio, as well as less relative delta and beta across all regions. Another cluster had elevated slow wave activity and reduced fast wave activity. The third cluster was characterised by excess beta activity as well as deficiencies in delta and alpha activity. In a replication study with the inattentive subtype of ADHD (n = 100) (Clarke, Barry, McCarthy, Selikowitz, & Brown, 2002) similar patterns to the first two clusters were identified but not the third, excess beta, pattern. Both of these studies were conducted only in boys, so a further study (Clarke et al., 2003) investigated EEG clusters in a sample of girls with ADHD. There were two subgroups, which were less separated than the three boys’ subgroups, emphasising the importance of the gender in ADHD research. The larger cluster of girls had greater total power, more relative theta, and less relative delta and beta than control subjects and the smaller cluster had a greater amount of high amplitude theta activity and deficiencies in all
other bands. The interpretation of the EEG results has led to the proposal of two main models of ADHD, which are described below.

The maturational lag model: As the name of this model indicates, it proposes that ADHD results from a developmental lag in CNS functioning (Kinsbourne, 1973). It proposes that EEG measures from a child with ADHD would be normal for a younger child (John et al., 1990). Developmental studies undertaken in normal children have previously demonstrated a decrease of theta activity with increasing age and also that the rate of this decrease occurs more slowly over the anterior-central regions compared with the posterior (Lazzaro et al., 1999). The maturational lag model of ADHD is supported by all EEG findings, which have presented dominant slow wave activity especially in frontal areas and reduced fast waves in children with ADHD compared to typically developed children. For instance, Lazzaro et al. (1998) found increased absolute theta and alpha activity in frontal regions and decreased relative beta in posterior regions in adolescents with ADHD. As described in the previous section, the second cluster of children found by Clarke et al. (2001a) had EEG that was quite similar to this pattern and he interpreted this as indicative of maturational lag in CNS development. Doehnert, Brandeis, Imhof, Drechsler, and Steinhausen (2010) examined the development of neuropsychological markers of attention and inhibition in ADHD and control groups from childhood to adolescence for support of the developmental lag hypothesis of ADHD. The result of this longitudinal study did not support the developmental lag hypothesis for attentional dysfunction in ADHD. However, they found partial evidence that developmental lag contributes to inhibitory brain dysfunction during early adolescence.

Developmental deviation model: In the developmental deviation model, ADHD is caused by a developmental abnormality in CNS functioning. From this perspective EEG features of a child with ADHD would not be normal even for a younger child. High levels of beta band activity have been observed during both physical and mental activity in neurotypical children (Andreassi, 1995). This beta increase is linked to alertness and mainly occurs when a person is actively thinking, concentrating or motivated. This increased beta can, therefore be seen as an indication of “cortical arousal”. In contrast, a lack of increase in beta activity has been found in children with ADHD (Mann, Lubar, Zimmerman, Miller, & Muenchen, 1992). Inadequate beta enhancement when it is required in children with ADHD might have serious consequences such as lower levels of attention and arousal. These EEG
abnormalities in children with ADHD are not improved with age and cannot be considered normal in children of any age (Klinkerfuss, Lange, Weinberg, & O’leary, 1965). The developmental deviation model can be also termed a ‘hypoarousal model’, which proposes that ADHD is a result of cortical underarousal in this disorder (Satterfield, Cantwell, Lesser, & Posodin, 1972). Luba (1991) found a link between increased theta and decreased beta activity in ADHD. A more recent study by Lansbergen, Arns, van Dongen-Boomsma, Spronk, and Buitelaar (2011) showed that previous findings of increased theta/beta ratio in ADHD may reflect individuals with slow alpha peak frequencies in addition to individuals with true increased theta activity. As noted earlier, Clarke’s (2001a) findings of the cluster with high levels of theta and low levels of delta and beta in ADHD is also consistent with this model.

According to Clarke (2001a), a cluster of EEG profiles in ADHD was found with a high level of beta activity that was labelled as an ‘over-aroused’ group. Neither of the previous models (the maturational lag model and developmental deviation model) include an explanation for the existence of such EEG measures. Limitations in both of these two models suggest that they are too simplistic to account for the symptom profile in ADHD, and that further developments in the EEG models of ADHD are required (Barry et al., 2003).

One of the major problems of most EEG studies in ADHD subtypes is that they assume their clinical subtypes are homogenous. Whereas, as noted before, several studies have described distinct EEG groups within specific ADHD subtypes. Chabot and Serfontein (1996) investigated 407 children and found two sharply opposite neurophysiological subtypes within ADHD: the first group showed fluctuating levels of slow wave activity specially in frontal regions (hypoarousal model), and the second group displayed an increase in EEG activity particularly in frontal regions (hyperarousal model). These EEG features were quite homogenous within the groups, which differed in the nature of the clinical symptoms of inattention, impulsivity, hyperactivity and learning problems. These various EEG profiles of children with ADHD are likely to reflect different underlying neural abnormalities.

1.5 Summary

ADHD is a common childhood disorder that might be classified in three subtypes (ADHD-I, ADHD-HI and ADHD-C) or can be considered as a spectrum of the symptoms. The neuropsychology of ADHD showed abnormalities on both the neuroanatomical and the
neurochemical levels that can clarify some underlying processes of different symptoms of ADHD. EEG and ERP studies in ADHD groups also displayed abnormalities on the neurophysiological level for these children compared to control children. Deficits in cognitive functions and in particular executive functions have been considered as a major source of the disability associated with ADHD. The behavioural inhibition factor of executive functions is presumed to be the core problem in children with ADHD.

If a fundamental problem shared by all the ADHD subtypes is dysfunction of the behavioural inhibition, we would expect to see some common abnormalities between the two subtypes, despite some heterogeneity in EEG of children with ADHD. In the following sections, we will briefly go over the behavioural inhibition concept in general and elaborate particularly on Gray’s theory of Behavioural Inhibition System (BIS), which we are going to focus on in the design of our study.

1.6 Theories of Behavioural Inhibition in ADHD

The concept of inhibition and the nature of its processes have been studied at the psychological, neurophysiological, and cognitive levels. According to Smith (1992) inhibition has been present in the scientific literature since the beginning of the 19th century to explain a wide range of phenomena from simple spinal reflexes to more abstract psychological processes. The literature shows the essential role of behavioural inhibition deficits in ADHD.

Barkley (Barkley, 1997a; Barkley, Grodzinsky, & DuPaul, 1992) in the “hybrid model,” presumed a hierarchical relationship of impairments in ADHD and put inhibition deficits at the highest level. He suggested that this impairment in behavioural inhibition leads to secondary impairments in the other four neuropsychological areas: working memory and self-regulation of affect; motivation and arousal; internalization of speech; and reconstitution of behaviour. These impairments then, in turn, lead to deficits in motor control, self-directed action and sustained attention. According to Barkley (1997a), this hierarchical model predicts that improvement in the inhibitory deficits should result in the normalization of each of the four executive functions and of motor control. The next section will expound on behavioural inhibition in particular in children with ADHD.
Quay (1997) also proposed a theory of ADHD in which behavioural disinhibition was considered to be a core deficit of the disorder. He argued that ADHD symptoms might be due to underactivity in Gray’s Behavioural Inhibition System (BIS) (Gray, 1972, 1982; Gray & McNaughton, 2000), described in the next section. The original application of BIS theory to ADHD predicted that these children would show longer stop signal reaction times (SSRTs) during SST tasks (Quay, 1997). SSRT reflects the time it takes to internally suppress a response (Aron, Fletcher, Bullmore, Sahakian, & Robbins, 2003). Consistent with this, children with ADHD have slower and more variable median reaction times (MRTs) and SSRTs relative to typically developing children (Nichols & Waschbusch, 2004). This view of the BIS theory would also predict that anxious children should show shorter SSRTs due to being over-inhibited. This was not observed in a study by Oosterlaan & Sergeant (1996). However, comorbidity of anxiety with ADHD may result in normalisation of the ADHD SSRT to match that of control (non-anxious, non-ADHD) children (Manassis, Tannock, & Barbosa, 2000). Lipszyc and Schachar (2010) also examined SST performance in patients with various psychiatric disorders to determine the magnitude and generality of deficient inhibition. They found that compared to an ADHD group, SSRT was less impaired or normal for patients with anxiety, autism, major depression and oppositional defiant disorder, pathological gambling, reading disability (RD), substance dependence, and Tourette syndrome. According to their, study comorbid ADHD had different effects on SSRT in patients with each of these disorders. They observed a large SSRT deficit for comorbid ADHD + RD. However SSRT was less than moderately increased for ADHD + ANX and ADHD + ODD/CD.
1.7 Gray’s Behavioural Inhibition System

1.7.1 What is Gray’s BIS?

The BIS theory was developed to explain the effects of anxiolytic drugs (Gray, 1977, 1982). The BIS is conceived as a brain system that impacts on not only behavioural inhibition, but also arousal and attention (see figure 1.1). According to Gray and McNaughton (2000), the BIS is activated by any inputs that generate conflict between competing goals. The BIS resolves conflict by inhibiting pre-potent behaviour, incrementing arousal, and incrementing attention. The processes in which the BIS is involved underlie the inhibition of pre-potent conflicting behaviours, the engagement of risk assessment processes, the scanning of memory, and the environment to make the goal conflict resolution possible; and will eventually generate the emotion of anxiety (Corr & McNaughton, 2015). Note that sensitivity to anxiolytics is the defining property of the BIS (Gray, 1977).

The BIS theory describes three motivation/emotion systems that interact with each other and result in approach, avoidance, and conflict resolving behaviours, respectively. It is assumed that each state has a separate underlying neural system that mediates reactions (Gray & McNaughton, 2000). The Behavioural Approach System (BAS) is activated by all
appetitive stimuli and results in approach towards the goal. Impulsiveness as a factor of personality is associated with this system especially when it is highly re-active (Corr & McNaughton, 2015). The Fight-Flight-Freeze System (FFFS) is engaged by all aversive stimuli and controls withdrawal from them. The FFFS mediates the emotion of fear, not anxiety (Gray & McNaughton, 2000). The Behavioural Inhibition System (BIS), as noted above, is responsible for goal-conflict resolution when the goal elicits both approach and avoidance systems equally and neither of them can produce the adaptive outputs (McNaughton & Corr, 2004). Thus the pre-potent response will be inhibited as a result of activation of the BIS. The pre-potent response can be the result of the activation of either FFFS (active avoidance) or BAS (simple approach) systems that both will be inhibited.

The activity of the BIS depends on the absence or presence of aversive stimuli and the nature of the new information associated with the stimuli. In fact, activation of the BIS will amplify the value of threat and so increase anxiety as a consequence. BIS activity will cause detecting the negative information associated with aversive stimuli. Extreme levels of passive avoidance behaviour is caused by over-reactivity of the BIS, which is the case of trait anxiety in anxious individuals (Gray & McNaughton, 2000). Thus, in normal conditions the behavioural outputs of BIS activation can vary in the direction of being approached or avoided (see figure 1.2).
Figure 1.2 Overall relations of the Behavioural Inhibition System (BIS), Fight, Flight, Freeze System (FFFS) and Behavioural Approach System (BAS) – an updated model. To activate the BIS one must face an approach–avoidance (or approach–approach, or avoidance–avoidance) conflict. Both simple approach and simple avoidance will then be inhibited and replaced with increased attention, risk assessment and internal scanning of memory. Note that all of these operations are aimed at detecting affectively negative information and involve a selective increase (stippled arrow) in the salience and value of aversive information. As a result, a secondary consequence of activation of the system is normally a shift of the balance between approach and avoidance tendencies in the direction of avoidance. However, when danger proves to be absent the approach–avoidance conflicts resolved in favour of approach. The inputs to the system are classified in terms of the delivery (+) or omission (−) of primary positive reinforcers (PosR) or primary negative reinforcers (NegR) or conditional stimuli (CS) or innate stimuli (IS) that predict such primary events. The stippled areas in the model are all points at which general personality factors could operate. Figure and legend from Corr and McNaughton (2012), modified from Gray and McNaughton (2000).
1.7.2 Neuropsychology of the BIS

Each of these three motivational systems (BAS, FFFS and BIS) consists of a hierarchy of neural structures. Lower neural levels control immediate “quick and dirty” responses while higher neural levels control more complex “slow and sophisticated” ones. In the case of the BIS, the lowest neural level starts with the periaqueductal gray – with higher levels being the hypothalamus, hippocampus and posterior cingulate cortex and finally the dorso-lateral prefrontal cortex. The greater the defensive distance is, the higher the neural levels that are engaged. As you can see in figure 1.3, defensive behaviour is controlled by the FFFS and BIS in opposite directions: defensive avoidance (fear) and defensive approach (anxiety), respectively. Note that these two parallel systems are distinct. So deficiencies in the BIS only result from abnormalities in the structures on the right hand side of the figure.

Figure 1.3 Distinct neural representations of the Fight, Flight, Freeze System (FFFS) and the Behavioural Inhibition System (BIS). The BIS is defined by its sensitivity to both novel serotonergic, anxiolytic drugs such as buspirone (Bus) and classical anxiolytic drugs such as benzodiazepines (BDZ). The hierarchical levels are ordered from high to low (top to bottom) with respect both to neural
level and to functional level, in the sense of the immediacy with which a response is required (defensive distance). Defensive avoidance is more likely with urgent simple situations and defensive approach with more complex ones, as indicated by the shading of the boxes. Each level is associated with specific classes of behaviour and associated syndromes and symptoms. OCD = Obsessive Compulsive Disorder; GAD = Generalized Anxiety Disorder. Syndromes are associated with hyper-reactivity of a structure and symptoms with high activity. Both systems are modulated by the monoamines serotonin (5HT) and noradrenaline (NA). Figure and legend adapted and modified from (McNaughton & Corr, 2004) and (Gray & McNaughton, 2000).

### 1.7.3 Rhythmical Slow Activity (RSA) and the BIS

One way to distinguish between the involvement of BIS and other systems would be by using what is termed Rhythmical Slow Activity (RSA) as a biomarker. In rodent studies, the 4-12 Hz rhythm recorded from the hippocampal system is often called hippocampal ‘theta’, although it is more defined by the fact that its sources results from rhythmic firing of hippocampal neurons than being in the human EEG theta range (Mitchell, McNaughton, Flanagan, & Kirk, 2008). Thus, such hippocampal rhythmicity is better termed ‘RSA’ to include all species unconstrained to the precise frequency band observed and avoid conflict with the conventional use of the term ‘theta’.

The BIS theory (Gray & McNaughton, 2000) is fundamentally an animal model and RSA was initially discovered in animals in which hippocampal rhythmicity was the same as But later researchers have found evidence of existence of a human homologue of RSA (Neo, Thurlow, & McNaughton, 2011).

RSA rhythmicity is a core functional construct of the BIS theory. Gray and McNaughton (2000) suggest that RSA is crucial for effective transmission of information during goal-conflict resolution. The septo-hippocampal system is the fourth level of the hierarchical neural model of the BIS (see figure 1.3), which Gray and McNaughton (2000) proposed is a key nexus of a neural system involved in behavioural inhibition. The arousal state of the septo-hippocampal system is reflected by RSA (4-12Hz in rats) in depth recordings of EEG (Gray & McNaughton, 2000). The anxiolytic drugs, the action of which, defines the (Gray, 1982) also reduce the frequency of RSA (McNaughton, Kocsis, & Hajos, 2007).
Assessing the BIS involvement in humans is difficult. Unlike animal studies, the cellular sources cannot be certainly determined. In the next section, we describe a biomarker that is assumed to be a marker of BIS activation.

### 1.7.4 Goal-Conflict-Specific Rhythmicity (GCSR) and the BIS

According to BIS theory, initiating goal conflict resolution via the BIS should be mediated by the human homologue of RSA (Neo & McNaughton, 2011). Neo et al (2011) observed similar rhythmicity at the right frontal area in humans using the Stop-Signal Task (SST). They measured human scalp EEG during three task phases dominated by approach, conflict and avoidance, respectively. They subtracted the average power in approach and avoidance from that in conflict to measure what they termed ‘goal conflict-specific rhythmicity’ (GCSR). They suggested that the effect could be related to the BIS. The specific frontal cortical rhythm generated by goal-conflict in human superficial EEG is called GCSR. Later on McNaughton et al (2013) showed that GCSR was affected by anxiolytic drugs.

The current thesis focuses on GCSR and assumes it is a homolog of the RSA in rodent studies. The term ‘GCSR’ avoids confusion both between animal studies and human ones and between alpha/theta band rhythmicity that is not related to goal conflict and similar frequency rhythmicity that is related to goal conflict. In contrast to animal studies, in human studies rhythmic activity is referred to by its frequency bands since the cellular sources cannot be easily recognized. In human studies, theta is mostly defined as 4 to 7 Hz; alpha as 8 to12 Hz and beta as 12 to14 Hz rhythmic activities. The theta frequency in the human EEG is defined as an intermediate frequency band (4-7 Hz) between delta and alpha (Walter & Dovey, 1994). ‘Theta’ in rats studies is synonymous with RSA and spreads across the human theta and alpha bands.

GCSR is recorded in right frontal cortex. Several rat studies have linked hippocampal RSA to rhythmicity recorded in the frontal cortex (Jones & Wilson, 2005; Siapas, Lubenov, & Wilson, 2005; Young & McNaughton, 2009). Like RSA, GCSR is sensitive to anxiolytic drugs. GCSR is also correlated with both neuroticism and trait anxiety (Neo et al., 2011).

### 1.7.5 Right frontal cortex and behavioural inhibition

A variety of techniques and approaches have been used to investigate the neural substrates of behavioural inhibition. A lot of neuroimaging studies have indicated the right Inferior Frontal
Gyrus (IFG) as the main location of behavioural inhibition (Aron, Robbins, & Poldrack, 2004; Nakata et al., 2008; K. Rubia, Smith, Brammer, & Taylor, 2003). In line with these data, patients with cortical damage including the right IFG, appeared to have longer SSRTs (Aron et al., 2003). MRI and fMRI data emphasized the role of the right IFC in behavioural inhibition, but also more medial structures and their connections to the basal ganglia (Chambers, Garavan, & Bellgrove, 2009).

A recent review (Aron, Robbins, & Poldrack, 2014) conceptualised right IFG as a general brake rather than a ‘stopping node’ that can explain its general effects on not only rapid stopping but also all the situations where exogenous, endogenous, unconscious, and automatic stimuli elicit a brake. The extended network can help explain the implication of this brain system in all disorders which include impaired self-control and impulsiveness, such as ADHD. However, this evidence does not specifically implicate the BIS in the pathophysiology of the disorder.

1.7.6 Applying Gray’s BIS model to ADHD impairments

If ADHD symptoms are primarily the consequence of dysfunction of the BIS, we would expect to observe a reduction in behavioural inhibition, attention (to negative stimuli) and arousal as these are the main outputs of the BIS. But we would not expect changes in simple approach and active avoidance as they are controlled by the BAS and FFFS respectively. In other words, the question is whether ADHD symptoms are related to the abnormalities of the BIS that directly produce the inhibition deficit as it is reported in the literature; or whether other kinds of systems are affecting action stopping – for example, a strong approach system could make stopping difficult.

ADHD has been broadly associated with deficits in withholding a response in Go/Nogo tasks, which are defined as “passive avoidance”. Passive avoidance is considered as withholding a response to avoid punishment or the aversive frustration of omission of an expected reward (Gray, 1982). In fact, the BIS would be involved in a wide range of situations creating conflict between two opposite motivations (approach and avoidance) and would result in a range of output behaviours depending on the defensive distance. It mediates passive avoidance at a short defensive distance and defensive approach at a long defensive distance.
Comparing the hierarchical neural structure of the BIS and neural abnormalities in ADHD shows some partial commonalities. Seidman (2005) reviewed volumetric imaging studies of children with ADHD and concluded that significantly smaller volumes in dorsolateral prefrontal cortex, caudate, pallidum, corpus callosum, and cerebellum have been replicated in most of the studies, while the hippocampus and amygdala have been unchanged. This is consistent with a view that the BIS dysfunction in ADHD is mediated by abnormalities in the dorsolateral prefrontal cortex, which can impact on hippocampal related functions – but without direct involvement of the hippocampus.

Studies in ADHD patients who have serious impairments in response inhibition tasks like the SST have also found some abnormalities in right IFC functioning (Schachar & Logan, 1990). Their inability to recruit PFC regions in a similar manner to healthy participants during an inhibitory task is associated with immaturity in cognitive control (Bunge, Dudukovic, Thomason, Vaidya, & Gabrieli, 2002). Generally children with ADHD show abnormal right IFC activation in behavioural inhibition tasks (Casey et al., 1997; Castellanos et al., 1996; Cubillo et al., 2010; Carin C. E. Overtoom et al., 2002; Sowell et al., 2003). Such abnormalities in right IFC may be the stem of a common pathologic process underlying response inhibition and working memory deficits in both adult ADHD patients and patients with right frontal damage (Clark et al., 2007).

Stopping can be produced by output of the BIS to the motor system when there is a conflicting goal which has activated both approach and avoidance systems and prevents either of them. In this context, it might be better conceptualised as inhibition which is affected by anxiolytic drugs. However, there are also inhibitory processes that are not controlled by the BIS, as they are not sensitive to the anxiolytic drugs. One of them is action stopping (Corr & McNaughton, 2015). In fact, action stopping is generated without involving the BIS as action withholding and so is not sensitive to anxiolytic drugs (McNaughton et al., 2013). In the next section, we will briefly review the SST which has been widely used as a simple test to measure the BIS.

1.8 Stop Signal Task

The SST is a variation on the standard go/no-go task. In standard go/no-go paradigms, there are stimuli that should be responded to and also there are stimuli that should absolutely not be responded to. Go.nogo is typically an easier task to do than the SST. The SST involves a go
task and the occasional condition to stop the already initiated response because the stop signal comes after the imperative stimulus.

The SST requires participants to respond differentially to two distinct go-stimuli (in our study, an arrow pointing left or right) using the left or right mouse button as fast as they can. Mean reaction times to the go-stimulus (MRT) are calculated by measuring the latency between the presentation of the stimulus and the response. Then on a predetermined number of trials (25%) they are instructed to withhold the response if it is followed by a specific stop signal such as a tone. The stop signal is introduced on some trials at various times generating a range of stop signal delays (SSD).

The SST involves a dual-task paradigm in which it is assumed that going and stopping are independent of each other (Logan, Cowan, & Davis, 1984). Thus two separate processes of going and stopping take part in a competitive “horse race” model. According to Logan’s race model, inhibition occurs only if the stop process overtakes the go process. That implies that the neural activity of Go responses during Stop trials is the same as their distribution during non-Stop trials. The “horse race” model provides the unique ability of the SST is to capture cognitive processes of inhibition by means of the stop-signal reaction times (SSRT) metric. The SSRT measures the average time between the stop signal and the stopping of the response. The slower the reaction time to the stop stimulus that a person has, the lower the probability that the stop-process will overtake the go-process. The relationships between MRT, SSRT and SSD are graphically portrayed in figure 1.4.

![Figure 1.4 A schematic portraying the relationships among mean reaction time (MRT), stop-signal delay (SSD), and stop-signal reaction time (SSRT) in the stop-signal paradigm. Figure taken from (Alderson, Rapport, Sarver, & Kofler, 2008)](image-url)
1.9 Aim of the current thesis

Our main question in the current study is whether Gray’s BIS theory can explain some of the deficiencies seen in ADHD. We tested the theory by looking at GCSR as the biomarker of the BIS activity during an auditory SST. Based on the literature, we hypothesised that the ADHD-C would show close to normal levels of GCSR, because of high level of BAS activation countering the effect of reduced BIS sensitivity. As mentioned earlier, higher levels of BAS (behavioural approach system) activation relative to FFFS (fight, flight, freeze system) activation, will result in approach towards the goal and vice versa, avoidance. A highly re-active BAS is associated with impulsive behaviours as can be seen in ADHD-C (see section 1.7.1). The BIS acts as a detector of conflict between approach goals and avoidance goals when they are equally strong. Increased BAS would lead to higher motivation values at FFFs and so more activation of BIS which responds to them as inputs. The stronger inputs would counter the reduced BIS sensitivity. The idea is that with a strong BAS activation, we will only get conflict when we also have a strong FFFS activation relative to normal. So, the BIS will receive stronger inputs than normal (but with normal output from BIS since it is weaker than normal). On the other hand, ADHD-C would not involve any dysfunction of arousal level as a BIS output. However it was expected that ADHD-I would show lower levels of GCSR due to low levels of arousal and decreased attention resulting from low BIS sensitivity. The ADHD-I and ADHD-C results would be relative to the controls.

Two studies were conducted to test our hypothesis, an initial study (n= 34) and a main study (n= 66). The brain waves of three groups of children (ADHD-I, ADHD-C and neurotypical) were recorded while they were doing the SST. Then the diagnostic groups were compared in terms of their behavioural performance and GCSR activity during the test.

Chapter 3 represents our initial study’s results using a small number of participants in New Zealand. Chapter 4, the main study, follows the same method as chapter 3, but with a larger number of participants in Iran. In chapter 5, we ran another study using the same data as previous chapters and examined ERPs between the three groups for only the Iran study. Based on former literature, we hypothesised that children with ADHD would show reduced N2 and P3 amplitudes during stop trials in comparison to control children (Table 1.1). In the final chapter, implications of the current findings are discussed.
2 General Methods

The task, EEG recording and data processing procedures across the initial and the main experiment were the same in the two replications reported in this thesis. These and variations in participant recruitment between the replications are detailed below.

2.1 Participants

Participants with ADHD were the same as participants in the control group in terms of age and other entrance criteria except they had received a diagnosis of ADHD by a clinical psychologist or psychiatrist. Some of them were receiving medical treatment during that time but they were asked to be drug free for 24 hours before the test. They were divided into two groups on the basis of this clinician diagnosis: inattentive (ADHD-I) and combined (ADHD-C; i.e. with hyperactive-impulsive and inattentive symptoms). As in previous experiments with adults (Neo et al., 2011) and children (Stevenson, 2011) in the Dunedin laboratory, the children received no reward of any kind. All the procedures and the recruitment of participants were approved by the University of Otago Ethics Committee; approval number: (10/043).

Table 2.1 is a summary of participant numbers in both the initial and main study.

Table 2.1 Details of participants in the initial (New Zealand) and main (Iran) studies.

<table>
<thead>
<tr>
<th></th>
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<th></th>
<th></th>
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<td>Combined</td>
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<td>7</td>
<td>8</td>
<td>10</td>
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<td>13</td>
</tr>
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</table>

2.1.1 Initial study - New Zealand

Participants in the control group were selected by a research assistant from the Early Learning Database (ELD). The ELD consists of details of families who live in Dunedin and are interested in taking part in studies about child development and was created by developmental researchers at the Psychology Department at the University of Otago and paid for by their grants. The control children were between 7-12 years old, right handed, with no skin allergies, normal IQ and free from any symptoms of deficits in attention and inhibitory control. Participants in clinical groups were recruited from the University of Otago database at the Department of Psychology. Some of them were also referred to the researcher by a
Paediatric Consultant from the Department of Psychological Medicine. Parents were first contacted by phone and then an information package was sent out by email. Parents were given a $10 dollar petrol voucher in recognition of the time and costs involved in attendance and parents and children signed the consent form (English version, see Appendix A) before starting the test.

2.1.2 Main study - Iran

Participants in the control group were children selected from a primary school in Tehran. They were between 7-12 years old, right handed, with no skin allergies, normal IQ and were free from any symptoms of deficits in attention and inhibitory control. Participants in the clinical groups were children with ADHD selected from the data base of the Atieh Clinic, a childhood psychological disorders clinic in Tehran. The data base holds contact details of families who go to the clinic to undertake treatment. The average age for each of the three groups was around 9 years old. Families were firstly contacted by phone and then, if they were interested, an information package was sent out by email. Parents were also asked to discuss about experiment with their children. Parents were given 20,000 toman in recognition of the inconvenience of taking part in the experiment and parents and children signed the consent form (Farsi version, translated from the English, see Appendix B) before starting the test.

2.2 Apparatus

2.2.1 Stimulus presentation

The stimuli were presented on a 14-inch monitor at eye level at a distance of about 90-120cm from the face and the tone was presented by headphones worn over the ears. All aspects of the experiment were controlled by a program written in Visual Basic 6.
2.2.2 EEG Recording

The details of the sampling rate and the band pass range in both experiments are described in the table 2.2 below.

Table 2.2 Details of EEG Machine Used for two Experiments Used in This Thesis.

<table>
<thead>
<tr>
<th>EEG Machine Filter (Hz)</th>
<th>Sample Rate (Hz)</th>
<th>Low Pass Filter (Hz)</th>
<th>High Pass</th>
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<td>WinEEG</td>
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<td>30</td>
</tr>
<tr>
<td>ASA Neurotechnology</td>
<td>256 (resampled to 128)</td>
<td>2.0</td>
<td>36</td>
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</table>

2.2.2.1 Initial study - New Zealand

All participants were fitted with a Wave Guard Cap in which mastoid reference electrodes were put on the cap as A1 and A2 like other electrodes. The position of the other electrodes was according to the International 10-20 electrode placement system. EEG data were recorded from 19 channels including F7, F3, Fz, F4, F8, T3, C3, Cz, C4, T4, T5, P3, Pz, P4, T6, O1, O2, Fp1 and Fp2. Electro-gel (Electro Cap International, USA) was used to fill the electrodes on the cap and aid the conductance from the scalp. The gel was inserted by a 3ml syringe with a Precision Glide 16 gauge blunt needle (Becton & Dickenson & Co, USA). Impedances were checked in the ASA software. ASA software controlled ANT Neurotechnology hardware to capture and amplify the EEG signals. The cap was connected to an ANT Neurotechnology amplifier system.

2.2.2.2 Main study - Iran

EEG recording in the main experiment was almost the same as the initial experiment except that a different electrode cap (Electro Cap International, USA) of a small size (500-540 mm) was used for recordings. Also we used a different EEG machine (WinEEG). Electro caps were mounted with pure tin electrodes.

Electrode recordings from the scalp were referenced to activity averaged from the two earlobes, recorded through two pure tin ear electrodes (A1, A2). Impedances were checked via WinEEG software. WinEEG software is designed to work with Mitsar-EEG hardware to capture and amplify the EEG signals. The cap was connected to a Mitsar-EEG amplifier system.
2.2.3 Testing area

2.2.3.1 The initial study - New Zealand

All participants were tested in the same body-protected room. They sat on a chair and researcher accompanied them to ensure following test instructions.

2.2.3.2 The main study - Iran

All conditions were the same as in the initial study.

2.3 Procedure

Children arrived at the laboratory with a parent for a 40 minutes session. Parents and children were asked to sign the consent form. Then they were moved into the testing room. Participants put on the electrode caps and the connection of the electrodes was checked. Impedances were checked and improved to set them below 5 kΩ. Impedance adjustment was carried out by the researcher and an assistant together in order to reduce the time taken in order to preventing children getting bored and restless before starting the test. The whole process generally took about 15 minutes. After fitting with the cap, they first completed an alpha rhythm task to ensure the EEG recording set up was in an appropriate condition. For the alpha test, participants were told to close their eyes and relax for 10 seconds to produce relaxation-induced alpha rhythm. The EEG was also checked visually to detect noise in the records before starting the main experiment.

All participants performed the Stop Signal Task (SST; see next section) as the main task which lasted around 25-35 minutes depending on the length of break times after each block. The instructions of the task were presented on screen before starting the SST task. They were the same as what used by Aron and Poldrack (2006). In Iran the instructions were translated into Farsi:

English:

*Remember to respond as FAST as you can once you see the arrow. Press the left mouse button if you see the left arrow “<”. Press the right button if you see the right arrow “>”. However, if you hear a beep, your task is to stop yourself from pressing. Stopping and Going are equally important.*
Participants responded to the stimuli by pressing a right or left button of a standard computer mouse using their right hand. After completion, participants were cleaned up and thanked for their participation.

2.4 The Stop Signal Task

The version of SST used in the current thesis is mainly based on Aron & Poldrack (2006) with the primary program being a translation into Visual Basic of C code kindly provided by Dr Aron. It included some minor adjustments to the control of stop signal delays as in a previous adult experiment from our laboratory (McNaughton et al., 2013) and further modifications to the rest periods and provision of feedback introduced by Stevenson (2013) in his adjustment of the task for children; and which has been retained in more recent improvements of the adult version of the task (Shadli et al, 2015).

As in the previous versions of the SST, there were two kinds of trials: Go trials and Stop trials (See figure 2.1). At the start of the test a fixation circle was presented in the centre of the screen against a black background. 500 ms later a Go stimulus appeared within the circle that was a left arrow («) or a right one (»). Participants were instructed to make a left or right click in response to the left or right arrows respectively, as quickly as possible. The circle and the arrow disappeared after 1500ms whether a response was made during the time or no response was made. The Stop trials were exactly the same as Go trials except that a 1000Hz tone was also presented that lasted for 500ms. The tone was the Stop stimulus requiring the participants to withhold responding to the arrow. Participants were informed that stopping and going were equally important.

The current version of the SST was as developed by Stevenson (2013) for children and differed from previous adult versions (Neo & McNaughton, 2011) in that:
1) The stop signal delay delivery at the beginning of each block for the present study were centred on the mean stop signal delay of the previous block (see section 2.4.1 Stop Signal Delay).

2) The task consisted of 6 blocks of 64 trials, instead of 3 blocks of 128 trials and thus included 2 more break periods. This was intended to reduce the time during which concentration had to be exerted and so prevent children from getting restless and introducing movement artefacts into the EEG record.

3) Four short humorous GIF clips were provided at each rest time with different clips for each of the 6 rest periods.

4) The maximum duration of Go stimulus presentation was increased from 1000ms to 1500ms as initial experiments reported by Stevenson (Stevenson, 2011) had found significant failure of normal children to complete the Go response with the 1000ms time limit.

5) After each trial, performance feedback was presented briefly (250ms). If the participant responded quickly enough (<1500ms) and was correct on Go trials or if the participant withheld a response successfully on Stop trials then a smiling face was shown. But if the participant did not respond within 1500ms on Go trials or if the participant failed to inhibit their response on Stop trials then a frowning face was shown (see Figure 2.1). This modification was introduced by Stevenson (2011) in our laboratory to increase motivation for correct responses, and also is now standard in our latest improved adult version of the SST (Shadli, Glue, McIntosh, & McNaughton, 2015).
Figure 2.1 The trial sequence in the child version of the SST. At the start of each trial a fixation circle is presented at the centre of the screen; a left or right arrow (Go stimulus) appears within the circle and participants respond by pressing left or right mouse key. Stop trials are exactly like Go trials except that a 1000HZ tone is presented as a cue to withhold responding. A smiley or frowney face is presented as feedback depending on participant's performance. Figure modified from Crosbie et al. (2013) with permission.
2.4.1 The Stop Signal Delay

There is an interval between the presentation of the Go stimulus and the onset of the Stop stimulus: the Stop Signal Delay (SSD). The SSD is controlled by a tracking system made up of four "staircases". They started at different SSDs: 100, 150, 200, and 250ms and then ran in parallel. Successfully inhibiting a response on a Stop trial increased the SSD for that trial’s staircase by 50ms and failing to inhibit a response on a Stop trial decreased the SSD by 50ms. As a result the staircase values converge to a common value that produces 50% correct stopping. Each staircase controlled responding 4 times during a block of 16 stop trials. There is one Stop trial in every four trials with a total of 64 trials in each block.

This version of SST is based on Aron and Poldrack’s version (2006) and is exactly like that during block one. But in the later blocks, the mean SSD of each block was calculated at the end of that block and this value was set as the base from which all SSDs were generated. When the staircase delivered the mean SSD then the next trial in that staircase was shifted by 100ms up or down rather than the 50ms which is usually programmed. The accuracy of the response to the intermediate SSD trial determined the direction. The 100ms increment only applied when SSDs were moving away from the mean SSD, not when moving towards and also did not occur in block 1.

2.5 Data Processing and Analysis:

2.5.1 Behavioural Data

Identification number, age, gender and handedness of each participant were recorded. Names and other personal identifying details were not recorded. Experimental measures recorded for each trial included trial and block number, trial type (Go or Stop), SSD value, reaction time, staircase index (1-4), staircase moves for each staircase, physical response (left/right/null) and inter-trial intervals. Based on Aron and Poldrack's (2006) study, three measures of behaviour were derived: first, the median reaction time of Go trials (Go RT) across all trials in ms; second, mean SSD over the last 12 moves of the four staircases in ms; third, the Stop Signal Reaction Time (SSRT) in ms was calculated by subtracting the mean SSD from the median Go RT of each participant.
Average SSDs from the first and second staircases were correlated with the average SSDs from the third and fourth staircases to check for stable estimates of SSD values. The 50% probability of withholding or responding had stabilized by the last 12 changes of each staircase. The 48 Stop trials (four staircases x last 12 changes) were arranged in order of ascending SSD for each participant then divided into three levels of SSD (early, intermediate and late). Trials with the same SSD were always put in the same band which caused unequal numbers of trials in each band for some participants. The number of trials in each band can differ from 5 to 24. Then the probability of successful inhibition ($P_{\text{inhibit}}$) of the four staircases in the last 12 moves was calculated to verify that $P_{\text{inhibit}}$ had converged at 50%. The $P_{\text{inhibit}}$ was then calculated for each group of SSDs.

As a result a distribution of trials was created that are considered early, intermediate or late in terms of the onset of the Stop stimulus. Late onset of Stop stimulus were expected hard to withhold and associated with a long SSD. Early onset of Stop stimulus was expected easy to stop and associated with a short SSD. Intermediate onset of Stop stimulus was expected balanced in that tendency to respond or stop was even and associated with intermediate SSD times.

This distribution was necessary for analysis of the power spectrum derived from the EEG. Quadratic power was calculated for each frequency (4-12 Hz) by subtracting the average power of the intermediate Stop trials from the average of the early and late Stop trials.

### 2.5.2 EEG artefacts removal

EEG data processing was carried out using a purpose-built program in Visual Basic 6. The raw data (128Hz) were first low pass filtered (using a 3-point running mean, effective cut off 43Hz) to remove residual high frequency noises including 50HZ electrical noise from the recordings. Then an automatic eye blink removal program (Mitchell, McNaughton et al. 2008; Neo, Thurlow, et al. 2011) was used to remove artefacts associated with eye blinks and followed by manual removal of any uncorrected eye blinks or other movement artefacts. The automatic eye blink removal program used an algorithm to recognize artefacts and remove them. The algorithm was based on EEG signals in Fp1 that matched a flexible eye blink template to account for variations between eye blinks and participants. After fitting the template to the specific detected eye blink on Fp1, linear regression in the form of a slope
coefficient was carried out to determine size and the direction of the eye blink component for each channel (Gratton, 1998). The rescaled eye blink template values were then subtracted from each channel to leave residual EEG.

Once the automatic eye blink removal was completed for analysis channels, the original Fp1 record was retained for the experimenter to facilitate visual checking for correct eye blink removal from the recordings. Any missed eye blinks or muscle-related or other artefacts were then replaced manually with missing data markers in the EEG segments across all the channels.

### 2.5.3 Processing spectral power

Raw EEG data were first converted to microvolt values then a power spectrum was calculated, focussing on the 0.5 second period after the tone in Stop trials and on the same 0.5 second period in the Go trial which preceded the Stop trial (or if the preceding trial was a stop trial, then the following Go trial was used). The early, intermediate and late SSDs were taken from the last 12 trials of each staircase (when $P_{\text{inhibit}}$ converged at 50%) and averaged separately.

Each segment of analysed data consisted of 32 samples before the start of the stop signal, 64 samples during presentation of the 500ms tone, and 32 samples after the end of the tone. The Hanning Window is a cosine wave and so extracted most power from the middle 0.5s period with much less power from the two outlying 0.25ms periods. This doubles the frequency resolution (to 1 Hz) compared to an equivalent (0.5s) square window. The procedure was the same for the matching Go trial. The power spectrum was calculated in relation to the point in time where the stop signal had been presented in the adjacent Stop trial. A log transform was performed for each power spectrum to normalize error variance before averaging procedures. Any missing data in window resulted in the entire spectrum for that period of EEG being marked missing. When more than 30% of the trials of an average of spectral power were missing, the average was replaced with missing data markers. This is the standard amount used in all previous research with this test. Participants were excluded from the analysis when more than 10% of their overall data were missing.
2.5.4. ERP Analysis

ERP analysis was performed using the ERPLAB toolbox (http://erpinfo.org/erplab), which is an open-source Matlab package for analysing ERP data. ERPLAB is integrated with EEGLAB, which is a popular open-source toolbox for EEG processing.

The same EEG data were used as for power analysis but prior to segmentation. That is, complete EEG files, processed through to after removing eye blinks, were sent to ERPLAB. Data analysis was locked to the stop signal, and epochs were extracted from 200ms before to 800ms after the stop signal. Baseline correction was also done. ERPs for correct and incorrect stop trials were produced at each of the 15 electrode sites (F7, F3, Fz, F4, F8, T3, C3, Cz, C4, T4, T5, P3, Pz, P4 & T6) averaged separately for each diagnostic group. The largest evoked potentials were observed at Cz (see Chapter 6), thus detailed statistical analysis focused on correct and incorrect stop ERPs at Cz only. ERP differences during correct and incorrect stop trials were acquired, particularly for two late positive peaks that appeared 500-750ms after the stop signal. These peaks were identified and labelled as P5 and P6. These peaks were not observed in Go trial ERPs. Analysis did not focus on any negative peaks since group differences were less noticeable in these ERP components, compared to the two late positive peaks. Analysis at P5 and P6 focused on ERP amplitude and latency differences, although P5 and P6 displayed only small latency variations but showed markedly different amplitudes across trial conditions and diagnostic groups.

2.5.5 Statistical Analysis – Analysis of Variance (ANOVA)

EEG analysis: ANOVAs were performed using the IBM SPSS package 21. Variables were the SSD (early, intermediate and late), frequency (4-12Hz), trial type (Stop and Go) and channel (F7, F3, Fz, F4 and F8). The intermediate SSD was considered as the condition of the maximum conflict as the point when stopping and going were equally activated. Two other levels of SSDs, late and early, represent lower levels of conflict. The differences between the three levels of SSD therefore allowed conflict to be calculated as an orthogonal quadratic contrast of SSD. This component compared the difference between the intermediate SSD with the average of two short and long SSDs. So the term “quadratic” is descriptive and does not imply the presence of underlying quadratic function. The amount of variation between the three levels of SSD (short, intermediate and long) independently was calculated by contrast
analysis. The log power was averaged across all early, intermediate and late SSDs to measure the overall stop signal power at the five frontal electrodes.

While all five frontal electrodes were analysed initially to test for channel variation, hypothesis testing was restricted to the right frontal channel, F8 as Neo et al. (2011) observed neuroticism and trait anxiety correlations with GCSR power only at F8, and McNaughton et al. (2013) found the clearest anxiolytic drug effects at F8. Also Shadli et al. (2015) developed and characterized an improved test appropriate for testing the anxiety biomarker (GCSR) at F8.

**ERP analysis:** ANOVAs were performed using the same package. An analysis of variance (ANOVAs) was performed on mean amplitude values for correct/incorrect stop ERP differences (mean correct stop ERP amplitude - mean incorrect stop ERP amplitude) across P5 and P6. There was a single between subjects factor, diagnostic group. There were two repeated measures factors: Stop response (correct/incorrect) and peak (P5/P6).
3 Goal-conflict processing in Children with ADHD in New Zealand (initial study)

3.1 Introduction

The aim of this study was to explore goal-conflict-specific rhythmicity (GCSR) in the Stop Signal Task (SST) in children with ADHD compared to a control group. To date there have been no experiments examining this effect in children with ADHD and only pilot experiments with neurotypical children. As discussed in Chapter 1, according to the behavioural inhibition theory of ADHD (Barkley, 1997a; Quay, 1997) deficits in behavioural inhibition are considered to be a core feature of ADHD and this has been explicitly suggested to be the form of behavioural inhibition described in BIS theory (Quay, 1997). As described in chapter 1, it was predicted that:

1) children with the combined subtype of ADHD could show close to normal levels of GCSR, due to a high level of arousal and resultant BAS activation counteracting the effects of reduced BIS sensitivity;

2) In contrast, children with the inattentive subtype of ADHD would show lower than normal levels of GCSR, because of low levels of arousal and decreased attention resulting from low BIS sensitivity.

The experiment reported in the current chapter compared GCSR in the SST among three groups of children in Iran: control; ADHD-inattentive; and ADHD-combined.

3.2 Methods

All details of participants, experimental testing, and analysis are given in Chapter 2.

3.3 Results

3.3.1 Exclusions

This study involved a large number of exclusions. There were 58 participants in total (25 control, 13 inattentive, 20 combined) at the start of testing. Ten of the control group were excluded due to lower than 50% of correct responses in stop trials, which shows that they did not get involved in the test and do it properly. In the ADHD subtype groups, they were excluded if their correct responses in stop trials were less than enough to divide them into short, medium and long SSDs. So 8 of them were excluded. There were also 5 more
exclusions due to excessive (>15%) artefacts in their EEG recordings. 35 participants (15 control, 10 inattentive, 10 combined) remained for analysis. Of these, 14 completed all three blocks of the task and 20 of them (58% of the whole sample) completed the first two blocks of the task. Accuracy when responding on go trials in both those completing two blocks and those completing three blocks was above 80%.

### 3.3.2 Behavioural data

ANOVA were carried out on each of Median Reaction Time (MRT), Stop Signal Reaction Time (SSRT), Go correct% and Probability of Inhibition ($P_{inhibit}$) in short, intermediate and long Stop Signal Delay (SSD) testing for differences between the three diagnosed groups (control, inattentive and combined subtype of ADHD) and the two genders. Detailed behavioural data are presented in Table 3.1 at the end of this section.

**MRT** was not systematically affected either by diagnosis (diagnosis: F (2, 28) = 0.206, p = 0.815; diagnosis x gender: F (2, 28) = 0.758, p = 0.478) or gender (gender: F (2, 28) = 2.072, p = 0.161) (Figure 3.1).

![Figure 3.1](image)

**Figure 3.1** Effects of diagnosis and gender on MRT. Error bars are 2 standard errors of the mean for each group.

**SSRT** showed a different trend from MRT (Figure 3.2). Both ADHD subtypes showed longer SSRTs compared to the control group particularly in males (diagnosis: F (2, 28) = 8.208, p = 0.002; diagnosis x gender: F (2, 28) = 4.227, p = 0.025). However, the two genders did not
differ when pooled across diagnosis (gender: F (1, 28) = 0.140, p = 0.712) similarly to the MRT results.

Figure 3.2 Effects of gender and diagnosis on SSRT. Error bars are 2 standard errors of the mean for each group.

When we tested for the relation between MRT and SSRT, MRT on Go trials was not related to SSRT (r (33) = 0.068, p > 0.005).

Go correct% showed a non-significant trend to a reduction in males (Figure 3.3; gender: F (1, 28) = 3.483, p = 0.073) but the apparent variation with subtype was not significant (diagnosis: F (2, 28) = 2.292, p = 0.120; diagnosis x gender: F (2,28) = 1.97, p = 0.157).

\( P_{\text{inhibit}} \) was analysed with short, intermediate and long SSD trials as separate levels of a delay factor. As expected there was a steady decrease of \( P_{\text{inhibit}} \) as the stop signal delay increased, with values in the region of 50% at intermediate SSDs (Table 3.1). There was also a similar pattern across the three levels of delays between the 3 groups, which mean that the staircase procedures are working similarly in all cases. When the three \( P_{\text{inhibit}} \) values were analysed as levels of a delay factor in a single ANOVA, neither gender nor diagnosis had a significant effect on \( P_{\text{inhibit}} \) (gender: F (1, 28) = 0.574, p = 0.455; diagnosis: F (2, 28) = 0.005, p = 0.995); gender x \( P_{\text{inhibit}}, \text{dev x quad} \): F (1, 28) = 1.370, p = 0.252; diagnosis x \( P_{\text{inhibit}}, \text{dev x quad} \): F (2, 28) = 1.562, p = 0.228); diagnosis x gender x \( P_{\text{inhibit}}, \text{dev x dev x quad} \): F (2, 28) = 1.161, p =0.328).
Figure 3.3 Effects of diagnosis and gender on Go correct%. Error bars are 2 standard errors of the mean for each group.

Table 3.1 MRT, median reaction time; SSRT, stop signal reaction time; Go correct%, the percentage of correct responses on Go trials; $P_{inhibit}$ short, probability of correct response on Stop trials in short SSDs (stop signal delay); $P_{inhibit}$ intermediate, probability of correct response on Stop trials in intermediate SSDs (stop signal delay); $P_{inhibit}$ long, probability of correct response on Stop trials in long SSDs (stop signal delay); N, number of participants in each group. The table represents behavioural outputs for different groups divided by gender and ADHD subtypes versus control group.

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
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<th>Male</th>
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<tr>
<td></td>
<td></td>
<td>Inattentive</td>
<td>Inattentive</td>
</tr>
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<td>MRT (S.D) ms</td>
<td>587 (42)</td>
<td>633 (55)</td>
<td>610 (46)</td>
</tr>
<tr>
<td>SSRT(S.D) ms</td>
<td>287 (79)</td>
<td>291 (43)</td>
<td>330 (6)</td>
</tr>
<tr>
<td>Go correct (S.D)%</td>
<td>94 (2)</td>
<td>91 (6)</td>
<td>95 (3)</td>
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<tr>
<td>$P_{inhibit}$ short(S.D)%</td>
<td>75 (6)</td>
<td>95 (11)</td>
<td>79 (11)</td>
</tr>
<tr>
<td>$P_{inhibit}$ intermediate(S.D)%</td>
<td>56 (5)</td>
<td>56 (8)</td>
<td>55 (8)</td>
</tr>
<tr>
<td>$P_{inhibit}$ long(S.D)%</td>
<td>36 (5)</td>
<td>37 (9)</td>
<td>40 (9)</td>
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<tr>
<td>N</td>
<td>6</td>
<td>2</td>
<td>2</td>
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</table>
3.3.3 EEG Analysis

More than half of the participants (58%) did the task only up to the end of block 2 and did not proceed to block 3. In addition, all participants showed stabilized SSDs in block 2 even those who completed block 3. SSDs were not stable in block 1 as this is a period when the SST is being learned. EEG analysis, therefore, focused on block 2 (both for those who have done the whole task up to block 3 and those who have done only up to block 2) to maximize the number of participants included. The EEG analysis involved 34 children who completed block 2 of the task with less than 10% artefact and also showed an acceptable accuracy during stop trials.

The primary focus of the analysis was on conflict power (i.e. stop-go x quadratic of SSD) at F8. This is discussed in section 3.3.6. Section 3.3.4 provides a larger scale picture of the overall data and section 3.3.5 looks at stop-signal-specific effects to provide context for the more focused comparison.

3.3.4 Go and Stop Trial Power at Fz, F4 and F8

Log power was averaged across participants separately for each SSD level at sites Fz, F4 and F8 to explore overall Stop-Go effects. Figure 3.4, 3.5 and 3.6 show for each of control, ADHD-inattentive and ADHD-combined, respectively, the variation in log power for Go, Stop and for the difference between them (Stop-Go) all on the same scale set to match Neo et al (2012). Figure 3.7 shows the Stop-Go differences for all three groups on a larger scale.

Figure 3.4 shows the variation in log power in the 4-12 Hz frequency range across the three right frontal sites (Fz, F4, and F8) for the control group. Intermediate SSDs (grey bars) are where the conflict effect should occur – that is their value should be increased relative to the white and black bars. Inspection of the Go trials at F8 shows there is no such increase in the region of 5-11 Hz except at 5 and 7-8 Hz where it can be seen that the grey bar is above both the white and the black bars, i.e. the power at intermediate SSDs (grey) is increased relative to both early (white) and late (black) SSDs, providing evidence of a conflict effect. It is almost the same with Stop trials at F8. It should be remembered that Go trials are exactly the same as Stop trials except for the onset of the Stop stimulus in the middle of the Stop trials. Go trials therefore provide a control for all on-going process during the trials except those elicited by the stop signal. To show stop-signal-specific effects we subtracted the log power in Go trials from Stop trials. The resultant, purified, Stop signal effect is shown in the
Stop-Go graph (third row). This shows a stop-signal specific effect at the intermediate SSDs relative to both early and late SSDs at 5 and 12 Hz at F8 (see also Figure 3.7).

**Control group**

**Figure 3.4** Variation in log power for Go, Stop and the Stop-Go difference for the control group for short (white) intermediate (grey) and long (black) SSDs. The first row (Go) is the power in Go trials that came immediately before (or after if the preceding trial was also a Stop trial) Stop trials of the SST. The second row (Stop) is the power in the Stop trials; and third row (Stop-Go) is the power difference between stop and matching go trials. The scales of the log power axes have been set to match Neo et al. (2012). Stop-Go differences for F8 are plotted on a larger scale in Figure 3.7.

Figure 3.5 shows the Go, Stop and Stop-Go data for children diagnosed as the inattentive subtype. There was a decreasing trend in power as frequency increased as in the control group. The power difference between Go and Stop trials (third row), shows the largest conflict effect at 8, 9 and 11 Hz. Surprisingly, there is an increase in the power at intermediate SSDs in Go trials at F8 in some frequencies (5, 6 and 12) and at 8-9 and 11-12 Hz in Stop trials.
Figure 3.5 Variation in log power for children diagnosed as inattentive subtype. Other details as Fig 3.4.

Figure 3.6 shows the variation in log power in the 4-12 Hz frequency range for children diagnosed as the combined subtype. Intermediate SSD power (grey) was generally not raised relative to short and long SSDs (white and black) in Go trials at F8 except at 5 Hz. This was almost similar to the control group Go trials. There was also an increase in the Stop trials: grey is above both black and white at 4, 5, 6, 10 and 11 Hz. When we subtracted Go trial power from Stop trial power, there was an F8 conflict effect at 6, 7 and 11 Hz.
Combined subtype

**Figure 3.6** Variation in log power for children diagnosed as combined subtype. Other details as Fig 3.4.

### 3.3.5 Stop Stimulus Effects

Figure 3.7 redisplay the Stop-Go graphs at F8 with an expanded scale. Variation in log power difference after subtracting the Go trials from Stop trials looked dissimilar between the three diagnostic groups both in relation to absolute values and in relation to the conflict-specific differences. Intermediate SSDs (grey) were associated with higher power at different frequencies. The control group displayed increased power at 7 and 12 Hz but the long SSD is above the intermediate SSD at 7 frequency. The inattentive subtype showed increased power at 8, 9, 11 and 12 Hz. The combined subtype showed higher power for intermediate SSDs in the different frequency bands (4-7 and 10-12 Hz). To provide a clearer picture of the differences in overall power, we averaged power across the three SSD levels for each group. The resultant overall effect of the stop stimulus is shown in Figure 3.8 (Conflict-specific effects are detailed in the next section).
As can be seen in figure 3.8 the effect of the stop signal on overall power at F8 varied with frequency somewhat differently for each group. Basically, the control group has increased power at 5-8 Hz with some fluctuation. The inattentive subtype has noticeably decreased power at 4-11 Hz. The combined group has somewhat decreased power at 7-10 Hz and increased power at different frequencies (5-6 and 10-12 Hz). The apparently different patterns between three diagnostic groups were not reliable.
3.3.6 Goal-Conflict-Specific Rhythmicity

Figure 3.9 shows Goal-conflict-specific rhythmicity (GCSR), which is assessed statistically as the quadratic component of the variation in the stop-go power difference across the three levels of SSD. This quadratic, since it is fitted to only 3 values, is equivalent to subtracting the average for the short and long SSDs from the intermediate SSDs. An additional simplification, relative to figure 3.7 is that a 3 point running average was used to smooth the data for display in the figure. Although our main focus is on F8, Fz and F4 are also shown because they were sites where conflict effects have been previously detected (Neo et al., 2011). The largest GCSR for the control group appeared at F8 in comparison with F4 and Fz. Similarly, the combined subtype group demonstrated the largest GCSR at F8. Following the original study, detailed analysis was focussed on GCSR at F8. Figure 3.9 displays the smoothed GCSR across frequencies at Fz, F4 and F8 in Block 2.
3.3.7 Detailed Analysis of F8

Figure 3.10 shows three perspectives on the same data. Part A displays the variation in GCSR at F8 for the three diagnostic groups (control, combined and inattentive subtypes) without the 3 point smoothing of figure 3.9. As can be seen, the predicted goal-conflict effect appeared at
F8 for the control group between 7-10 Hz. The combined group looks fairly like the control
group with higher amplitudes, which started from 6 Hz, peaked at 8-9 Hz and continued up to
10 Hz. However, the inattentive group has a noticeably different pattern with sharp
fluctuations mostly in negative zone and two short peaks at 8-9 Hz and 10-11 Hz but power
suppression at 7 and 9 Hz. Nonetheless, the differences between the three groups were not
reliable.

There was a reliable order 5 (reflecting a curve with four inflection points, e.g. two
peaks and two troughs) frequency variation in GCSR between the diagnostic groups in the
main experiment (see next Chapter); but there was no reliable order 5 difference between the
three groups in the current study when analysing the original data (diagnosis x stop-go x SSD
x frequency, dev x dev x quad x order 5: F (2, 30) = 0.667, p = 0.521).

To allow comparison with the main study, we extracted the individual order 5
coefficient for each participant at F8, although it was not reliable in the current study. The
order 5 difference between the three groups is visually complex and occurs together with
other frequency-related variations. We, therefore, first extracted the individual order 5
coefficient for each participant at F8\(^1\), and then used this coefficient to clarify the nature of
the differences between the inattentive, combined and control groups. Figure 3.10 B displays
the deviation values of the extracted order 5 component of GCSR for each frequency
averaged across all participants for the three diagnostic groups. As can be seen, there is no
noticeable difference between the three groups, with the control group tending to an opposite
pattern to inattentive and combined subtype groups.

Part C of the figure shows the residual effect in the three groups after removal of the
order 5 component. That is, the result of the subtraction of the order 5 component differences
shown in part B from the scores shown in Part A. As was expected, the ADHD subtype
groups did not change and the control group had much the same increased power at 7-11 Hz
with some variations after removal of the order 5 component. The quadratic polynomial trend
lines in the figure show the same patterns of the control and ADHD subtypes.

\(^1\) We took the order 5 weighted values from a standard table of orthogonal polynomial contrasts [-4, +11, -4, -
9, 0, +9, +4, -11, +4; divisor = 3/20], multiplied those into the data for each individual, summed and divided by
the sum of the squared contrast values to generate each participant’s order 5 coefficient.
Figure 3.10 Variation in GCSR at F8 for the control, combined and inattentive groups. (A) Mean values for the data as in Figure 4.9 but without 3 point smoothing. (B) Order 5 component only of the data in A. (C) Data with the order 5 component removed from the means and with polynomial trend lines for the combined and control groups demonstrating the same quadratic trend between them. That is, (C) is equal to the data in (A) minus the deviations in (B).
3.3.8 Goal-Conflict Effects and Behaviour (SSRT)

GCSRs for each individual were entered as the predictor variable in a stepwise regression to predict SSRT. There was no relationship between SSRT and GCSR at F8 during block two of the present experiment (GCSR, SSRT: \( r(33) = 0.007, \text{NS} \)).

3.4 Discussion

3.4.1 Behavioural results

The performance of the three diagnostic groups suggests a difference in pattern of doing the test for each group. However, these differences did not reach acceptable levels of significance for any of the variables including MRT, Go correct and \( P_{\text{thibit}} \). The only behavioural parameter in which the control group had reliably lower scores was SSRT. We also looked at gender as a variable that can affect behaviour in ADHD samples. We did not find any significant difference between the two genders in terms of behavioural responses, possibly due to small numbers of females in the ADHD subtype groups. The inattentive group and the combined group did not differ on behavioural measures.

3.4.2 EEG analysis

According to previous studies, the goal-conflict effect (GCSR) is mostly observed at the F8 site. In this study, the predicted GCSR at F8 appeared at 5-11 Hz for the control group. As you can see in figure 4.9 there is an even higher level of GCSR at 7-10 Hz for the combined group compared to the control. However the inattentive group appeared to have a reverse trend at 5-10 Hz. Moreover, GCSR is observed at lower levels at Fz and F4 compared to F8 in the current study. So, we kept our main focus on F8 for further analysis.

To determine the reason for this different kind of reaction to the conflict, we performed some more detailed analysis for a focussed comparison by looking at the stop signal effect itself. The three groups appeared to vary in averaged Stop-Go log power over all levels of SSD at F8, but this was not statistically reliable. The combined group showed a somewhat different pattern to the control. The control group had some variation across frequencies with two peaks at 5-6 Hz and 7-9 Hz. The inattentive group appeared to have an almost opposite pattern to the control group with a decrease in power from 4 to 11 Hz.

Consistent with other studies, SSRT could not been predicted by GCSR.
4 Goal-conflict processing in Children with ADHD in Iran (main study)

4.1 Introduction

The aim of this study was to replicate the initial study (described in chapter 3) in Iran. Thus, as in the initial study, goal-conflict-specific rhythmicity (GCSR) in the Stop Signal Task (SST) in children with ADHD was examined compared to a control group. The same predictions also were applied to this study.

The experiment reported in the current chapter compared GCSR in the SST among three groups of children in Iran: control; ADHD-inattentive; and ADHD-combined.

4.2 Methods

All details of participants, experimental testing, and analysis are given in Chapter 2.

4.3 Results

4.3.1 Exclusions

There were 78 participants in total at the start of testing, with 12 excluded due to excessive (>15%) artefacts in their EEG recordings. 66 (27 control, 18 inattentive, 21 combined) participants remained for analysis. Of these, 37 completed all three blocks of the task and 29 of them (44% of the whole sample) completed only the first two blocks of the task. Accuracy when responding on go trials in both of these groups was above 80%.

4.3.2 Behavioural data

ANOVAs were carried out on each of Median Reaction Time (MRT), Stop Signal Reaction Time (SSRT), Go correct% and Probability of Inhibition ($P_{inhibit}$) in short, intermediate and long Stop Signal Delay (SSD) testing for differences between the three diagnosed groups (control, inattentive and combined subtype of ADHD) and the two genders. Detailed behavioural data are presented in Table 4.1 at the end of this section.

MRT was not systematically affected by diagnosis (diagnosis: F (2, 60) = 0.953, p = 0.391; diagnosis x gender: F (2, 60) = 0.927, p = 0.401), although the inattentive subtype tended to have a larger MRT than the combined subtype and control group (Figure 4.1). For
each of the diagnostic groups, females were significantly slower than males (gender: $F(1, 60) = 4.713, p = 0.034$).

![Graph showing MRT for different groups](image)

**Figure 4.1** Effects of diagnosis and gender on MRT. Error bars are 2 standard errors of the mean for each group. Line and fill coding is chosen to match display of the conflict EEG data below.

**SSRT** showed similar trends to MRT (Figure 4.2). The inattentive subtype tended to show the largest SSRTs, but this did not achieve conventional levels of significance (diagnosis: $F(2, 60) = 2.55, p = 0.086$; diagnosis x gender: $F(2, 60) = 0.851, p = 0.432$). However, females had significantly longer SSRTs than males in all three subgroups (gender: $F(1, 60) = 9.588, p = 0.003$) similar to the MRT results.

Given the strong similarity in pattern of results for MRT and SSRT, we tested for the relation between them. MRT on Go trials was highly reliably related to SSRT ($r(64) = 0.422, p < 0.001$). So we did an analysis of covariance to see how far SSRT changes could be explained by MRT changes. The gender effect on SSRT appeared slightly weaker after adjustment for MRT as a co-variate but it was still reliable (gender: $F(1, 59) = 5.500, p = 0.022$). The apparent but non-significant ($p = 0.086$) difference between diagnostic groups was even smaller after adjustment of SSRT by MRT (diagnosis: $F(2, 59) = 1.861, p = 0.164$).
Figure 4.2 Effects of gender and diagnosis on SSRT. Error bars are 2 standard errors of the mean for each group.

Go correct% was higher in males than females (Figure 4.3; gender: $F (1, 60) = 6.193, p = 0.016$) and lower in ADHDs than controls (diagnosis: $F (2, 60) = 4.364, p = 0.017$). The effect of diagnosis appeared somewhat weaker in the males than the females but this was not reliable (gender x diagnosis: $F (2, 60) = 0.818, p = 0.446$).

Figure 4.3 Effects of diagnosis and gender on Go correct%. Error bars are 2 standard errors of the mean for each group.

$P_{inhibit}$ (i.e. the probability of a correct stopping response on stop trials) was analysed with short, intermediate and long SSD trials as separate levels of a delay factor. As expected there was a steady decrease of $P_{inhibit}$ as the stop signal delay increased, with values in the
region of 50% at intermediate SSDs (Table 4.1). There was also a similar pattern across the	hree levels of delays between the 3 groups, which means that the staircase procedures are
working similarly in all cases. When the three $P_{\text{inhibit}}$ values were analysed as levels of a
delay factor in a single ANOVA, neither gender nor diagnosis had a significant effect on
$P_{\text{inhibit}}$ (gender: F (1, 60) = 0.005, p = 0.941; diagnosis: F (2, 60) = 0.110, p = 0.896); gender
x $P_{\text{inhibit}}$, dev x quad: F (1, 60) = 1.231, p = 0.272; diagnosis x $P_{\text{inhibit}}$, dev x quad: F (2, 60) =
0.375, p =0.689); diagnosis x gender x $P_{\text{inhibit}}$, dev x dev x quad: F (2, 60) = 1.933, p =0.154).

Table 4.1 MRT, median reaction time; SSRT, stop signal reaction time; Go correct%, the percentage of
correct responses on Go trials; $P_{\text{inhibit}}$ short, probability of correct response on Stop trials in short SSDs (stop
signal delay); $P_{\text{inhibit}}$ intermediate, probability of correct response on Stop trials in intermediate SSDs (stop
signal delay); $P_{\text{inhibit}}$ long, probability of correct response on Stop trials in long SSDs (stop signal delay); N,
number of participants in each group. The table represents behavioural outputs for different groups divided by
gender and ADHD subtypes versus control group.

<table>
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<tr>
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<td>Combined</td>
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<td>Combined</td>
</tr>
<tr>
<td>MRT (S.D) ms</td>
<td>613 (61)</td>
<td>635 (93)</td>
<td>627 (32)</td>
<td>597 (46)</td>
<td>611 (67)</td>
<td>560 (71)</td>
</tr>
<tr>
<td>SSRT(S.D) ms</td>
<td>351 (97)</td>
<td>407 (99)</td>
<td>326 (67)</td>
<td>269 (45)</td>
<td>321 (66)</td>
<td>300 (89)</td>
</tr>
<tr>
<td>Go correct (S.D) %</td>
<td>88 (8)</td>
<td>70 (16)</td>
<td>73 (31)</td>
<td>92 (4)</td>
<td>87 (8)</td>
<td>81 (20)</td>
</tr>
<tr>
<td>$P_{\text{inhibit}}$ short(S.D) %</td>
<td>70 (18)</td>
<td>67 (13)</td>
<td>74 (16)</td>
<td>75 (7)</td>
<td>71 (13)</td>
<td>64 (11)</td>
</tr>
<tr>
<td>$P_{\text{inhibit}}$ intermediate(S.D) %</td>
<td>53 (10)</td>
<td>49 (6)</td>
<td>50 (9)</td>
<td>52 (6)</td>
<td>55 (13)</td>
<td>51 (9)</td>
</tr>
<tr>
<td>$P_{\text{inhibit}}$ long(S.D) %</td>
<td>36 (10)</td>
<td>36 (11)</td>
<td>42 (15)</td>
<td>36 (11)</td>
<td>37 (10)</td>
<td>36 (17)</td>
</tr>
</tbody>
</table>

| N                | 17 | 7 | 8 | 10 | 11 | 13 |
4.3.3 EEG Analysis

Almost half of the participants (29 out of 66) did the task only up to the end of block 2 and did not proceed to block 3. As in the previous experiment, all participants showed stabilized SSDs in block 2 even those who completed block 3. As in previous experiments, SSDs were not stable in block 1 as this is a period when participants are learning and the staircases are adjusting to each individual. EEG analysis, therefore, focussed on block 2 to maximise the number of participants included. The EEG analysis involved 66 children who completed block 2 of the task with less than 10% artefact.

The primary focus of the analysis was on conflict power (i.e. stop-go x quadratic of SSD) at F8. This is discussed in section 4.3.6. Section 4.3.4 provides a larger scale picture of the overall data and section 4.3.5 looks at stop-signal-specific effects to provide context for the more focussed comparison.

4.3.4 Go and Stop Trial Power at Fz, F4 and F8

Log power was averaged across participants separately for each SSD level at sites Fz, F4 and F8 to explore overall Stop-Go effects. Figure 4.4, 4.5 and 4.6 show for each of control, ADHD-inattentive and ADHD-combined, respectively, the variation in log power for Go, Stop and for the difference between them (Stop-Go) all on the same scale set to match Neo et al (2012). Figure 4.7 shows the Stop-Go differences for all three groups on a larger scale.
Figure 4.4 Variation in log power for Go, Stop and the Stop-Go difference for the control group for short (white) intermediate (grey) and long (black) SSDs. The first row (Go) is the power in Go trials that came immediately before (or after if the preceding trial was also a Stop trial) Stop trials of the SST. The second row (Stop) is the power in the Stop trials; and third row (Stop-Go) is the power difference between stop and matching go trials. The scales of the log power axes have been set to match Neo et al (2012). Stop-Go differences for F8 are plotted on a larger scale in Figure 4.7.

Figure 4.4 shows the variation in log power in the 4-12 Hz frequency range across the three right frontal sites (Fz, F4, and F8) for the control group. Intermediate SSDs (grey bars) are where the conflict effect should occur – that is their value should be increased relative to the white and black bars. Inspection of the Go trials at F8 shows there is no such increase in the region of 5-11Hz. However, with Stop trials at F8 it can be seen that the grey bar is above both the white and the black bars from 6-10Hz, i.e. the power at intermediate SSDs (grey) is increased relative to both early (white) and late (black) SSDs providing evidence of a conflict effect. It should be remembered that Go trials are exactly the same as Stop trials except for the onset of the Stop stimulus in the middle of the Stop trials. Go trials therefore provide a control for all ongoing process during the trials except those elicited by the stop signal. To
show stop-signal-specific effects we subtracted the log power in Go trials from Stop trials. The resultant, purified, Stop signal effect is shown in the Stop-Go graph (third row). This shows a stop-signal specific effect at the intermediate SSDs relative to both early and late SSDs at 6-11 Hz at F8 (see also Figure 4.7).

**Inattentive subtype**

![Graph of Inattentive subtype](image)

**Figure 4.5** Variation in log power for children diagnosed as inattentive subtype. Other details as Fig 4.4.

Figure 4.5 shows the Go, Stop and Stop-Go data for children diagnosed as the inattentive subtype. There was a decreasing trend in power as frequency increased as in the control group. However the power difference between Go and Stop trials (third row), shows the largest conflict effect at lower frequencies (6-7 Hz) compared to the control group. There is an increase in the power at intermediate SSDs in Go trials at F8 in the 8-9 Hz frequency range and also at a range of other frequencies in Stop trials (4, 8, 11 and 12).
Figure 4.6 Variation in log power for children diagnosed as combined subtype. Other details as Fig 4.4.

Figure 4.6 shows the variation in log power in the 4-12 Hz frequency range for children diagnosed as the combined subtype. Intermediate SSD power (grey) was generally not raised relative to short and long SSDs (white and black) in Go trials at F8. This was similar to the control group Go trials. There was a different pattern to controls in the Stop trials: grey is above both black and white but this is at 4-6 Hz and not in the middle frequency band (8-10 Hz) like the control group. When we subtracted Go trial power from Stop trial power there was an F8 conflict effect at 4 and 6 Hz as well as 8-9 Hz and at 12 Hz.
4.3.5 Stop Stimulus Effects

Figure 4.7 Variation in log power Stop-Go difference with frequency at each level of SSD at F8 comparing the 3 diagnostic groups (from top to bottom: control, inattentive, combined).

Figure 4.7 redisplay the Stop-Go graphs at F8 with an expanded scale. Variation in log power difference after subtracting the Go trials from Stop trials looked dissimilar between the three diagnostic groups both in relation to absolute values and in relation to the conflict-specific differences. Intermediate SSDs (grey) were associated with higher power in different frequencies. The inattentive subtype showed increased power in the 6-7 Hz range, which was the largest stop-signal-specific effect in all three diagnostic groups. The combined subtype and the controls showed higher power for intermediate SSDs in the middle frequency band. To provide a clearer picture of the differences in overall power, we averaged power across SSD levels for each group. The resultant overall effect of the stop stimulus is shown in figure 4.8. (Conflict-specific effects are detailed in the next section)
As can be seen in figure 4.8 the effect of the stop signal on overall power at F8 varied with frequency somewhat differently for each group. Basically, the control group has increased power at 4-5 Hz and 8-12 Hz. In contrast, the inattentive subtype has mainly increased power at 5-7 Hz and is only slightly increased at higher frequencies. Unlike the two other groups, the combined group has generally moderately increased power with some fluctuation across frequencies. The generally opposite pattern of the control and the inattentive group was reliable (diagnosis x Stop-Go x frequency, dev x dev x cub: F (2, 63) = 3.256, p = 0.045).

4.3.6 Goal-Conflict-Specific Rhythmicity

Figure 4.9 shows Goal-conflict-specific rhythmicity (GCSR), which is assessed statistically as the quadratic component of the variation in the stop-go power difference across the three levels of SSD. This quadratic, since it is fitted to only 3 values, is equivalent to subtracting the average over the short and long SSDs from the intermediate SSDs. An additional simplification, relative to figure 4.7 is that a 3 point running average was used to smooth the data for display in the figure. In the initial experiment, the effect of GCSR during the SST at F8 was smaller than F4 and Fz for the control group. However, in the present experiment, the largest effect of GCSR during the SST was found at F8 and in the 6-10 Hz frequency range. Figure 4.9 displays the smoothed GCSR across frequencies at Fz, F4 and F8 in Block 2. There appears to be a steady trend to increasing GCSR in the controls across the three sites,
with F8 showing increased power at 7-10Hz. Therefore, detailed analysis was focussed on GCSR at F8.

**Figure 4.9** Variation in goal-conflict specific rhythmicity (GCSR) for each frequency averaged across all participants for three groups (control, combined and inattentive subtype) for Block 2 of the SST. The data have been smoothed with a 3 point running average. Data are graphed separately for Fz, F4, and F8.
4.3.7 Detailed analysis of F8

Figure 4.10 shows three perspectives on the same data. Part A displays the variation in GCSR at F8 for the three diagnostic groups (control, combined and inattentive subtypes) without the 3 point smoothing of figure 4.9. As can be seen, the predicted goal-conflict effect appeared at F8 for the control group between 6-11Hz. The combined group looks fairly like the control group with somewhat more variation between frequencies. However, the inattentive group has a noticeably different pattern with almost the same amount of power as controls at 6-7 Hz but power suppression at 5 and 9 Hz (diagnosis x stop-go x SSD x frequency, dev x dev x quad x order 5: F (2, 63) = 4.432, p = 0.016). Post hoc ANOVAs of the individual diagnostic groups found a significant order 5 effect only in the inattentive group (stop-go x SSD x frequency, dev x quad x order 5: F (1, 17) = 8.917, p = 0.008) and not in the combined (stop-go x SSD x frequency, dev x quad x order 5: F (1, 20) = 0.864, p = 0.364) or the control group (stop-go x SSD x frequency, dev x quad x order 5: F (1, 26) = 0.453, p = 0.527).

To picture clearly the order 5 component for each diagnostic group, we first extracted the individual order 5 coefficient for each participant at F8; and then used this coefficient to clarify the nature of the differences between the inattentive, combined and control groups. Figure 4.10 B displays the deviation values of the extracted order 5 component of GCSR for each frequency averaged across all participants for the three diagnostic groups. As can be seen, the primary difference is between the inattentive group and the other two, with the combined group tending to an opposite pattern to inattentive and, perhaps, control (which had very little order 5 variation). We carried out an ANOVA on the order 5 coefficient scores as a manipulation check and obtained the same F ratios as previously.

Part C of the figure shows the residual effect in the three groups after removal of the order 5 component. That is, it is the result of the subtraction of the order 5 component differences shown in part B from the scores shown in Part A. The control group has much the same increased power at 5-11 Hz with a peak at 7-8 Hz as prior to removal of the order 5 component. The combined group remains mostly like the control group with positive power in the 6-11Hz range. In contrast to these groups, the inattentive group showed a tendency to reduced, and even negative, power at intermediate frequencies. The quadratic polynomial trend lines in the figure show the opposite patterns of the control and inattentive more clearly but the difference between these curves did not achieve conventional levels of significance in the original analysis (diagnosis x stop-go x SSD x frequency, dev x dev x quad x quad: F (2, 63) = 2.192, p = 0.12).
Figure 4.10 Variation in GCSR at F8 for the control, combined and inattentive groups. (A) Mean values for the data as in Figure 4.9 but without 3 point smoothing. (B) Order 5 component only of the data in A. (C) Data with the order 5 component removed from the means and with polynomial trend lines for the inattentive and control groups demonstrating the quadratic deviation between them. That is, (C) is equal to the data in (A) minus the deviations in (B).

4.3.8 Order 5 coefficient – relation to overall scores

Diagnostic group averages obviously involve a mixture of participants with different quadratic (order 2) scores and with different order 5 scores. Moreover, order 5 component
scores were not reliably related to order 2 component scores accounting for less than 1% of their variance (r (64) = 0.078, NS). This suggests that these two components are controlled by different neural systems. We therefore investigated the structure of the components within the groups. Figure 4.11 shows the cumulative distribution of order 2 (Figure 4.11A) and order 5 (Figure 4.11B) across all participants in Block 2.

Figure 4.11 Cumulative distribution of GCSR order 2 coefficient score (A) and order 5 coefficient score (B) for the control, inattentive and combined groups. The box drawn in part B indicates that at the point where 28% of the inattentive group had a value of -0.0189 or less, only a small proportion (5%) of the combined group, and none of the control group, had similar values.

As shown in figure 4.11, the inattentive group have a larger number of extreme negative scores than the controls for both order 2 (panel A) and order 5 (panel B). However, in both cases there is substantial overlap with some inattentives having scores well into the 80th percentile of the control distribution. For order 2 (which was not significant in ANOVA), the combined group are generally intermediate between inattentives and controls. For order 5 (Panel B), the cumulative distribution of order 5 scores of the combined group is almost the opposite of the inattentive group with the control group falling in the middle. The data within the box drawn in figure shows that more than 25% of the inattentive group had low conflict scores with only a very small proportion of the combined and none of the control group are distributed in this zone. Generally the inattentive group has a bigger distribution in the negative zone of conflict effect compared to two other groups. Despite the fact that the groups differ in terms of their order 5 averages, both low and high order 5 values occur within each group. So the distributions overlap fairly strongly. This fact suggests that the groups cannot be categorically separated in terms of their order 5 scores.
As in the initial study, we extracted three groups characterised by their order 5 scores. Two methods were used: first, we ranked all the participants on the size of their order 5 component and regardless of their clinical diagnosis and then divided them into 3 equal sized groups (Figure 4.12A); Second, we also created two groups with matched average positive and negative order 5 values and one with a zero average in the middle (Figure 4.12B).

Figure 4.12 Variation of GCSR for participants selected for high, medium and low order 5 component scores, ignoring diagnostic group. There was a range from +0.0283 to -0.0296 order 5 scores across all participants. (A) Participants were ranked and then divided into 3 groups each with 22 participants according to their order 5 score. Participants with mostly negative scores were in the “low” group (mean order 5 = -0.0016), participants with around 0 scores were in the “medium” group (mean order 5 = 0.000) and participants with higher positive scores were in “high” group (mean order 5 = +0.0011). (B) The selection process was similar to A but we tried to make up even more equivalent groups in terms of the value of order 5 score. Each participant with a large positive order 5 component was matched with a participant with the same value of order 5 component but a negative sign – this matching generated the high (mean order 5 = +0.0016) and low (mean order 5 = -0.0016) groups. Participants with a zero, or close to zero, order 5 score were put into the medium order 5 group in such a way as to produce a zero order 5 mean. As a result of this matching selection there was a smaller number of participants in each group (10) but a clearer demonstration of the effects associated with extreme positive and negative order 5 scores.
As the figure indicates, there are three distinct different patterns and none are typical of the experimental groups. There appears to be a positive peak in power, which shifts from lower frequencies in the low order 5 group to higher frequencies in the high order 5 group, but surprisingly, the medium order 5 group, rather than having a peak at intermediate frequencies show almost no increase in power at any frequency.

In order to compare participants with the three different sorts of order 5 more precisely, we matched participants with more extreme scores in high and low groups and sorted them so that the lower and the higher order 5 groups had an almost equal average value of 0.0016 in the two opposite directions (positive and negative) and the medium order 5 group that had an average close to zero and was selected to include only people with values close to zero. There were only 10 participants in each group who met the matching criteria. Figure 4.11 B demonstrates the variation of the GCSR for each frequency averaged across 10 participants in each group (as compared to 22 with the simple split by rank). The graphs for these more homogeneous groups in part B were generally similar to the graphs of all participants in part A – but with a clearer positive peak (with essentially no negative values) in the two extreme groups and more clearly negative values in the zero group. The results are consistent with the conclusion that strongly negative or positive order 5 scores are associated with shifts in the position of the peaks in power from lower frequencies to higher ones, respectively. Intermediate order 5 scores, surprisingly do not appear to reflect an intermediate frequency peak.

### 4.3.9 Goal-Conflict Effects and Behaviour (SSRT)

The order 2 and order 5 components for each individual were entered as predictor variables in a stepwise regression to predict SSRT. There was no relationship between SSRT and the order 2 or order 5 component at F8 during block two of the present experiment (GCSR, order 2: (r (64) = 0.007, NS) and (GCSR, order 5: (r (62) = 0.027, NS).  

### 4.4 Discussion

#### 4.4.1 EEG analysis

In the present study, the predicted GCSR appeared at F8 for the control group between 6-11Hz. Figure 4.9 shows there is a similar increase in the 6-10Hz range for the control and the combined groups. However the inattentive group had a different pattern with an increase only
at 6-7 frequencies at F8 and a reverse trend at 7-10Hz with decreased power peaking at 9Hz. It is difficult to determine the cause of this complex different reaction to the conflict. So we undertook a range of additional analyses.

To provide a context for the more focused comparison we first looked at the simple stop signal effect (ignoring conflict-related variation). The three groups varied reliably in log power Stop-Go averaged over all levels of SSD at F8. The inattentive group repeatedly showed the opposite pattern to controls. The combined group had some fluctuations across frequencies. Elevated levels of slow wave activity in the EEG of ADHDs in comparison to normal children have repeatedly been found in other studies. Thus, the apparent reduction in conflict-related activation at F8 for the inattentive group may in part reflect the more general EEG pattern that has been described before for ADHDs (Barry et al., 2003).

The population as a whole had variation detected as an order 5 polynomial. As can be seen in figure 4.10 B, this is a complex pattern in the means that is likely to represent the average of a similar individual pattern. Detailed analysis of the individual data and their possible relation to the order 5 polynomial suggested that its presence in the differences of the group means reflects frequency shifts in simpler peaks across individual data. Comparing the diagnostic groups based on the order 5 components of their respective means showed that the main deviation is of the inattentive group from the controls and the combined group is only marginally opposite to the controls (figure 4.10 B).

There was clearly a mixture of participants with different order 5 scores within the diagnostic group averages (see figure 4.11 B). Furthermore, order 5 component scores were not reliably related to order 2 component scores and these two components might be controlled by different neural systems. Thus, to examine the order 5 component effect independently, we grouped all the participants according to their order 5 factor and regardless of their clinical diagnosis. As a result, three different pattern of GCSR activation appeared across frequencies at F8 for the 3 order 5 factor groups (high, medium and low). The apparent reduction in GCSR activation at F8 for the inattentive group was also observed for the low order 5 group (figure 4.12 A). They both have a peak at lower frequency (5-7Hz) unless the low order 5 group has bigger power at this area and also both have the same amount of trough at higher frequencies (8-10Hz) which can be argued as the lower level of arousal. On the other hand, participants with high or positive order 5 factor scores represented different kind of pattern which almost looks like combined group graph (see figure 4.12 A) in terms of
having peak at higher frequencies (7-10Hz). This pattern also looks somewhat like the control group. The rising trend in higher frequencies can also be considered as the higher level of arousal which is consistent with stronger approach tendency and shorter median reaction time for the combined and the control group compared to the inattentive group. The group with medium order 5 component’s graph showed a quite different pattern from the two other groups. These participants showed no increase in conflict effect but decrease in negative zone of power. That was unlike any of the diagnostic groups. That might be considered as a state in which no conflict has been experienced.

Past studies examining GCSR and behaviour (SSRT) in adults found no relationship between GCSR at 4-11 Hz and SSRT. Previous studies in adults used block three as the period of interest for EEG-behaviour analysis because this is where the $P_{\text{inhibit}}$ for intermediate SSD trials stabilized. There is only one study in children (Stevenson, 2013) and this found a similar stabilization at block 2 to the current experiment and used block two as a period of interest. It produced a similar result to the adult data. In the current study, not all children completed the task and 43% of them did not proceed to block three after finishing block 2. In addition in the present study, the probability of inhibit during intermediate SSD trials was stabilized at 50% during block two. So we also chose block 2 as a period of interest. Consistent with other studies, SSRT could not been predicted by either order 2 (quadratic) or order 5 components.

### 4.4.2 Behavioural results

The behavioural performance of the participants in the main study (Iran) was compared for the three diagnostic groups. The ADHD-I and the ADHD-C did not differ on behavioural measures, suggesting that the SST might not be effective in differentiating the subtypes (Adams, Milich, & Fillmore, 2010). There may be differences among the groups, however none of the variables, including MRT, SSRT and $P_{\text{inhibit}}$, showed reliable differences. According to the literature, some researchers get longer SSRTs for ADHD and some don’t. In sum, a recent meta-analysis by Alderson, Rapport, and Kofler (2007) argued that SSRT are more variable for ADHDS. Consistent with this, Lijffijt, Kenemans, Verbaten, and van Engeland (2005), found slower and more variable SSRTs in children with ADHD compared to normal children. Also, our results suggested longer SSRT for ADHD children compared to controls but they weren't reliable, which may have been a result of having small N. The only behavioural parameter on which the control group had reliably higher scores was the
percentage of correct responses in Go trials. The gender comparisons imply that males generally had a better performance than females in terms of their behavioural responses. They were faster than females with shorter MRT and SSRT. They also responded more accurately than females on Go trials.
5 EVENT RELATED POTENTIAL ANALYSIS OF ADHD SUBTYPES

5.1 Introduction

The review of previous ADHD-ERP literature in Chapter 1 (section 4.1) described ERP differences in children with ADHD. It noted, in particular, reduced N2 and P3 components during SSTs. Some of the studies described in the review (Lazzaro et al., 2001; Senderecka, Grabowska, Gerc, Szewczyk, & Chmylak, 2012) also investigated the latencies of the peaks and reported relatively longer latencies for children with ADHD compared to neurotypical children.

The primary aim of the present chapter was to analyse ERPs during the auditory SST. Based on the previous literature, it was predicted that children with ADHD would show reduced N2 and P3 amplitudes during stop trials, compared to control children (Table 1.1). The correct and incorrect stop trials were analysed separately in order to compare the brain activity during successful trials with unsuccessful trials.

There were no clear ERPs in the New Zealand (initial) study (data not shown). Data from the Iran (main) study are reported in the current chapter, comparing ERPs among three groups of children: control; ADHD-I; and ADHD-C.

5.2 Methods

The raw data analysed in this chapter are the same as in Chapter 4 with the only difference being averaging of raw EEG to obtain ERPs rather averaging of Fourier power. All details of participants, experimental testing, and analysis are given in Chapter 2.

5.3 ERP results in the main study (Iran)

5.3.1 Exclusions

We used the same EEG data analysed for GCSR in chapters 3 and 4 only the analysis differed. We, therefore, excluded the same participants due to excessive (>15%) artefacts in their EEG recordings as before resulting in 66 participants (controls=27; ADHD-I=18; ADHD-C=22) for the final analysis.
5.3.2 Preliminary Descriptive Findings

Figure 5.1 displays the averaged ERPs, for correct and incorrect stop trials, obtained at each of the 15 electrode sites (F7, F3, Fz, F4, F8, T3, C3, Cz, C4, T4, T5, P3, Pz, P4 and T6) averaged separately for each diagnostic group. Variation in ERPs across frontal (F7, F3, Fz, F4 and F8), central (C3, Cz and C4) and posterior (P3, Pz, and P4) electrodes within each group is more marked than the between group variation in waveforms. It seems that ERPs for the control group are generally stronger than the ADHD groups at the frontal, central and parietal zones. The largest evoked potentials for the control group emerged at Cz (Section 5.5).

Inspection of Figure 5.1 reveals ERPs were clearest at latencies later than 200 or 300ms after the presentation of the stop signal. Two late positive peaks particularly occurred in the region of 500-750ms after the stop signal. The first of these late positive peaks presented 508-540ms after the stop signal; it will be referred to below as P5. The second peak appeared 640-672ms after the stop signal and will be referred to below as P6. ERP amplitude differences were observed between groups in these two peaks and are subjected to analysis below. ERP group differences were less prominent at negative peaks. Therefore analysis focused only on group differences in the two positive peaks.

At P6, the control group showed the largest correct and incorrect stop ERP amplitudes whereas the ADHD-I group had the smallest correct and incorrect stop ERP amplitudes. ADHD-I participants had the largest correct and incorrect stop ERP amplitudes at P5, while ADHD-C participants showed almost equal correct and incorrect stop ERP amplitudes at P5 and P6.

Before proceeding to the statistical analysis on P5 and P6, scalp distributions of the evoked potentials were examined in the next section for the three groups for the main study.
Figure 5.1. Average stop signal related ERPs, at each of the 15 electrode sites analysed for the control group (A), the ADHD-I (B) and the ADHD-C (C). Black vertical line at 0ms=stop signal presentation. Black line = correct stop responses; Red line = incorrect stop responses.
5.4 Scalp distribution of ERPs

5.4.1 Scalp distribution of ERPs in the main study (Iran)

The scalp distribution of the evoked potentials is shown in Figure 5.2. Mean latency for correct stop trials at P5 and P6 was calculated for each group. That was calculated by estimating individuals’ latencies at the time window for each peak and averaged across all of them in a group. The distribution of potential values at these latencies was determined for each electrode and then plotted as an interpolated map by EEGLAB.

**Figure 5.2.** Scalp distribution of ERPs at the latency of the positive peaks for the control group (A), the ADHD-I (B) and the ADHD-C (C) for correct stop trials. The scale values show a specific domain of amplitudes at different latencies of P5 and P6 for each group.
Figure 5.2 shows that P5 and P6 were occurring maximally in the region of Cz except for P6 in the inattentive group. Although relatively large ERPs extend posteriorly to Pz in the control group, analysis focused on group comparisons solely at Cz, since the central zone and particularly Cz showed large ERPs more than any other site across the three groups at both P5 and P6.

5.5 ANOVA findings in the main study (Iran)

Further analysis was conducted of each of P5 and P6 as a particular time window that included the largest amplitude value for all the groups over both the correct and incorrect conditions. A ‘peak window’ was defined for analysis of each of P5 and P6 as the time period that included the largest mean sample value for every waveform, i.e. for the diagnostic groups over both the correct and incorrect conditions. This window included the values from 500ms to 555ms for P5 and from 630ms to 700ms for P6. Each participant had their own amplitude and latency assessed within this time period for correct and incorrect stop trials separately. The amplitude values at Cz were averaged for each of P5 and P6 across participants for each group. The resultant group ERP amplitudes are shown in figure 5.3. The difference in correct versus incorrect stop ERPs for both P5 and P6 are shown in figure 5.4.

![Figure 5.3. Average correct and incorrect stop ERP amplitudes at P5 (A) and P6 (B) at Cz. Grey bars = Average correct stop ERP amplitude at peak; Black bars = Average incorrect stop ERP amplitude at peak. The data are shown separately for the three diagnostic groups (control, inattentive, combined). Error bars are 2 standard errors of the mean for each group.](image)

There is a similar pattern of decreased amplitude in incorrect stop trials compared to correct stop trials for the three diagnostic groups at P5. However, a trend to the reverse was observed at P6 - with an increased amplitude in incorrect stop trials compared to correct ones for the controls and, perhaps, the combined group. The correct versus incorrect stop ERP
differences between the three groups were not reliable at either P6 (diagnosis x correct/incorrect, F (2, 61) = 2.068, p = 0.135) or P5 (diagnosis x correct/incorrect, F (2, 61) = 2.579, p = 0.084). Generally, the difference in correct versus incorrect stop trials was strongly significant at P5 (correct/incorrect, F (1, 61) = 16.101, p < 0.001). This shows there is a consistent increase in amplitudes in correct stop trials versus incorrect stop trials at P5, which does not vary between the three groups. However, the correct/incorrect difference was not reliable at P6 (correct/incorrect, F (1, 61) = 1.114, p = 0.239). The diagnostic groups did not differ significantly on average ERPs at P6 (diagnosis, F (2, 61) = 5.423, p = 0.007” p = 0.105, NS Bonferroni corrected) or at P5 (diagnosis, F (2, 61) = 2.579, p = 0.084, NS).

Figure 5.4. Average correct stop ERP amplitude at peak - average incorrect stop ERP amplitude at peak at position Cz. Grey bars= P5; Black bars= P6.

The averaged incorrect stop ERP amplitude at P5 and P6 was subtracted from the averaged correct stop ERP amplitude (Figure 5.4) to illustrate the residual effect at these peaks. The control group showed a large positive correct/incorrect stop ERP difference at P5, but had a large negative correct/incorrect stop ERP difference at P6. Both of the ADHD subtype groups displayed positive correct/incorrect stop ERP differences at P5 and in both ADHD subtypes this difference was larger at P5. However they differed from each other in the value at P6. The inattentive subtype group had a positive value while the combined subtype group showed a negative correct/incorrect stop ERP difference, which was more like the control group than the inattentive subtype.

We also ran an analysis comparing between the two peaks although P5 was not significantly different between three groups. The diagnostic groups were reliably different when interaction between peaks and correct/incorrect stop ERP difference were analysed
Following this analysis, we subtracted the correct/incorrect stop ERP difference at P6 from the correct/incorrect stop ERP difference at P5. Figure 5.5 shows ADHD subtype groups had the similar amplitude after subtraction between the peaks and the control group displays larger amplitude compared to them.

**Figure 5.5.** Subtraction average correct stop ERP amplitude - average incorrect stop ERP amplitude at P6 from P5 at position Cz.

There were no major differences between the diagnostic groups in the latencies for P5. The latencies at P6 looked longer for the ADHD subtype groups than the control. However the difference was not at all reliable (diagnosis x latency x correct/incorrect, \( F(2, 61) = 1.052, P = 0.355 \)). Figure 5.6 displays the averaged latencies at P5 and P6 for correct and incorrect stop trials across all participants at each group.

**Figure 5.6.** Average correct and incorrect stop ERP latencies at P5 (A) and P6 (B) at Cz. Grey bars = Average correct stop ERP latency at peak; Black bars = Average incorrect stop ERP latency at peak. Error bars are 2 standard errors of the mean for each group.
5.6 Discussion

Taking together all the ERP results in the main study, there were no consistent differences between the controls and the ADHD subtypes. There were two late positive peaks (P5 and P6) in both studies. However, the variation of these peaks between the three groups was not in line with our hypothesis and the ADHD subtypes were not distinctive from the control. Furthermore, these peaks appeared later than previously reported P2 (200ms) or P3 (300ms) ERP components.

Correct/incorrect Stop ERP differences at two late positive peaks (P5 and P6) were also observed. In the main experiment, an absolute correct/incorrect difference in stop trials was observed at P5. However, the ADHD subtypes were not distinguishable from the control group based on the correct/incorrect differences at either P5 or P6 in this study.

Correct/incorrect stop ERP differences at P5 and P6 obtained positive values for three groups in the Iran study. Correct stop ERPs at the latency of the positive peaks were somewhat centralized at Cz in Iran study (figure 5.2).
6 General Discussion

6.1 Overview

The primary focus of this study was to evaluate whether ADHD deficiencies are related to BIS dysfunction. Although impairments in behavioural inhibition have been hypothesized to be at the core of ADHD (Barkley, 1997b; Quay, 1997), little research, to our knowledge, has focused on whether and, if so how, the neuropsychological function of Gray’s BIS in children with ADHD differs from normal children. This study examined the differences between ADHD-I, ADHD-C and control groups by looking at their GCSR activity, which is believed to be a biomarker of BIS function (McNaughton, 2014; McNaughton et al., 2013), during an auditory SST.

Two studies were undertaken, one in New Zealand (initial study) and one in Iran (main study). They demonstrated that ADHD-C showed GCSR activity at F8 similar to that in control groups obtained from the general population. However, ADHD-I showed less GCSR activity than controls. In both studies, instead of positive GCSR, there were negative scores at F8 for ADHD-I particularly at 7-9 Hz. We found GCSR activity at Fz and F4 in the initial study control group but not in the main study control group. Neo et al. (2011) also found co-activation of the medial right frontal regions (Fz and F4) during the SST. They suggested that the varying speed of Go responses across trials could lead to the co-activation of different regions of Fz, F4 or F8. In both studies, GCSR activity for the ADHD subtypes at Fz and F4 looked somewhat similar to their F8 GCSR (see figure 6.2 and 6.3).

ERPs of the main study (Iran) were also assessed. Two late positive peaks (P5 and P6) were observed for all three diagnostic groups. However, these peaks appeared later than previously reported N2 or P3 ERP components and, to our knowledge, have not been described before. There were no obvious amplitude or latency P5 and P6 differences between control and ADHD subtype groups except from the averaged ERP amplitudes at P6 in the main study in which the three diagnostic groups reliably differed. Post hoc ANOVAs of the individual diagnostic groups found a significant difference only between the ADHD-I and the control but not between the ADHD-C and the control group or the between the subtypes.

Stopping behaviour was assessed via SSRT. Both ADHD subtypes had significantly longer SSRTs than the control group in the initial study, which is consistent with Lijffijt et al. (2005), who found slower and more variable SSRTs in children with ADHD compared to
normal children. In the main study as in the initial study, ADHD-I had longer SSRTs than the control group. However, in contrast to the initial study, the ADHD-C female group had shorter SSRTs than the controls. Other studies (Johnstone, Barry, et al., 2007; K. Rubia, et al., 2005) have also found shorter SSRTs for ADHD-C.

In the main study, the control group achieved a reliably higher level of correct responses in Go trials than the ADHD subtypes, consistent with Zeeuw et al. (2008). Similar results did not achieve statistical significance in the initial study.

6.2 EEG findings

GCSR can be calculated by subtracting the average of the stop-go power difference over the short and long SSDs from that of the intermediate SSDs. GCSR has been proposed as a biomarker of BIS activity in human superficial EEG (McNaughton, 2014; McNaughton et al., 2013). The BIS is activated by goal-conflict when approach and avoidance are equally important. Previous studies in adults (Crosbie et al., 2013; Neo et al., 2011) have found GCSR at F8. Consistent with this, we observed GCSR at F8 for the control group at 5-11 Hz in the initial study and at 5-10 Hz in the main study. This confirms the preliminary observation of GCSR in children by Stevenson (Stevenson, 2011). The current thesis is the first study that examines GCSR in ADHD children and compares them to neurotypical children.

We will start by focusing on F8 in this section as it is the primary site of interest in the current thesis. There were some major commonalities between the two studies: a positive GCSR activation for both the ADHD-C and the control group and a negative GCSR activation for the ADHD-I subtype. To make the commonalities clear, figure 6.1 displays the average of the two studies at F8 and compares it with the previous separate data.
Figure 6.1 Variation in goal-conflict specific rhythmicity (GCSR) at F8 for each frequency averaged across all participants for the three diagnostic groups (control, combined and inattentive subtype) for Block 2 of the SST. The data have been smoothed with a 3 point running average. A: an average of the results from the two centres. B: results of initial study taken from chapter 3 (figure 3.9) and C: results of main study taken from chapter 4 (figure 4.9).
As can be seen in figure 6.1A, the pooled control group shows positive GCSR from 5 to 11 Hz at F8, with a moderate peak at 6-8 Hz. The pooled ADHD-C shows a similar, positive GCSR at 7-11 Hz peaking at 8 Hz. In contrast, the pooled ADHD-I has negative GCSR from 7-10 Hz with maximal negativity at 8 Hz. The ADHD-I pattern is clearly distinct from ADHD-C particularly at 8-9 Hz.

In the initial study, we found higher GCSR activity for ADHD-C at 7-10 Hz at F8 while the highest GCSR for the control group was found at 6-8 Hz. However, in the main study, ADHD-C showed a very similar GCSR in the 5-10 Hz frequency range to the control group. Overall, then, ADHD-C may have somewhat greater GCSR than controls; but the key finding, in both cases, is that ADHD-C do not have lower values than controls and, unlike ADHD-I, do not have negative values in the 5-10Hz range.

In the initial study, ADHD-I showed a noticeably different pattern to the main study from 5-9 Hz; with a decrease in power. The results showed some similarity to the main study, ADHD-I appeared to have a distinct pattern from the other groups. The ADHD-I showed an opposite trend to the ADHD-C and the control with a noticeable decrease in power at 7-10 Hz and an inflection at lower frequencies (6-8 Hz) at F8. The differences between the two sets of results, and the complex shape observed in both cases, suggest that the detailed form of the ADHD-I curve in figure 6.1A should be treated with caution.

The two ADHD subtypes show distinct patterns of GCSR variation at all of the three sites (Fz, F4 and F8) in both studies (see figure 6.2 for F4 and figure 6.3 for Fz). The ADHD-I generally show decreased power at 7-9 Hz while the ADHD-C tend to show increases. Although the results of the two studies appear to differ in some respects, they were not significantly different in terms of the observed overall differences between the diagnostic groups at F8(GCSR averaged over frequencies at F8: Centres x diagnosis: F (1, 93) = 0.681, p = 0.509).
Figure 6.2 Variation in goal-conflict specific rhythmicity (GCSR) at F4 for each frequency averaged across all participants for three diagnostic groups (control, combined and inattentive subtype) for Block 2 of the SST. The data have been smoothed with a 3 point running average. A: an average of results from the two centres. B: taken from chapter 3 (figure 3.9) and C: taken from chapter 4 (figure 4.9).
Figure 6.3 Variation in goal-conflict specific rhythmicity (GCSR) at Fz for each frequency averaged across all participants for three diagnostic groups (control, combined and inattentive subtype) for Block 2 of the SST. The data have been smoothed with a 3 point running average. A: an average of results from the two centres. B: taken from chapter 3 (figure 3.9) and C: taken from chapter 4 (figure 4.9).
There was also some apparent dissimilarity between the two centre’s results. In particular, GCSR was generally higher over the frequency band (5-11 HZ) for the initial study control group compared to the main study control group at F8. There are a number of possible reasons for this. We used two different electro caps in the two centres and these had different electrode types. In the initial study, silver/silver chloride (Ag/Agcl) electrodes were used, while in the main study, tin electrodes (which tend to produce more artefacts) were used. Additional sources of variation between two centres could include other equipment differences, variations in sample composition, different diagnostic procedures, comorbidity, cultural and race effects. Given the small number of participants in the initial study, we could expect to see spurious large (or small) values as a result of more variability. However, the initial study’s control group had relatively lower GCSR activity at F4 and particularly Fz, compared to F8. It should be noted that previous adult experiments have reported varying peak frequencies for GCSR (McNaughton et al., 2013; Neo et al., 2011). It is also important to bear in mind that participants in the initial study had generally faster reaction times (MRT = 585 ms) in Go trials than the participants in the main study (MRT = 604 ms). As mentioned earlier, according to Neo et al. (2011) the extent to which right or midline frontal areas are involved in behavioural inhibition depends on the Go response speed. F8 has a bigger contribution when responses are slower. F4 and Fz have a bigger impact when the response is fast.

To sum up, we found solid evidence of normal GCSR activity in children, of the type previously observed in adults, for the control and ADHD-C groups; and also clearly abnormal GCSR activity for the ADHD-I subtype. GCSR was consistently observed at F8 for the control and ADHD-C subtype across the two experiments. This observation rules out the detection of GCSR by chance for these two groups and shows that the qualitative result is robust in the face of differences in geography, race, culture, size of urban area, and diagnostician. Moreover, some decrease in GCSR was consistently found for the ADHD-I group across the two experiments although its precise form varied. This also rules out the possibility of abnormal GCSR by chance in ADHD-I. Hence, the BIS bio marker differentiates, at least on a group basis, between the subtypes (ADHD-I, ADHD-C). While it is possible that the ADHD-I results could be due to some unmatched variable such as comorbidity, IQ, SES, etc, it is difficult to see why the same variable should have shown the same sample bias in two such different centres.
Figure 6.4 Variation in log power Stop-Go difference with frequency averaged over all levels of SSD at F8 for 3 groups. A: an average of the two centres results, B: taken from chapter 3 (figure 3.8) and C: taken from chapter 4 (figure 4.8).

Simple stop-signal-specific effects (i.e. averaged across all SSD values) were also compared between the three diagnostic groups in the two centres. This effect was calculated as the variation in log power difference after subtracting the Go trials from Stop trials. The resultant absolute values seemed dissimilar between the three diagnostic groups in both
experiments but the precise form of the data varied between the studies and appeared quite complex. Figure 6.4A shows an averaged graph of the two centres and comparison with each separately (Figure 6.4B, C).

As the figure shows, the control group had higher amplitude compared to the clinical groups in both studies. The clinical groups showed higher amplitude in the main study compared to the initial study. If we take the averaged graph as representative of both studies, in ADHD-I power is increased at 7 Hz, while in ADHD-C it is shifted to higher frequencies and the control group has steady positive amplitude across frequencies. To our knowledge, there has not been any other study investigating stop-signal-specific effect in EEGs in children with ADHD.

6.3 ERP findings

Researchers studying Event Related Potentials (ERPs) in children with ADHD have observed reductions in ERP amplitude compared to controls during tasks that require inhibitory control (Albrecht et al., 2005; Brandeis et al., 1998; Johnstone, Barry, et al., 2007; Liotti et al., 2007; C. C. E. Overttoom et al., 2002; Pliszka et al., 2000b; Senderecka, Grabowska, Szewczyk, et al., 2012). This suggests that specific ERP components might be used either to distinguish ADHD from neurotypical participants or to discriminate subtypes of ADHD.

In contrast, in the current thesis, there were no consistent differences between the control and the ADHD subtypes considering all the ERP results in the main study. There were two late positive peaks (P5 and P6) that appeared later than the previously reported N2 (200ms) or P3 (300ms) ERP components. Correct/incorrect Stop ERP differences in the two late positive peaks (P5 and P6) were also observed in both studies. However, the ADHD subtypes were not consistently distinguishable from the control group based on the correct/incorrect differences at either P5 or P6 across studies. The diagnostic groups only differed at P6 on averaged ERP amplitudes. Post hoc ANOVAs of the individual diagnostic groups showed that the significant difference was between the ADHD-I and the control group.

6.4 Behavioural findings

Stop-signal reaction time (SSRT) has been widely seen as the essential measure characterizing behavioural inhibition performance in ADHD. However, a recent meta-
analysis by Alderson et al. (2007) argued that SSRT reflects a more generalised deficit in cognitive processing rather than behavioural inhibition (see section 3.4.1 for more details).

In the current thesis, ADHD subtypes tended to longer SSRTs than the control groups across studies with only one exception. In the main study, the ADHD-C female group showed slightly shorter SSRTs than the control group (see figure 4.2). However, none of these apparent differences were reliably significant. Finding longer SSRTs for ADHD groups is consistent with previous studies' (Alderson et al., 2008; Lipszyc & Schachar, 2010) findings of significantly slower and more variable SSRTs for ADHD groups.

ADHD subtypes were not distinguishable from the normal groups in terms of the Go response speed in either the initial study or the main study. Previous studies have found contradictory MRT results for children with ADHD. According to Alderson et al.'s (2007) results, ADHD groups had significantly slower MRT while a study by de Zeeuw et al. (2008) showed ADHD groups had reliably faster MRT. We found more inaccurate responses in Go trials for ADHDs than controls in the main study, which fits with the results of de Zeeuw et al. (2008).

We also found a significant gender effect on MRT, SSRT and Go correct responses in the main study. Females were reliably slower in median reaction times in Go trials, longer in stop-signal reaction time in Stop trials and had more errors than males. This does not fit with Crosbie et al.’s (2013) findings of minimal effects for gender in studying ADHD traits using the stop task. In contrast, there were no effects of gender in the initial study. This is consistent with Thakkar et al.’s (2014) result of no sex differences in overall accuracy or response inhibition in healthy adults during the SST. Finding a reliable gender effect in one study and not in the other will raise a question of the role of other variables that might have an indirect effect on the results. The initial study was run in New Zealand and the main study in Iran. The varying gender effect in the initial and the main studies could be due to culturally related gender differences in the two centres. Other studies have also shown the importance of role of the culture in diagnosis and treatment of ADHD symptoms (Bussing, Gary, Mills, & Garvan, 2003; Ghanizadeh, 2009; Norvilitis, Ingersoll, Zhang, & Jia, 2008).
6.5 Does GCSR provide evidence for the BIS producing ADHD?

Quay (1997) proposed a model of ADHD in which the symptoms would be the result of abnormality in Gray's BIS (Gray, 1972, 1982; Gray & McNaughton, 2000). According to Gray's BIS model, a reduction in the main outputs of the BIS in ADHD would be expected to change behavioural inhibition, attention to negative stimuli and arousal. However, these changes would only happen when there is a balanced goal conflict between two opposite motivations (approach and avoidance). GCSR is generated by goal conflict resolution (Neo et al., 2011); and is a human biomarker for BIS activity as it is affected by drugs that share only anxiolytic action (McNaughton, 2014; McNaughton et al., 2013), which define the BIS (Gray & McNaughton, 2000).

In both the initial and the main study, reduced GCSR was observed for ADHD-I. The current results with ADHD-I, therefore, support Quay’s (1997) view that ADHD symptoms might be due to underactivity in Gray’s BIS. However, our findings with ADHD-C do not fit with Quay’s theory: there was no evidence of reduced BIS activity for ADHD-C in either of the studies. The ADHD-C group appeared to show similar GCSR activity to the control group, with perhaps a slight tendency to greater not lesser GCSR. The current ADHD-C results are also inconsistent with Barkley’s (1997a) hierarchical model of impairments in ADHD where inhibition deficits are primary and lead to secondary impairments in the other four neuropsychological areas – if “inhibition” is restricted to the sense of BIS output. In contrast, finding normal BIS activity for the ADHD-C subtype is consistent with Nigg’s (2006) suggestion that hyperactive-impulsive behaviours (which are more common in ADHD-C than ADHD-I) are an expression of a high approach tendency rather than behavioural inhibition impairments. Solanto et al. (2001) also suggested that impulsivity of ADHD symptoms might be better conceptualized as a choice to avoid delay, not as an inability to inhibit the response. They argued that delay aversion is associated with a broad range of ADHD characteristics compared to inhibitory deficits.

Longer SSRTs in children with ADHD have been interpreted as a proof of the BIS deficits (Quay, 1997). In the initial study, both ADHD subtypes had longer SSRTs than the control group. This is consistent with some previous studies (Nichols & Waschbusch, 2004). In contrast, in the main study, SSRTs for ADHD subtypes did not differ significantly from the control group. In the main study, both genders with ADHD-I tended to show somewhat
longer SSRTs than the control group but females with ADHD-C showed shorter SSRTs than the control.

Figure 6.5 Postulated neural control of going and stopping. Motor inhibition uses both fast and slow routes (Nachev, Kennard, & Husain, 2008) to modulate the go circuit (Nachev, Rees, Parton, Kennard, & Husain, 2005; Nachev, Wydell, O’Neill, Husain, & Kennard, 2007). We propose that goal inhibition involves, in addition, the slower BIS circuit (Gray & McNaughton, 2000). avPFC = anteroventral prefrontal cortex; rlFG = right inferior frontal gyrus; preSMA = presupplementary motor area. Connections have been simplified, and circuits and structures in the BIS, other than the hippocampus, are not shown (e.g., the Papez circuit is omitted). Figure and legend taken from (Neo et al., 2011) with permission.
However, it should be noted that McNaughton et al. (2013) demonstrated that SSRT was not affected by anxiolytic drugs despite the fact that GCSR was reduced. In accordance with this finding, GCSR did not predict inhibition times (SSRT) during the SST in any of our experiments. Consistently, in a previous study (Neo et al., 2011) there was no correlation of SSRT with GCSR, or trait anxiety, or neuroticism. Neo et al. (2011) suggested that the SST is a speeded response task involving actions but not goals. It is possible that goal-conflict related information could not reach the motor system in time to affect behaviour. Figure 6.5 shows Neo’s model of neural stopping circuits at different speeds in Go and Stop trials. In line with this suggestion, we found that the largest GCSR appeared in a specific range of speed (570-650 ms), which has been a medium MRT in both studies. We also observed reduced GCSR activity for faster participants. Thus, the resultant abnormal GCSR activity does not seem to be the output of a real BIS abnormality for fast participants. But it is rather related to their behavioural strategy that doesn’t allow the BIS to get involved. These results lead us to the conclusion that SSRT and GCSR are not necessarily measuring the same thing. In other words, BIS activation would not affect SSRT in this speeded case.

Given these results, SSRT in the SST paradigm can be seen as involving different processes (act and action stopping) from behavioural inhibition of the type controlled by the BIS (resolution of goal conflict). SSRT depends on the outcome of a race between the "go" process and the stopping process. If MRT is faster than SSRT, the individual emits the response; if the SSRT is faster than MRT, the response is inhibited. As a result, SSRT is measuring the processes that are related to action stopping. In fact, action stopping is generated without involving the BIS and is not sensitive to anxiolytic drugs (McNaughton et al., 2013). However, under less time pressure, stopping can be produced by output from the BIS to the stopping system. The BIS can cause stopping when there is a conflicting goal which has activated both approach and avoidance systems and prevents either of them. Thus, SSRT may be better conceptualised as a measure of action withholding and stopping while GCSR is best characterised as a measure of conflict and behavioural (goal) inhibition.

In conclusion, ADHD-I symptoms, which involve attention and arousal problems included some that can be explained by abnormality in the BIS. However, ADHD-C symptoms (and some ADHD-I symptoms), which are characterised by impulsive behaviours, may be better explained by abnormality in action stopping, the BAS system or other executive functions, since they do not appear to show BIS abnormalities. The BIS will be
activated when the BAS and the FFFS are equally and strongly activated. When the BIS is activated, neither the BAS nor FFFS can produce its usual behaviour (approach or avoidance respectively). An over active BAS will produce stronger approach that would not allow equal approach and avoidance to be experienced. As a result, the BIS will detect less conflict or may not be activated appropriately to stop the behaviour. Thus, BAS over activity can result in disinhibited behaviours even in the presence of normal BIS activation for ADHD-C.

6.5 ADHD: subtypes or spectrum?

A dimensional, or spectrum, approach is used for a mental disorder when its causes or symptoms show a smooth range of distributed conditions with no clear boundaries between groups of cases. On the other hand, a categorical, or subtype, system is more appropriate when distinct collections of typical clinical profiles can be identified that do not overlap with each other. According to the APA (2000), a categorical classification of subtypes is best when: (1) all the members of a subtype are homogeneous; (2) there are clear borders between subtypes; and (3) the different subtypes are reciprocally exclusive. The current results raise the question of the validity of the usual division into subtypes in ADHD. Is ADHD-I better conceptualised as a less severe variation of ADHD-C or as a distinct diagnostic entity from ADHD-C? In either case, is there a clear separation into distinct categorical groups or are there features that are smoothly distributed across the entire population. There is some evidence for both sides of this argument. Some studies have supported a categorical distinction between three subtypes (Glutting et al., 2005; Proctor & Prevatt, 2009). Other studies have claimed that the overall similarities between the subtypes are greater than the dissimilarities (Baeyens et al., 2006; Lemiere et al., 2010; Miller et al., 2010). Neuropsychological methods also have failed to identify critical neurological substrates for the subtype differences (Solanto et al., 2007).

It has been suggested that ADHD can be understood via a bifactor model (Martel et al., 2010). According to this model, there is an important unitary component in ADHD that captures common variance in subtypes. There are also two additional orthogonal factors of inattention and hyperactivity/impulsivity that capture unique variance between cases. This model has potential implications for distinct etiological inputs, as well as differential assessment (Martel et al., 2010). However, ADHD symptoms in the bifactor model could be distributed according to a spectrum or as subtypes. Figure 6.6 displays the ADHD symptoms according to the bifactor model in these two different ways.
6.6 Bifactor model of ADHD symptoms. The model includes three dimensions: 1. g factor, 2. Inattention, 3. Hyperactivity-Impulsivity. A: Spectrum: the symptoms are scattered throughout the dimensions. B: Subtype: the symptoms are clustered in each subtype (inattentive, hyperactive-impulsive, and combined). n = neurotypical, h = hyperactive-impulsive, c = combined and i = inattentive.

Our results support a spectrum of ADHD symptoms. When we investigated the structure of GCSR measures within the groups using cumulative graphs, in both studies there was no clear separation between the diagnostic groups (or between them and controls) – both low and high GCSR values occur within all three groups. Thus, the distributions overlapped extensively. This means that no group can be categorised reliably in terms of their GCSR score. Participants with normal and abnormal GCSR can be found in each of diagnostic groups. It should be noted that we obtained similar results with SSRT. Our results, therefore, support the concept of ADHD as an extreme of continuous traits rather than as a categorically separate disorder.
Our findings also somewhat support the idea of a unitary component (a "g" factor) in ADHD as we found no differences between the ADHD-I and ADHD-C regarding their behavioural outputs in the SST. They varied from the control to some extent in terms of the accuracy of responses and SSRTs. However ADHD-I and ADHD-C were not different on these behavioural measures. Previous studies that compared how ADHD-I and ADHD-C perform on the SST, found similar results. For instance, Huang-Pollock et al. (2007) reported no differences were observed between ADHD-C and ADHD-I during SST in terms of intentional, pre-potent motor inhibition. It seems that, although the stop-signal paradigm has been a highly influential model for studying basic inhibitory deficits in ADHD, the model has limitations in its ability to differentiate the ADHD subtypes (Adams, Derefinko, Milich, & Fillmore, 2008). Similarly, Nigg et al. (2002) and Geurts et al. (2005) compared executive functions among ADHD-I and ADHD-C and found that, on most domains, ADHD-I and ADHD-C did not differ. These result may also relate to subtype instability (Lahey, Pelham, Loney, Lee, & Willcutt, 2005). Neuropsychological findings on executive functioning of children with ADHD-I and ADHD-C have not produced evidence for distinctiveness of subtypes so far. This is all consistent with a linkage of these measures to the g factor.

However, we found some evidence for differences between ADHD-I from ADHD-C that can be linked to the postulated specific additional factors of inattention and hyperactivity-impulsivity. The averaged GCSR, the biomarker of the BIS activity, decreased for the ADHD-I but not for the ADHD-C. Thus, the BIS biomarker, GCSR, can be a potentially practical tool to locate ADHD-I in relation to ADHD-C on the inattentive dimension.

According to our findings, two different motivational systems can be involved in the aetiological aspects of some ADHD symptoms like behavioural disinhibition. Goal conflict resolution problems for ADHD-I can be explained by BIS abnormality. A lower level of attention, arousal and behavioural inhibition can be the consequences of the BIS abnormality in ADHD-I. However, BIS activity for ADHD-C appeared normal consistently across the two studies. Superficially similar behavioural problems for ADHD-C characterised as impulsivity would be better conceptualised as a combination of action stopping problems and excess of action producing by the BAS. As mentioned earlier, the BAS may produce stronger approach in conflict that interferes with the balance between approach and avoidance. As a result, conflict would not be experienced to activate the BIS. In another words, if the BAS is suppressed in ADHD-C, then the BIS will be stimulated in conflict and can result in
behavioural inhibition. Therefore, two different specific factors (the BIS and the BAS abnormality) are involved in behavioural inhibition deficits in ADHD-I and ADHD-C. This fact implies that different treatment approaches for each of ADHD-I and ADHD-C would be appropriate.

Overall, the unitary component of the bifactor model (g factor) can be responsible for common variance between ADHD-I and ADHD-C found in their behavioural outputs and be reflected in a failure of, e.g., action stopping. However, ADHD-I and ADHD-C cannot be deemed as a single entity by looking at the averaged GCSR values for each group (see figure 6.1). The BIS abnormality may be considered as one of the specific factors of the bifactor model, i.e. the ADHD-I specific factor that explains low levels of arousal, attention and inhibition in conflict for ADHD-I. In contrast, BAS abnormality may be the basis of the ADHD-C specific factor of the model – this needs further investigation. BAS over activity can produce excessive approach that results in some aspects of ADHD-C like hyperactivity and impulsivity.

**6.6 ADHD: maturational lag model or Developmental deviation model?**

As mentioned earlier (see section 1.4.2), two main models have been proposed to interpret the EEG features of ADHD studies. The maturational lag model suggests that ADHD results from a developmental lag in CNS functioning whereas, in the developmental deviation model, ADHD is caused by a developmental abnormality in CNS functioning. Our findings are more consistent with the developmental deviation model. According to this model, EEG abnormalities in children with ADHD are not improved with age and cannot be considered normal in children of any age (Klinkerfuss et al., 1965). Consistent with this latter suggestion, we found abnormal BIS activation in ADHD-I. However, further investigation would be needed to prove that this abnormal pattern is not normal in very young children.

**6.7 Limitations and future directions**

There are some limitations to the conclusions that can be drawn from the current thesis. First of all, because of recruitment problems, we did not have access to a sufficiently large sample of participants in the initial study (New Zealand). There were not equal numbers of both genders in each diagnostic group because of the generally limited number of participants in both the initial and the main studies. As a result, we could not control gender effects across subtypes in both studies. Due to lack of access to large samples, we also did not screen and
exclude comorbid factors, such as behavioral problems or learning disabilities. We also did not have access to the clinical characterization of the ADHD groups, including comorbidities and symptoms severity. Unfortunately, we did not record the proportions of our samples that were medication free. Using larger samples in each subtype group with equal number of each gender and comorbidities excluded would clarify the role of gender, IQ, etc and strengthen the results.

In addition, there were different diagnosis systems, cultural and race effects in two countries that could not be controlled. Moreover, different EEG hardware and software were used in the initial study (ASA Neurotechnology) and in the main study (WinEEG) for EEG recording. Two different kinds of EEG caps were also applied in each center to suit with each EEG machine (the initial study: silver/silver chloride (Ag/Agcl) electrode cap and the main study: Tin electrode cap). All these uncontrolled variables could have had an impact on the final results. However, given the overall consistency of the results obtained, these uncontrolled differences make our results stronger by demonstrating generality across the varying conditions.

The current investigation on ADHD subtypes using the BIS biomarker has raised several issues that future studies should address. From our results, it is possible that two different motivational systems are involved in ADHD-I and ADHD-C symptoms: the BIS abnormality in ADHD-I, which causes goal conflict resolution problems and the BAS abnormality in ADHD-C, which causes action stopping problems. Further research is needed in ADHD subtypes to compare them in terms of the BAS activity by EEG recordings using appropriate tasks to activate this system and explore this possibility.

6.8 Conclusion

Is BIS dysfunction the main cause of ADHD symptoms as hypothesized by many researchers (Barkley, 1997b; Quay, 1997)? Our findings answer this question with a clear ‘no’. We found some aspects of ADHD symptoms that could be related to BIS dysfunction. In particular, averaged GCSR activity, the BIS biomarker, tended to be consistently lower for the ADHD-I groups across the two studies. In contrast, averaged GCSR activity was consistently high for the ADHD-C and the control groups in both studies. Thus, ADHD-I symptoms such as low level of attention and arousal could be due to BIS under activity since these are the BIS outputs. However, action stopping problems in ADHD-C cannot be explained by BIS abnormality as there was no evidence of abnormal BIS activity for ADHD-C in any of the
studies and action stopping is not sensitive to the anxiolytic drugs that define the BIS. BAS over activity may better explain ADHD-C hyperactivity and impulsivity symptoms. We conclude from all this that ADHD-I differs from ADHD-C and normal groups in terms of their BIS activity. Thus, ADHD-I and ADHD-C cannot be seen as a single entity.

We also found some evidence supporting the concept of a spectrum for ADHD symptoms rather than categorical divisions. The distribution of GCSR, and other measures for the three diagnostic groups overlapped fairly strongly. Thus, ADHD-I and ADHD-C would be better viewed as extremes of distinct continuous traits that also share a common factor between them.
7 References


Lansbergen, M. M., Arns, M., van Dongen-Boomsma, M., Spronk, D., & Buitelaar, J. K. (2011). The increase in theta/beta ratio on resting-state EEG in boys with attention-deficit/hyperactivity disorder is mediated by slow alpha peak frequency. *Progress in Neuro-Psychopharmacology and Biological Psychiatry, 35*(1), 47-52. doi: [http://dx.doi.org/10.1016/j.pnpbp.2010.08.004](http://dx.doi.org/10.1016/j.pnpbp.2010.08.004)


Stevenson, M. (2011). *Do phenylketonuria and attention deficit/hyperactivity disorder share a common dysfunction? A “behavioural inhibition system” hypothesis.* (MSc Master), University of Otago.


Appendix A: Information sheet and consent forms (English version)

The information and consent form follow as 7 un-numbered pages.
Inhibition Mechanisms in Children  
The Stop Signal Task computer game with EEG  
INFORMATION SHEET FOR PARENTS / GUARDIANS

Dear Parents/Guardians,

Thank you for showing an interest in this project. Please read this information sheet carefully before deciding whether or not to participate. If you decide to participate we thank you. If you decide not to take part there will be no disadvantage to you of any kind and we thank you for considering our request.

What is the Aim of the Project?

We would like to invite your family to take part in an experiment that tests a computer game version of a cognitive task. The task tests the capacity to inhibit behaviour and we want to use it later in a study we are carrying out that will investigate electrical brain activity in children with attention deficit hyperactivity disorder. The project focuses on theta band (4-8Hz) changes under situations of high conflict between two competing goals. The overall project is being undertaken by Sima Sadeghi and the results will be written up as her PhD thesis and we hope will also be published in a research journal.

What Type of Participants is being sought?

We are looking for children aged 7-12 years (years 4-8 in school). We need them to be right handed (because the brain effects we are interested in are lateralised), and have no difficulties with attention or inhibitory control. Children with a history of allergic skin reactions will not be able to participate in the project because, in the opinion of the researchers and the University of Otago Human Ethics Committee, it may involve an unacceptable risk to them from the electrode gel that we use to get a good electrical contact between the head and our electrode cap.

What will Participants be asked to do?

Should you and your child agree to take part in this project, you will be asked to bring them to the psychology department for a one-hour testing session. We will provide you with a $10 petrol voucher as compensation for the costs of bringing your child to us.

Your child will first be fitted with an electrode cap. This will involve measuring points on their head, putting a dot on their forehead, fitting the cap and checking each electrode with an impedance meter, which your child can help read. To ensure the electrode has good contact with the scalp we use an electro-conductive gel that is squeezed through the electrodes using a blunt syringe. We then rub the small part of the scalp under the electrode, while checking impedance, to get a good connection. If this process is too uncomfortable your child may withdraw at any time.

Your child will then be taken to a specially designed booth where they will be connected to an EEG machine that records their brain rhythms. They will be made comfortable in a chair facing a computer monitor where the game is to be presented. They will be instructed to perform two brief pre-tests (eye-blink and relaxation) to ensure the cap is reading clearly.

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The computer game your child will be playing involves clicking the right or left mouse button in response to a signal that come up on the computer's screen. The task will last roughly 25 minutes in total.

Then we will take the cap off and help your child clean off the gel. Please bring a camera if you would like to take a photo of your child while they are wearing the cap.

**What Will You Be Asked To Do**

Providing that you are still happy to participate in the study we ask you to:

- Discuss the study with your child (a child information sheet is provided for your child to read, or for you to read to them) and to gain your child's assent (verbal agreement) to participate.
- Sign the parent consent form before test.

**Can Participants Change their Mind and Withdraw from the Project?**

You or your child may withdraw from participation in the project at any time and without any disadvantage to yourself of any kind.

**What Data or Information will be collected and What Use will be made of it?**

Your child’s responses and brain rhythms will be recorded, transcribed, and viewed only by the researchers directly involved in this study. They will be identified by an arbitrary code, not by name, and all computer files will be kept confidential. Results of this project may be published, but any data included will in no way be linked to any specific participant.

You are most welcome to request a detailed copy of the overall results of the project should you wish.

The data collected will be securely stored in such a way that only those directly involved in the project will be able to gain access to it. At the end of the project any personal information will be destroyed immediately, except the raw data on which the results of the project depend, which will be retained in secure storage for five years. This is a requirement of the University’s research policy, and all data may be completely destroyed after this compulsory five years.

Every attempt will be made to protect the anonymity of your child, you and your family.

**What if Participants have any Questions?**

If you have any questions about our project, either now or in the future, please feel free to contact either:-

Prof. Neil McNaughton  
Department of Psychology  
Phone: 479 7634

or

Sima Sadeghi  
Department of Psychology  
Phone: 479 5835  
Sadeghi.sima@yahoo.com

This study has been approved by the University of Otago Human Ethics Committee (Approval Number: 10/043; 23 March 2010). If you have any concerns about the ethical conduct of the research you may contact the Committee through the Human Ethics Committee Administrator (ph 03 479 8256). Any issues you raise will be treated in confidence and investigated and you will be informed of the outcome. Please keep this Information Sheet for future reference.
INHIBITION MECHANISMS IN CHILDREN
The Stop Signal Task computer game with EEG

Parent/Family Consent Form

If you have any concerns or questions about the study please contact Sima Sadeghi (027 2442300) or Professor Neil McNaughton (03 479 7634).

I have read and I understand the Information Sheet for volunteers taking part in the “Inhibition Mechanisms in Children study. I understand the nature and purpose of this research, the time required in taking part, and the fact that it involves electrical recording. I have had the opportunity to discuss this study and to ask questions which have been answered to my satisfaction.

I understand that taking part in this study is voluntary and that I may withdraw from the study at any time without any penalty of any kind for my family or my child.

I understand that my taking part and my child’s taking part in this study is confidential and that no material that could identify my child, my family, or me will be used in any public reports on this study. No personal identifying data will be stored and individual raw data will be stored securely and only averaged data published. Every attempt will be made to protect the anonymity of my child, my family and me.

I have had sufficient time to consider whether to take part in the current study.

I have discussed this study with my child and my child is happy to take part.

I, ......................................................... hereby consent for my child,
(Parent’s/Guardian’s full name)

......................................................... to take part in this study.
(Child’s full name)

Signature of Parent/Guardian ............................ Date ............................

Current Address Details: ..........................................................

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

Current Phone Number(s) and good times to contact: ..........................................

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

This study has been approved by the University of Otago Human Ethics Committee (Approval Number: 10/043). If you have any concerns about the ethical conduct of the research you may contact the Committee through the Human Ethics Committee Administrator (ph 03 479 8256). Any issues you raise will be treated in confidence and investigated and you will be informed of the outcome.
INHIBITION MECHANISMS IN CHILDREN
The Stop-Signal and Choice computer games

Investigator Contact Details

Principal Investigators: Professor Neil McNaughton (03) 479 7634
Co-investigators:
Sima Sadeghi (03) 479 7621

This project has been reviewed and approved by the University of Otago Human Ethics Committee

[Reference Number 10/043 23 March 2010]
Inhibition Mechanisms in Children
The Stop Signal Task computer game

Would you like to take part in a research study?

Hi there,

We have designed a new computer game and we are writing to ask you if you would like to come to the University to play this computer game.

What will I be asked to do?

We will ask you to play a computer game. In this game you have to sit in a chair and watch the screen closely. The game involves concentrating on the screen and pressing the right mouse button or the left mouse button as fast as you can when you see a symbol on the screen that will tell you which button to press. You will sometimes hear a tone that will signal different rules for button pressing. You will get points whenever you press (or don’t press) the correct button.

We will ask you to wear an Electrocap while you are playing the game. This allows us to record your brain activity. It has holes in it (the white spots in the pictures) that we will fill with special gel that allows us to connect to your brain rhythms. It will take a while to get this fitted to you and we will have to rub the gel into your hair to get a good connection. You can stop us at any time if you are not comfortable with this. After you have played the game we will take the cap off and help you clean off the gel. If you want a copy of your brain waves, or a photo of you in the chair with your cap on, ask your mum or dad to bring a camera along!
How do you feel about taking part?

Have a think about it before you say “yes” or “no”, and talk to your mum, dad, or the person who cares for you. You don’t have to take part if you don’t want to, and you can stop at any time. You shouldn’t take part if your skin often gets irritated by creams like sun block. If you would like to say “yes” and take part in the study, please tell your mum, dad, or carer. There is a consent form that they will have to sign that even has a place where you can sign your name to say that you want to take part.

Who are we?

These are the names of the researchers involved in this study. If you want to ask us something please do – our phone numbers are below!

Sima Sadeghi (479-5835)  Neil McNaughton (479-7634)

Thank you, we hope to hear from you soon
INHIBITION MECHANISMS IN CHILDREN
The Stop Signal Task computer game with EEG

Child Consent Form

I have been told about this study and understand what it is about. All my questions have been answered in a way that makes sense. I know that:

1. Participation in this study is voluntary, which means that I do not have to take part if I don't want to and nothing will happen to me. I can also stop taking part at any time and don't have to give a reason;

2. Anytime I want to stop, that's okay.

3. Sima will take electrical recordings from my head but these will not have my name linked to them.

4. If I don't want to answer any questions she asks, that's fine.

5. If I have any worries or if I have any other questions, then I can talk about these with Sima.

6. The computer file with my recordings and my responses during the computer game will only be seen by Sima and the people she is working with. They will keep everything private.

7. Sima and the people she is working with will write up the results from this study for their University work. The results may also be written up in journals and talked about at conferences. My name will not be on anything they write up about this study.

8. I know that Sima will put a cap on my head, put sticky electro gel into holes in the cap and rub it into my scalp. If I think this is uncomfortable I can ask Sima to stop at any time.

I agree to take part in the study.

...........................................................................  ......................................
Signed                                        Date

Family Consent form 4 March 2012
Appendix B: Information sheet and consent forms (Farsi version)

The information and consent form follow as 5 un-numbered pages.
مکانیزم های بایزرداری رفتاری در کودکان

تست کامپیوتری علامت توقف با نوار مغزی

فرم اطلاعاتی بیای ولادتین

والدین گرامی

منونن برای نشان دادن علاقه به مطالعه مدا. لطفا این فرم را یا دقت بخوانید قبل از اینکه باید شرکت در این مطالعه تصریح بگیرید. اگر تصمیم می‌شود بود، اقدامی می‌کنیم و اگر منفی بوده، هیچ گونه زیانی نتوانید بگذارید. بود و ما باز هم از توجه که به درخواست ما نشان داده اید، منونن خواهیم بود.

هدف این مطالعه چیست؟

ما خانواده شما را دعوت می‌کنیم تا در این مطالعه شرکت کنید. این تست نسخه کامپیوتری یک تست نشان‌دهی است. تست، ظرفیت بایزرداری رفتاری را بررسی می‌کند، یعنی می‌خواهیم از آن در مطالعه فعالیت‌های مغزی کودکان بیش از نهایت ضعیف به نظر توجه و بهبود فعالیت‌های استفاده کنیم. این پروژه روی چگونگی زندگی تنش (4-8 هرتن) امواج مغزی متمرکز می‌شود در شرایطی که تعارض با آبی مان در هدف رقابت کنند و وجود دارد. تمام این پروژه توسط سیما صادیقی انجام می‌گیرد و نتایج آن به عنوان ترکیبی از چاپ خواهند شد.

چه نوع آزمون‌هایی یا مورد نیازند؟

ما در جستجوی کودکان 7-12 سال هستیم. ما نیازداریم که این کودکان راست دست باشند. (به دلیل کاهش قدرت پژوهش‌های کودکان این موضوع دارد) و مشکل عمدی ای در زمینه توجه و کنترل رفتار نداشته باشند. اگر سابقه ابتلا به حساسیت‌های پوستی داشتند، ما نمی‌توانیم از او در این مطالعه استفاده کنیم. چون این موضوع ممکن است کودک را در معرض خطرات پیشین بیش نشده قرار دهد.

آزمون‌ها چه خواهند کرد؟

در صورت موافقت شما و فرزندتان با شرکت در این مطالعه، شما برای یک جلسه یک ساعت به بانوان مطالعه مورد شده خواهید. شما، ما مبلغ 20 هزار تومان برای مزیت سوخته به شما پرداخت خواهیم کرد.

فقط شما، یک کلاس ثبت نوار مغزی به سر خواهد گذاشت. این مرحله شامل اندازه‌گیری‌های سر هم خواهید بود. برای برقراری ارتباط بهتر با امواج مغزی، سویاکه‌ها روزی کلاه با زل مخصوصی پر خواهید شد. این سازگاری‌ها که برآورده می‌شود، در بنای این فرزند شما این مطالعه را خیلی آزاد می‌کند. می‌توانید از ادامه دادن انتظار دهید.

SST - Parent Information Sheet 18 Nov 2013
مکانیزم‌های بازداری رفتاری در کودکان
تست کامپیوتری علائم توقف با نوار مغزی

دانت می‌خواهید در مطالعه ما شرکت کنید؟

سلام,

ما یک بایز کامپیوتری طراحی کرده‌ایم و این فرم را برای تو می‌فرستیم تا از تو دعوت کنیم در این بایزی شرکت کنی.

چه کاری قرار است انجام بدهم؟

ما از تو می‌خواهیم یک بایز کامپیوتری انجام بدهی. در این بایزی روی یک صندلی مقابل کامپیوتر می‌نشینی.بازی شامل تمرکز روی صفحه کامپیوتر خواهد بود. یک علامت فلش به سمت چپ با راست روی صفحه می‌آید و تو باید با سرعت هر چه تمام تر دکمه چپ با راست موس را فشار بدهی. گاهی اوقات صداي بوک می‌شنوی. در این مواقع تو باید از فشار دادن دکمه موس خودداری کنی. اگر دکمه چپ با راست را به موقع فشار بدهی و موقعیت به توقف بعد از شنیدن صدا یاب شوی، امتیاز می‌گیری.

ما از تو می‌خواهیم خواست کلال مخصوصی را به سر بگذاری. این کلالی به ما اجازه می‌دهد، امواج مغزی تو را ثبت کنیم. روی کلاه سوراخ‌های وجود دارد، همانطور که در این شکل می‌بینی، ما نیاز داریم سوراخ‌های کلاه را با یک مخلوطی پر کنیم. این کار مدتی زمان خواهد برد. ما باید یک دلیل برای سرنگه‌های مخصوصی که سر آنها تنی نیست در سوراخ‌های تزریق کنیم. اگر در طول این کار احساس ناگهانی داشتی، می‌توانی از ما بخواهی که کارا موفق کنیم.

بعد از اینکه تست تمام شد، کلال را از سرت داریم و موها را تعریف می‌کنیم. اگر بخواهی می‌توانی یک کمی از نوار مغزی ات داشته باشی و اگر دوست داری یا این کلاه عكس بگیری، حتما یک دوست به خودت بیاور.

SST – Information Sheet 18 Nov 13
چه احساسی در مورد شرکت در این مطالعه داری؟

قبل از اینکه جواب مثبت یا منفی به این سوال بدیهی، کمی فکر کن. با پدر یا مادر یا برادر گذری که مرافقت توست، حرف بزن. تو مجبر به شرکت در این مطالعه نیستی و هر زمان که بخواهی می توانی آن را متوافق کنی. بهتر است در این مطالعه شرکت نکنی، اگر پوستت به استفاده از کرما حساس است. اگر تصمیم مثبت بود به خانواده ات بگو. بک فرم رضایت برای تو در نظر گرفته شده که پایان آن را امضا کنی.

ما کی هستیم؟

اینها اسم محققانی است که این مطالعه را به عهده دارند. اگر سوالی از ما داشتی، حتی با ما تماس بگیر.

شماره تماس ما این است!

سیما صادقی (09125434236)
نیل مک نوتن (006434797634)

ممنون، منتظر شنیدن خبری از طرف تو هستیم.

SST – Information Sheet 18 Nov 13
مکانیزم های بازداری رفتاری در کودکان
تست کامپیوتری علامت توافق با نوار مغزی
فرم رضایت خانواده

در صورت داشتن هرگونه سوال در مورد این مطالعه لطفاً با سیما صادقی (0912) گفتگو کنید.

من فرم اطلاعاتی برای داوطلبان را مطالعه کرده و فهمیده‌ام. می‌دانم شرکت در مطالعه بازداری رفتاری در کودکان داوطلبانه است. می‌دانم طبعاً این مطالعه به جهت ترتیبی است و اینکه شامل نتیجه‌گیری از آموزش‌های متغیر می‌شود. من برای طرح سوالاتم با محقق و گرفتن پاسخ راضی کننده فرصت کافی داشته‌ام.

من می‌دانم که در صورت تمایل می‌توانم از مشارکت در این مطالعه صرف نظر کنم و این هیچ گونه زیانی را متحمل

من و خانواده‌ام نمی‌کنم.

من می‌دانم که مشارکت من و فرزندم در این مطالعه محرمانه خواهد بود و هیچ گونه اطلاعات شخصی در مورد من و

فرزندم منتشر نخواهد شد. هیچ گونه اطلاعات هر یک از من و فرزندم جایی نیستند، داده‌ها حق خاصی از جایی

نگهداری شده و فقط میانگین نتایج منتشر خواهد شد. هر گونه تلاش‌های مربوط به این مراقبت از ناشناخته بودن داده‌ها مربوط به

ما انجام خواهد شد.

من زمان کافی برای در فکر کردن به شرکت در این مطالعه داشته‌ام.

من در مورد این مطالعه با فرزندم بحث کرده‌ام و فرزند من از شرکت در این مطالعه راضی است.

فاز 1-------بدین سبب وسیله رضایت می‌دهم-------فرزندم...

در این مطالعه شرکت کنند.

امضاء و تایید......

تاریخ......

آدرس:......

تلفن و زمان مناسب برای تماس:

این مطالعه توسط کمیته اصول اخلاقی مطالعات انسانی دانشگاه اوتاگو تایید شده است (10/043). اگر گروه نگرفتی

ای در مورد مسائل اخلاقی این مطالعه دارید، با کمیته اصول اخلاقی مطالعات انسانی ارتباط برقرار کنید (نامه: 03

479 6285). شما با رعایت اصول محرمانه بررسی خواهید شد و شما از نتیجه تحقیق باخبر خواهید شد.

Family Consent form 4 March 2012
مکانیزم‌های بازدارنده رفتاری درک‌وکان
نست کامپیوتری علامت نتوانف به نواز مغز

فرم رضایت کودک

همه چیز در مورد این مطالعه به من گفتگو شده و من فهمیدم ام که این مطالعه در مورد چیست. تمام سوالات من به شیوه قابل فهمی باش و حادثه شده اند.

1. شرکت در این مطالعه داوطلبانه است و این یعنی من می‌پویان به شرکت در این مطالعه نیستم و اگر نخواهم هنگام اتفاقی نخواهم افتاد. من خود می‌توانم نست را در هر کجا که دلمن خواست منتفی کنم و می‌پویان نیستم همیشه برای ان پایوت.

2. هر زمان که نخواهم نست را منتفی کنم، ابرادی نخواهم داشت.

3. سیما امواج مغز مرا ضبط نخواهد کرد و این نتایج هنگامی از من روی آن نخواهد داشت.

4. اگر من نخواهم به سوالاتی که از من می‌پرسند، پاسخ بدهم، هیچ ابرادی نخواهد داشت.

5. اگر من نگرانی با سوالی در مورد نست داشته باشم، می‌توانم از سیما پرسیدم.

6. فایل کامپیوتری امواج مغز من فقط توسط سیما و کسی که او با او کار می‌کند، دیجیتال نخواهد شد.

7. سیما پاسخ این است که اگر کار دانشگاهی اش استفاده نخواهد کرد. آنها همچنین در مراحل علمی و کنفرانس‌ها مطرح نخواهد شد اما هنگامی از من در این مطالعه برد نمایه شود.

8. من می‌دانم که سیما به کلید سر من نخواهد گذاشته و سوالاتی که کلیه را با ژل مخصوصی بر نخواهد کرد. اگر این کار باعث ضارتی من بشود می‌توانم از سیما بخواهم ان را منتفی کنم.

من موافقت شرکت در این مطالعه هستم.

امضا

................................. نام

Family Consent form 4 March 2012