An Event-Related Potential (ERP) study of symptomatic and asymptomatic adults with Attention Deficit Hyperactivity Disorder (ADHD)

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September 2003

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Word Count: 28,620

"A report submitted as a requirement for the degree of Master of Cognitive Science at The University of Western Australia."

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I, Stas Simon Krupenia, herewith agree to being an author on publications that may arise out of the work reported in a Masters thesis submitted to the School of Psychology in 2003.

_____ 18/11/2003

Signature Date

Acknowledgments

There are several people to thank that have contributed to the completion of this thesis in a variety of forms. For academic input, Allison Fox has been invaluable. Zyron Krupenia has provided extensive academic feedback as well as motivation and encouragement. Thank you also Andrew Whitehouse and Janet Williams for providing feedback on earlier versions of this thesis. Freda Krupenia has provided me with her unlimited patience and support for which I will be forever grateful. Tammy Ellis has once again helped me feel good when I didn't and feel great when I felt good. Finally, thank you to all my friends who have ensured I lead a balanced life, insisting that good work is also a product of a healthy body and a positive outlook on life.

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Abstract

This study recorded Event Related Potentials (ERPs) during completion of a Continuous Performance Task (CPT) in order to identify the contribution of response inhibition, working memory, and response monitoring to the pattern of hyperactive and impulsive and inattentive behaviour observed in patients with Attention Deficit Hyperactive Disorder (ADHD). Four ERP components, Nogo N2, Nogo P3, Go P3, and the ERN were examined and compared using a symptomatic and asymptomatic ADHD sample, and a healthy control group. The Nogo N2 had the expected frontal scalp distribution and was affected by changes to inhibitory demands. It was also suggested that this component was not wholly determined by inhibitory processing and may have been influenced by differing presentation rates of the Go stimulus, a template matching process or an in-depth response strategy. Source localisation analysis suggested a right frontal generator for this component. The Nogo P3 had the expected central distribution and had equal amplitude for those participants that were more efficient at inhibiting behaviours compared to those participants that were less efficient inhibitors. Contrary to expectations, the Nogo P3 was not affected by increasing the inhibitory demands of the task and was suggested as being a less reliable indicator of response inhibition in the present study. The Go P3 had the expected centro-parietal distribution, and appeared to provide a reliable index of working memory. Response inhibition and working memory were not impaired in the sample of symptomatic and asymptomatic ADHD adults used in this study. The symptomatic group elicited a slightly enhanced ERN compared to the asymptomatic and control groups, indicating that deficits in response monitoring may contribute to the pattern of problematic behaviour observed in people with ADHD.

Introduction

Despite many studies which have examined the nature of cognitive deficits in adults and children with ADHD, very few have compared these processes between patients currently exhibiting ADHD symptoms and those adults diagnosed as having the disorder but who no longer experience such problematic behaviour. Currently, the most widely used treatment for ADHD involves the administration of stimulant medication. This form of treatment yields high response rates in children and adolescents with the disorder, with around 70% of patients experiencing a significant decrease in symptoms. In adults, the response rate is less robust, with between 25% and 78% responding positively to medication (Wilens, Biederman, & Spencer, 1998, as cited in Paterson, Douglas, Hallmayer & Krupenia, 1999). A gap that remains in the literature relates to the nature of the deficits that persist in a group of symptomatic adults with ADHD compared to asymptomatic ADHD adults. Aside from providing a greater understanding of ADHD, the identification of the persistent deficits can allow for the development of novel treatment techniques aimed at normalising the specific dysfunctions. This study attempted to identify the nature of cognitive differences between the symptomatic and asymptomatic groups, using Event-Related Potentials (ERPs) that enable the examination of these cognitive processes. ERPs are recordings of brain electrical activity and possess extremely high temporal resolution. They can be used to observe rapid changes in brain activity associated with specific cognitive functions. The Continuous Performance Task (CPT) has been widely used in ADHD experiments and allows for the analysis of working memory, response inhibition, and response monitoring.

By recording ERPs and examining waveform components elicited during the completion of the CPT, this study will examine the difference in working memory, response inhibition and response monitoring capabilities between symptomatic and asymptomatic ADHD adults, as well as a non-ADHD control group. The components identified as being of particular relevance to the present study are the Nogo N2, Nogo P3, Go P3 and the Error Related Negativity (ERN).

In chapter one, several theories aimed at explaining the three cognitive processes of interest to this thesis are presented. Chapter two will address how ERPs are obtained and which ERP components are associated with response inhibition, working memory and response monitoring. In the third chapter, a review of localisation studies is presented. This chapter identifies which brain regions are involved in activation of the cognitive processes of interest. Chapter four uses the information presented in the previous three chapters to identify the contribution of differing cognitive deficits to the pattern of hyperactive, impulsive and inattentive behaviour displayed by persons with ADHD.

Chapter One: Cognitive models of response inhibition, working memory, and response monitoring

Response inhibition

According to Barkley (1997), response inhibition is a three-fold process involving: 1) the prevention of a prepotent (or secondary) response from interfering with a primary task, 2) the stopping of an ongoing response, in order to provide a delay period necessary to assess the situation, and 3) the maintenance of this period free from competing events and responses. Barkley defines the prepotent response as that for which positive or negative reinforcement is available, or has been previously associated with that response.

Logan and Cowan (1984) developed the Horse-Race Model of inhibition. This model likens response inhibition to a horse race between two competing processes – the primary action (the initially performed, or action of most importance) and the prepotent (or secondary) action. If the processing for the primary action finishes before that of the prepotent action, then the primary response is executed. If processing for the prepotent action finishes first, then the primary action is stopped, and the prepotent response is performed. The likelihood of inhibition is thus determined by the probability of one response being processed before the other.

Inhibition has been extensively studied using the Stop-Signal paradigm (Schachar, Mota, Logan, Tannock, & Klim, 2000; Schachar, Tannock, Marriot, & Logan, 1995) and the CPT (Johnson et al., 2001; Seidman, Biederman, Weber, Hatch, & Faraone,

1998; Seidman et al., 1997). Both the stop-signal task and the CPT are controlled laboratory tasks designed to observe inhibitory processes.

The CPT, which is used to assess attentive, vigilant and impulsive processing (Spreen & Strauss, 1998), was initially introduced by Rosvold and colleagues in 1956 (Rosvold, Mirsky, Sarason, Bransome, & Beck, 1956). It has since been modified in several ways. The CPT-AX is one variant often used to study inhibitory processing amongst ADHD and other clinical populations (Overtoom et al., 1998; Strandburg et al., 1996). The CPT-AX requires participants to respond to the target letter 'X' when it follows the presentation of the cue letter, 'A'. The 'X' in the AX sequence is referred to as the Go stimulus. If the cue stimulus is not followed by the Go stimulus, but instead the Nogo stimulus (the letter 'Y'), no response is required.

CPT performance is typically analysed in terms of hits (correctly responding to Go stimuli), omission errors (missed response to Go stimuli), and false alarms, or commission errors (incorrectly responding to Nogo stimuli). Reaction times to hits and false alarms are also recorded. Performance errors on the CPT can be broken down into two sub-categories, i.e., inattention – by number of missed targets, and impulsivity – the number of false alarms (Overtoom et al., 1998).

The inhibitory demands of the CPT-AX can be manipulated in two ways. Firstly, by stressing the need to perform rapidly (versus accurately), participants are more likely to fail to inhibit their response to the Nogo stimuli (Jodo & Kayama, 1992). In this situation, reaction times for hits will be faster, however, the number of errors will be greater. Alternatively, if accuracy is emphasised (over speed), then correctly

inhibiting responses becomes more frequent, errors are reduced and reaction times to target stimuli increases.

Secondly, inhibitory demands can be manipulated by varying the likelihood of the Go stimulus appearing. When the Go stimulus appears at a high-density (for example, on 90% of trials) then inhibition to Nogo stimuli is more difficult than when the Go stimulus occurs at a lower density (on 50% of trials).

When a Go stimulus is presented there is a specific pattern of neural activation associated with production of the Go response. With increasing presentations of the Go stimuli, the neural network associated with response production experiences greater rehearsal within working memory. Because of the increased activation and working memory rehearsal the neural network responsible for the Go response becomes increasingly primed and thus the response is more readily elicited. In the high-density condition, participants find it increasingly difficult to withhold responses to the Nogo stimulus. With reference to the horse-race model, the processes that are involved in executing the Go responses are primed and are consequently more rapidly completed than the Nogo process.

A benefit of the CPT is that it is not influenced by practice effects. In fact, performance at the end of each testing session tends to decline (Spreen & Strauss, 1998), attributed to the tedious and repetitive nature of the task. The inattention and impulsivity measures derived from the AX version of the task have adequate split-half and test-retest reliabilities (Gordon, 1993, as cited in Spreen & Strauss, 1998; Seidel & Joschko, 1991). The CPT has also been shown to distinguish between

people with head injuries, conduct disorder, childhood ADHD and normal control subjects (Ballard, 1997). Studies have found that CPT performance is influenced by the age of the participant such that older adults tend to exhibit decreased reaction time on commission errors compared to younger adults and children. Recently CPT performance has been associated with IQ score and academic performance (Ballard, 1997). Consequently, any between-group study involving a CPT must use age and academically matched samples.

The Stop-Signal Task (SST) has also been used to observe response inhibition. Here, participants are required to respond to a Go stimulus, but must inhibit the response if the Go stimulus is immediately followed by a stop signal. Inhibitory demands can be manipulated by varying the time delay between presentation of the response signal and stop signal. When the time between the Go stimuli and stop signal is small (e.g. 50 ms), inhibiting the response is easier than when that time delay is greater, (e.g. 500 ms) (Logan & Cowan, 1984). Performance data on the SST approximates a psychometric function, such that when the time delay is below a certain figure, inhibition is inevitable. Similarly, when the time delay is above a certain period, a failure of inhibition is almost certain.

Schachar and colleagues (Schachar et al., 2000) have developed a method for calculating the stop-signal reaction time (SSRT) by using a novel tracking algorithm. The algorithm increases the stop-signal delay following a successful inhibition and decreases the delay when the participant has failed to inhibit. The algorithm converges on a stop-signal delay period such that inhibition successfully occurs

approximately 50% of the time. This allows the SSRT to be estimated by subtracting the stop-signal delay from the mean Go signal reaction time. The SSRT thus provides a precise measure of latency of an internally generated, unobserved inhibitory control process. People with poor inhibitory processes exhibit longer SSRTs (Schachar et al., 1995; Schachar et al. 2000).

Performance on the SST can be explained using the Horse-Race Model. When the time delay between the Go and Stop signals is large, then the processing undertaken to perform the Go action might be completed before the presentation of the stop signal. When the delay is short, it is likely that the processing required to stop the action will be completed before the response action processing had been completed.

Working memory

Working memory represents a temporary limited capacity store of information used when performing mental operations (Gazzaniga, Ivry, & Mangun, 1998) and is thought to underlie a range of higher cognitive processes including hindsight and forethought. It is used, for example, when remembering a phone number or having a conversation. It has been referred to as a mental scratchpad (Kimberg, D'Esposito, & Farah, 2000). Impairment in working memory has been hypothesised as constituting a core deficit in ADHD (Karatekin & Asarnow, 1998).

Alan Baddeley, believing that the current models of memory were not capable of explaining short-term information processing, constructed a three-part model of working memory, composed of a central executive, a phonological loop and a visuospatial sketchpad (Baddeley, 1986). The phonological loop is a two-part

mechanism by which information is acoustically coded in working memory whilst the visuospatial sketchpad is responsible for the initiation, storage, and manipulation of representations of visual and spatial information. Overseeing these two processes is the central executive, thought of as the command component of working memory. The central executive presides over the functioning of the phonological loop, the visuospatial sketchpad and their interactions with long-term memory (see Figure 1).

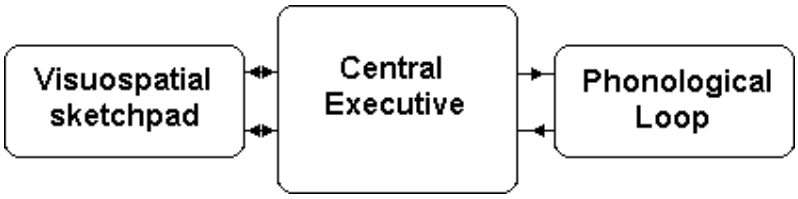

Figure 1. A simplified representation of Baddeley and Hitch's working memory model.

Unlike the subordinate components, the central executive is modality free and along with coordinating processes in working memory, it is involved in the controlling of actions. Many recent studies of working memory have examined the relationship between central executive functions and the frontal lobe, which is the proposed neuroanatomical region of the central executive (Carpenter, Just, & Reichle, 2000; Goldman-Rakic, 1995). By testing persons with known frontal lobe lesions, researchers have sought to identify tasks that are wholly dependent upon the central executive. A product of these studies has been the realisation that the central executive plays a role in a range of cognitive processes. To accommodate for the range of processes dependent upon central executive processing, Baddeley has recently conceded that "the central executive itself will need to be fractionated into a number of separable executive processes" (Baddeley, 2000, p301).

Goldman-Rakic (1995) uses primarily non-human primate studies to argue that the central executive itself is composed of multiple, modular, special purpose processing systems (see Figure 2).

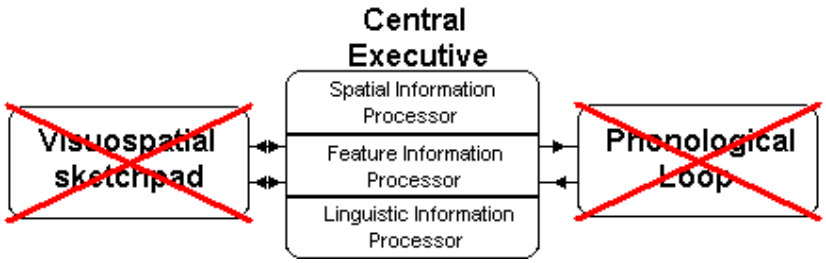

Figure 2. Schematic representation of the working memory model introduced by Goldman-Rakic (1995).

In this model, the central executive need not communicate with other working memory subsystems as the central executive contains all the necessary domain-specific working memory modules. Each of these modules can register information, maintain that information for immediate processing, and process this information by interacting with related sensory and motor areas with which each module is connected. In addition, each module contains individual sensory, mnemonic and motor control features. Deeper information processing requires interactions either with more modules or with modules located further, in both an anatomical and cognitive sense, from the initial module. In the cases involving deeper processing, a greater number of neurons become activated, due to increased activity within each module as well as between modules (Goldman-Rakic, 1995).

The central executive proposed by Baddeley and Hitch is similar to the Supervisory Attention System (SAS), initially introduced by Norman and Shallice (1980). The

SAS operates in conjunction with *contention scheduling*, and is responsible for action control using conscious awareness, as opposed to automatic responses initiated by contention scheduling. The SAS makes use of stored knowledge to prioritise actions, irrespective of environmental cues. Whilst contention scheduling is implicated in the initiation of automatic, impulsive and implicit behaviours, the SAS has the capability to oversee contention scheduling and offer more controlled and explicit behaviours. According to Shallice, a deficit in the functioning of the SAS would result in contention scheduling dominating behaviour determination. Behaviour would thus become more impulsive and reliant upon environmental cues (Shallice, Burgess, Schon and Baxter, 1989).

Pennington and colleagues introduced a theoretical framework of working memory. They define the primary characteristics of working memory as involving action selection based upon the satisfaction of key constraints, which are both context-specific and transient. Within their framework, there are seven factors capable of influencing the functioning of working memory (Pennington, Bennetto, McAleer, Roberts, 1996). These are; 1) the *capacity* of working memory; 2) the degree of c*onnectivity* between working memory and other cognitive systems; 3) the *interconnectivity* between bits, or chunks of information stored in working memory; 4) the degree of relationship between each bit or chunk information (*complexity*); 5) the *maintenance* of the information within each element, that is, the time period before decay occurs; 6) *priming* or the previous arousal of working memory elements; and 7) the general *arousal* level of the working memory system. The overall arousal of the system is thought to be influenced by the levels of dopamine in the prefrontal cortex. The authors concede that what they present is only a limited

theoretical model, and that further work is required before the model can be fully accepted. One question that remains unresolved is what occurs within each working memory element. Both the working memory elements (the bits or chunks of information) and indeed the entire collection of working memory elements, performs a similar function to Goldman-Rakic's central executive. Pennington's framework has placed the central executive into a model of executive functions and the prefrontal cortex.

Currently, there are several laboratory methods that can be used to investigate working memory. One such method is the n-back task (Grune, Metz, Hagendorf, & Fischer, 1996). The n-back task is a cognitively demanding task requiring participants to maintain representations of stimuli, such as letters, numbers or symbols in working memory and to compare these stored representations to the representations of newly presented items (for an illustrated example, see Figure 3). For example, a one-back trial occurs when the target stimulus is presented one stimulus after the cue stimulus. As the number of intervening stimuli increases, a greater number of representations must be stored in working memory and thus the task becomes more difficult.

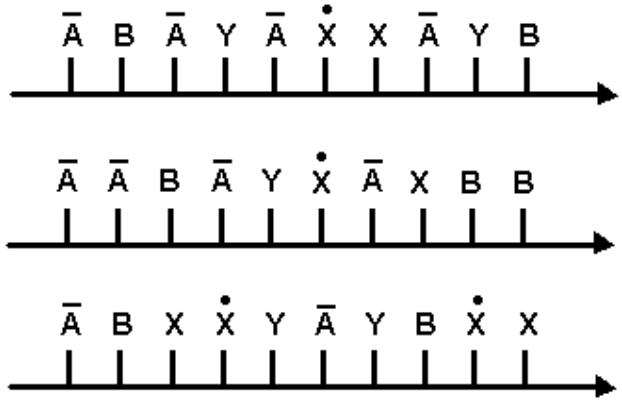

Figure 3. Example of a 1-back (top), 2-back (middle) and 3-back (bottom) task. Stimuli are presented on a screen, one at a time from left to right. Target stimuli (X) are indicated by the '•', cue stimuli (A) by the '¯'.

The n-back test has often been used to successfully reflect working memory capabilities. The n-back test incorporated into the CPT-AX can be manipulated to alter the working memory demands of the continuous performance task. As explained previously, the CPT-AX requires participants to respond to a letter 'X', only if it has been preceded by the letter 'A'. Participants must maintain representations of each letter in working memory and compare it to representations of subsequent items. When presented with an 'A', participants must maintain a representation of this item in working memory and refer to it when presented with the following stimulus. If the n-back increases – that is, increasing the number of stimuli between the cue and target variables, participants must retain this representation over a longer period, and concurrently rehearse the newly presented items, thereby increasing the working memory demands of the task. Ruchkin and colleagues (Ruchkin, Johnson, Grafman, Canoune, & Ritter, 1992) using a working memory task similar to the n-back test found that both reaction times to target stimuli and error rates increased significantly when information load (the number of

consonant-vowel syllables in a pronounceable non-word) was increased from three to five elements.

Monitoring response execution

A third cognitive process examined in this thesis is one that broadly involves the monitoring of behavioural responses. More specifically, this thesis will examine the monitoring of *error* responses. Error response monitoring is an important cognitive function through which people are able to identify errors in behaviour and to adjust their behaviour accordingly. Coles Scheffers and Holroyd (2001), used research performed Falkenstein and colleagues (Falkenstein, Koshlykova, Kiroj, Hoorman, & Hohnsbein, 1995) and by Gehring and Knight (2000) to construct a model of error processing involving both a monitoring system and a remedial action system. This is presented in Figure 4.

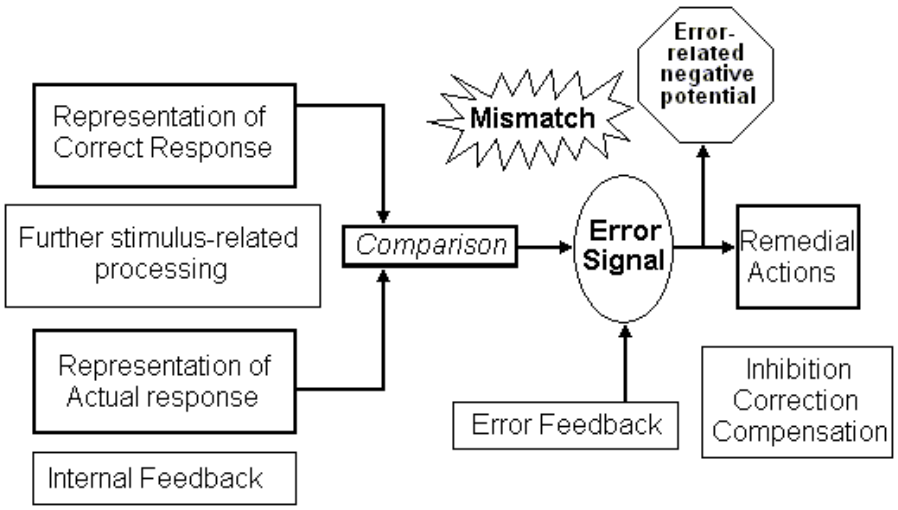

Figure 4. Schematic representation of response monitoring theory involving a comparator process (Coles et al., 2001).

According to this model, a comparative process compares the representation of the correct response with representations of the actual response. When there is a mismatch between these two representations, at least two things happen. Firstly, a signal is sent from the comparator to the remedial action system, a system designed to correct errors. Secondly, an error related negative electrical potential, is produced by the basal ganglia in the ventral bank of the anterior cingulate cortex (Coles et al., 2001). A discussion on what this negative potential represents is presented in detail in Chapter 3.

Now that each cognitive process of interest has been discussed, it is necessary to explain how they will be observed in the present study. The following chapter begins with a description of how ERPs are generated and recorded followed by a discussion relating to the use of ERPs in the study of each cognitive process in turn.

Chapter Two: Psychophysiological measurement techniques

Recording brain electrical activity

Electrical potentials are generated by the ongoing activity of brain neurons. When neurons communicate with one another there is a change in the placement of potassium and sodium ions surrounding each cell. This movement of ions can results in either a positive or a negative electrical potential to flow through the cell (Mader, 1995). By using electrodes attached to the scalp, the electricity generated by neural activity can be recorded. When passed through a powerful amplifier, the pattern of voltage variation (that is, positive or negative variations) can be observed (Coles & Rugg, 1995). The recording of the voltage variation is known as an 'electroencephalogram', or EEG. The EEG is a recording of the postsynaptic potentials of millions of similarly oriented pyramidal cells (Hillyard, 2000).

Event-related potentials (ERPs) are typically constructed by averaging EEG recordings over many trials using response- or stimulus-locked trials (Klorman, 1991). Most often, the electrophysiological data is continuously recorded. Epochs, or samples, of electrical activity are extracted from the recording and averaged over all occurrences of like stimuli (or responses). The result of this process is a sample of electricity associated with a specific response or stimuli characterised by a series of peaks and troughs of positive and negative electrical potential. When describing a feature of the ERP waveform, the polarity of the potential (negative or positive) is given alongside either the latency of that peak or its position in the waveform. Of additional importance is the scalp distribution of the component.

Unlike magnetic resonance imaging and positron emission tomography, ERPs possess high temporal resolution and as such allow the study of cognitive processes associated with specific events. By using ERPs, it is possible to follow the pattern of neural activation is it spreads over the scalp. Using new technologies, such as Brain Electrical Source Analysis (BESA) and Low Resolution Electromagnetic Tomographies (LORETA), the source of the electrical potential can now be identified, aiding in locating neural regions responsible for initiating specific cognitive processes. A significant advantage of using ERPs in studies of cognition is that they allow for the observation of component stages of cognitive processing. For example, sensory ERP components occur early in the waveform - auditory brain stem responses are recorded at latencies up to 10 ms, whilst processing of abstract attributes and assigning meaning to stimuli occurs later (Coles & Rugg, 1995). Thus, ERPs can be used to identify the timing, order and interactions that occur whilst specific cognitive activities are carried out.

Because disorders in response inhibition, working memory, and error monitoring are three cognitive theories associated with the pattern of problematic behaviour seen in patients with ADHD, of particular interest to the present study are the ERPs elicited whilst performing these cognitive processes.

Response inhibition and the Nogo N2

The Nogo N2 is a peak in the ERP waveform characterised by a negative shift maximum at frontal sites with a latency of 200 – 400 ms (Falkenstein, Hoormann, & Hohnsbein, 1999; see Figure 5).

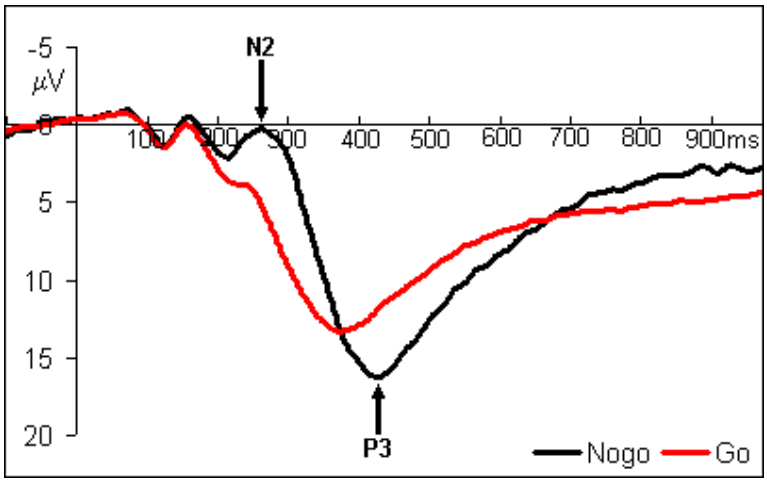

Figure 5. Sample ERP generated by Go and Nogo stimuli showing the N2 and P3. X axis denotes 100 ms increments of time, from 100 ms pre-stimulus to 1000 ms post-stimulus. Stimuli were presented at time = 0.

The N2 is generally accepted as being the most negative deflection occurring at some time between 150 and 500 ms (Fox, Michie, Wynne, & Maybery, 2000; Pliszka, Liotti, & Woldorff, 2000). The N2 is one of several peaks regularly elicited by tasks that require inhibitory processing (Jodo & Kayama, 1992). The Nogo N2 has its maximum amplitude occurring over frontal electrode sites (Yong-Liang et al. 2000).

There are other negative potentials over this time period reflecting different cognitive processes. Stimulus probability also modulates the amplitude of the Nogo N2. The negative component associated with stimulus probability is the mismatch negativity (MMN). As most inhibitory tasks (such as the stop-signal procedure, and Go/Nogo task) require participants to respond to some (frequent) stimuli and inhibit that response when presented with other, rare stimuli, it may be that the N2 is representing the difference between the physical attributes of the inhibitory stimulus and those of the response stimulus. It has been claimed that the Nogo N2 reflects an

automatic discrimination of a change in stimulus type or the initiation of an orienting response (Näätänen, 1986). Orienting responses involve a reflexive reaction of skeletal, physiological, and behavioural change arising due to presentations of unexpected or significant stimuli (Näätänen & Gaillard, 1983). In tasks such as the auditory oddball procedure, where a frequently presented tone stimulus (for example, a 600 Hz tone presented at 60 dB occurring 80 percent of the time) is occasionally replaced by a 'rare' tone stimulus (a 1500 Hz tone presented at 70 dB which occurs 20 percent of the time), the N2 may indicate a mismatch between the neural representation of the current 'rare' stimuli and that of the previous, frequently presented stimuli.

To a degree, Eimer (1993) provides support for this argument. Following completion of a Go/Nogo task, he found that Nogo stimuli elicited a frontal N2 that was greater when those stimuli were 'rare' events compared to when they appeared at equal presentation rates to the Go stimuli (Eimer, 1993). Upon closer inspection of Eimer's data, however, it appears more likely that the N2 was reflecting inhibitory processing. In Eimer's second experiment, Go and Nogo stimuli appeared at equal presentation rates. In this experiment, Nogo stimuli elicited an enhanced N2 component, even when inhibitory stimuli appeared at equal presentation rates to the Go stimuli. It is thus unlikely that the Nogo N2 was reflecting either an orienting response, or a mismatch between neural representations. Were this the case, then the amplitude of the N2 would be equal following presentation as Go and Nogo stimuli. As the amplitude of the N2 was greater following Nogo than Go stimuli in the equal presentation rate condition, this experiment provides support for the argument that the frontal Nogo N2 reflects inhibitory processing.

Further support for the argument that the Nogo N2 reflects inhibitory processing can be obtained by examining the relationship between reaction times and the N2. Faster response rates to Go stimuli were coupled with predictable Nogo N2 changes. Participants who responded faster to Go stimuli had larger Nogo N2 amplitudes than those participants recording slower Go reaction times. When responding faster, inhibition is more difficult as the response behaviour is highly primed, it consequently has a 'head start' compared to the inhibition behaviour (see the 'race-model' of inhibition). Thus the fast responders required earlier, or greater inhibitory processing to successfully prevent a false alarm from being performed. The difficulties in inhibiting the behaviour were reflected by enhanced N2 amplitudes for participants with fast reaction times to Go stimuli (Eimer, 1993). Because of this, it seems that the N2 is at least not wholly due to a mismatch between the neural representations of frequent and rare stimuli, but is reflecting inhibitory processing.

Van Boxtel, van der Molen, Jennings and Brunia (2001) examined two ERPs associated with the completion of a stop-signal task and a Go/Nogo task. These researchers examined the frontal N2 (associated with inhibition) as well as an ERP component associated with response activation (a lateralised readiness potential – the LRP). They found that the relationship between the LRP and the N2 provided a neurophysiological correlate of the processes described in the horse-race model introduced by Logan and Cowan (1984), whereby the timing relationship between the go and stop processes was capable of predicting a complete, partial or no response. If the LRP occurred much earlier than the N2, a motor response was more likely. Importantly, the researchers also found that the frontal N2 elicited by the Nogo stimuli in the Go/Nogo task was similar to that elicited by the stop signal in the

stop-signal task. They concluded that for both the Go/Nogo and SST tasks, the inhibition stimulus (Nogo or stop-signal) activates a central mechanism of inhibitory control. Further support for the argument that the frontal N2 reflects inhibitory processing comes from Jodo and Kayama (1992), who separated participants completing a Go/Nogo task into two groups – a high response inhibition group (HI), and a low response inhibition group (LI). Participants in the HI group were required to make their responses to Go stimuli within a shorter time period following stimulus presentation than was required of the LI group (300 ms versus 500 ms respectively). When responses are made quickly, it becomes more difficult to inhibit the Go response to inhibitory stimulus as discussed previously. The authors found that participants in the HI group elicited a significantly larger Nogo N2 than that elicited by the LI group. For both groups, the Nogo N2 was larger at the frontal electrode site than either the central or parietal sites. They concluded that at least to some extent, the Nogo N2 was reflecting the activity of a response inhibitory system within the brain.

In a population with suspected inhibitory deficits (ADHD), Pliszka et al., (2000) found a correlation between N2 amplitude and performance on a stop-signal task, such that poor inhibition (reflected in longer stop signal reaction times) was coupled with decreased N2 amplitude. Yong-Liang and colleagues (Yong-Liang et al., 2000) examined ERPs generated by a Go/Nogo task performed by children with and without ADHD and reported that the frontal Nogo N2 was larger following Nogo stimuli than Go stimuli. In a similar experiment, Falkenstein and colleagues (Falkenstein, et al., 1999) using a non-clinical population, found that subjects who performed well on the Go/Nogo task elicited a Nogo N2 about twice as large as those

that performed poorly. As the Nogo N2 amplitude was greater for people that sufficiently inhibited their behaviour compared to those displaying inhibitory deficits their results supported the idea that the Nogo N2 reflected inhibitory processes.

Finally, Bokura and colleagues (Bokura, Yamaguchi, & Kobayashi, 2001) used a modified CPT to study ERPs in 13 healthy subjects. To increase the inhibitory demands of the task, Nogo stimuli appeared on only 30% of trials. The authors observed a Nogo N2 component consistently elicited during Nogo trials, but only variably elicited by Go stimuli. In addition, the neuroanatomical data gathered by the research team was consistent with previous data concerning localization of inhibition and is discussed further in chapter three.

In conclusion, the data gathered by Bokura et al., (2001), Eimer (1993), Falkenstein et al., (1999), Jodo and Kayama (1992), Pliszka et al., (2000), and Yong-Liang et al., (2000) and others provides strong support for the frontally distributed Nogo N2 as an electrophysiological index of inhibitory processing.

Working memory and the Go P3

The P300 is an endogenous ERP component the amplitude of which is determined by psychological reactions to sensory events. The P300, or P3, is a positive peak in the waveform occurring between 300 ms and 1000 ms after stimulus presentation (see Figure 5) and was one of the earliest ERP components to be identified (Sutton, Braren, & Zubin 1965). Sutton and colleagues discovered a late positive ERP component that was reliably elicited following the delivery of significant information to the participant.

There have been many interpretations regarding the significance of the P3, and associations have been established with decision-making, signal probabilities, attention, discrimination, information delivery, inhibition and memory. Andreassi (2000) has stated that a common thread between all these associations is the need for *information processing* on behalf of the participant.

A popular interpretation of the posteriorly distributed Go P3 is that it is associated with working memory (Donchin & Coles, 1988; Fabiani, Karis, & Donchin, 1986; Kok, 2001; Squires, Wickens, Squires & Donchin, 1976). Donchin and Coles (1988) introduced the context updating hypothesis and argued that the P3 reflected the updating of working memory. They suggested, using a number of experiments as validation that the amplitude of the P3 is the product of activity occurring whenever a persons' model of the environment undergoes revision. They also claim that the amplitude of the P3 is indicative of the amount of working memory required to process any given stimulus, and that the amplitude of the P3 reflects the degree to which a person's model of the environment needs to be modified. The authors state that for rare events, the amplitude of the P3 is inversely related to the probability of the event occurring. In other words, when expected stimuli are presented only a small amount of working memory revision is required. However, when infrequent stimuli are presented, a greater amount of environmental modification takes place so as to 'remind' the participant of this stimulus. When there is greater revision occurring, a larger P3 is produced. Thus, infrequent, task relevant stimuli are associated with larger P3 amplitudes. According to Donchin and Coles (1988), there is a strong relationship between the P3 amplitude and working memory.

Verleger has criticised the context updating hypothesis (Verleger, 1988), proposing a contradiction exists between the P3-evoking stimuli being initially unexpected but later becoming expected and the generalised statement that the P3 reflects the updating of expectancies. Verleger has suggested an alternative hypothesis, namely the context closure hypothesis. Verleger claims that the P3 indicates a "deactivation" of the parietal areas that control perception. He suggests that it may be a physiological indicator of excess activation being released from perceptual control areas. Thus according to Verleger, the P3 is not closely associated with working memory.

The context closure hypothesis assumes that the repetitive methodologies intrinsic to ERP studies are both necessary and favourable to the generation of P300s. Verleger claims that when dealing with a highly repetitive, structured environment, participants combine successive stimuli to create a meaningful context for the preceding stimuli. When stimuli are presented, the participant creates and maintains an internal template of the context. Verleger suggests that it is the closing of this context that elicits the P3. An argument that contradicts part of Verleger's theory was put forth by Cohen and Polich (Cohen and Polich, 1997). Cohen and Polich found that using both auditory and visual stimuli occurring at either 20% or 80% they were able to produce a P3 that stabilised after only 20 trials. Verleger has suggested that it is only through the averaging of *large numbers* of stimuli that the P3 can be produced, Cohen and Polich have shown otherwise.

Kok (2001) presents an alternate view of what the P3 represents, describing the amplitude of the component as a measure of processing capacity. According to Kok,

the P3 is elicited following a process called *event categorisation*. This process is essentially a matching, or comparison processes, the outcome of which leads to a stimulus being judged as a match or a non-match to a previously stored internal representation. According to Kok, the amplitude of the P3 is wholly determined by event categorisation, but event categorisation is in turn influenced by the amount of attentional capacity invested into the categorisation procedure (see Figure 6).

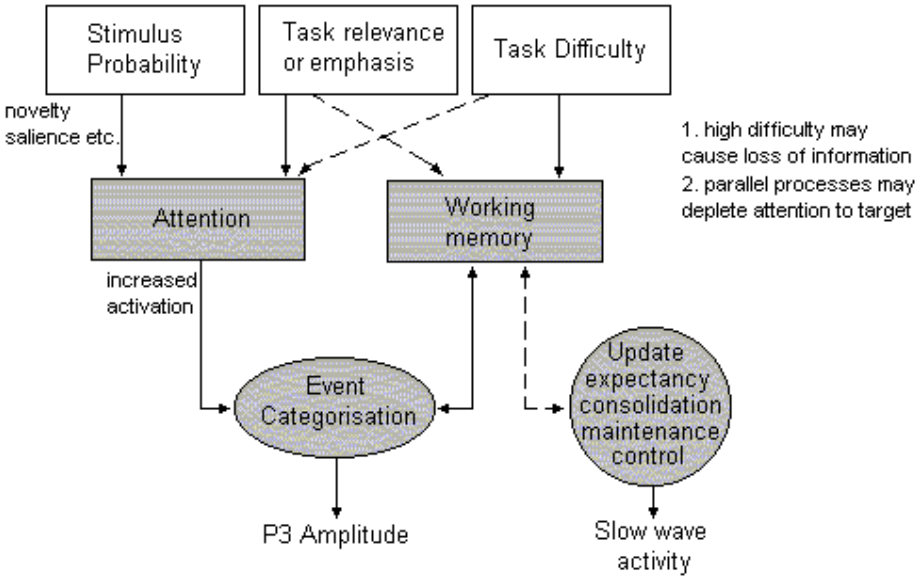

Figure 6. Diagram showing determinants of P3 according to Kok (2001, p 571).

Kok claims that the strength of the categorisation activation (and thus P3 amplitude) depends upon both the closeness of the match between the present stimulus and the internal representation of the target stimulus as well as on the amount of attention that is paid to the stimulus. It is this degree of attention that Kok refers to as the *capacity allocation* determinant of the P3 amplitude. Whilst both attention and working memory have a clear impact upon event categorisation the impact of working memory upon P3 amplitude was described as being less direct.

Kok acknowledges that for any comparison of stimuli to take place, working memory is implicated in the storage and maintenance of the representations. He claims, however, that the executive functions that control working memory activate a neural system that is distinct from that involved in event discrimination. The P3 amplitude is determined by event categorisation, and influenced by attention, however as this system operates separately from working memory, it is not influenced by processing of the working memory system. The impact of the working memory system is claimed to be reflected in negative slow wave activity. A problem with this model, and one acknowledged by Kok, is that whilst there may be separate neural systems (such as for event categorisation and working memory) the processes and subsequent ERP components may overlap in time. A consequence of this is that it becomes almost impossible to confidently separate the ERP components related to the different systems.

Kok also claims that according to his model, the updating of working memory is not essential for the generation of the P3. He does however say that the updating mechanism mentioned by Donchin and Coles (1988) *could* play a role during involuntary orientating to novel stimuli. In these situations, Kok claims, a revision of the neural network is required, following a mismatch between the present stimulus and the internally stored representation. Kok claims that the parietal P3 investigated by Donchin and Coles (1988) may be reflecting the revision of internal representations *whilst learning to categorise initially novel events.* This final statement regarding Donchin and Coles' study suggests that there may exist a stronger relationship between the P3 and updating mechanisms than is suggested by Kok.

Whilst Kok claims that the P3 reflects event categorisation, he claims that the impact of working memory upon this process does not modulate the P3 amplitude. Secondly, he claims that the parietal P3 investigated by Donchin and Coles does not represent the updating itself, but rather updating occurring whilst event categorisation takes place. Yet as Kok concedes that these processes may activate separate neural networks, and the ERP components associated with such events may overlap in time. A consequence of these issues is that it seems difficult to come to the conclusion that recordings of parietal P3 activity does not, at least partially, reflect some working memory processing.

Currently, Donchin and Coles' (1988) context updating hypothesis has been more influential within the scientific community, and fewer studies have examined the P3 component in relation to Kok's (2001) claims. As Kok's ideas regarding processing capacity are more recent, it is not to say that it won't receive significant attention in the future. Currently, there exist a number of studies that are consistent with the theory of working memory updating introduced by Donchin and Coles (1988). Squires, Wickens, Squires and Donchin (1976) obtained data which showed that the P3 amplitude is inversely proportional to the probability of the eliciting event occurring. More frequently presented stimuli required less processing to maintain the representation of that item in working memory (Squires, et al., 1976). This experiment supports Donchin's hypothesis because representations in working memory decay over time (Karatekin & Asarnow, 1998) and thus detection of rare stimuli would be accompanied by an increase in the updating of its mental representation and the subsequent P3 elicitation would be greater. When less

updating is required, due to greater target presentation frequency (and an increased retention of the target representation), a smaller P3 results.

Further support for the use of the P3 as an indicator of working memory comes from Fabiani and colleagues (1986) who found that the amplitude of the P3 correlated with performance during recall of verbal stimuli (Fabiani et al., 1986). This was found to be true for subject utilising a simple rote learning strategy. A rote strategy implies updating the contents of working memory with the salient attributes of the to-be-remembered items, such as shape and form. Participants that entertained an elaborative strategy utilised additional processes for encoding the stimuli. The elaborative strategists relied less upon the salience of the stimulus attributes and depended mostly upon the success of their memory strategy. The elaborative strategists were thought to have reduced the influence of working memory updating on the encoding of stimulus properties, whilst the former relied almost entirely on working memory processes. Less updating, according to Donchin, would result in the elicitation of a smaller P3 amplitude, which is what the researchers found for items not subsequently recalled.

Ruchkin and colleagues found that the P3 amplitude varied significantly with information load during a memory recall test (Ruchkin, et al., 1992). They performed a study that examined localization, amplitude and latency differences in the P3 for visuospatial and phonological information processing. During the phonological memory task, non-words of three, four or five syllables were displayed for 1.5 seconds. At the end of the set, a probe stimulus was presented to which subjects responded whether it was or was not included in the memory set. The authors found

that the amplitude of the parietal P3 increased significantly with increasing information load, such that the P3 was greatest for the five-syllable condition and smallest for the three-syllable condition.

Two other studies which provide contrasting views on the use of the P3 as an indicator of working memory are those by Grune (Grune, et al., 1996) and a German paper he reports on (Gross, Metz, and Ullsperger, 1992, as cited in Grune et al., 1996). Gross et al. (1992) used ERPs to examine mechanisms of encoding and storage during increasing working memory loads. Sequences of consonants three to seven stimuli in length were presented to participants for 800 ms followed by a retention interval of 2000 ms. After the final consonant was presented, participants were asked to recall the sequence of stimuli. The authors found that the P3 amplitude was larger for stimuli presented later than for stimuli presented first or second. They suggested that the amplitude of the P3 was influenced by the cognitive effort required to encode and store each additional stimulus. When presented with a greater number of stimuli, increased working memory was required to process the newer items and thus a larger P3 was elicited. Grune et al., however, argued that the increase in P3 amplitude accompanying the later presented stimuli might have been due to the variation in set sizes, which was unknown to the subjects in advance.

In his own study, Grune et al. (1996) had subjects retain a set of seven sequentially presented consonants and recall the set immediately after the final stimulus was presented. He found that the largest P3 amplitudes were recorded at the parietal site and the smallest at the frontal site. In addition, he found that the later a consonant was presented, the smaller the P3 elicited, being in opposition to Gross' results. The

argument presented was that with each additional stimulus presentation, less working memory resources were available for processing the following stimuli. Thus, these authors issue an argument contrary to Gross et al. (1992) and Ruchkin et al. (1992) in that the P3 amplitude is inversely related to the cognitive load for retention of information stored in working memory.

On the basis of the literature reviewed, the amplitude of the P3 is a useful tool to observe working memory processes, with the size of the component reflecting the degree to which a persons representation of the environment undergoes revision (Donchin & Coles, 1988). If performing a simple one-back task to compare working memory processes between groups, it would be expected that participants with better working memory systems would elicit a larger P3 compared to those participants with working memory dysfunctions.

Response inhibition and the Nogo P3

In addition to suggestions that the frontal N2 may reflect inhibitory processing, other studies have found that an anteriorly distributed Nogo P3 may reflect similar processes (Pfefferbaum, Ford, Weller, & Kopell, 1985; Eimer, 1993; Bokura, et al., 2001). Pfefferbaum and colleagues (1985) used a modified Go/Nogo procedure to examine response production and inhibition in twelve healthy subjects. Consistent with previous research, they found that the N2 was larger following Nogo stimuli than following Go stimuli. In addition, they observed a parietally maximal Go P3 that was distinctly different to the centro-parietally Nogo P3. As the Go and Nogo P3 topographies had different scalp distributions it was speculated that the Go and Nogo P3 were reflecting different cognitive processes (Pfefferbaum, et al., 1985). Whilst

the posterior Go P3 may have been reflecting working memory processes or possibly event categorisation (Kok, 2001) the anteriorly distributed Nogo P3 was thought to reflect inhibitory processing. To support the case for the existence of a Nogo P3, evidence can be obtained via further examination of Eimer's (1993) study. He found that Nogo stimuli elicited a P3 with a more anterior distribution than that elicited by Go stimuli. The Go P3 had an amplitude that was equally maximal at central and parietal sites, whilst the Nogo P3 had a central maximum only.

Bokura and colleagues found that in addition to the frontal Nogo N2, a mid-frontocentral Nogo P3 was also elicited by Nogo stimuli (Bokura, et al., 2001). This anteriorly distributed Nogo P3 was topographically different to the Go P3, which was maximal mid-centro-parietally. In addition to different ERP topographies, the source of the Go P3 was localised to the medial part of the parietal lobe and the left superior prefrontal cortex whilst the Nogo P3 was found to originate from the left lateral orbitofrontal cortex.

Kopp, Mattler, Goertz and Rist (1996) used a novel task to investigate motor inhibition and its electrophysiological correlates. They constructed a hybrid choice reaction and Go/Nogo task involving visually presented stimuli whereby the target stimuli (a right or left pointing arrowhead) was flanked by simultaneously presented stimuli appearing both above and below the target. The flanker stimuli were designed to prime the associated response and were either right or left pointing arrowheads. The authors did obtain the standard set of results, such that a frontally distributed N2 component was present following Nogo trials. They also observed a

Go P3 that was maximal at parietal sites and a Nogo P3 maximal at central sites. Kopp et al. (1996) suggest, however, that the interpretation of the Go/Nogo P3 effect as indicating that the Nogo P3 reflects inhibitory processing is 'undesired', suggesting that motor potentials occurring on Go trials, but not Nogo trials interfere with the data. They also mention that because Nogo stimuli appeared on a third of trials, and Go stimuli appeared on two-thirds of trials, the difference in stimulus presentation rates may have altered the effects of motor inhibition upon the electrophysiological components. They also highlight the effect of priming upon the ERP components, noting that unlike the Nogo N2, the Nogo P3 was not affected by the presentation of erroneous response priming. They suggest that because the P3 did not vary as a function of this priming, it is unlikely that the component is associated with inhibition or stopping of the erroneous actions. The authors fail, however, to suggest what the component may then reflect. These authors used a novel task to suggest that the Nogo P3 was not a product of inhibitory processing. Further examination of the task should be employed so as to either validate or argue against their findings.

All these studies observed a Nogo P3 with a more frontal maximum than that recorded by the Go P3. The data gathered by Pfefferbaum et al. (1985), Eimer (1993), Bokura et al., (2001) and others, provides support for the theory that in addition to the frontal Nogo N2, the anteriorly distributed Nogo P3 can be used to observe inhibitory processing.

Error Related Negativity

The Error Related Negativity (ERN) is a negative potential in the ERP waveform that peaks between 50 and 100 ms following an incorrect response. It is maximal centrally, or fronto-centrally and symmetrical around the midline (Falkenstein, Hoormann, Christ, & Hohnsbein, 2000; Pailing, Segalowitz, Dywan, & Davies, 2002). This section will identify two leading theories of what cognitive processes the error-related negativity may represent and also discuss some issues regarding ERN component extraction. One current theory of the ERN is that it represents some aspect of a comparator process, identifying a mismatch between the actual and desired motor responses (Falkenstein et al., 1999; Coles et al., 2001). A second theory is that the ERN is the outcome of recognition of a response competition (Carter, et al., 1998; Botvinick, Braver, Barch, Carter, & Cohen, 2001).

On the basis of earlier work suggesting that the ERN is a correlate of either error detection or inhibition, Falkenstein et al. (1999) began their study with the presumption that the ERN was reflecting a late and unsuccessful attempt to inhibit responses to non-target stimuli, thus being similar to the Nogo N2. Two results of their study can be used to suggest the independence of the Nogo N2 and the ERN. Firstly, the amplitude of the Nogo N2 was affected by the modality of the stimuli presented; an effect not seen with the ERN. Secondly, the ERN and Nogo N2 had different scalp topographies. The Nogo N2 was maximal at frontal electrode sites, whilst the ERN was largest centrally. On the basis of this, they concluded that the N2 was reflecting a more stimulus-specific inhibition process, whilst the ERN was reflecting a more response-specific inhibitory process. In addition, they added that

the ERN might have been reflecting something other than inhibitory process, possibly error detection.

Whilst Falkenstein initially argued that the ERN represented a mismatch between these actual and desired response (Falkenstein, Hoormann, Hohnsbein, & Blanke, 1991) he later suggested that the ERN was not reflecting the *outcome* of this process, that is the mismatch between the responses, but rather *the comparison process itself* (Falkenstein et al., 2000). To support this argument, the authors described two experiments where the amplitude of the ERN decreased when time pressure was enhanced. They suggested that under a high time pressure, the time reduction forced a less thorough comparison of the actual and desired responses to take place. The authors also compared error types and found that the ERN was smaller when the two response options were similar (e.g. using either middle or index finger to respond), compared to when they were less similar (e.g. using either left or right hand to respond). The ERN when participants responded with the incorrect finger was smaller than the ERN elicited when participants responded with the incorrect hand.

Falkenstein et al (2000) suggests that if the ERN was simply reflecting this process, then the ERN is unlikely to differ according to the correlation observed in more recent research (Falkenstein et al., 2000). It would not explain why in conditions with small differences in response types the ERN was smaller than in conditions with large differences in response types. They suggest rather that the ERN is more likely reflecting the comparison process itself, rather than the mismatch. A third set of supporting data for this argument came from the results that a small ERN was observed following correct responses, a finding that contradicts the error detection

hypothesis. Falkenstein et al. (2000) used this finding to support the idea that the ERN is the product of a response comparison process and not the outcome of that process. They added that the larger ERN following incorrect responses may be due to a combination of this response monitoring process and an overlaid error signal.

Coles, et al. (2001) also observed an ERN following correct responses and put forward a similar claim to that issued by Falkenstein and colleagues. They claimed that the ERN observed following correct trials might be due to either the occurrence of error-processing on correct trials and/or contamination by negative components evoked by the stimulus. To explain the presence of the ERN following correct trials, they presented a theory of the ERN such that the negative potential arises when the error signal, generated by a comparison of the correct-response representation and the actual-response representation, arrives at a remedial action system. These authors claimed the ERN to be elicited when there exists a mismatch between correct and actual responses. They described a situation whereby the ERN is elicited on correct trials. If participants have been instructed to respond as fast as possible, they may form a representation of the correct response, which involves both a motor response, as well as a time frame for this response. Thus if they perform the correct response but do so slower than desired, the representation of the actual response will still differ from the representation of the desired response, and thus an ERN on the correct trial may be elicited. Luu, Flaisch, and Tucker (2000) provided supporting data, reporting a linear increase in the amplitude of the ERN with increasingly late responses.

A competing theory comes from Carter and colleagues in Pittsburgh. Carter et al., (1998) performed a functional Magnetic Resonance Imaging study, observing neural activity associated with completion of a Continuous Performance Test-AX. The authors used fMRI to examine neural activity during a task for which an ERN has been reliably elicited. They found that incorrect responses were accompanied by temporally and anatomically significant activation of the anterior cingulate cortex (ACC) and a smaller increase in activity following correct responses under conditions of greater response competition. Thus, whilst not recording the ERN directly, they observed increased ACC activity under conditions during which an ERN was expected. They suggest that ERN studies, and those studies involving ACC activation involve similar cognitive procedures to one another. By examining those studies investigating the role of the ACC in response monitoring, the authors developed a theory as to what the ERN may represent.

Carter et al., (1998) claimed that the ACC is involved in the compensation and monitoring of errors. To perform these processes, a representation of the intended correct response must be compared to a representation of the actual response. Consequently, they proposed that the ERN does not reflect the implementation of this comparison process, but rather monitors competition between response processes that conflict during task performance. It was suggested that ACC activity was representing a process that recognises the presence of conflicting response possibilities. They argued that one reason for the strong relationship between ACC activity and error responding is that errors occur when there is strong conflict between different response options. If this were the case, then ACC activity would be

expected for trials on which even correct responses were made. This was found under conditions involving greater response competition.

In a more recent paper, Botvinick, et al., (2001) expanded upon the significance of the ERN with reference to three other findings. They report on a study by Gehring, Coles, Meyer and Donchin (1993, as cited in Botvinick et al., 2001), in which Gehring et al. (1993), recorded both ERPs and response-related electromygraphic activity and observed large ERN responses following trials in which a response reversal took place. The EMG was used to observe when a response was started with the incorrect hand. When the incorrect response was started, but was stopped and completed by the correct hand, this was referred to as a response reversal. On these trials, there is assumed to be strong evidence for late activation of the correct response, and thus a high degree of response competition. In this study, Gehring et al. observed ERNs on correct trials, however as described previously, this may be due, not to a response competition monitoring system, but a difference between the representation of the actual response from the desired response. Finally, Botvinick et al. refer to a study by Dahaene, Posner, and Tucker (1994, as cited in Botvinick et al., 2001) in which participants, withholding responses for two seconds after stimulus presentation, failed to elicit an ERN. In this condition, it is assumed that incorrect responses were unlikely to have been accompanied by any degree of response competition. The view of the ERN representing a process identifying response conflict has been supported by further research examining the ACC and the timing of response monitoring (van Veen and Carter, 2002).

Over the last half century, much research has been performed examining ERPs and their use in observing working memory and response inhibition and more recently, error response monitoring. On Go/Nogo, stop signal and continuous performance tasks, the frontal Nogo N2 has proven a reliable indicator of inhibitory processing, so too has the central or centro-frontal Nogo P3. A more posterior Go P3 has been used to observe the level of working memory processing. This study also examined a negative potential associated with processing error response, a function mediated by the dopaminergic system. It has been alleged that the ERN represents the outcome of a response monitoring system, whereby a specific system compares representations of the actual response to those of the desired response (Falkenstein et al., 1999; Coles et al., 2001). Alternatively, the ERN has been claimed to reflect the outcome of a process identifying the presence of response conflict (Carter et al., 1998; Botvinick et al., 2001; van Veen & Carter, 2002).

The present study used these four ERP components (Nogo N2, Nogo P3, Go P3 and the ERN) to compare working memory, response inhibition and error monitoring between a group of symptomatic and asymptomatic ADHD adults, as well as a non-ADHD normal control group. The following chapter describes some possible neuroanatomical regions responsible for the activation of the three cognitive processes of interest to this study.

Chapter Three: Neuroanatomical substrates

The earliest known brain map was discovered on an Egyptian papyrus and has been dated to between 3000 and 2500 years BC (cited in Carter, 1998). Processes such as planning, problem-solving, and conceptualisation are all executive functions and are thought to be primarily products of the frontal lobes and prefrontal cortex (Dubois et al., 1995; Carter, 1998). The anatomical study of executive functions and their relationship with the frontal areas does not share as long and elaborate history as that of the entire brain. There exists the classic case of the nineteenth century railway worker Phineas Gage, who lost a large portion of his forebrain when a steel rod was thrust though his skull. Despite the severity of the accident, Gage survived and appeared to be functioning normally, however with some marked changes in behaviour. He changed from a hard worker to a drifter and according to his treating doctor, as quickly as he made plans for the future, they were abandoned. He also became childlike in his intelligence and the most striking feature of the new Phineas Gage was said to be his complete inability to direct or control himself. Recent advances in neuroimaging techniques have enabled the study of neuroscience to progress without the need for the examination of such drastic physical trauma. Imaging techniques, such as function Magnetic Resonance Imaging (fMRI), Positron Emission Tomographies (PET), and source localization software in conjunction with ERPs, have enabled researches to localise neural generators responsible for executive functions.

Localising response inhibition

Response inhibition is considered to be an executive function. The neural structures responsible for this process have been localised to within frontal brain regions. Cummings (1995) reported that disorders of the orbitofrontal cortex (see Figure 7) were associated with disinhibition in the patient. Patients with orbito-prefrontal dysfunction will often display socially inappropriate behaviours and exhibit environmental dependency, relying upon environmental cues to direct behaviour (Cummings, 1995). He also stated that inhibitory dysfunction is a feature of damage to the medial frontal lobe. Whilst exhibiting few other neuropsychological symptoms, difficulty in inhibiting responses to Nogo stimuli has been observed in patients with damage to medial aspects of the frontal lobe (Drewe, 1975, as cited in Cummings, 1995).

Boller et al. (1995) reports that the outcome of executive functions depends upon the integrity of the prefrontal cortex. They cite an early PET study by Pardo, Pardo, Janner, and Raichle (1990) in which they observed increased activation of the anterior cingulate cortex (see Figure 7) during completion of the Stroop task, an inhibitory task described in further in the following chapter.

When using functional Magnetic Resonance Imaging (fMRI) to examine neural activity associated with completion of a Go-Nogo task, Casey and colleagues (1997, as cited in Nigg, 2001) found an increase in activity in inferior regions of the dorsolateral prefrontal cortex in response to Nogo stimuli. They also observed greater orbito-prefrontal cortex activity in persons who made fewer false alarm errors, suggesting greater inhibitory capabilities. This supports the notion that these

areas are involved in inhibitory processes. The dorsolateral-prefrontal cortex is presented in Figure 7. The dorsolateral-prefrontal cortex and the orbito-prefrontal cortex are closely related anatomically, and both form part of the frontal lobe.

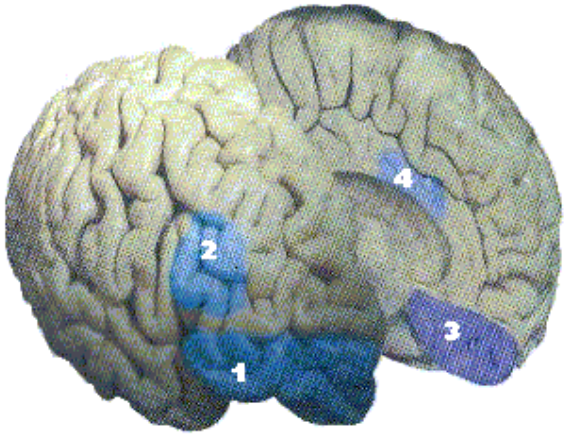

Figure 7. Figure of brain showing (1) Orbito-frontal Cortex (2) Dorsolateral prefrontal cortex (3) Ventromedial cortex and (4) Anterior cingulate cortex (from Carter, 1998, p. 182).

Support for response inhibition being a function of the frontal regions can be obtained by examining data recorded during ERP studies. Pliszka reported that normal children produced a large negative wave over the right inferior frontal cortex when responding to an inhibitory stimulus (Pliszka, et al., 2000). The amplitude of this wave was significantly reduced in children with inhibitory disorders (ADHD). The authors suggest that in addition to a reduced slow positive ERP component over the right frontal hemisphere in the ADHD group, the results implicate involvement of the right inferior prefrontal cortex in inhibitory processes. The argument for right frontal cerebral involvement based upon the scalp topography of ERP components in not convincing, and requires deeper analysis.

Obtaining similar results to Pliszka et al., (2000), Bokura et al. (2001) used a Go/Nogo task and observed the same negative ERP component (the Nogo N2) elicited in response to Nogo stimuli and found it to be clearly localised to the right hemisphere. More specifically, using a low-resolution electromagnetic tomography (LORETA), Bokura et al. located the source of the Nogo N2 as being predominantly in the right lateral orbitofrontal cortex and also in the cingulate cortex. Additionally, they identified a Nogo P3, which was localised to the left lateral orbitofrontal cortex. Using a CPT in conjunction with three-dimensional source localization software (LORETA), Strik and colleagues investigated the P300 and found that there was significantly more neural activity occurring in the right frontal lobe following presentation of the Nogo stimulus than there was following the Go stimulus (Strik, Fallgatter, Brandeis, & Pascual-Marqui, 1998).

All of these studies have found inhibitory processing to occur in frontal brain regions. Some studies have additionally located the source of this process to be in the right hemisphere. A detailed examination suggests that the process is more specifically a function the prefrontal cortex, including the dorsolateral prefrontal cortex, and also the orbito-frontal cortex.

Localising working memory

Within the field of localising working memory, there is little consistency between the type of neuroimaging system utilised and the tasks performed by the participants. There is still however, some degree of similarity between the results obtained.

One region that appears to be related to working memory processes is the dorsolateral pre-frontal cortex (DLPFC; Van der Linden et al., 1999). Van der Linden et al., attempted to study working memory by differentiating between different working memory subcomponents. They presented a combination of four different items in a 'running span task' at the end of which participants were required to serially recall a specified number of items. The authors argued that as the memory load was low, the task would not require any intervention by the storage components of working memory and participants would rely solely on central executive processes. Using scans of regional cerebral blood flow (rCBF) the most significant increase in activity occurred in the left frontopolar cortex, an area of the prefrontal cortex. In addition, enhanced activation was recorded at the left medial frontal cortex and the right frontopolar cortex.

Bokura et al. (2001) utilised LORETA for analysis of ERPs elicited during a Go/Nogo task. The authors located the source of Go P3, thought to reflect working memory, to the medial part of the parietal cortex, which was different to the source of the Nogo P3, thought to reflect response inhibitory processes.

Goldman-Rakic acknowledges that locating working memory is not a particularly easy process. She does however provide both human and primate data supporting prefrontal localisation of working memory (Goldman-Rakic, 1995). According to her model, however, the central executive comprises multiple components, each designed to represent and maintain specific information that can be shared with other

components. For Goldman-Rakic, the localisation of working memory would entail broad activation of the prefrontal areas. She suggests that in order to identify regions responsible for specific functions of working memory, such as spatial working memory, there needs to be high demands placed upon that specific working memory module. Any task that broadly requires the use of the central executive would thus result in broad activation of prefrontal areas, with no specific region being particularly active. Using a number of both human and non-human studies, Dubois et al., (1995) demonstrated that working memory elicits enhanced activation of the dorsal part of the prefrontal cortex. They claimed that this area enables the disruption of automatic stimulus-responses (as would be dictated by contention scheduling) creating a temporary buffer during which information can be analysed using past experiences, forethought and other higher cognitive functions.

Whilst some studies claim to have located specific regions associated with working memory, other studies have found a broader activation of neural regions. One conclusion is that working memory does not seem to be particularly localised to a specific hemisphere. Secondly, as working memory typically involved multiple connections with other neural regions, unless particularly high demands were placed upon a specific working memory component, it would appear that broad activation across frontal regions would result.

Localising the source of response monitoring

The anterior cingulate cortex (ACC) has been frequently identified as experiencing increased activation following error responses. Carter et al., (1998) had thirteen people complete a CPT-AX whilst undergoing a fMRI. They observed an increase in

ACC activity occurring during incorrect responding. In this study, the inhibitory demands of the task and thus the degree of response competition were maintained at a high level, with the target stimuli (AX) appearing on 70% of trials, and three non-target stimuli (AY, BX, and BY) each appearing on 10% of trials. In addition to increased ACC activation during incorrect responses, this study also reported increased ACC activation following correct responses. Carter et al., uses this data as support for his theory of the ACC and ERN reflecting response conflict detection.

Botvinick, Nystrom, Fissell, Carter and Cohen (1999) performed another study identifying the ACC as being implicated in the detection of response conflict. They performed a version of the flanker task, whereby participants were required to indicate by a button press in which direction a central arrow was facing when presented within a row of five arrows. On compatible trials the arrows pointed in the same direction (for example, <<<<<), whilst on incompatible trials, the target arrow was presented in the opposite direction to the flanker arrows (for example, <<><<). They found that activity within the ACC was greater during trials that featured high levels of response conflict, that is, when the flanker variables were identical to the target variable, compared to the low response conflict condition, when target and flanker variables differed.

Menon, Alderman, White, Glover and Reiss (2001) used a Go/Nogo task in conjunction with fMRI to investigate error-related brain activity in fourteen healthy subjects. Menon et al. (2001) used a reduced presentation rate of the target variable compared to Carter et al., (1998) with the Go stimuli appearing on only 50% of trials and the Nogo stimuli appeared on the remaining 50% of trials. Unlike Carter et al.,

who obtained specific activation of the ACC, this study identified a network of brain regions responsible for error processing. The left and right insular cortices, the rostro-ventral anterior cingulate cortex and adjoining medial prefrontal cortex, as well as the posterior cingulate cortex, all experienced increased activation during incorrect Nogo responses compared to correct Nogo inhibitions. Their results suggest an error-processing system, not confined to the ACC, but rather distributed across the brain and incorporating brain regions associated with response inhibition and competition. A possible explanation for the difference between results may be the different presentation rates utilised by the two sets of authors. Having target stimuli appear more frequently may be associated with conditions of greater response conflict when presented with the inhibitory stimuli. A possible consequence of this is greater ACC involvement.

Like Botvinick et al., (1999), Hazeltine, Poldrack and Gabrieli (2000) performed a flanker task to examine response monitoring in eight healthy males. Using fMRI, the researchers found that in situations involving response conflict, there was increased activation in four separate areas: the right ventrolateral prefrontal cortex, the supplementary motor area, the left superior parietal lobe, and the left anterior parietal cortex. The authors suggest that the frontal regions were responsible for inhibitory processes whilst the posterior regions related to the activation of inappropriate response representations.

In conclusion, Carter et al. (1998) employed a Go/Nogo task to observe neural activity during situations in which the ERN is known to be elicited. They found an increase in activation in the ACC following both correct and incorrect responses, a

result replicated by Botvinick et al. (1999). Menon et al. (2001) used the same task as Carter et al. but had Go and Nogo stimuli appear at equal presentation rates. These researchers observed more widespread neural activation however, increased ACC activity was observed. Hazeltine et al. (2000) used a novel version of the flanker task, to identify neural regions activated during situations involving response competition. Whilst these authors failed to identify specific ACC involvement, several frontal brain regions were identified as experiencing increased activation during response competition conditions.

Botvinick et al., (1999) and Hazeltine et al., (2000) observed a range of brain regions activated during conditions of high response conflict, regions that have been associated with other executive functions, such as response inhibition. The activation of these regions may represent sub-processes that operate during response monitoring, such as the comparison process (see Chapter One), or the representations of the actual and desired responses being maintained in working memory.

Chapter One provided theories regarding three cognitive processes (response inhibition, working memory and error monitoring/response conflict detection) deficits in which are thought to contribute to ADHD. The second chapter identified methods by which these processes can be observed and highlighted the four ERP components (Nogo N2, Nogo P3, Go P3, and the ERN) that were examined in this study. The third chapter addressed these cognitive processes from a neurological point of view, identifying several brain regions thought to be responsible for the initiation of the three cognitive processes. The final chapter provides arguments and theories for why each of these processes are thought to contribute to the pattern of

hyperactive, impulsive and inattentive behaviour observed in people with ADHD. In presenting arguments for each theory, it is necessary to draw upon information presented during the previous three chapters so as to enable a better understanding of the concepts and principals involved.

Chapter Four: Diagnosis and classification of cognitive impairments in ADHD

The disorder currently known as ADHD was first mentioned by George Still in 1902 and was described as a 'major deficit in moral control' (cited in Barkley and Murphy, 1998). It later became known as minimal brain damage (MBD) attributing abnormal behaviour to non-specific brain damage. Because of the vagueness and over-inclusiveness of its explanations, the diagnosis of Minimal Brain Dysfunction was destined to lose favour amongst the scientific community, with the final contribution to the theory being Wender's (1971) Theory of Minimal Brain Dysfunction (cited in Barkley and Murphy, 1998). Later, the term Hyperactive Child Syndrome surfaced and was the precursor to Douglas' Model of Attention Deficit. Douglas (1972, cited in Barkley and Murphy, 1998) argued that deficits in sustained attention and impulse control were more likely contributing to the symptomatology of ADHD than was hyperactivity. Her work was the grounding for a significant amount of subsequent research on ADHD, and was a contributing factor to the inclusion of 'Attention-Deficit Disorder' in the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorder, Third edition (DSM-III; American Psychiatric Association, 1980).

A more recent version of the manual, the DSM-IV (American Psychiatric Association, 1994), describes ADHD as a disorder involving a persistent pattern of inattention and/or hyperactivity-impulsivity being at a level that sets if apart from individuals of comparable levels of development in terms of frequency and severity. Within the DSM-IV, three ADHD subtypes are mentioned; ADHD predominantly

inattentive, ADHD predominantly hyperactive-impulsive, and ADHD combined type.

Symptoms listed within the DSM-IV of predominantly inattentive ADHD include; failing to pay close attention to detail, making careless mistakes at work or during other activities, and not seeming to listen when spoken to directly. Hyperactive symptoms include fidgeting with hands or feet, being ‘on the go’, acting as if ‘driven by a motor’, and often talking excessively. The three impulsive symptoms listed in the DSM-IV are: blurting out answers before the question has been completed, experiencing difficulty awaiting turn, and frequently interrupting or intruding on others.

Persons with ADHD are also likely to suffer from a range of emotional, interpersonal and psychiatric problems. Adult subjects with the disorder are more likely to be divorced or separated and tend to be of lower socio-economic status (Biederman et al., 1993). Sufferers of ADHD also are far more likely to drop out of school (seen in 32-40% of people with the disorder), have few or no friends (50-70%) and engage in antisocial activities (40-50%) than are non-ADHD individuals (Barkley, 2002). Adults with ADHD show a greater prevalence of oppositional, conduct, and substance abuse disorders, and greater illegal substance use than adults without the disorder (Murphy & Barkley, 1996). They tend to exhibit a broad spectrum of comorbid psychiatric conditions, including Axis-II disorders (for example, antisocial personality disorder, borderline personality disorders, obsessive-compulsive disorder, and narcissistic personality disorder), as well as anxiety, depression and other mood disorders.

The DSM-IV stipulates that in order to obtain a diagnosis of ADHD, the individual must have displayed either the hyperactive-impulsive or inattentive symptoms for at least six months to a degree being deviant from normal development and these symptoms must have been present no later than seven years of age. At least six of the nine inattention symptoms mentioned, or six of the nine hyperactive-impulsive symptoms must be considered abnormal for an ADHD diagnosis to be given. If the patient has six or more symptoms from only one of the two subtype criteria, they are said to have ADHD-predominantly Hyperactive-Impulsive or ADHD-predominantly Inattentive. Alternatively, if six or more symptoms from both categories are present the diagnosis ADHD-Combined Type is given.

In a prevalence study of DSM-III disorders in preadolescent children, Anderson found ADHD to be the most prevalently diagnosed childhood disorder (Anderson, Williams, McGee, & Silva, 1987). Prevalence estimates of childhood ADHD range from 1.3% to 13.3% and is generally accepted as a disorder occurring in between three to seven percent of children (Dulcan, 1997), with roughly two thirds of these being boys. Adult ADHD occurs in around 4% of the population with around 0.9% being Combined Type, 2.5% Hyperactive-Impulsive, and 1.3% Inattentive (Murphy & Barkley, 1996).

Mannuzza and colleagues performed a prospective follow-up study of boys with ADHD initially having a mean age of 7.3 years and just under 17 years later, when the mean age was 24.1 years (Mannuzza, Klein, Bessler, Malloy, & LaPadula, 1998). They found that in only 4% of the initial ADHD cases was the disorder present in adulthood. Additionally, none had partial symptoms in the adult sample. These

studies help illustrate that in many cases, symptoms associated with childhood ADHD remit in adulthood. In some cases however, the persistence of symptoms into adult hood is best treated through clinical intervention, and in many cases this is achieved via the use of stimulant medication. For some, however, ADHD symptoms persist despite the use of such medication.

This study began by highlighting a gap in the literature regarding ADHD. Little information is available which discusses the differences between symptomatic and asymptomatic adults with ADHD. By identifying which deficits persist in a group of symptomatic adults, compared to an asymptomatic group, better treatment strategies may be devised. As this study represents the first ERP investigation comparing symptomatic and asymptomatic ADHD adults, it is not possible to present a review of previous research specific to these groups. However, a summary of ADHD and control group differences in response inhibition, working memory, response monitoring and their associated ERP components will be presented.

Because cognitive and neuropsychological functions are frequently impaired in children and adults with ADHD (Seidman et al., 1998), theories regarding the underlying cognitive deficits of the disorder currently receive much attention from the scientific community. In addition, cognitive performance measures, such as the CPT and Go/Nogo tasks do not share the same degree of variance found in other scientific measures, such as self-report tests, which may be influenced by biased recall and other confounding factors. Two recent cognitive explanations for the range of symptoms displayed by people with ADHD are a deficit in response inhibition (Barkley, 1997; Johnson et al., 2001; Nigg, 2001; Pliszka et al., 2000;

Schachar et al., 1995; Schachar et al., 2000, Strandburg, 1996; Yong-Liang et al., 2000) or working memory (Johnson et al., 2001; Karatekin & Asarnow, 1998; Klorman, 1991; Overtoom et al., 1998; Schweitzer et al., 2000; Strandburg, 1996; Walker, Shores, Trollor, Lee, & Sachdev, 2000).

ADHD and response inhibition

Russel Barkley (1997) proposed that ADHD is primarily a product of problematic inhibition. During the mid 1990's, Barkley felt that current theories of ADHD failed to describe the basic nature of the disorder. He also felt that the clinical view of ADHD at the time failed to account for the multitude of cognitive and behavioural deficits associated with the disorder. He constructed a 'unifying theory' of ADHD in which he presented a hybrid model of the disorder based on theories relating to the neuropsychological functions of the prefrontal lobes. In his model, the primary deficit of inhibition had both a direct and indirect impact upon behaviour. Indirectly, deficient inhibitory mechanisms resulted in abnormal communication with four other executive functions: Self-regulation of affect, internalization of speech, reconstitution, and working memory. Self-regulation of affect refers to the wilful separation of emotion from communication. Resulting from behavioural inhibition deficits, a deficit in self-regulation of affect would present itself in a lack of emotional self-control, an inability to take an objective perspective in social situations, and a failure to regulate arousal in the undertaking of goal directed action. The internalization of speech is thought to contribute to self-restraint, guidance, and to provide a means for reflection, and self-questioning. Reconstitution refers to procedures that require accurate and efficient communication of information. Despite seeming to be unable to stop talking most of the time, children with ADHD produce

less speech in response to confrontational questioning (Tannock, 1996, as cited in Barkley, 1997). Finally, with respect to working memory, Barkley cites several studies that have established a relationship between ADHD and working memory deficits. These include examples of ADHD patients exhibiting deficits in mental arithmetic (Zentall & Smith, 1993), on the backward digit task (Barkley, Murphy & Kwasnik, 1996) and on a memory task for spatial location (Mariani & Barkley, 1997). Barkley is convincing in establishing the relationship between working memory deficits and abnormal behaviour, as well as the relationship between working memory deficits and ADHD, yet provides little support for the notion that working memory is a secondary process, that exists 'downstream' of inhibition. Barkley failed to acknowledge the importance of this and remains a loose thread in his unifying theory of ADHD. It is possible that working memory may at least operate in parallel to inhibition on a hierarchical system. Alternatively, according to Norman and Shallice, working memory (the SAS) oversees inhibition (contention scheduling), and only when the former becomes dysfunctional does behaviour become more impulsive (Shallice, et al., 1989).

Whilst Barkley does present a highly plausible unifying theory of ADHD, he acknowledges it to be a somewhat premature notion. Whilst not being the first theory to identify response inhibition as being a core deficit of ADHD, the theory is unique in that it is the first to introduce the linkage of inhibitory deficits to the disruption of the four other executive functions. Additionally, the executive processes referred to by Barkley are unique to his study and further justification of these processes as executive functions is required.

As a consequence of these disruptions, the behaviour of people with ADHD is controlled primarily by the 'here and now', that is, by immediate situations and stimuli. This behaviour contrasts with that of people without the disorder, whose actions are controlled by internal representations of information used for hindsight, forethought, time awareness, self-motivating behaviour and other cognitive operations.

In support of Barkley's theory, many other researchers have identified inhibitory processes as being deficient in persons with ADHD. In an early study, Schachar and colleagues (Schachar, et al., 1995) used a stop-signal task to identify inhibitory deficits in children with pervasive ADHD - where symptoms where identified in a home and school setting - compared to children where ADHD symptoms were significant either at home or in a school only. No ADHD patients were taking stimulant medication at the time of testing. They also examined these inhibitory processes in a normal control group. The researchers found that the pervasive ADHD group exhibited significantly longer stop-signal reaction times compared to the normal control group. In addition, the pervasive and school-only ADHD groups had flatter response inhibition slopes. This means that with a decreasing time delay between the Go and Stop signals (designed to facilitate inhibition) the increase in the probability of successful inhibition was significantly different to the other two groups. The ADHD group did not experience as rapid an increase in correct responding as did the control group. This study supports the notion that at least in children with pervasive ADHD there exists a significant impairment in inhibitory processing.

In a later study, Schachar and colleagues examined inhibitory control in normal children, children with ADHD or Conduct Disorder (CD) and in children with both ADHD and CD (ADHD+CD; Schachar, et al., 2000). As with the previous study, children with ADHD were asked to withhold their stimulant medication for 48 hours prior to testing. This study utilised a tracking version of the Stop-signal task mentioned earlier. The tracking algorithm manipulated the time delay between to Go and Stop signals until inhibition was occurring on around 50 percent of trials. The authors propose that when inhibition was successfully occurring on half of the trials, the stop signal delay is reflecting the time taken to internally inhibit the behaviour. This algorithm thus allowed for a time to be given to an event that doesn't occur. Using this algorithm, the authors compared the two groups, and as with their previous study, found that people with ADHD exhibited significant inhibitory deficits, as reflected in longer stop-signal reaction times.

An ERP study by Pliszka et al., (2000) utilised a 64-channel electrode-cap to record electrophysiological activity whilst ten ADHD and ten control children completed a stop-signal task. Patients consuming stimulant medication were asked to withhold that medication for 24 hours prior to testing. The researchers found that the ADHD group was less accurate to Go stimuli, recording a greater number of misses, representing a deficit in vigilance, than the control group. Pliszka et al. also obtained ERP data supporting the hypothesis that inhibitory deficits are present in children with ADHD. For both groups, the authors found a negative peak in the waveform occurring at 200 ms after the stop-signal was presented (the Nogo N2) which was approximately equal for both groups at all sites other than over the right inferior frontal cortex. Over the right anterior inferior scalp region, the ADHD group

exhibited an N2 that was significantly smaller than that of the control group. As described earlier, the frontal Nogo N2 can be used to reflect inhibitory processing, and thus the results of this study would suggest that a key deficit in ADHD lie in the reduced activity of inhibitory centres, as recorded over right hemisphere, inferior frontal scalp regions.

Yong-Liang et al., (2000) used a Go/Nogo task to examine inhibitory processing in normal, healthy boys and never-medicated ADHD boys. The children were required to respond to black arrows (appearing on two-thirds of presentations) and withhold that response when presented with blue arrows (appearing on a third of presentations). In addition to the behavioural data, the researchers also recorded ERP data from 30 scalp electrodes. As with Pliszka et al., (2000), Yong-Liang found that the ADHD children recorded a greater number of misses, suggesting reduced attentional capacities. In this study, the authors found that the ADHD group exhibited more false alarms to Nogo stimuli than the control group.

Walker and colleagues (Walker, et al., 2000) examined a range of cognitive functions in ADHD adults and healthy non-ADHD adults. Additionally, in an attempt to identify a specific profile of neuropsychological dysfunction of the disorder, a third group, composed of non-ADHD individuals with either mood or anxiety disorders was included in the study. Using a CPT, they found that the ADHD adults recorded a greater number misses and false alarms compared to the control group but not compared to the psychiatric group, suggesting that behavioural results of the CPT alone were not sufficient to differentiate between these groups in terms of inhibitory capabilities. Thus, whilst the ADHD group was less efficient than the control group

at inhibiting behaviours, they did not display inhibitory deficits to an extent that could be used to differentiate between the other psychiatric disorders. In addition, the ADHD group performed worse on the backward digit task (a measure of working memory ability) and on the Stroop Test (a measure of inhibition) compared to the control group, but as with CPT performance, there was no difference between the ADHD and the non-ADHD psychiatric group. Correct responses on the Stroop test requires the participant to inhibit reading a word that spells a certain colour, but to name the colour in which that word was printed. For example if presented with the word “Green”, printed in blue ink, the participant must inhibit saying the word ‘Green’ but must instead repeat ‘blue’, the colour in which the word was printed. There was no difference between the ADHD and psychiatric groups on this measure of inhibition. Whilst Walker obtained validating data for both response inhibition and working memory deficits to contribute to ADHD, the authors attributes the set of ADHD symptoms in adults to be mostly due to a deficit in attention and working memory.

Data reported by Johnson et al., (2001) support this hypothesis. They observed performance on a Gordon Diagnostic System (a version of the CPT-AX using number instead of letters) completed by adults with and without ADHD and found no differences between these adults and the control sample on the number of false alarms recorded.

Similar results have been obtained by Seidman et al. (1998), who performed a battery of executive function tests on a large sample (64 participants) of non-medicated ADHD adults and an age- and sex-matched control sample. Included in their study

was an auditory CPT, selected in part because it has been previously used to identify cerebral metabolic abnormalities in ADHD adults (Zametkin et al., 1990). The authors found that the ADHD sample obtained a greater number of misses and slower reaction times than the control sample, but there was no difference in the number of false alarm errors. This suggests that inhibitory processing was not different between the two groups but there may have been a deficit in vigilance and/or attention in the ADHD group.

In conclusion, impairments in response inhibition are relatively consistently observed in children with ADHD, evidenced by increased and alarms and reduced Nogo N2 components. This is consistent with Barkley's model such that impairments in response inhibition may contribute to other executive function deficits. In contrast, much of the literature regarding adult ADHD had argued that despite some evidence for impaired inhibition (as seen in the Stroop and CPT results), these results are more likely to reflect working memory or central executive impairments, contributing to the inhibitory problems.

An alternate theory to response inhibition being a core feature of ADHD is one claiming deficient working memory to underlie the pattern of problematic behaviour seen in people with the disorder.

ADHD and working memory

Using the Digit Span sub-test of the WISC and the Dot Test of Visuospatial Working Memory, Karatekin and Asarnow (1998) examined verbal and spatial working memory in two clinical populations (ADHD and schizophrenic patients), and an age-

matched control sample. The authors found that the ADHD group did not differ to the schizophrenic group on either of the tasks. Collapsed over forward and backward digit span tasks, normal children recalled significantly more digits than the schizophrenic children did, and slightly more digits than the ADHD group. For immediate recall on the spatial working memory task, the ADHD children performed worse than both other groups, although there was little variation amongst the three groups. Significant impairments did become apparent in the delayed recall condition, where ADHD children performed worse than both other groups, and significantly worse than the normal group. The results of the study suggested that both ADHD and schizophrenic children had deficits in verbal and spatial working memory that set them apart from the control group.

Overtoom and colleagues (Overtoom et al., 1998) collected ERPs as non-medicated children with ADHD and a control group completed a CPT-AX. As with Seidman et al., (1998) the ADHD children obtained a significantly greater number of misses than the control group, yet there was no difference in the number of false alarms. A major finding of the study was that whilst both groups elicited a parietally distributed P3 to target stimuli, the amplitude of the P3 was significantly smaller in the ADHD group than in the control group. In addition, there was no difference between the two groups in the frontal N2 amplitude elicited by Nogo stimuli, suggesting that the ADHD group maintained intact inhibitory processes.

In a study of medicated ADHD children, withholding their stimulant medication, Strandburg and colleagues (Strandburg et al., 1996) recorded ERPs during the completion of a simple and dual CPT. The simple CPT required the child to respond

to the digit ‘8’, whilst the dual CPT required a response when any digit was repeated upon successive presentations. As with previous studies, the ADHD group scored more misses and more false alarms than the control group. For both groups, a parietal P3 was elicited in response to target stimuli in both the simple and dual CPTs. When the age was considered as a covariance, the authors found the target P3 to be significantly smaller in the ADHD group than in the control group. As with Overtoom’s study, thus supports the idea of working memory deficits in ADHD patients.

In an early review of ERP studies, Klorman (1991) examined memory and cognitive performance in children with Attention Deficit Disorder (ADD) and compared this data to healthy control sample data. As with later studies, Klorman illustrated that the P3b was significantly reduced in persons with ADHD compared to control samples. An interesting follow-up finding is that, compared to a placebo, stimulants led to a significant increase in accuracy and speed of processing. In addition, the reduction in P3b amplitude observed in ADHD patients was normalised upon the administration of stimulant medication.

In a novel study, Johnstone, Barry and Anderson (2001) examined ERPs elicited by children and young adults with either ADHD-predominantly inattentive type, or ADHD-combined type and in normal healthy control participants as they completed an auditory oddball task. Their task required participants to respond to rarely presented target stimuli (1500 Hz tones) by pressing a response button as quickly as possible. Tasks such as the oddball task utilise working memory in that representations of the target stimulus must be rehearsed during presentations of the

standard stimuli. The infrequently presented target stimuli require greater working memory processing to maintain the representation of that item in working memory compared to the standard stimulus, which is presented more frequently. A typical P3 to target stimuli was observed in the control group. In this situation, the posterior P3b was greater than the frontal P3b. In the ADHD group, however, this posterior > frontal effect was diminished. As P3 amplitude has been used to reflect working memory processing, this supports the idea that working memory deficits occur in people with ADHD.

A recent neuroimaging study by Schweitzer et al. (2000) utilised Positron Emission Tomography (PET) to compare regional Cerebral Blood Flow (rCBF) associated with working memory in adults with and without ADHD. To assess working memory, the authors used a paced auditory serial addition task, which required participants to add consecutively presented single-digit numbers and provide a total at the end of the trial. They found that there was a significant difference in the activation of brain regions between the ADHD and control groups. The control group obtained results that were consistent with pre-established models of working memory, implicating involvement of right frontal regions, assumed to be central executive activity, and temporal region, assumed to reflect phonological loop activity, used in the rehearsal of the previously presented digit and the subtotal. In comparison, the ADHD group exhibited a more diffuse pattern of activation with less frontal involvement. The authors concluded that the ADHD group tended to recruit novel neural pathways and were less efficient at solving the working memory tasks, as measured by the Paced Auditory Serial Addition Task, where participants were required to add single-digit numbers presented binaurally.

Finally, Cohen & Servan-Schreiber (1992) constructed a computational network designed to model performance on some linguistic and cognitive dependent tasks, including the Stroop task and a CPT. The authors reported that when the representations held in computational working memory were systematically degraded, the model simulated the behaviour of schizophrenic patients on the two mentioned tasks. As mentioned earlier, ADHD and schizophrenic children did not differ significantly on tests of verbal and spatial working memory – yet both performed worse than a normal control sample (Karatekin & Asarnow, 1998). It may be possible to extrapolate this, such that, the degradation of working memory representations could produce results similar to those obtained from an ADHD sample, as opposed to the schizophrenic sample used in this study.

In conclusion, impairments in working memory have been consistently observed in children and adults with ADHD, evidenced by impaired performance on working memory tests such as the digit forward and digit backwards tests (Karatekin & Asarnow, 1998) and by greater misses to target stimuli in a CPT-AX (Overtoom et al., 1998). Additionally, people with ADHD have been shown to elicit a reduced P3 component is response to target stimuli during completion of a CPT (Klorman, 1991; Strandburg et al., 1996). A final cognitive process thought to be impaired in patients with ADHD is the ability to behavioural monitor responses.

ADHD and response monitoring

There are several reasons why this study has chosen to examine response monitoring in addition to response inhibition and working memory. According to the model of response monitoring introduced above, this process is strongly reliant upon

successful utilisation of working memory. For the comparator process to correctly compare actual and desired responses, the representations of these responses must be maintained in working memory. The comparator process acts upon these representations, the outcome of which contributes to the determination of what action is to be taken by the remedial action system. If the central executive is unable to provide correct representations to the comparator process then both the ERN and the processes performed by the remedial action system will be abnormal. By examining working memory and the response monitoring system, it becomes possible to correctly identify where in the cognitive chain of command response errors may be occurring.

An additional reason why this component has been examined in the present study is that the ERN has been associated with the level of dopamine found in the brain. De Bruijn, Hulstijn, Verkes, Ruigt and Sabbe (2002) found that compared to a placebo, benzodiazepine and an antidepressant, amphetamine consumption resulted in a clearly enlarged ERN amplitude. The authors took this to provide strong evidence for the involvement of the dopaminergic system in error monitoring. Given that people with ADHD have been claimed to exhibit reduced levels of dopamine particularly in the striatum (Grace, 2001) it seems likely that non-medicated ADHD patients will exhibit a reduced ERN compared to a control sample as a result of a reduced capability for response monitoring.

A central part of this thesis is to examine the cognitive differences between symptomatic and asymptomatic adults with ADHD, an aspect of the study that renders it unique. A consequence of this is that it is not possible to report on studies

investigating similar ideas. Some limited insight into the cognitive differences between these two groups can be obtained by examining the effects of stimulant therapy on the behaviour of patients with ADHD.

Stimulant therapy has been found to be effective in between 25% and 78% of adults with ADHD (Wilens at al., 1998 as cited in Paterson et al., 1999). Kolko, Bukstein and Baron (1999) have found that the core symptoms of ADHD (inattention and hyperactivity) underwent significant decreases following administration of methylphenidate to a group of children with the disorder, suggesting that methylphenidate targets the dysfunctional areas associated with the abnormal cognitive functions.

Clarke, Barry, McCarthy, Selikowitz, and Croft (2003) sought to investigate the effects of stimulant medication on the EEG of children with ADHD-predominantly inattentive type. Whilst initially abnormal, the researchers found that stimulants normalised EEG, but failed to achieve complete normalisation. They found that the best results were achieved in children who were initially hypoaroused, suggesting that the stimulants increased neural activation.

In a double-blind, placebo-controlled trial of dexamphetamine in adults with ADHD, Paterson et al. (1999) found that these drugs where effective in alleviating inattentive symptoms. The researchers were unable to draw firm conclusions regarding the efficacy of this treatment for hyperactive symptoms as only one participant in the sample was in the hyperactive ADHD subtype. Overall, dexamphetamine was shown to be a useful method for alleviating ADHD symptoms in adults over the short term.

However, of the 45 participants in the Paterson et al. study, five people formed neither a positive nor negative reaction to the drug, whilst two people were dissatisfied. Additionally, two people showed only a partial reduction in their inattentive symptoms (and none in their hyperactive symptoms). Five of the people tested experienced no response to the dexamphetamine.

This study seeks to address what cognitive processes remain dysfunctional in a subgroup of adults who report abnormal hyperactive, impulsive or inattentive behaviours, via a self-report measure.

Aims

Based on the literature reviewed, the present study therefore has the following aims:

1. To identify changes in the number of false alarms, reflecting inhibitory processes, by increasing the target density.

2. To identify and examine the latency, amplitude and topographic distribution of the Nogo N2, Nogo P3, Go P3 and ERN, considered to be indices of response inhibition, working memory and error monitoring during completion of a CPT.

3. To identify the neural sources of the Nogo N2 and Go P3 ERP components.

4. To examine whether response inhibition, working memory, or error monitoring are impaired in symptomatic and asymptomatic adults with ADHD, using behavioural and ERP indices.

In summary, this study thus aims to identify differences in a number of cognitive processes, between a symptomatic and asymptomatic ADHD sample and a control sample. This is done in order to provide support for one of three theories of ADHD, that is, whether the disorder is related to deficient inhibitory processing, working, memory or error monitoring processes. This study also aims to explore several related issues including the localisation of working memory and response inhibition.

Hypotheses

The specific hypotheses for the present study are:

1. Increasing the target density will result in an increase in the number of false alarm errors recorded.

2 Nogo stimuli will elicit a frontal Nogo N2 and a central Nogo P3 that will increase in amplitude following an increase in target density. Go Stimuli will elicit a Go P3 with a parietal distribution, which will decrease in amplitude following an increase in target density. Additionally, averaging epochs associated with failed inhibitions with enable the identification of an ERN.

3. The source of the Nogo N2 will approximate the orbito-prefrontal cortex. The source of the Go P3, whilst being less clearly defined, will lie in the frontal cortex.

If inhibitory deficits contribute to the ADHD type behaviour, then:

4. The symptomatic group will exhibit more false alarms, a decreased Nogo N2 and a decreased Nogo P3 amplitude compared to the asymptomatic and control groups.

If working memory deficits contribute to the ADHD type behaviour, then:

5. The symptomatic group will record a greater number of misses and a smaller Go P3 amplitude than the asymptomatic and control groups.

If deficits in error detection or response-competition contribute to the ADHD type behaviour then:

6. The ERN amplitude for the symptomatic group will be smaller than that of the asymptomatic and control groups.

Method

Participants

Nine adults with ADHD (eight males and one female, age range 21 to 50 years, one person was predominantly left-handed) volunteered to participate in the study. Nine age-, sex-, and education-matched control participants (all predominantly right-handed), whose age range was from 21 to 53 years also completed this study. They were contacted through friends and family of the research team. The control and ADHD groups were matched on age and their years of education. All participants had normal, or corrected to normal, vision and none received payment for their services.

Participants initially recruited to form the ADHD sample were to have a current diagnosis of ADHD as provided by their psychiatrist or other qualified clinician. The clinician providing this diagnosis was not associated with the study. Participants reporting substance abuse were excluded from the study. Current symptomatology was based upon results of the ADHD rating scale. Inclusion in the symptomatic group was limited to people who were currently reporting six or more symptoms of hyperactivity/impulsivity or inattention, (occurring either ‘often’ or ‘very often’), as recorded on the ADHD behaviour rating scale (Barkley & Murphy, 1998). If six or more symptoms were rated as occurring often, or very often, then this score was considered as being clinically significant, given that it exceeds the recommended threshold of six out of nine symptoms for this list published in the DSM-IV (Barkley & Murphy, 1998). The asymptomatic group was composed of individuals diagnosed as having ADHD who no longer exhibited symptoms associated with the disorder to

the level described above. Finally, the control group included those participants who had not received a diagnosis of ADHD and who reported less than six symptoms of either hyperactivity/impulsivity or inattention occurring either ‘often’ or ‘very often’.

Of the ADHD sample, three met the criteria for inclusion in the symptomatic group. Additionally, one person from the control group met the criteria for inclusion in the symptomatic sample, (for further discussion of the impact of this inclusion, see the Discussion section). These four participants formed the symptomatic group. Three participants exhibited primarily predominantly inattentive symptoms and one participant exhibited both hyperactive and inattentive symptoms. The asymptomatic group was composed of the remaining six ADHD participants that did not form part of the symptomatic group, and the control group was composed of the remaining eight participants.

All participants with ADHD were receiving stimulant medication at the time of testing (average time since last administration = 6.7 hours). Two of the nine were suffering from clinical depression and were consequently receiving anti-depressive medication (one adult from the symptomatic group, and one from the asymptomatic group). One person from the control group suffered from anxiety, depression and panic attacks and whilst he was receiving cognitive and behavioural therapy, that participant was not receiving medication as part of the treatment program. For the purpose of this study, it was deemed inappropriate to interfere with treatment regimes for either ADHD or depression.

Stimuli and Apparatus

All participants completed a brief screening questionnaire to provide information regarding current physical attributes (height, weight, handedness), psychiatric diagnoses, medication (dosage, hours since previous dosage, hours until following dosage), and education. Following this, an ADHD Current Symptoms Scale – self-report form was administered. The checklist is a four-point Likert Scale adapted from the DSM-IV diagnostic criteria for Attention Deficit Hyperactivity Disorder (Barkley and Murphy, 1998). Respondents select the frequency (ranging from 'never or rarely' to 'very often') that they experience the nine inattentive and nine hyperactive-impulsive symptoms mentioned in the DSM-IV. This simple and easy-to-complete checklist provides a rapid overview of the severity of ADHD type symptoms and has been previously used in a study of adult ADHD and stimulant medication (Paterson et al., 1999).

The Continuous Performance Task

The CPT involved the random presentation of 300 trials each involving the presentation of a cue and trial stimulus, each appearing for 100 ms and having a stimulus onset asynchrony of 1000 ms. The cue stimuli, A, B, C or D was followed by either an 'X' or a 'Y'. AX sequences were referred to as Primed Go trials, whilst AY sequences were called Primed Nogo trials. Unprimed Go trials occurred when the 'X' was preceded by a non-'A' cue stimulus. All other trials were Unprimed Nogo trials.

Participants were required to respond with a button press to the Primed-Go stimulus and inhibit responding when presented with the any Nogo stimulus. In the low-

density condition, Primed Go trials were presented on 150 trials (50%) and Primed Nogo on 60 trials (20%). The number of Primed Go trials increased to 240 (80%) in the high-density condition, whilst the number of Primed Nogo trials decreased to 24 (8%). All letters had equal dimensions, subtending a visual angle of approximately 1.62 degrees, and appeared in white on a black computer screen (NEC Multisync E1100 Microtouch; 35 cm x 30 cm) in the middle of a centred fixation rectangle.

To assess task performance, the number of hits (Primed-Go stimuli correctly responded to), false alarms (Primed-Nogo stimuli incorrectly responded to), and misses (Primed-Go not responded to) were recorded, as was reaction times to hits and false alarms.

Procedure

Each adult was tested individually in an acoustically dampened room. The experiment was explained to the participant and written consent obtained. After fitting the electrode cap (Elecro-Cap International) a standard set of instructions was read to the participant. The instructions were constructed so as to emphasise the need to respond rapidly. Participants were required to respond to Primed Go stimuli by pressing the space bar with one hand for the first half of each condition and with their other hand for the second half of that condition. The distribution of participants completing low- and high-density conditions first is presented in Table 1.

Table 1. Number of participants from each group that completed the low- and high-density conditions first.

	Symptomatic	Asymptomatic	Control
Low-density first	2	4	4
High-density first	2	2	4

Participants were assigned to groups in a sequential order according to either ADHD or non-ADHD diagnosis. There was no significant difference between the number of participants completing the low- or high-density condition first (χ^2 (2) = 0.45).

For each condition, participants were given a practice set of twenty stimuli, for which the experimenter remained present. Any errors were identified and the participant was informed at the end of the practice set. Where necessary, instructions were re-clarified.

This study was approved by the Human Research Ethics Committee at the University of Western Australia (Reference Number RA/4/3/0059).

EEG acquisition and processing

Electrophysiological methods

Data were continuously sampled using a Neuroscan EEG SYNAMPS system and Scan version 4.0 software (Neuorosoft, Inc. USA.). The nineteen tin cap electrodes were arranged according the International 10-20 electrode system, (see Figure 8) and

measured electrical potentials from sites Fz, Cz, Pz, Fp1, Fp2, F3, F4, C3, C4, P3, P4, O1, O2, F7, F8, T3, T4, T5, and T6 with the tip of the nose as the reference.

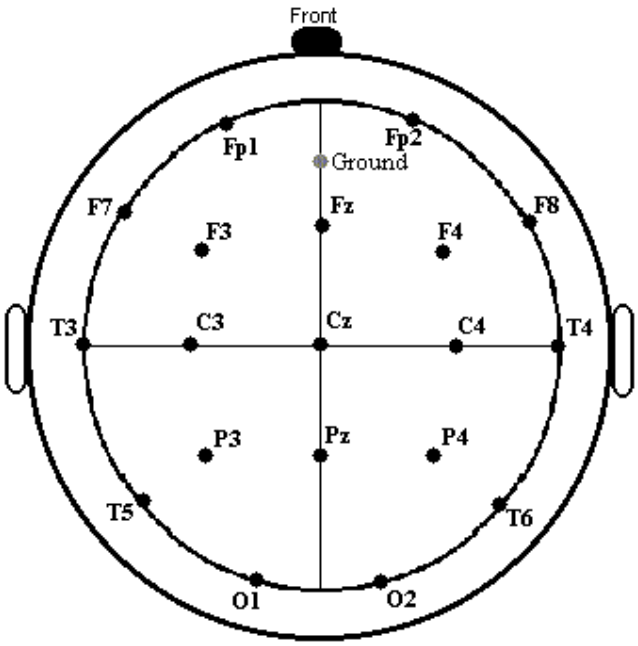

Figure 8. View from above head of the 19 electrodes, as per the International 10-20 electrode system.

Electrooculogram (EOG) was measured vertically (VEOG) using tin electrodes placed 1 cm above and below the left eye. The EEG was sampled at 2 ms/channel using a gain of 75,000 and a bandpass of 0.05 Hz to 30 Hz (-6 dB down). For the EOG, a reduced gain of 22,500 was used. Due to limitations in some software, individuals' ERP data was transformed such that every second data point in the recording was sampled and analysed. This transformation resulted in a 4 ms/channel sampling rate. Participants were grounded by the cap ground electrode (see Figure 8) and impedance was maintained at or below 5kΩ. Trials where EOG potentials interfered with the ERP were corrected using an automated procedure provided by

the Scan (version 4.0) software. Artefacts and signals larger than 100 μV were rejected from the ERP averages.

ERP component extraction

Only trials on which Go stimuli were correctly responded to and trials on which the response to Nogo stimuli was correctly inhibited were included in the analysis. The N2 and P3 components were extracted using stimulus locked ERPs, such that for each ERP epoch, the stimulus was presented at time = 0 ms. For the stimulus-locked ERPs, an ERP epoch from 200 ms pre-stimulus to 1000 ms post-stimulus was extracted and averaged. Mean amplitudes as well as peak amplitude and latency of the N2 and P3 were analysed within the following time intervals: N2 from 200 to 300 ms; P3 from 325 to 625 ms. Mean and peak P3 amplitudes and latencies were obtained with the use of an automated extraction program and verified by manual inspection. Mean N2 amplitudes were also extracted using the automated procedure although there were difficulties with the identification of the peak N2 because the component emerged from the increasing positivity of the P3. A consequence was that the automated procedure would identify a more negative aspect of the P3, occurring before the N2 was elicited as the peak of the N2. To obtain the peak N2 values a combination of manual extraction and automated extraction was required. For manual extraction, the peak N2 was considered as the most negative point occurring within the latency window, consistent across nine electrode sites (F3, Fz, F4, C3, Cz, C4, P3, Pz, P4).

ERN extraction

The ERN epoch was constructed using a response-locked method, such that, time = 0 was defined as the time at which a false alarm response was recorded. The ERN epoch was from 600 ms before stimulus onset through to 1000 ms post-stimulus. Trials where the EOG interfered with the ERN were corrected using the SCAN procedure. Artefacts larger than 100 μV were removed from the ERPs. Only trials where subjects responded incorrectly to Nogo stimuli (false alarms) were included in the analysis. Baseline correction was performed from –600 to –400 ms. The mean and peak ERN values were obtained using an automated procedure, as too was the peak latency. Data was visually inspected for consistency and where errors seemed possible, the peak amplitude and peak latency were manually extracted, following the procedure described for ERP component extraction. An error in the data was considered as possible when the peak occurred at the start of the latency window in which the automated procedure operated.

Brain Electrical Source Analysis

BESA (version 4.0) works on the premise that only a distinct number of brain areas are active during the epoch for any particular cognitive activity. The software uses different dipoles to describe the activity in each functionally different brain region and places these dipoles into an approximate location within a fixed electrical head model. The BESA serves three purposes, to estimate the number of active sources during an activity, to locate the appropriate dipoles or sources of this activity, and to determine the strength of activity occurring at each of these areas as a function of time. The manufactures of the BESA software acknowledge that due to the use of a

simple head model, the natural variation in scalp and skull thickness as well as individual head geometry, localising the source of the activity is not exact and may be up to 2 cm wrong in some cases.

Statistical Analyses

All statistical comparisons were performed using SPSS (v 9.0.1) for windows (SPSS Inc. Chicago, IL, USA).

Behavioural Analyses

Statistical comparisons were performed with separate between- and within-groups repeated measures analysis of variance (ANOVA) for accuracy and reaction time scores. Stimulus type (Go and Nogo) and Condition (low-density and high-density) were used as the within subject measure, with Group (symptomatic, asymptomatic and control) as the between subjects measure. Type I errors were maintained below 0.05.

ERP Analyses

For the purposes of the present study, the analysis of Primed stimuli only was judged as being sufficient. Thus, as only ERPs for Primed-Go and Primed-Nogo trials were included in the analysis, these shall be shortened and referred to as Go and Nogo trials. Unprimed trials, both Go and Nogo will be referred to in full. Peak amplitude, mean amplitude and peak latency for the N2 and P3 were subjected to separate multivariate analysis of variance (MANOVAs), with electrode site (F3, Fz, F4, C3, Cz, C4, P3, Pz, P4), density (Low, High), and stimulus (Go, Nogo) as repeated measure factors. Group (Symptomatic, Asymptomatic, and Control) was used as a

between subjects factor in the analysis. Follow-up comparisons were conducted with t-tests where appropriate, using a Bonferroni corrected adjustment to maintain alpha at 0.05.

ERN Analyses

ERN amplitude and latencies were subjected to a separate repeated multiple analysis of variance (MANOVA), with electrode Site (F3, Fz, F4, C3, Cz, C4, P3, Pz, P4), and density (Low, High) as repeated factors. Group (Symptomatic, Asymptomatic, Control) was a between subjects factor. This resulted in a 9 x 2 x 2 (Electrode x Group x Density) MANOVA.

BESA Analyses

For each of the three groups, a BESA was performed for both Go and Nogo stimuli summed across both low- and high-density conditions. The number of raw data points included in the BESA was 550 for each analysis and digitisation was limited to 4 ms/sample in a sweep that began at time = 0 (when the response was recorded) and ended when time = 396 ms.

A spatial principal component analysis was employed so as to estimate the minimum number of dipoles that should be included in the model. One dipole was used in the Go condition and was initially set on the midline within inferior aspects of the temporal lobe. For the Nogo stimuli, two dipoles were used. These initial source placements (starting points of dipoles before analysis has been performed) were set to approximately the right orbitofrontal cortex, and the anterior cingulate cortex.

These initial source locations were used as they resulted in the least amount of variance unaccounted for by the source dipoles, and are presented in Figure 9.

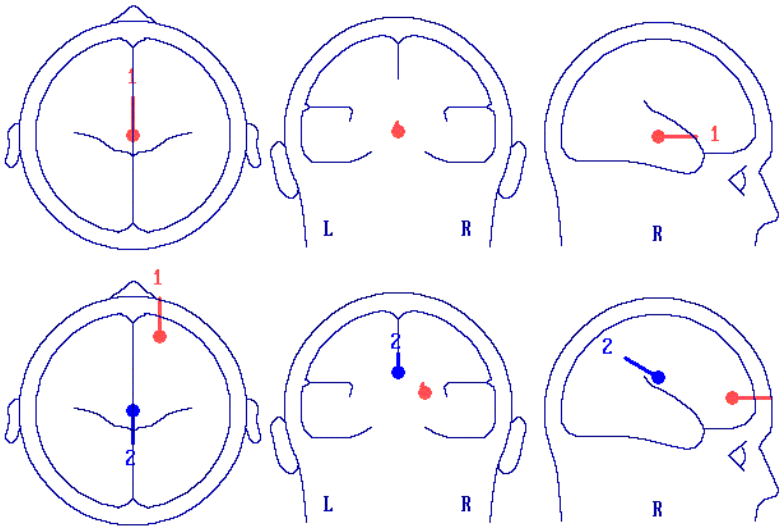

Figure 9. Initial source placement for Go P3 (top) and Nogo N2 and Nogo P3 (bottom).

No statistical comparisons were performed using data gathered from the BESA, there is however, a discussion based upon visual inspection of the data.

Results

Group data

The demographic and clinical attributes of the sample are presented in Table 2. There were no significant differences in age and education between the three groups (main effect of age F (2, 15) = 0.19, p = .83; main effect of education F (2, 15) = 0.63, p = .55). A one-way ANOVA identified significant differences between groups for the scores obtained on the ADHD behaviour rating scale (main effect of ADHD rating scale score F (2,15) = 61.17, p < .001). Follow-up t-tests identified the Symptomatic group as scoring significantly higher than both the Asymptomatic group (t (8) = 10.27, p < .001) and Control group (t (8) = 9.45, p < .001) on this measure. Additionally, the Asymptomatic group scored significantly higher than the Control group (t (8) = 4.24, p = .001). Based on the effect size for the difference in the false alarm rate between symptomatic and control groups, approximately seventy participants in each group would be required to attain a power level of 0.8.

Table 2. Means and standard deviations (SD) for age, years of education, mg of dexamphetamine per kilogram of body mass consumed and score on the ADHD Behaviour Checklist of the Symptomatic, Asymptomatic and Control Groups. Also included is the gender distribution (m = male, f = female) and group sizes (N).

Group	N	Gender M:F	Age	Years Education	mg dex/ kg body mass	ADHD score
Symptomatic	4	4 : 0	32.8 (11.7)	14.75 (1.89)	2.91 (2.56)	27.75 (2.75)
Asymptomatic	6	5 : 1	31.3 (12.5)	13.33 (2.00)	4.75 (1.45)[a]	13.67 (1.63)
Control	8	7 : 1	35.4 (12.8)	13.00 (3.16)	0.0 (0.0)	6.13 (4.09)

[a] Two participants were receiving stimulant medication other than dexamphetamine.

There was no significant difference between the symptomatic and asymptomatic groups on the milligrams of dexamphetamine per kilogram of body mass (mg/kg) consumed (t (6) = 1.24, p = .26).

Behavioural data

Table 3 presents the accuracy and reaction times for the three groups. For all groups, accuracy to Go stimuli was high, and very few misses were recorded. Changing the target density did not affect the hit accuracy (t (17) = 1.70, p = .11). It did, however, increase the number of false alarms recorded. Significantly more false alarms were made in the high-density condition compared to the low-density condition (main effect of density F (1, 15) = 32.80, p < .001). The groups did not differ significantly on reaction times to Go stimuli (main effect of group, F (2, 15) = 1.94, p = .19; group x density interaction, F (2, 15) = 0.70, p = .51).

Table 3. Means and standard deviations for Symptomatic, Asymptomatic and Control groups measuring percentage of misses, false alarms and reaction times (RT) to Go stimuli (ms) during the Low-density and High-density conditions.

	Symptomatic	**Asymptomatic**	**Control**
% Misses			
Low-density	5.2 (7.3)	2.5 (1.7)	1.3 (1.5)
High-density	5.0 (6.7)	1.5 (1.0)	1.0 (1.0)
% False Alarms			
Low-density	9.2 (10.2)	5.8 (4.6)	8.1 (8.3)
High-density	31.3 (21.9)	23.6 (11.1)	22.3 (17.8)
RT to Go stimuli			
Low-density	401 (50)	404 (30)	382 (26)
High-density	322 (39)	384 (44)	369 (32)

The false alarm rate did not differ significantly between groups (main effect of group F (2, 15) = 0.32, p = .72; group x density interaction F (2, 15) = 0.5, p = .60).

Electrophysiological data

The ERPs generated by averaging across Group and Density are presented in Figure 10.

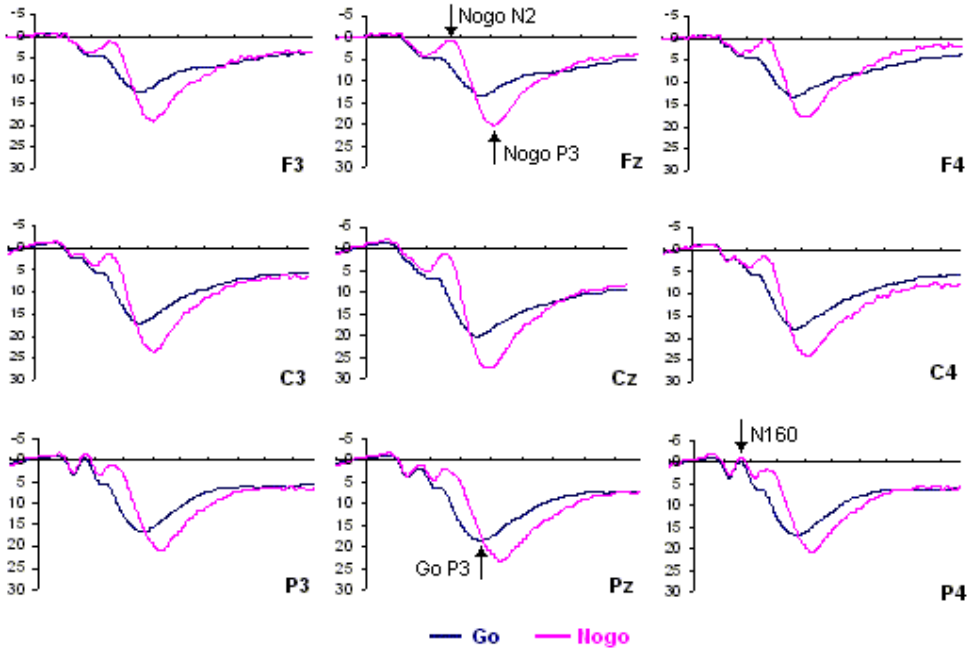

Figure 10. ERPs for Go and Nogo stimuli recorded from nine electrode sites averaged across Group and Density. Nogo N2, Nogo P3, Go P3 and N160 are indicated.

N160 Component

A negative component with a peak latency of approximately 160 ms was identified (see Figure 10). The mean amplitude of the N160 was larger following Nogo stimuli compared to Go stimuli (main effect of stimulus F (1, 15) = 4.4, p = .05) and showed a mostly parietal distribution (main effect of electrode F (8, 120) = 2.91, p = .08, ε = 0.20).

N2 Component

Nogo stimuli elicited an N2 component largest at F4 and peaking at 235 ms. The mean N2 amplitude was larger for Nogo stimuli than for Go stimuli (main effect of stimulus F (1, 15) = 37.25, $p < .001$) and was somewhat more frontally distributed (main effect of electrode F (8, 120) = 2.99, $p = .06$, $\varepsilon = 0.26$). The mean amplitude of the Nogo N2 was somewhat larger in the high-density condition than in the low-density condition (main effect of density F (1, 15) = 3.59, $p = .08$). ERPs elicited in response to Nogo stimuli occurring in the low- and high-density conditions are presented in Figure 11.

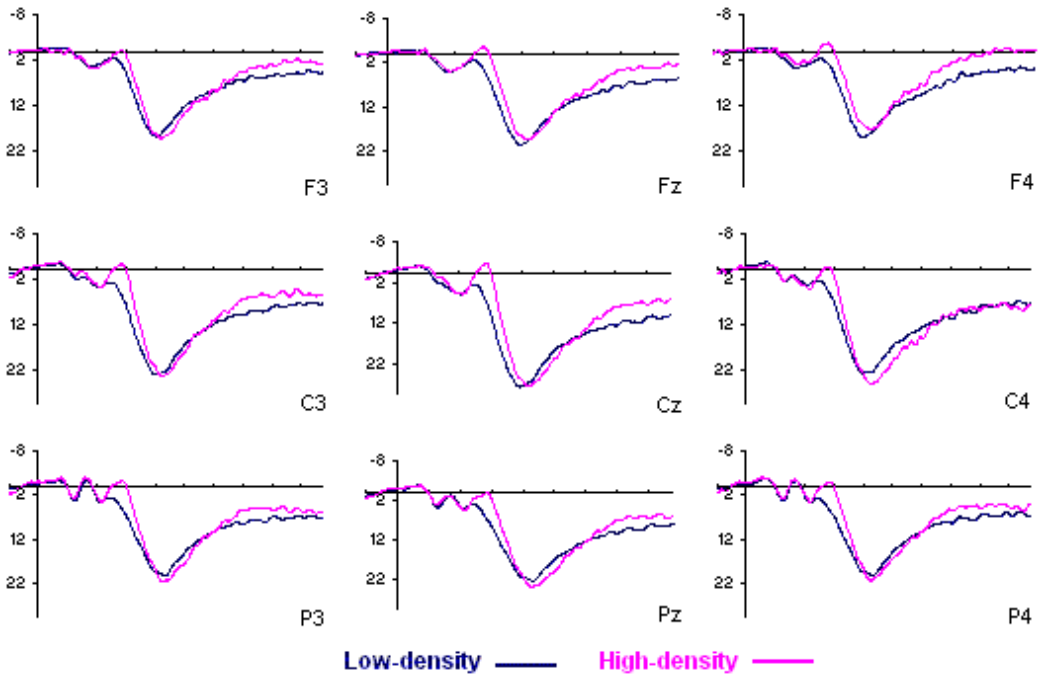

Figure 11. ERP elicited in response to Nogo stimuli in the low-density condition and in the high-density condition.

The difference between the Go and Nogo N2 remained the same for all groups (N2 group x stimulus interaction F (2, 15) = .807, p = .465). Similarly the difference between the Nogo N2 in the low-density condition and high-density condition remained constant between groups (Nogo N2 group x density interaction F (2, 15) = .027, p = .974).

P3 Component

The mean amplitude of the P3 was larger following Nogo stimuli than following Go stimuli (main effect of stimulus F (1, 15) = 15.24, p < .001) and was largest at central electrode sites (main effect of electrode F (8, 120) = 20.84, p < .001. Additionally, Go and Nogo components where analysed separately. The mean Go P3 was centro-parietally distributed (main effect of electrode F (8, 120) = 25.56, p < .001, ε = 0.211) and was larger in the low-density condition than in the high-density condition (main effect of density F (1, 15) = 6.35, p = .02; density x electrode interaction F (8, 120) = 2.67, p = .06, ε = 0.347). The Nogo P3 was centro-parietally distributed (main effect of electrode F (8, 120) = 11.39, p < .001, ε = 0.259). ERPs elicited for Go stimuli recorded during the low- and high-density conditions are presented in Figure 12.

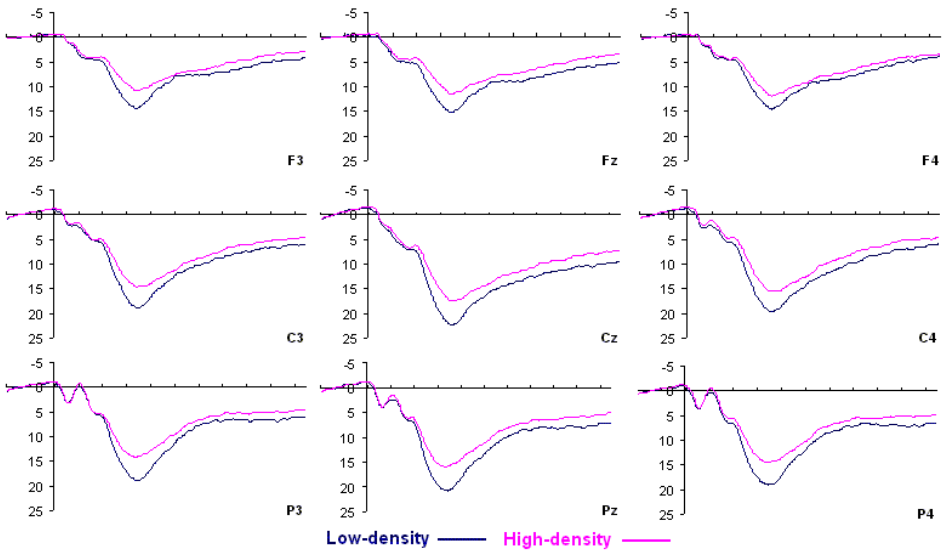

Figure 12. ERPs in response to Go stimuli recorded during the low- and high-density conditions, averaged across group.

The same pattern of results was obtained from the peak amplitude of the P3 component. The peak amplitude of the P3 was larger following Nogo stimulus than following Go stimuli (main effect of stimulus F (1, 15) = 27.57, $p < .001$) and was also largest at central electrode sites (main effect of electrode F (1, 15) = 16.72, $p < .001$, $\varepsilon = 0.252$). The peak Go P3 amplitude was centro-parietally distributed (main effect of electrode F (8, 120) = 31.01, $p < 0.001$) and was also larger in the low-density condition than in the high-density condition (main effect of density F (1, 15) = 8.816, $p < .01$); density x electrode interaction F (8, 120) = 2.685, $p < .05$, $\varepsilon = 0.404$). As with the mean Nogo P3, the peak Nogo P3 was centro-parietally distributed (main effect of electrode F (8, 120) = 8.106, $p = .002$, $\varepsilon = 0.302$).

As was the case with the Nogo N2, no group differences were observed for the mean amplitude of the Nogo P3. The increased amplitude for the Nogo P3 compared to the

Go P3 remained constant between groups (P3 group x stimulus interaction F (2, 15) -.449, p = .647). Similarly, the effect of density upon the mean amplitude of the Go P3 remained constant between groups, such that all groups had approximately the same enhancement of the Go P3 in the high-density condition compared to the low-density condition (Go P3 group x density interaction F (2, 15) = 0.142, p = .869).

Comparison of good and poor inhibition groups

The Poor Inhibition sample was constructed by averaging the ERPs elicited by Nogo stimuli from the five participants across all groups that recorded the greatest number of false alarm errors. Similarly, the Good Inhibition group was composed of five people scoring the least number of false alarm errors. For the Poor Inhibition group, the false alarm errors were occurring 31.17% of the time, for the Good Inhibition group, this value was 5.50%. Collectively, the Good Inhibition and Poor Inhibition samples are called the inhibition groups. The Poor Inhibition group scores significantly more false alarms than the Good Inhibition group (t (8) = -3.8, p < .0.01).

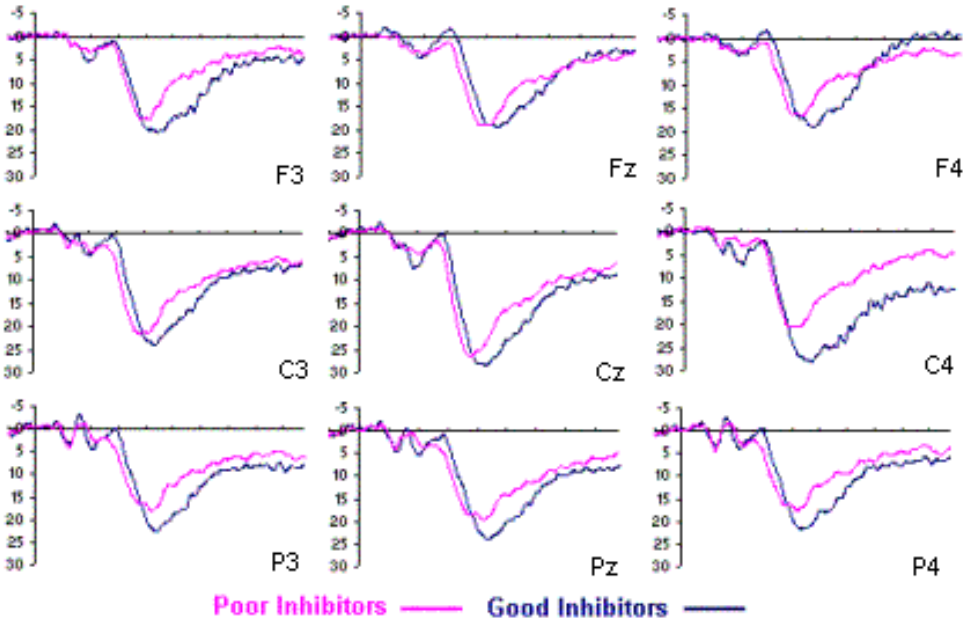

Figure 13. ERPs elicited by Nogo stimuli for Poor Inhibitors and Good Inhibitors recorded from nine electrodes averaged across Density.

ERPs comparing participants who were good inhibitors to poor inhibitors were constructed, these are presented in Figure 13. For both inhibition groups, ERPs were constructed following the presentation of Go and Nogo stimuli. These ERPs are presented in Figure 14.

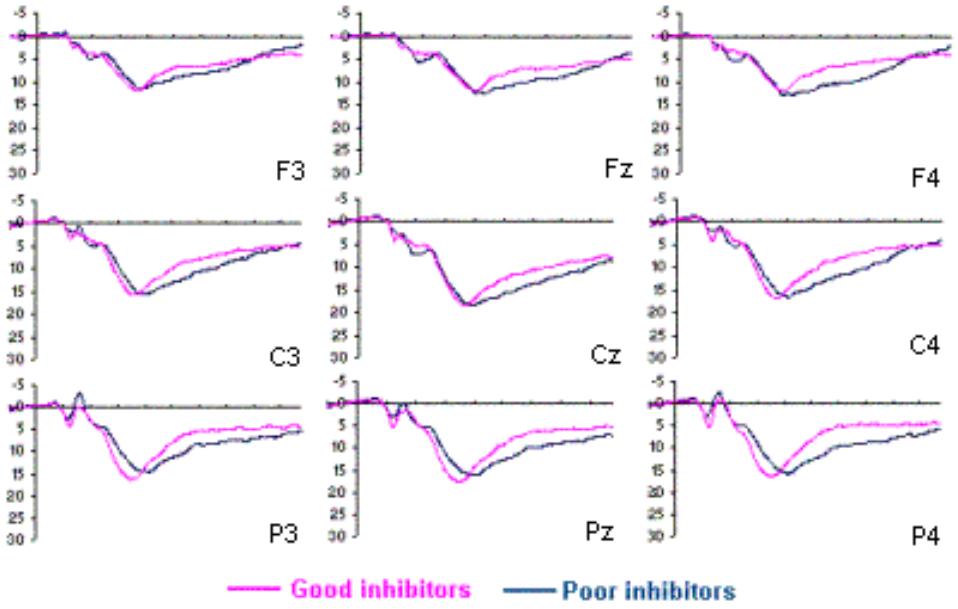

Figure 14. ERPs constructed for Poor Inhibitors and Good Inhibitors in response to the Go stimuli, recorded from nine electrodes.

There was no difference between the inhibition groups on the mean amplitude of any electrophysiological component (main effect of inhibition group upon Nogo N2 mean amplitude F (1, 8) = 0.66, p = .82; main effect of inhibition group upon Nogo P3 mean amplitude F (1, 8) = 0.54, p = .48; main effect of inhibition group upon Go P3 mean amplitude F (1, 8) = 0.16, p = .70). Neither were the differences on the peak amplitude of any component (main effect of inhibition group upon Nogo P3 peak amplitude F (1, 8) = 0.82, p = .39; main effect of inhibition group upon Go P3 peak amplitude F (1, 8) = 0.01, p = .92).

Difference waveforms

Difference waveforms were constructed by subtracting the Go waveform from the Nogo waveform, this is presented in Figure 15.

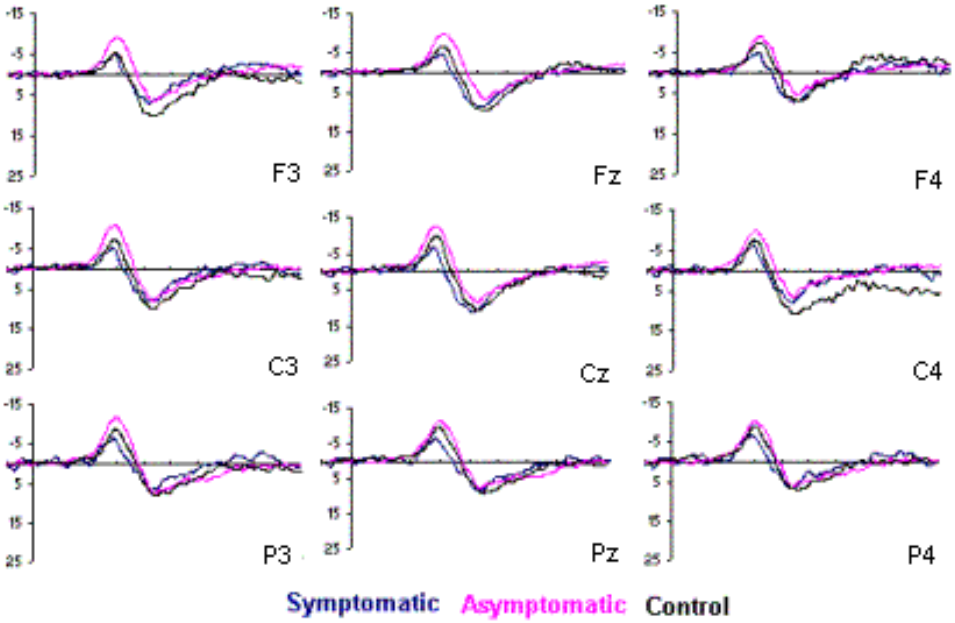

Figure 15. Difference waveform for Symptomatic, Asymptomatic and Control groups, constructed by subtracting the Go waveform from the Nogo waveform, shown at nine electrodes, averaged across density.

The mean amplitude of the difference waveform over the epoch defined by the N2 was not different between groups (main effect of group F (1, 5) = 1.83, p = .19; group x density interaction F (2, 15) = 0.01, p = .99; group x electrode interaction F (16, 120) = 0.68, p = .81; group x density x electrode interaction F (16, 120) = 1.34, p = .19).

The mean amplitude of the difference waveform over the epoch defined by the P3 was not different between groups (main effect of group F (1, 5) = 1.21, p = .33; group x density interaction F (2, 15) = 0.36, p = .71; group x electrode interaction F (16, 120) = 0.55, p = .29; group x density x electrode interaction F (16, 120) = 1.19,

p = .29). The mean amplitude of the difference P3 was equally distributed across the scalp (main effect of electrode F (8, 120) = 2.59, p = .80, ε = 0.294).

Error Related Negativity

The number of trials for which an ERN could be recorded was limited by the number of incorrect responses made to Nogo stimuli, as well as by the degree to which artefacts interfered with the data. The number of acceptable trials for each group is presented in Table 4.

Table 4. Number of trails for which an ERN was recorded for each group and condition.

	Number of trials accepted	
Group	Low-density	High-density
Symptomatic	29	39
Asymptomatic	33	49
Control	37	52

Two participants failed to record any false alarms during the low-density condition, whilst one participant did not record any during condition two. The ERN averaged over all groups and density conditions is presented in Figure 16.

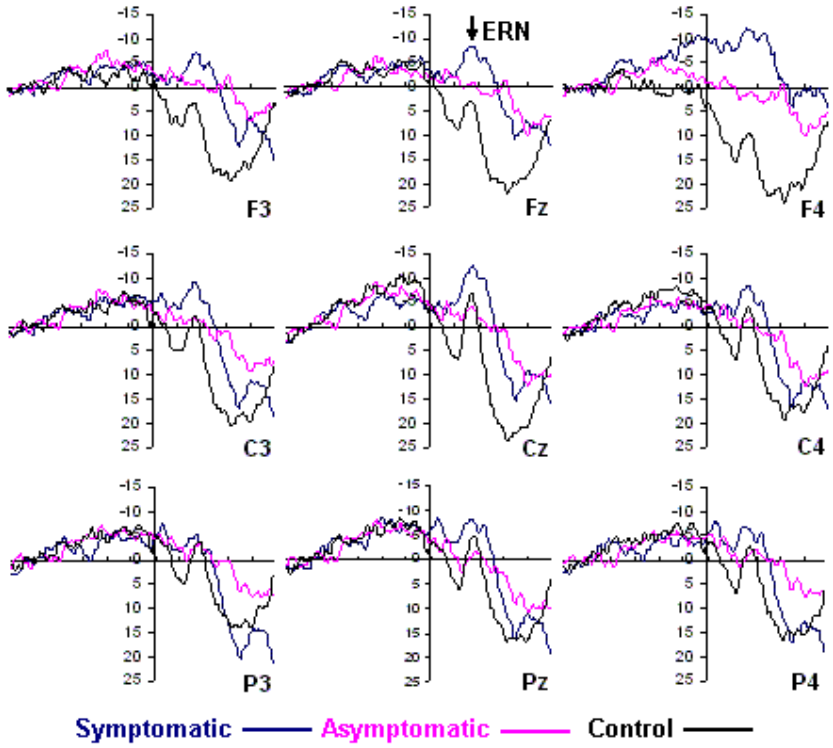

Figure 16. Waveform (from –600 ms prior response to 500 ms post response) showing the ERN for the Symptomatic, Asymptomatic and Control averaged across density. ERN indicated by the arrow. Responses were made at time = 0.

There were no differences between groups on the mean amplitude of the ERN and changing the density did not affect the difference between the groups (main effect of group F (1, 13) = 1.35, p = .29; group x density interaction F (2, 13) = 0.67, p = .53). The difference between groups was greatest at frontal sites and particularly at F4 (group x electrode interaction F (16, 104) = 2.05, p = .08, ε = 0.369; group x density x electrode interaction F (16, 104) = 0.97, p = .45, ε = 0.29). Similarly, there were no differences between groups on the peak amplitude of the ERN and again, changing the density did not affect the difference between the groups (main effect of group F (1, 13) = 0.18, p = .84; group x density interaction F (2, 13) = 0.26, p = .80;

group x electrode interaction F (16, 104) = 1.53, p = .20, ε = 0.334; group x density x electrode interaction F (16, 104) = 1.01, p = .42, ε = 0.27). The ERN had a peak latency that was recorded earlier at central electrode sites compared to frontal and parietal sites (main effect of electrode F (8, 104) = 2.84, p = .03, ε = 0.526).

Brain Electrical Source Analysis

The estimated sources for the Go P3 and Nogo N2 and P3 summed across all participants is presented in Figure 17.

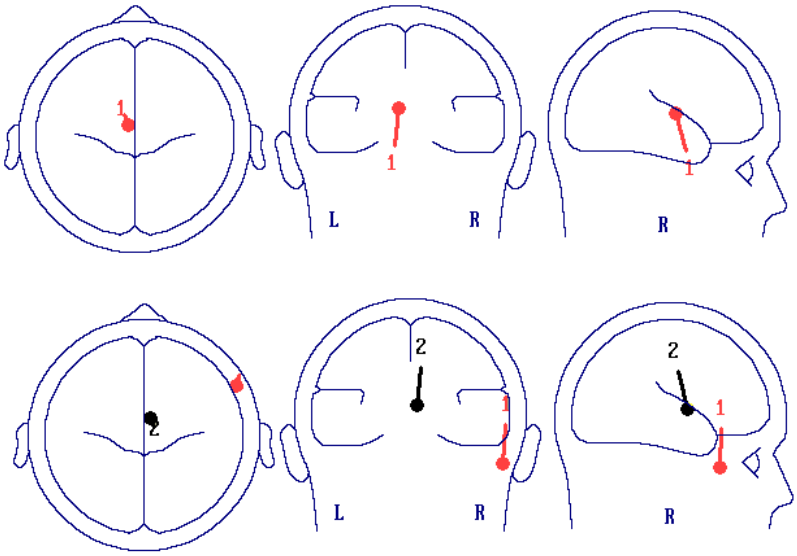

Figure 17. View of top, back and side of head showing the source of Go P3 in the top panel, and the Nogo N2 and Nogo P3 sources in the bottom panel, summed across all participants.

The Go source remained close to the midline, slightly to the left hemisphere. The source approximates central brain regions possibly including structures such as the caudate nucleus, the putamen and the possibly the thalamus of the left hemisphere.

This source accounted for 85.2% of the variance. Of the two sources identified following Nogo stimuli the primary source, accounting for a majority of the variance was located just outside the brain, whilst the second source remained along the midline. The second source can be approximated to similar regions to that of the source of the Go P3, this time, however, in the right hemisphere. The residual variance remaining following the identification of these sources was 8.7%.

The source of the Go P3 was similar for all three groups, as can be seen in Figure 18.

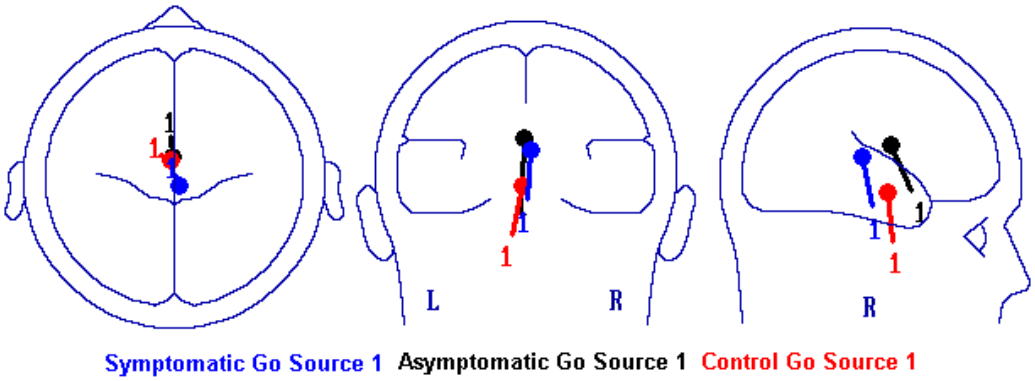

Figure 18. View from top, back and side of head, illustrating the position of the Go P3 source for the Control, Asymptomatic and Symptomatic groups.

As can be seen in Figure 18, the source is located furthest anteriorly in the asymptomatic group, and most inferiorly in the control group. For all groups, the source is located along the midline. For the symptomatic and control groups, the percent of variance not accounted for by the source is high, 32.6% and 31.3 % respectively, comparatively at 7.27% that of the asymptomatic group is low.

The similarity of the Go P3 source seen between groups is not found when comparing the Nogo N2 and Nogo P3 sources between groups, a difference which can be easily seen in Figure 19.

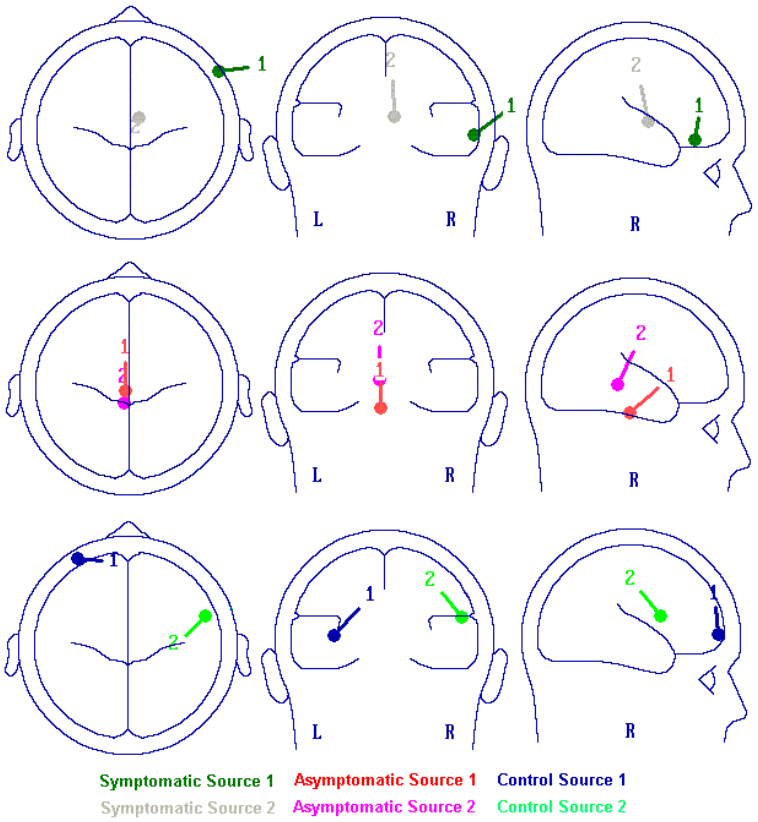

Figure 19. Sources of Nogo N2 and P3 for symptomatic (top), asymptomatic (middle) and control (bottom) groups.

The residual variances unaccounted for following this source localisation procedure are presented in Table 5.

Table 5. Residual variances following source localisation for three groups.

Group	Residual Variance (%)
Symptomatic	12.3
Asymptomatic	3.78
Control	12.7

Of the sources, two were identified as possibly existing outside the brain, a ‘source one’ in the symptomatic group, and a ‘source two’ in the control group.

For the symptomatic group, source one was located outside the brain. BESA is however, susceptible to error of up to 2 cm in some cases. Given this, source one in the symptomatic group can be approximated to right hemisphere inferior regions of the prefrontal cortex. The second source remained similar to its initial placement and remained nearby to brain structures such as the splenium, globus pallidus, third ventricle and possibly the thalamus. For the asymptomatic group, the primary source was located at middle inferior aspects of the temporal lobe, a region of close proximity to the hippocampus, whilst the second source was similar to that of the symptomatic group, albeit slightly more inferior and posterior. The control group recorded a primary source in the left hemisphere within inferior aspects of the prefrontal cortex. The second source was located slightly anterior to the central and lateral sulci most likely within the motor cortex.

Discussion

This study had the following four aims. Firstly, to identify changes in the number of false alarms associated with changes to the frequency at which target stimuli were presented. Second, to identify and examine the Nogo N2, Nogo P3, Go P3 and ERN, electrophysiological components associated with response inhibition, working memory and response monitoring. Third, to identify the neural sources of the Nogo N2 and Go P3 ERP components. And finally, using the information gathered from the first three aims, the fourth aim was to identify whether deficits in response inhibition, working memory or response monitoring contribute to the pattern of hyperactive/impulsive and inattentive behaviour observed in people with ADHD.

The first aim of this study was to identify whether changes would occur in the number of false alarms when increasing the target density. This was done in order to observe whether changes in inhibitory capabilities were associated with changes in inhibitory demands. Hypothesis one, which stated that increasing the target density would result in an increase in the number of false-alarm errors, was supported by the data. Previous research has suggested that the ability to inhibit responding to Nogo stimuli can be manipulated in several ways. Firstly, inhibition becomes more difficult when increasing the speed of responding required by the participant (Jodo & Kayama, 1992). Secondly, the inhibitory demands of the task can be manipulated by changing the presentation rates of the stimuli. When the Go stimuli occur more frequently, the neural network associated with the response process is primed, and thus inhibiting responses to the Nogo stimuli becomes more difficult compared to when the Go stimuli appear less regularly, and the Go response network is less

primed. As the false alarm rate reflects failures of inhibition, it can be concluded that conditions in which more false alarms are recorded are conditions involving either reduced capacity for inhibiting behaviour, or increased inhibitory demands. All groups recorded significantly more false-alarm errors in the high-density condition, compared to the low-density condition, supporting the idea that increasing the target density increased the inhibitory demands of the task. Whilst the results failed to identify a significant difference between the groups on the number of false alarms recorded, it is necessary to consider the small number of participants included in this study. The effect size for the comparison between the symptomatic and control groups on the high density false alarm error rate was the highest of all false alarm rate effect size comparisons (*d* (pooled SD) = 0.47). Effect size and power analyses have identified that approximately seventy participants would be required to establish a power level of 0.8. Given this, it is not possible to conclude that the failure to identify group differences on the number of false alarms is attributable to a lack of group difference, and as was expressed earlier, these results should be interpreted cautiously, with further research strongly encouraged.

The second aim of this study was to identify and examine the latency, amplitude and topographic distribution of the Nogo N2, Nogo P3, Go P3 and ERN. This was performed in order to examine the use of these components as indices of response inhibition (Nogo N2, Nogo P3), working memory (Go P3) and response monitoring (ERN). Given that the final aim was to identify cognitive differences between a symptomatic ADHD sample and an asymptomatic ADHD sample it was necessary to establish that in the present study, the ERP components were reflecting the desired cognitive functions.

As part of the second hypothesis, it was expected that Nogo stimuli would elicit an N2 component that was not elicited following Go stimuli. This was supported by the data. By examining the ERPs following Go and Nogo stimuli, there was a clear N2 component following Nogo stimuli, which was not present following Go stimuli. This result supports the use of the Nogo N2 as a reflection of inhibitory processing which is consistent with other research, such as Eimer (1993), Bokura et al. (2001), van Boxtel et al. (2001) who have similarly reported the existence of an N2 component following the presentation of Nogo stimuli, but absent following Go stimuli.

It was also expected that the Nogo N2 and Nogo P3 would have greater amplitude in the high-density condition compared to the low-density condition. If the Nogo N2 and Nogo P3 components are indeed reflections of inhibitory processing, then it is likely that increasing the inhibitory demands of the task would result in an increase in the amplitude of these components. This was only partially supported by the data. As expected, the mean amplitude for both components was greater in the high-density condition compared to the low-density condition although this effect was only marginally significant. For the Nogo N2 component, the increase in mean amplitude following an increase in target density was approaching significance, providing support for the use of this component as an indicator of response inhibition.

Maintaining consistency with previous research, it was expected that the Nogo N2 would have a frontal distribution and would be greatest over the right hemisphere. Support for this hypothesis would add further weight to the argument that the Nogo

N2 reported in this study was reflecting the same inhibitory processes associated with the Nogo N2 observed in previous studies. This hypothesis was partially supported. The results suggested that the Nogo N2 had a widespread distribution, albeit with a small frontal enhancement. That this frontal enhancement was observed is encouraging and adds support for the use of the Nogo N2 in this study as an indicator of inhibitory processing.

Many studies using this version of the CPT and other similar tasks have identified a frontally distributed N2 component that has been well established as reflecting inhibitory processing. Typically, the component is maximally distributed over frontal electrode sites (Eimer, 1993; Jodo & Kayama, 1992) and is larger over the right hemisphere (Bokura, et al., 2001; Pliszka, et al., 2000).

An explanation for the failure to identify a more significant frontal distribution, as reported in previous research, may be that in addition to inhibitory processing, the Nogo N2 was reflecting other cognitive processes. Recent studies have identified the existence of a parietal N2 component and several theories regarding the functional significance of this component can be found. In 1994, Luck and Hillyard described an attentional related, parietally distributed N2 component, which they labelled the N2pc. The researchers added the *pc* to reflect the maximally *posterior* distribution of the component in the hemisphere *contralateral* to the visual field in which the stimulus was presented. This study used a fixation rectangle to direct attention such that stimuli were intended to be presented centred within each participant's visual field. A result of presenting stimuli centred within the visual field is the absence of a contralateral distribution. The failure to identify a clear frontally distributed Nogo N2

may be the result of this interfering N2pc component. The N2pc has been related to the selection and inhibition of distractor stimuli (Luck and Hillyard, 1994a, 1994b, Luck, 1995), as well as to a template matching process (Wijers, Lange, Mulder, & Mulder, 1997).

The majority of studies investigating the functional significance of the N2pc have highlighted its relationship with focusing attention during a visual search. Luck and Hillyard (1994a) argued that by suppressing competing information from distracting items, it becomes easier to identify target items in a visual search array. They claimed that a product of this filtering process is the elicitation of the N2pc. According to them, this component reflected an attentional filtering process, occurring in the occipital cortex. They suggested that due to the late timing of this component, the filtering process is presumed to be under control of higher cognitive functions. In a similar study, Luck and Hillyard (1994b) used current source density maps to identify the topographic distribution of the N2pc, and found its peak to occur over the occipital lobe. They went further to suggest that the source of this component is also located in the occipital lobe. The theory put forward by Luck and Hillyard in 1994 which aimed to explain the functional significance of the N2pc can not however be applied to the present study as no obviously distracting stimuli were used.

Wijers et al. (1997) on the other hand, provided a theory of the N2pc that may help explain the reduced significance of the frontal enhancement observed in the present study. They argued that the N2pc was reflecting an early, semi-automatic process involving a template matching process. Contrary to Luck and Hillyard (1994a),

Wijers et al. suggested that the N2pc was the product of an object identification process, not related to a filtering process. They support this argument by presenting an N2pc elicited by single attended and single unattended targets. Of the theories presented to explain the presence of a parietally distributed N2 component, that presented by Wijers et al. seems the more applicable to the present study. As no distracting items were presented and this study did not display an array of variables through which to identify the target and other stimuli, the N2 could not have been a product of the processing described by Luck and Hillyard (1994). Wijers' theory seems more plausible, as participants were required to maintain representations of each stimulus in working memory so as to compare that representation to the preceding stimulus as well as the following stimulus. It may be that participants were maintaining representations of the Nogo stimulus, as opposed to the Go stimulus, in working memory and matching each item to that representation. Thus, one explanation for the marginally significant increase in mean N2 amplitude following an increase in target density, and for the slightly (as opposed to significant) frontal enhancement may be that the Nogo N2 was being influenced by other cognitive processes, possibly a template matching process as explained by Wijers et al.

No studies have been published which examine the existence of the N2pc elicited during completion of a CPT. One possible explanation for the smaller than expected frontal Nogo N2 enhancement may be that unlike previous studies, a fixation rectangle was used to direct each participant's attention to the location of the stimulus. No reported studies used this feature and thus it may be the reason for observing the widely distributed Nogo N2. In the light of this, Luck and Hillyard's

(1994a) theory becomes somewhat more plausible. If the fixation rectangle is assumed to be a distracting stimulus, then the suppression of this visually 'distracting' information may be the reason for limiting the impact of a frontal N2. Whilst it seems unlikely that the use of a fixation rectangle has such an impact upon the ERP, given the relatively more complex cognitive processes being performed, such a possibility cannot be excluded. An interesting follow-up study that could provide data to help explain this situation would be one examining threshold effects upon elicitation of the N2pc. Such a study could examine the minimum level of distracting stimuli required to elicit the N2pc.

Instead of representing a template matching process, another explanation as to why this study identified only a small frontal Nogo N2, may be that the N2 was not wholly reflecting inhibition, but rather an aspect of inhibition. As this study involved the visual presentation of stimuli to participants, most of the studies reported herein have been of a similar nature. Interestingly, the Nogo N2 is not consistently found in auditory Go/Nogo tasks, suggesting perhaps that this component is not completely determined by inhibition. Fox et al. (2000) failed to observe a Nogo N2 enhancement when participants were required to inhibit responses to a stimulus created by conjoining features represented in Go stimuli. In their study, the letters N, J, and W, when presented in blue, were the Go stimuli, so too was the letter O presented in any colour other than blue, thus being a combination of the two Go stimulus features. Nogo stimuli included the letter O presented in blue. In that study, the researchers did not observe the typical Nogo N2 enhancement to these Nogo stimuli. They suggested that in this task, response inhibition depended upon the application of a rule, as opposed to the detection of novel stimulus features. They

claimed that response inhibition was clearly required following presentation of the blue O, and as no enhancement in the N2 was observed, suggests that the Nogo N2 is not necessarily always elicited during response inhibition. They do not, however, suggest that inhibitory processes fail to contribute to the elicitation of the N2 when it is observed.

Given that the task used in this study has been previously used to observe an enhanced frontal N2, it would have been expected that similar results would be obtained. That the N2 did not have the expected degree of frontal enhancement may be due to the frontal Nogo N2 experiencing interference from a posterior, template matching processes (as per Wijers et al.), or due to participants using independent strategies to guide their responding (as per Fox et al.).

A further explanation for the more evenly dispersed Nogo N2 distribution than was expected may be that the component is a product of stimulus probability. As Go and Nogo stimuli were never presented at equal rates, the density effects upon the N2 and P3 components could possibly be attributed to differences in the presentation rate. The enhanced amplitude of the Nogo N2 may occur simply because the Nogo stimulus occurs more often than the Go stimulus. Eimer (1993) found that at frontal electrode sites, changing the density did not have as large an effect upon the Nogo N2 as was found at other sites. He used this result to suggest two things. Firstly, he claimed it supported the case for a frontal Nogo N2 reflecting inhibition, and secondly, that the N2 enhancements associated with stimulus probability had a broader distribution than the frontally distributed, inhibition-related N2. Given that the frontal enhancement in the present study was less than expected, it seems likely

that the Nogo N2, as an index of response inhibition, was being affected by differences in stimulus probability. This explanation is highly plausible and there is at least one method that can be employed to observe the effect of different stimulus probabilities. By employing equal presentation rates for Go and Nogo stimuli, the problem of stimulus probability effects is removed. Whilst the present study had Primed Go stimuli occurring on 50% of trials in the low-density condition, the remaining 50% were composed of both Primed and Unprimed Go and Nogo stimuli, a result of which is that it is not possible to directly compare Go and Nogo stimuli at equal presentation rates. This is a suitable topic for future research.

In remaining consistent with previous research, the Nogo P3 was expected to have a central or fronto-central distribution and be greatest along the midline. This was supported by the data and adds to the argument that the Nogo P3 observed in this study reflects inhibitory processing, similar to that reported elsewhere (Pfefferbaum et al., 1985; Bokura et al., 2001; Eimer, 1993). As the Nogo P3 observed in the present study was consistent with previous studies, being greatest along the midline and at central electrode sites, it appears that the Nogo P3 may provide a good indicator of inhibitory processing that can be used to compare these capabilities between groups.

When examining the amplitudes of the Nogo N2 and Nogo P3, it was expected that they would be larger in participants who were more efficient at inhibiting their behaviour. Support for this would help substantiate the use of the Nogo N2 and Nogo P3 as providing accurate reflections of inhibitory processing. This information may then be used to compare inhibitory abilities between the three groups. This

hypothesis was partially supported by the data. For both the Nogo N2 and the Nogo P3, the amplitude of these components were larger in the Good Inhibition group compared to the Poor Inhibition group. The difference however, was not statistically significant.

The failure to identify a significantly enhanced Nogo N2 component in the Good Inhibition group can be explained by considering the argument discussed earlier, that is, that the Nogo N2 was not solely reflecting inhibition, but was possibly affected by a template matching process, or rule based responding. That the difference between the good and poor inhibition groups was in the expected direction was, however, encouraging.

From the second hypothesis, it was expected that the Go P3 would have a parietal or centro-parietal distribution. This was supported by the data and aids in validating the use of the Go P3 as an indicator of working memory. Several previous studies have identified the existence of separate Go and Nogo P3 components, each reflecting a different cognitive process. Whilst the Nogo P3 has been claimed to reflect inhibitory processing, it has also been suggested that the Go P3 reflects working memory capabilities. The exact interpretation of the Go P3 remains contentious, with convincing theories being put forward by Donchin and Coles (1988) as well as by Kok (2001). Whereas Donchin and Coles (1988) claimed the Go P3 reflected an updating of working memory, Kok claimed it reflected event categorisation. Whilst Kok (2001) did claim that event categorisation is *influenced* by working memory, he suggested however, that the Go P3 component is not. As discussed previously, Donchin and Coles' theory is currently more the widely accepted of the two. The Go

P3 obtained in the present study was equally maximal at central and parietal sites and is therefore similar to results reported by Donchin and Coles (1988). This result therefore helps to confirm that the Go P3 observed in the present study is reflecting working memory processes, similar to that reported by Donchin and Coles (1988).

Unlike the effect a change in density had upon the amplitude of the Nogo N2 and Nogo P3, it was expected that the amplitude of the Go P3 would decrease following an increase in target density. This hypothesis stemmed from Donchin and Coles' theory of the P3, that is, that the amplitude of the Go P3 is a reflection of the degree to which a person's model of the environment undergoes revision – a process dictated by working memory processing. This hypothesis was supported by the data. There was a clear decrease in amplitude of the Go P3 following an increase in the presentation rate of the Go stimuli. This conforms to previous studies, such as that by Donchin and Coles who identified the Go P3 as providing an index of working memory updating. That both the topographic distribution of the Go P3 was as expected, and that the component decreased in amplitude following an increase in target density provides much support for the use of the Go P3 recorded in this study as a reliable indicator of working memory processes.

In summary, therefore, the second aim of this study was to confirm that the Nogo N2 and Nogo P3 were reflecting response inhibition processing, whilst the Go P3 was reflecting working memory. The results obtained suggest that the Nogo N2 was at least partly reflecting inhibitory processing. This component, however, may not have been solely a product of inhibitory processing. Given that some of the hypotheses relating to this aim were not wholly supported, explanations have been provided

which discuss possible influences upon the Nogo N2. One explanation was that the N2 observed in this study was influenced by interference from an N2pc, as described by several other authors. Secondly, whilst the N2 may have been elicited by inhibitory processing, it may have been based upon rule based processes. Alternatively, the failure to identify a more significant frontally enhanced distribution of the N2 may be a product of different presentation rates of the Go and Nogo stimuli.

As with the Nogo N2, the electrophysiological data did not wholly support the hypothesis that the Nogo P3 was reflecting inhibitory processes. Whilst the distribution of the Nogo P3 was similar to that reported in previous studies examining the relationship between this component and response inhibition, the present study failed to identify any differences in amplitude associated with changes in target density. It is possible that the Nogo P3 was simply a product of differing presentation rates between Go and Nogo stimuli. Some support suggesting that the Nogo N2 and P3 were indeed reflecting inhibitory components, can be obtained by examining the data gathered from the Good and Poor Inhibition groups. The participants who were more capable of inhibiting their behaviour tended to elicit ERPs with a greater Nogo N2 and Nogo P3 amplitude, compared to people who were less efficient at inhibition. The difference in Nogo P3 peak amplitude between the two groups was greatest at central sites, which is consistent with results obtained identifying a central distribution of the Nogo P3, compared to the centro-parietal Go P3. Additionally, the differences between good and poor inhibitors appeared greatest over the right hemisphere, the hemisphere in which inhibitory processing is thought to dominate (Bokura et al., 2001).

To ensure that the enhanced Nogo P3 for good inhibitors was not a product of overall greater processing by that sample, the Go P3 amplitudes from these same groups can be compared. In these ERPs, there was no clear difference between the groups on the peak P3 amplitude, suggesting that the enhanced Nogo P3 by the good inhibitors was not simply a generic increase in amplitude, but rather, the product of increased inhibitory processing.

Whilst the pattern of the results obtained from the Inhibition group comparison does suggest that the Nogo N2 and Nogo P3 were reflecting inhibitory processes, it is important to note that the difference between the inhibition groups did not achieve statistical significance. Consequently, the second aim, which was to confirm that the Nogo N2 and Nogo P3 were reflecting inhibitory processes can not be wholly supported by these results.

An alternate view to the one suggesting that the Nogo P3 is a reflection of inhibitory processing, is one suggesting that the increase in the Nogo P3 amplitude is simply a product of differing stimulus presentation probabilities.

Thus far, the Nogo N2 has been explained as representing a possible combination of inhibitory processing, template matching processes, independent response guiding strategies, and the effect of using different presentation rates. Aside from the template matching theory, the same explanations have been given for the pattern of results found for the Nogo P3.

An additional aspect of the second aim was to confirm that the Go P3 was a product of working memory. Two expectations regarding this component were supported by the data. The Go P3 did have a more posterior distribution than the Nogo P3, and the amplitude of the component decreased following an increase in the presentation rate of Go stimuli. That these two established phenomena were observed provides support for the use of the Go P3 observed in the present study to afford a useful tool for comparing working memory processes between the symptomatic, asymptomatic and control groups.

A final part of the second aim was to identify an ERN component consistent with previously reported data. This is to ensure that a comparison between groups on the amplitude of the ERN will equate to a reliable comparison of error monitoring. Falkenstein et al. (2000) observed the ERN to have a central or fronto-central maximum, a result replicated by the present study. That the control group exhibited a reduced frontal ERN compared to other electrode sites, and compared to the other groups was surprising, and may indicate a more centralised response monitoring process. Also surprising was that the symptomatic group exhibited the largest ERN compared to the asymptomatic and control groups. Whilst this is discussed in further detail later, the ERN enhancement by the symptomatic sample may suggest a more complex neuroanatomical relationship between this component and response monitoring in ADHD populations. Aside from the neurological theories regarding this complex relationship, the increased ERN in the symptomatic sample may be the result of more stringent self-monitoring. No papers have been published examining this relationship and it is an exciting area of future research.

To conclude the second aim, it appears that there exists some evidence supporting the use of the Nogo N2 as an indicator of response inhibition, whilst less evidence exists supporting the use of the Nogo P3 as an indicator of inhibitory processes. The Go P3 component appears to provide a reliable index of working memory processes. Lastly, the ERN does appear to provide a reliable indicator of error-monitoring.

The third aim of this study was to identify neural sources responsible for generating the Nogo N2, Nogo P3 and Go P3. This aim was included to add further support for the argument that these electrophysiological components were reflecting the cognitive processes expected. As the present study sought to identify a Nogo N2 reflecting inhibitory processing, hypothesis 3 stated that using BESA, the Nogo N2 component would be localised to frontal brain regions approximating the orbito-prefrontal cortex. The results partially supported this hypothesis.

Several studies have established a relationship between frontal brain regions and inhibition. Cummings (1995) reported that disorders in the orbitofrontal cortex were associated with inhibitory deficits in patients. Bokura et al. (2001) used electromagnetic tomography to locate the source of the Nogo N2 to the right orbitofrontal cortex and also the cingulate cortex. Strik et al. (1998) using a similar three-dimensional tomography of ERPs found there to be greater right frontal lobe activity following Nogo stimuli than following Go stimuli. The results obtained in the present study are similar to previous studies, in that the source of the components could be approximated to the expected regions, given the possible error in BESA.

Whilst data produced by the BESA software located the source of the Nogo N2 as existing outside the brain, the software attributed a standard brain, scalp and skull size for all participants. As mentioned previously, in some cases, the variance of the BESA solution may be up to 2 cm misplaced. The nearest brain regions to where the Nogo N2 source was identified were the lateral and inferior regions of the temporal pole, which approximated Brodmann cytoarchitectural areas 11 and possibly 20 and 38. The source of this component also approximates extreme lateral aspects of the orbitofrontal cortex, which is what was expected. Whilst it was expected that the source of the Nogo N2 would be the right orbito-prefrontal cortex, this study found the source to be more lateral and slightly more medial and inferior than expected. Given the limitations of the software, however, it is still possible to suggest that the right orbito-prefrontal cortex was indeed the source of the Nogo N2 component.
As explained, this study sought to localise the source of the Nogo N2 reflecting response inhibition processing. The source of this component as identified by the BESA is consistent with previous hypotheses regarding the localisation of inhibitory processes. This result, however, must be interpreted with some degree of caution, given the inability of the BESA software to map neural sources to precise neuroanatomical landmarks using such a relatively small number of electrode sites.

Based upon the slightly enhanced frontal distribution of the Nogo N2 and on the slight increase in amplitude observed following an increase in target density, it was suggested that the Nogo N2 recorded in the present study was at least reflecting some aspect of response inhibition. That the Nogo N2 component was localised in the expected area, however, provides further support for the expectation that the Nogo N2 was reflecting response inhibition processing.

A second aspect of the third hypothesis was that the source of the Go P3 component would similarly be localised somewhere within the frontal cortex. The data did not support this hypothesis. Whilst there is much variation in the reported literature regarding the localisation of working memory, many studies report a significant frontal cortex involvement. Goldman-Rakic (1995) used support from both human and primate studies to suggest that activities requiring central executive involvement would result in broad activation of prefrontal areas. Similarly, Dubois et al. (1995) demonstrated that working memory processes were associated with enhanced activation of the prefrontal cortex. Van Der Linden et al. (1999) suggested that a common theme that emerges when examining the source of working memory is the activation of the dorsolateral-prefrontal cortex.

The results obtained in the present study were not consistent with these previous studies. They were however similar to those obtained by Bokura et al. (2001) who identified the source of the Go P3 as being the medial part of the parietal cortex. The source of the Go P3 in the present study does approximate medial aspects of both the parietal and frontal cortices. Functionally significant areas close to where the Go P3 source was located include frontal aspects of the hippocampus, the amygdala, and inferior aspects of the cingulate cortex. It may be possible that the source of this component was the hippocampus, a structure having established relationships with memory. The hippocampus has been associated with long-term memory, whereby information consolidated here is passed back to Brodmann area 28 for long-term storage. The hippocampus also plays a role in long-term potentiation, an associative phenomenon whereby specific stimuli become associated with specific neural responses. Such a process could be occurring in the present study, as participants

were required to form associations between the Go signal and the Go response. Thus, whilst the localisation of the Go P3 was not consistent with working memory theories, the results are similar to at least one previous study. Given the possible variance of the BESA, the Go P3 may be localised to the hippocampus, a structure involved in the creation of memories. The hippocampus, however, has not been demonstrated as playing an active role in working memory. Further study in this field could examine the relationship between long-term potentiation and completion of the CPT. Such a study would be considerably improved through the use of additional neuroimaging tools such as fMRI, which allow for the identification of activity in specific brain structures. Additionally, through the use of sophisticated electrode caps, recording from an increased number of electrodes, source localisation becomes more accurate.

To summarise the third aim, it appears that the source of the Nogo N2 can be approximated to inhibitory centres within the frontal cortex, possibly the right orbitofrontal cortex. This result, alongside the other results associated with the Nogo N2 further supports the idea that the Nogo N2 was reflecting inhibition. Whilst the source of Go P3 was not located in expected regions, an explanation for this was provided, in that the Go P3 may have originated, or at least be influenced by, activity occurring in the hippocampus.

The fourth aim of this study was to identify whether response inhibition, working memory or response monitoring deficits contribute to the pattern of hyperactive/impulsive and inattentive behaviour exhibited by persons with ADHD. Several hypotheses were constructed in order to establish whether a dysfunction in

one or more processes contributes to the problematic behaviour. For the present study, some evidence was obtained supporting the use of the Nogo N2 and Nogo P3 to reflect response inhibitory processes. No evidence, however, was obtained which suggested that inhibitory processing was impaired in people reporting ADHD symptomatology, nor in medicated ADHD adults.

Hypothesis four stated that if inhibitory deficits contributed to the ADHD type behaviour, then the symptomatic group would exhibit more false alarms, a decreased Nogo N2 and a decreased Nogo P3 compared to the asymptomatic and control groups. Many researchers have explained ADHD in terms of deficits in response inhibition. Barkley (1995) presented a hybrid theory of ADHD whereby the primary deficit in inhibition had both a direct and indirect effect upon behaviour. The existence of inhibitory deficits in patients with ADHD has also been supported by other researchers. Schachar et al. (1995), found that children with pervasive ADHD took longer to stop the response behaviour when presented with a stop-signal compared to a control sample. Walker et al. (2000) used a CPT and found that adults with ADHD scored more false alarms than the control group. ERP studies have also been used as supporting evidence for this hypothesis. Pliszka et al. (2000) found that compared to a control group, children with ADHD produced a significantly smaller Nogo N2 over the right inferior frontal cortex. Thus, if inhibitory deficits were a contributing factor to the symptomatology, this would support the hypothesis which stated that the symptomatic group would exhibit more false alarms on the CPT than either the asymptomatic or control groups. This hypothesis was partially supported by the data, in that whilst the symptomatic group scored the greatest number of false

alarm errors for both density conditions, the differences between their scores and the other groups were not statistically significant.

The failure to identify a significant difference between groups on the amplitude of the Nogo N2 may also be the result of interfering cognitive processes recorded in the waveform. A consequence of this is that it becomes impossible to determine whether or not inhibitory capabilities differed between the three groups on the basis of the Nogo N2. Much of the data, however, identify the Nogo N2 as providing at least a partial indicator of response inhibition. It is also necessary to note that the non-significant difference may be due to differences in the quantity of stimulant medication consumed between the groups as stimulants normalise behaviour (Kolko, Bukstein & Baron, 1999) and modify electrophysiological activity (De Bruijn, Hultijn, Verkes, Tuigt, & Sabbe, 2002).

The Nogo P3, however, did not seem to be as reliable a predictor of response inhibition as was the Nogo N2. Whilst the Nogo P3 did have the expected topography, it was not larger in the high-density condition, nor was it larger in the Good Inhibition group. The failure to support these points suggests that a comparison based upon the amplitude of the Nogo P3 could not be used to compare inhibitory capabilities between the three groups.

The failure to identify group differences on the number of false alarm errors recorded, in addition to the similarity between groups on the amplitude and distribution of the Nogo N2 suggests that inhibitory deficits do not contribute to the pattern of behaviour observed in adults with ADHD. This however must be

interpreted with some degree of caution, given that several factors identifying the Nogo N2 as an indicator of response inhibition were not at the level of statistical significance that was predicted based upon previous research. Additionally, it may be speculated that the failure to identify clear group differences on the amplitude of the Nogo N2 and Nogo P3 is due to the relatively small sample sizes utilised in the present study. A study of a similar nature to that presented here is strongly encouraged. A future study would benefit from additional participants in each of the three groups examined.

The fifth aim sought to identify whether or not working memory deficits contributed to the pattern of hyperactive/impulsive and inattentive behaviour. The existence of working memory deficits in people with ADHD has been previously identified. Karatekin and Asarnow (1998) found that children with ADHD performed significantly worse than a control sample on both verbal and spatial working memory tests. ADHD groups have also been identified as having a reduced P3 component. Overtoom et al. (1998) found that ADHD children elicited a parietal distributed Go P3 component that was significantly smaller than the control Go P3. A similar result was obtained by Strandburg et al. (1996) who found the target P3 in the ADHD group was significantly smaller than the control group on both simple and dual versions of the CPT.

The Go stimuli used in the present study did elicit a P3 component that had a similar distribution to that reported previously (Klorman, 1991; Bokura et al., 2001). It also followed an established trend whereby the amplitude of the Go P3 decreases following an increase in the presentation rate of Go stimuli. That no group

differences were observed for the amplitude of the Go P3 suggests that working memory was not impaired in the sample of symptomatic and asymptomatic adults, compared to the control group. Alternatively, it may be speculated that working memory deficits do exist, however, the relatively small sample size utilised in the present study was unable to sufficiently differentiate between the three groups.

The final aim of this study was to examine the ability of persons with ADHD or ADHD symptoms to monitor their responses following errors in inhibition. Hypothesis 6 stated that the symptomatic groups would elicit an ERN with a smaller amplitude than that elicited by both the asymptomatic and control groups. This hypothesis was not supported by the data. Contrary to expectations, the symptomatic group elicited the largest ERN of the three groups, whilst the asymptomatic and control groups elicited ERNs which were approximately equal. Unlike the other ERP components, the ERN is response-locked and the robustness of the component depends on the number of errors committed. Given the relatively low error rate and the small number of participants in the present study, the ERN waveforms must be interpreted with caution

Whilst the result was unexpected, similar results have been reported previously. Burgio-Murphy (2002) reported that children with ADHD had larger ERN amplitudes on error trials than children without ADHD. They suggest that children with the disorder may have been more vigilant at self-monitoring, possibly in order to achieve an average performance, than the non-ADHD sample. That the symptomatic sample in the present study recorded the largest ERN study conforms to the results reported by Burgio-Murphy (2002). This would not however account for

the difference between the symptomatic and asymptomatic samples. The failure to record a significant difference may be due to the small number of trials accepted for the analysis. As few errors were recorded, there were few trials that could be used. Additionally, this number was reduced when removing trials with significant artefact interference.

The finding in the present study, that the symptomatic sample recorded the largest ERN, deserves further study due to the relationship between the ERN, dopamine and the neurochemistry in ADHD. Error processing is thought to be a cognitive process operating under the influence of the neurotransmitter, dopamine. As dopamine is thought to be reduced in ADHD patients, it seems likely that this deficiency would impact upon the amplitude of the ERN. Unexpectedly, the symptomatic sample recorded the greatest ERN, suggesting a more complex relationship between the ERN and dopamine.

Dexamphetamines have been shown to increase the amplitude of the ERN (De Bruijn et al., 2002). Additionally, children with ADHD have been found to elicit greater ERNs than non-ADHD children (Burgio-Murphy, 2002). From these results, it would appear that administering dexamphetamines to people with ADHD would further accentuate their enhanced ERN component. Further research is encouraged to identify the relationship between the ERN, ADHD and stimulant drugs.

The small sample sizes were a limiting factor in interpreting the results obtained in this study. Given that this study was the first to explore cognitive and electrophysiological data obtained from a symptomatic and asymptomatic sample of

adults with ADHD, the results are best considered as exploratory, rather than confirmatory. Whilst the results obtained identified interesting group differences, particularly regarding the ERN, it is difficult to convincingly attribute this to the symptomatology status of the participants, given the small number of participants in each group. That this study involved so few participants limits the interpretability of the results and must be addressed when attempting to reproduce this study, or to extrapolate meanings from the results obtained herein.

Conclusion

This study had several aims, designed to identify ERP components associated with response inhibition, working memory and error monitoring and whether dysfunctions in these areas contributed to the pattern of hyperactive/impulsive and inattentive behaviour observed in adults with Attention Deficit Hyperactivity Disorder (ADHD). To examine these cognitive processes, a Continuous Performance Task (CPT) was completed whilst brain electrical activity was recorded using an electroencephalograph. Event-Related Potentials (ERPs) were constructed to observe response inhibition (Nogo N2 and Nogo P3), working memory (Go P3) and error-response monitoring (the ERN). Using a Brain Electrical Source Analysis (BESA) the Nogo N2 was localised to expected frontal and right hemisphere brain regions and whilst it was not as evident as has been previously identified, the Nogo N2 did have a small frontal enhancement. It was suggested that whilst being influenced by response inhibition, other cognitive factors may have affected the amplitude of the Nogo N2. The Nogo P3 did have the expected central distribution, but was not greater in the high-density condition nor in the Good Inhibition group, suggesting that it too was not wholly a product of inhibition, and was possibly affected by the differing presentation rates. The Go P3 had the expected centro-parietal distribution and was localised to a similar region to that which has been reported previously. As expected, the Go P3 was greater in the low-density condition compared to the high-density condition, supporting the use of this component as an indicator of working memory processes. The ERN did have the expected central maximum and was found to be significantly smaller at frontal electrode sites for the control group.

There was no evidence to suggest that working memory impairments or response inhibition impairments were contributing to the ADHD type behaviour reported by the symptomatic group. Interestingly, whilst not statistically significant, the symptomatic group, elicited the largest ERN component. An explanation for the failure to identify a statistically significant difference between the groups on the amplitude of the ERN may be that few behavioural errors were recorded and consequently, the ERNs were constructed using only a small number of trials. There are few studies that have reported on the ERN in ADHD populations and this is one area in which further research is suggested.

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