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Neuroanatomy of Executive Functions, Cognitive Control Processes and their Interactions using Functional Magnetic Resonance Imaging.

By

Catherine Fassbender

A dissertation submitted for the degree of Doctor of Philosophy of the University of Dublin, Trinity College, Dublin 2, Ireland.

This research was carried out in the Department of Psychology.

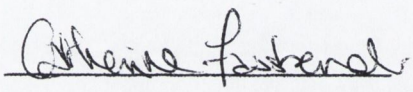
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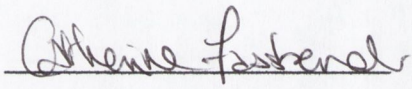


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Catherine Fassbender

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Summary

Human behaviour, though appearing seamless, is comprised of a number of differing and interacting cognitive processes. In this dissertation I attempted to establish the anatomical networks subserving a number of different executive functions, which are crucial for normal human learning and behaviour with the use of functional magnetic resonance imaging (fMRI). These functions were the maintenance of task set, sustaining attentional focus, inhibition of prepotent responses and the detection of errors or situations in which an error is likely to occur.

In the first study all of these executive functions were examined utilising a GO/NOGO paradigm and a mixed, block and event-related fMRI study, which facilitated the examination of tonic processes that were engaged throughout the task, and phasic events that were transient and active only at particular points during the paradigm. Response inhibition was seen to be subserved by bilateral prefrontal cortex (PFC) and right inferior parietal lobe (IPL). A right fronto-parietal network was believed to underlie sustained attention, whereas left PFC was thought to be involved in task set maintenance. A dissociation between error detection and response conflict monitoring was found along the midline, anterior cingulate cortex (ACC) reacting to errors, whereas more dorsal areas of ACC extending into presupplementary motor area (pre-SMA) were responsible for the detection of response conflict. A reciprocal relationship was also found between pre-SMA and left PFC in cognitive control; these areas were positively correlated phasically and individuals that enforced high tonic levels of cognitive control experienced lower amounts pf response conflict during errors.

This midline-prefrontal relationship was further explored in the next experiment, this time on a within-subject, trial-for-trial basis. A cued GO/NOGO paradigm and mixed fMRI study was used. Correct responses to NOGO stimuli (inhibitions) were examined in order to rule out any confounding error-related activation. Correct inhibition trials were divided into high or low control events on the basis of levels of activation in left PFC in the preceding cue period. High levels of control resulted in

lower subsequent levels of response conflict. Again, this relationship was seen for the left PFC and pre-SMA.

The third experiment was designed in order to investigate further the left PFC's role in top-down control. Once again cues were used, this time in a flanker paradigm. Mixed block and event-related analyses were again utilized. Left PFC was again seen to be particularly important in cognitive control, being active during preparation for an up-coming target event. Cues also resulted in subsequently higher levels of activation in response-pertinent areas during correct responses to targets. Finally, cues and correct responses shared a number of anatomical regions, suggesting that cues facilitate preparation of task-relevant areas for an up-coming event.

A similar anatomical network, namely a right fronto-parietal network is often seen to be active for a seemingly diverse array of cognitive paradigms. A final experiment was designed in order to ascertain the reason for this. A GO/NOGO task and mixed fMRI design was again used, on this occasion utilising randomly presented "cues-to-action" which were not predictive of an up-coming target but were associated with an instruction to concentrate on the task at hand. A similar network of right hemisphere frontal and parietal regions was active during both cues and the inhibitions themselves. This was interpreted as evidence to suggest that similar top-down control processes were involved during cues and inhibitions.

Thus from this thesis we can conclude that bilateral PFC may be involved in top-down control or allocation of attentional resources. A dissociation along the midline was noted for error detection, which is believed to be subserved by ACC, and response conflict monitoring, which is though to be the domain of the pre-SMA. Sustained attention and response inhibition both appear to involve largely right-hemisphere fronto-parietal networks, however, this may very possibly due to an underlying processing characteristic such as top-down attentional control.

Publications Resulting from the Present Work:

Articles:

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Fassbender, C and Garavan, H. A Review of Midline Activations Associated with Error Processing and Conflict Monitoring. NeuroImage, (HBM2003).

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Abbreviations used

ACC: anterior cingulate cortex

ADHD: attention deficit hyperactivity disorder

AFNI: Analysis of Functional Neuroimages

BOLD: blood oxygen level dependent

CPT: Continuous Performance Task

DLPFC: dorsolateral prefrontal cortex

EEG: electroencephalogram

ERN: error related negativity

HRF: haemodynamic response function

IFG: inferior frontal gyrus

IPL: inferior parietal lobe

IRF: impulse response function

fMRI: functional magnetic resonance imaging

LCD: liquid crystal display

LRP: lateralized readiness potential.

MFG: middle frontal gyrus

MPRAGE: magnetization prepared rapid gradient echo

N2: negativity associated with response inhibition

Ne: error negativity

OCD: obsessive compulsive disorder

Pe: error positivity

PET: positron emission tomography

PFC: prefrontal cortex

pre-SMA: pre supplementary motor area

ROI: region of interest

RT: reaction time

SART: Sustained Attention to Response Test

SEF: supplementary eye field

SFG: superior frontal gyrus

SMA: supplementary motor area

SPL: superior parietal lobe

STM: short-term memory

TBI: traumatic brain injury

TMS: transcranial magnetic stimulation

TOL: Tower of London

WCST: Wisconsin Card Sort Task

WM: working memory

%AUC: percentage area under the curve

%CS: percentage change score

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Chapter 1

General Introduction.

Humans are remarkable in their ability to ponder, plan and execute behaviour. We are able to reason and to adapt ourselves to novel and sometimes-difficult circumstances. This unique ability is thought to be largely due to our frontal lobes. The use of tools and rudimentary problem solving abilities are seen in our nearest relatives, the apes who also have relatively enlarged frontal lobes in comparison to the rest of the animal kingdom. Studies of patients with lesions and imaging studies have also implicated the prefrontal cortex (PFC) in "higher thought" or executive functioning. PFC has also been shown to be anatomically and reciprocally connected to practically all sensory and motor systems as well as a wide variety of subcortical structures (Miller, 2000), which makes it an ideal site for learning and adaptation of behaviour and goals as well as being able to exert a top-down influence on other brain structures in the facilitation of appropriate behaviours and allocation of attentional resources.

Although behaviour is facilitated by a number of different executive functions it appears smooth and relatively effortless. In fact it is only when a part of this system breaks down due to brain damage or psychological illness or distress that the importance of each individual process is seen. These functions include the ability to maintain attention on the entire task, to select between different response alternatives or indeed which aspect of the task to pay attention to, inhibition of distracting or irrelevant aspects of the task or items in the environment or indeed in the individual's mind, the ability to detect errors and subsequently correct them and adjust behaviour in order to minimize the possibility of making further errors. All these functions take place within the mental framework where past experience and current as well as future goals are kept on-line and influence behaviour. Additionally, minute-to-minute evaluations and strategic changes are also made. It is the goal of cognitive neuroscience to glean information about the nature of these functions, about their anatomical substrates and their interaction with each other. With this information it may be possible to alleviate the problems associated with clinical disorders and brain trauma.

In this chapter the literature on a number of these executive functions and their interactions will be examined. As mentioned, the ability to inhibit inappropriate mental states, distracting items in the environment and inappropriate motor responses are essential to behaviour. Inhibition will be examined with particular focus on the inhibition of prepotent motor responses. Efficient behaviour depends on the ability to firstly detect errors and subsequently adjust performance. Included within this framework is the notion that it may be important to monitor for situations where an error may be likely to occur and subsequently increase attentional control in order to

minimise the likelihood of an error occurring. To this end, error detection and conflict monitoring processes are examined. All these processes are reliant on the ability to pay attention, maintain task goals and rules and engage extra attentional processes when they are required. Top-down control, sustained attention and the interaction between error/conflict-monitoring processes and top-down control in the control of behaviour are all reviewed. Finally, a popular imaging method in the examination of these processes, functional magnetic resonance imaging (fMRI) is briefly detailed.

1.1 Inhibition

Inhibition is a complex concept, which is used as an umbrella term for a number of cognitive and behavioural processes that may in fact be functionally and anatomically distinct. Many higher-level cognitive processes and executive processes require or involve some aspect of inhibition, for example sustained and selective attention and working memory. It can be thought of as the suppression of an action, response, stimulus, thought, memory or learned way of performing a task. These competing thoughts or actions may often be inappropriate to a task and hence detrimental to performance and so they need to be suppressed in order to concentrate on the task at hand. The ability to inhibit facilitates control over and regulates our behaviour and impulses. This ability is thought to develop throughout childhood and declines again in late adulthood. This inhibitory decline with old age (Hasher, Stoltzfus, Zacks, & Rypma, 1991; Nielson, Langenecker, & Garavan, 2002) has been associated with a number of age-related cognitive deficits including poor memory. Problems with inhibition have also been implicated in clinical syndromes such as Tourette's syndrome (Peterson, Skudlarski, Anderson, Zhang, Gatenby, Lacadie, Leckman, and

Gore, 1998), Obsessive-Compulsive Disorder (OCD) (Enright & Beech, 1993) and Attention Deficit Hyperactivity Disorder (ADHD) (Barkley, 1997; Cairney, Maruff, Vance, Barnett, Luk, and Currie, 2001; Casey, Castellanos, Giedd, Marsh, Hamburger, Schubert, Vauss, Vaituzis, Dickstein, Sarfatti, and Rapoport, 1997). Due to its involvement in such a variety of complex cognitive functions and because of its importance in fostering a greater understanding of certain clinical syndromes, it is essential to garner a more comprehensive understanding of this complex construct.

A number of authors support the notion that the PFC controls behaviour by focusing activity in certain neural pathways to the detriment of other competing pathways (Miller & Cohen, 2001). This ensures that under certain circumstances particular responses will be favoured whereas other conflicting and presumably redundant response options will be dampened and less likely to be enforced. This is akin to the notion of Norman and Shallice's (Norman & Shallice, 1986) supervisory attention system. The PFC is like the contention scheduler which controls which schema will be active at a particular point in time. This concept will be discussed further later in the chapter. This view of the selection of certain behaviours while simultaneously suppressing others does not necessarily require the concept of a separate construct "inhibition". There may be no need for a dynamic inhibitory mechanism, which actively suppresses activation in conflicting response pathways or cognitive sets. However, evidence for distinct inhibitory processes (that is schema or response suppression) have been provided for memory retrieval (Anderson & Green, 2001) and task sets (Mayr & Kliegl, 2003). Furthermore, factor analytic studies in both normal (Chan, 2001; Miyake, Friedman, Emerson, Witzki, Howerter, and Wager, 2000) and clinical populations (Burgess, Alderman, Evans, Emslie, & Wilson, 1998) have

identified inhibition as a dominant component of executive functions. Inhibition as measured by its factor score was also correlated with performance on a number of tasks that are commonly used to measure executive functioning (e.g. the Tower of Hanoi and Wisconsin Card Sorting Task (WCST)) (Burgess et al., 1998; Chan, 2001; Miyake et al., 2000). Problems with inhibitory control have also been linked to a number of clinical syndromes such as ADHD (Barkley, 1997; Cairney et al., 2001; Casey et al., 1997), Tourettes Syndrome (Peterson et al., 1998), OCD (Enright & Beech, 1993) and has also been shown to follow a different developmental trajectory than selective attention (Booth, Burman, Meyer, Lei, Trommer, Davenport, Li, Parrish, Gitelman, and Mesulam, 2003). Therefore, it does seem that there is a distinct inhibitory mechanism in the brain, which actively suppresses inappropriate responses or cognitive states in the facilitation of behaviour.

1.1.1 Cognitive Inhibition

At this point it may be helpful to briefly mention different types of inhibition that may fall under this "umbrella term" and to point out that there is some degree of disagreement as to the nature of different types of inhibition. As mentioned at the beginning of this section, inhibition of inappropriate thought and cognitive sets is also important in efficient behaviour. This is very clear when the breakdown of these processes is seen in certain clinical syndromes such as schizophrenia (Curtis, Calkins, & Iacono, 2001) and OCD (Enright & Beech, 1993) and inappropriate mental states are no longer being inhibited severely hindering the individual's capacity to interact in society. However, the examination of these processes is a little more difficult than the study of response inhibition. There is some disagreement as to the nature of this type of inhibition. It may be (Rieger & Gauggel, 2002) that many studies that claim to

have found difficulties with inhibition have utilized tasks, which involved *interference* rather than inhibition *per se*. It has been argued that these two constructs may be somewhat different (Langenecker, Nielson, & Rao, 2004) in that interference deals with performance decrements under conditions of *distracting stimuli,* not necessarily involving the actual suppression of cognitive processes or contents (Rieger & Gauggel, 2002). To what extent, if any, performance in the face of distracting stimuli relies on the ability to inhibit is unclear. Langenecker and colleagues suggest that interference is a "measurable effect of cognitive load, while inhibition is a neural process of attentional selection that can serve to reduce interference" (Langenecker et al., 2004, pg 192).

Tasks such as the Stroop Task and WCST are considered to involve some degree of inhibition (Barkley, 1997; Burgess et al., 1998; Leung, Skudlarski, Gatenby, Peterson, & Gore, 2000; Miller & Cohen, 2001) although they have also been associated with interference (Langenecker et al., 2004). The Stroop Task is a popular paradigm that is used to measure a number of different executive functions. In this task colour words are presented in different coloured ink. Sometimes the ink colour corresponds to the colour name (e.g. the word RED written in red ink). This is known as the congruent condition. In the incongruent condition, the colour of the ink does not match the colour word (e.g. the word RED written in blue ink). The participant is asked to name the colour of the ink. This is particularly difficult, as the naming of the word has been shown to be the more automatic or dominant response (Lindsay & Jacoby, 1994). The WCST requires participants to sort a number of cards with different shapes, colours and numbers. The experimenter chooses the rule according to which the participant is required to sort the cards (e.g. sort by shape) and the participant must guess this rule

by trial and error. However, from time to time the experimenter will change the rule, unbeknownst to the participant, which requires the subject to inhibit the previously appropriate response set and search for a new one. This ability has been shown to be particularly compromised in frontal brain injury (Demakis, 2003; Goldstein, Obrzut, John, Ledakis, and Armstrong, 2004; Stuss, Levine, Alexander, Hong, Palumbo, Hamer, Murphy, and Izukawa, 2000).

1.1.2 Response Inhibition

Response inhibition is perhaps the most accessible form of inhibition in terms of the relative ease with which one can examine it in an experimental paradigm. The analogy of driving a car is often used in order to illustrate the concept of response inhibition. If we imagine ourselves driving in a car along a straight road and suddenly have to avoid something, we can picture ourselves slamming hard on the brakes. This is exactly what inhibitory processes are postulated to do in the brain. They are proposed to "slam on the brakes" and withhold an inappropriate motor response from being carried out.

The car-driving analogy is again useful as it is also used as an example of automatic or over-learned behaviour. Automaticity is a useful process because it means that cognitive resources are not engaged in unnecessary pursuits and are available for other thoughts and behaviour (Miller & Cohen, 2001) as will be described in more detail later in this chapter. When behaviour becomes automatic, it is less under conscious control. For example, while driving a car people often report getting to their destination without remembering any of their journey on the way. However, under situations such as this, inhibitory control is very important. When responding

becomes automatic a prepotency or tendency to carry out the response is built up. In situations where it is no longer appropriate to respond extra energy is needed in order to withhold that response and "slam on the brakes".

1.1.3 Anatomy of Response Inhibition

As mentioned, motor response inhibition is often examined in an experimental setting as it is arguably the clearest, most accessible and least controversial form of inhibition. As Rubia et al (Rubia, Russell, Overmeyer, Brammer, Bullmore, Sharma, Simmons, Williams, Giampietro, Andrew, and Taylor, 2001) point out it involves "all-or-none decisions about action or non-action" (page 251). Various brain-imaging techniques such as EEG and PET have previously been employed in an attempt to isolate the anatomical regions involved in response inhibition. In recent years, however, a new imaging technique, fMRI, has revolutionised the process of examining brain structures in the behaving human and animal brain. fMRI has excellent spatial resolution and deep brain as well as surface structures can be studied using this technique, which will be discussed in more detail later in the chapter. For this reason, a number of fMRI investigations of response inhibition have been conducted in recent years.

The GO/NOGO paradigm is often used in imaging studies to investigate the processes involved in response inhibition. This task requires the subject to suppress a prepotent response. In such an experiment participants are required to respond to a certain stimulus or set of stimuli (the GO stimulus) and withhold responding to another stimulus, or same stimulus under certain conditions (the NOGO stimulus). As automatic responding is more difficult to inhibit, the ratio of GO to NOGO stimuli is

manipulated in order to encourage participants to establish a pattern of responding. De Zubicaray et al (de Zubicaray, Andrew, Zelaya, Williams, & Dumanoir, 2000) demonstrate this effect in their GO/NOGO study in which numbers of NOGO responses were manipulated in three differing blocks in order to determine the cerebral activation connected with response suppression "load". The authors used a simple design consisting of two stimuli, one representing the GO response and the other the NOGO response. By intermittently presenting GO only blocks the authors both further built up a prepotency to respond and provided a baseline condition against which NOGO blocks were compared. The behavioural data displayed a trend in the direction of a decrease in errors with an increase in NOGO events, supporting the notion that an increase in the ratio of suppressions to responses decreases the prepotency to respond and makes inhibiting less difficult. There was also a tendency for response latencies to increase with an increase in NOGO events. It may be that as NOGO events increase or eventually reach 50/50, the task becomes more akin to a selective attention task where the subject must select between the equiprobable events of a response or a non-response. The number of errors to NOGO trials has also previously been shown to significantly increase with the number of preceding GO trials (Durston, Thomas, Worden, Yang, & Casey, 2002). Thus, we can conclude that an increase in the ratio of GO to NOGO events makes inhibition more difficult.

De Zubicaray and colleagues (de Zubicaray et al., 2000) found that differing regions were activated as a function of "load". An increase in activation was noted in right middle frontal gyrus extending over the mid-dorsolateral prefrontal cortex and in the frontal pole with an increase in NOGO events. Smaller activation foci were noted in left medial and superior frontal gyri and in the right orbital prefrontal cortex. Other

areas included the left pre-supplementary motor area (SMA) and left anterior cingulate cortex (ACC). Rubia et al (Rubia et al., 2001) also found a bilateral but predominantly left hemisphere pattern of activation associated with response inhibition in the GO/NOGO paradigm. Activation was observed in inferior frontal gyri, left and right mesial frontal cortex, including ACC and pre-SMA, left inferior parietal lobule, left precuneus and bilateral extrastriate cortex.

From these studies one might conclude that inhibition may involve both hemispheres. However both the De Zubicaray et al (de Zubicaray et al., 2000) and Rubia et al's (Rubia et al., 2001) studies utilised a block fMRI design. Block fMRI designs may include activations associated with error processing or tonic processes such as the maintenance of task set (D'Esposito, Postle, Jonides, & Smith, 1999). The inclusion of error-related processes in activation maps has been found to considerably compromise them (Murphy & Garavan, 2004). Event-related designs, on the other hand, enable one to examine the temporal dynamics of inhibition while ruling out confounds such as activation due to mental "set" for example (D'Esposito et al., 1999). This will be discussed in more detail later in the chapter.

A number of common areas have been implicated in the suppression of a motor response. Animal literature has implicated ventral frontal regions in inhibition. Iverson and Mishkin (Iversen & Mishkin, 1970) found that monkeys with lesions to the inferior convexity had difficulties withholding responses in auditory and visual inhibitory tasks. Animals with damage to this area also displayed perseverative behaviour. Ventral PFC has also been implicated in a number of inhibitory studies in humans (Casey et al 1997; Durston et al 2002; Garavan, Ross, and Stein, 1999;

Konishi et al, 1999; Liddle, Kiehl, and Smith, 2001). Casey et al (Casey et al., 1997) also found that volume of activity in this area correlated with correct performance in their GO/NOGO paradigm. When comparing studies of inhibition in humans and animals, the picture appears to be more complex in humans, possibly due to additional cognitive processes involved. Many other regions have been seen in addition to ventral PFC including dorsolateral, mesial, orbital and inferior frontal, temporal and parietal cortices as well as cerebellum, basal ganglia and regions of the ACC (Casey et al., 1997; Durston et al., 2002; Garavan et al., 1999; Kawashima, Satoh, Itoh, Ono, Furomoto, Goto, Koyama, Yoshioka, Takahashi, Takahashi, Yanagisawa & Fukuda, 1996; Konishi et al., 1999; Konishi, Nakajima, Uchida, Sekihara, & Miyashita, 1998; Liddle et al., 2001; Menon, Adleman, White, Glover, & Reiss, 2001). Activation in overlapping areas has been noted for inhibitions irrespective of whether the stimuli are presented aurally or visually (Klingberg & Roland, 1997). These areas were largely in right hemisphere and included superior and inferior frontal gyrus and frontal operculum (Klingberg & Roland, 1997).

The STOP paradigm requires participants to inhibit an already-triggered motor response. Participants are usually required to respond to a stimulus unless a stop signal immediately follows that stimulus, in which case they need to withhold their response. The difficulty of this task can also be tailored to each individual's response inhibition threshold (Logan & Cowan, 1984). Logan and Cowan (Logan & Cowan, 1984) propose that in the STOP paradigm, there is a race between the GO response and the STOP response. Each individual has a time threshold beyond which it is impossible to withhold responding because the GO response has already proceeded too far and will be carried out to its conclusion.

STOP paradigms have found activation in similar regions of prefrontal and parietal cortex as GO/NOGO studies (Rubia et al, 2000, 2001). Rubia and colleagues (2001) compared the GO/NOGO and STOP paradigms directly in one study and found similar prefrontal and parietal regions to be active during both tasks. However, the STOP task activated a more right lateralized network of regions. Rubia and co-workers (2001) argue that the GO/NOGO paradigm activates a larger network of regions due to additional processes that may be involved such as working memory (WM) processes. A good example of this is the Garavan et al study of response inhibition using a GO/NOGO task (1999). Here participants' responses were contingent upon remembering stimuli relatively far back in the stimulus train. This calls on WM processes and this may contaminate activation maps. Rubia and colleagues (Rubia, Smith, Brammer, & Taylor, 2003) suggest that inhibitory tasks such as this that purport to measure response inhibition are confounded by the fact that they also include other processes such as decision making, response competition/response selection, conflict monitoring, oddball effects and increased attentional demands. They suggest that the STOP paradigm is the best way to examine inhibitory processes, as it requires subjects to withhold a response that has already been triggered (Rubia et al, 2001, 2003). Because the STOP task allows the experimenter to tailor the task to each subject it ensures that everyone experiences equal task difficulty irrespective of individual differences in performance of the task. It also allows subjects' error rates to be controlled at around 50%. However, similar tailoring of performance has been utilised in both humans in a GO/NOGO task (Garavan, Ross, Murphy, Roche, & Stein, 2002) and in a saccade-countermanding task in animals (Ito, Stuphorn, Brown, & Schall, 2003).

Rubia et al (Rubia et al., 2003) argue that a comparison of the successful and unsuccessful STOPS in this paradigm controls for some of the confounding additional processes mentioned above, for example, it controls for the oddball effect, response selection and difficulty. However, other systems are also included by this comparison, for example error-related and motor processes; unsuccessful STOPS include motor and error-related processes that are not involved in the STOP itself. Thus the authors (Rubia et al., 2003) also compared the unsuccessful STOPS with baseline GO trials in order to control for motor confounds. Activation was noted in right inferior PFC when STOPS were compared with unsuccessful STOPS. When compared with baseline GO trials STOP activation was noted in medial frontopolar cortex, rostral ACC and bilateral posterior parietal cortex. At first flush, it may appear that only the right inferior PFC is the area that is responsible for inhibitions as this was the region that was active when comparing successful and unsuccessful STOPS. However, it has recently been shown that inhibitory areas may also be active during unsuccessful attempts to inhibit (Garavan et al., 2002). Inspection of the ERP waveforms associated with correct inhibitions and errors of commission revealed that the waveforms were identical but phase-shifted by 75msec. That is, the latency differed; when a response was successfully inhibited the process was activated a full 75msec faster than when the response was not inhibited. This suggests that when a motor response was successfully inhibited, the process was activated more quickly. Garavan and co-workers (2002) suggest that errors occur not due to a failure of relevant areas to activate, but because the inhibitory signal arrived too late. In fact, the reason that these attempts are unsuccessful may be that these areas are engaged too late in the process. This is in line with Logan's race model (Logan & Cowan, 1984). Therefore

Rubia and colleagues (2003) subtraction may not be an optimal one and may be disguising the true array of regions that are active during a successful STOP.

A recent study (Mostofsky, Schafer, Abrams, Goldberg, Flower, Boyce, Courtney,, Calhoun, Kraut, Denckla & Pekar, 2003) has supported Rubia and colleagues' (2001, 2003) argument that many studies of response inhibition include additional processes in activation maps. The authors utilised a "simple" GO/NOGO task with only two stimuli and consistent stimulus-response mapping. Also GO stimuli were green and NOGO stimuli were red, colours that are commonly associated with those particular responses. They also utilized a more complex counting version of the task, which used a semi-variable stimulus-response mapping. Here participants were required to respond to green and to red stimuli that were preceded by an even number of green stimuli. Although the authors found the usual right hemisphere regions associated with inhibitions in the more complex counting version of the task (pre-SMA, right dorsolateral prefrontal cortex (DLPFC), inferior parietal lobe (IPL) and insula) they found that these areas disappeared in the simple task. The only activation that remained was in the pre-SMA, which the authors interpreted as being a 'pure' inhibitory region after all other processes have been stripped away.

1.1.4 Anatomy of Cognitive Inhibition

Stroop tasks have been shown to activate prefrontal, parietal and anterior cingulate cortex (Bench, Frith, Grasby, Fristn, Paulesu, Frackowiak & Dolan, 1993; Carter, Mintun, & Cohen, 1995; Leung et al., 2000; Peterson et al., 1999). In their review of imaging studies of the Stroop task (Cabeza & Nyberg, 2000), Cabeza and Nyberg found activation in frontal, ACC and parietal cortex. Furthermore, they noted that in

most of the imaging studies reviewed activation in PFC was predominantly left lateralized. Stroop and Simon tasks were both seen to activate bilateral prefrontal and parietal cortex as well as ACC and SMA (Peterson et al., 2002). Jonides and colleagues (Jonides, Smith, Marshuetz, Koeppe, & Reuter-Lorenz, 1998) found activity in left PFC under conditions of high levels of interference in a verbal WM recognition task.

In summary, prefrontal and parietal regions are consistently active across a number of tasks designed to measure response inhibition (Aron, Fletcher, Bullmore, Sahakian, & Robbins, 2003; Braver, Barch, Gray, Molfese, & Snyder, 2001; Garavan et al., 1999; Kawashima et al., 1996; Konishi et al., 1998) irrespective of the nature of the paradigm. A similar network of areas is seen to be active during cognitive inhibition although there is evidence to suggest that the right fronto-parietal network is more heavily involved in response inhibition (Aron et al., 2003; Garavan et al., 1999). However, as a number of authors have argued (Mostofsky et al., 2003; Rubia et al., 2001; Rubia et al., 2003) the picture may be a little more complicated: These areas may not be directly involved in the actual inhibition of the response itself but may reflect additional cognitive processes that are necessary to complete the task. Thus it is of interest to examine other executive processes that are involved in the completion of such cognitive paradigms. As some of these processes are tonic, that is active throughout a particular task and others are phasic, that is active only at particular points throughout a task, it may be useful to examine both tonic and phasic aspects of response inhibition tasks. Additionally, as mentioned, many tasks that examine response inhibition compare successful withholds with errors of commission or the ongoing GO response. This comparison is confounded by the additional motor

response in a commission error. Therefore it would be useful to design a better control condition that equated the stimulus and response conditions of the successful NOGO.

1.2 Performance Monitoring

An important aspect of behavioural control is the ability to detect errors or potential errors and to subsequently adjust behaviour. The brain may also be able to recognize situations in which an error may be likely to occur. A common problem in patients with frontal trauma is the inability to change behaviour or adapt to novel circumstances (Stuss et al., 2000) and this can be extremely debilitating in everyday life. Hence it is important to understand the mechanisms by which errors are detected and behaviour is accordingly adjusted.

1.2.1 Error Detection

In order to successfully complete a task it is imperative that an organism is aware of errors during and after performance. This is important for the on-line adjustment of behaviour as well as behavioural amendment after the task has finished and remembering this changed behaviour for future occurrences of similar situations. In other words, this is crucial for learning. We can once again think of the example of driving a car. If one drives their car too quickly they are in danger of injuring themselves or others. Therefore, when someone exceeds the speed limit the police will stop the behaviour and impose a fine for speeding. That person will then drive more carefully in future in order to avoid further fines. We can think of our error-detection system as akin to the police in this example. First of all there is a need to detect that an error has taken place, and second of all corrective measures need to be

carried out to ensure that this does not happen again. All of this information may also be stored for future reference.

Rabbitt (Rabbitt, 1966) noted that subsequent to an error participants' reaction times (RT) slowed significantly. Errors in tasks such as the GO/NOGO task are commonly due to rapid, impulsive responding patterns. Therefore what Rabbitt (Rabbitt, 1966) is believed to have observed is amendment of behaviour subsequent to an error. A number of authors subsequently investigated error-related processes and its connection to behavioural adjustment (Gehring, Goss, Coles, Meyer, & Donchin, 1993; Scheffers, Coles, Bernstein, Gehring, & Donchin, 1996). Early studies into error detection involved mainly EEG and noted an error-related negativity (ERN) 80 to 150 msec after a participant has made an incorrect response (Falkenstein, Hoormann, Christ, & Hohnsbein, 2000; Gehring et al., 1993). It has been suggested that the ERN results from a mismatch as a consequence of a comparison between the actual response and an internal representation of the correct response (Falkenstein, 1990; Bernstein, Scheffers, & Coles, 1995).

1.2.2 Anatomy of Error Detection

Dipole modelling has implicated a medial-frontal generator of the ERN, generally thought to be the ACC (Dehaene, Posner, & Tucker, 1994) or SMA (Vidal, Hasbroucq, Grapperon, & Bonnet, 2000). Clinical disorders involving dysfunction of ACC, such as schizophrenia, have also been associated with problems in monitoring and responding to errors (Alain, McNeely, He, Christensen, & West, 2002; Holcomb, 2004). Additionally, opiate addicts have also been found to commit more errors and display reduced activation in ACC during errors of commission (but not correct

inhibitions) in a GO/NOGO paradigm (Forman et al., 2004). A similar result has been found in cocaine addicts (Kaufman, Ross, Stein, & Garavan, 2003).

Subsequent studies have utilised fMRI in the investigation of error-related processes. ACC has again been implicated in error detection (Braver et al., 2001; Garavan et al., 2002; Kiehl, Liddle, & Hopfinger, 2000; Menon et al., 2001; Ullsperger & von Cramon, 2001). Many of these studies have implicated the rostral portion of ACC in error detection processes (Braver et al., 2001; Kiehl et al., 2000; Menon et al., 2001). A number of authors have suggested that the error-related activity witnessed in ACC may be an affective or emotional response to an error (Falkenstein et al., 2000; Leung et al., 2000; Vidal et al., 2000) because of this. It is thought that ACC is divided into two separate functional regions, the rostral emotional/ affective division and the more caudal cognitive region (Bush, Luu, & Posner, 2000). Emotional, pain and mood disorders have often been associated with more rostral and ventral areas of ACC (Bush et al., 2000; Whalen, Bush, McNally, Wilhelm, McInerney, Jenike & Rauch, 1998). Additionally, ERN is usually reduced or absent when participants are unaware that they have made an error (Dehaene et al., 1994) and is present when subjects are given negative feedback on their performance (Badgaiyan & Posner, 1998). This is supportive of the notion that ERN reflects an emotional response to an error.

1.2.3 Error Detection and Behavioural Adjustment

Some authors have suggested that the ACC's error-related signal triggers behavioural adjustment. In a task where participants were required to squeeze zero-displacement dynamometers (which measure grip pressure) as a response to stimuli, Gehring et al (1993) noted that a larger ERN was produced when response force was less and the

incorrect response was likely to be followed by a correct response. Larger ERNs have also previously been associated with subsequent corrective behaviour (Scheffers et al., 1996) although this finding has subsequently been disputed (Nieuwenhuis, Ridderinkhof, Blom, Band, and Kok, 2001; Rodriguez-Fornells, Kurzbuch, and Munte, 2002; Rollnik, Schroder, Rodriguez-Fornells, Kurzbuch, Dauper, Moller, and Munte, 2004). Pailing and colleagues (Pailing, Segalowitz, Dywan, & Davies, 2002) also found that subjects who displayed larger ERNs also showed smaller RT differences between correct and error responses, which was indicative of less impulsive responding. The authors also found that individuals who showed a faster ERN produced fewer errors, suggesting that a fast ERN was able to intervene in behaviour and correct inappropriate responses before they were made. The authors therefore suggest that this supports the notion that the ERN reflects a monitoring system which influences systems that affect corrective behaviour.

1.2.4 Conflict Monitoring

Recently some controversy has arisen as to the nature of error-related processes in the ACC. In EEG studies this arose with the discovery that the ERN is often seen in correct as well as error trials (Coles, Scheffers, & Holroyd, 2001; Vidal, Burle, Bonnet, Grapperon, & Hasbroucq, 2003; Vidal et al., 2000). In an fMRI study Carter and colleagues (Carter, Braver, Barch, Botvinick, Noll & Cohen, 1998) noted that the ACC responded not only to incorrect trials but also trials that involved increased amounts of response conflict. Carter and colleagues have suggested that it is the detection of response conflict and not error-detection *per se* that is the trigger for performance amendment (Botvinick, Nystrom, Fissell, Carter, & Cohen, 1999; Botvinick, Braver, Barch, Carter, & Cohen, 2001; Carter et al., 1998; MacDonald,

Cohen, Stenger, & Carter, 2000). Response conflict is thought to arise when two conflicting response pathways are simultaneously activated. It has been suggested that errors simply reflect larger amounts of response conflict, the incorrect response pathway having the greater activation and hence succeeding in being carried out (Braver et al., 2001).

It is worth noting, however, that there is also evidence against a simultaneous priming of the correct and incorrect response on incorrect trials (Luu, Collins, & Tucker, 2000). Luu, Flaisch and Tucker (2000) used lateralized readiness potentials (LRPs) in order to investigate the degree of response conflict on a task which required left or right handed responses and compare it with the degree of ERN on both correct and error trials. LRP is measured as a difference between EEG over the motor cortex of the hemisphere contralateral to the responding hand and the ipsilateral motor cortex. Activation over both hemispheres would suggest that there is a motor priming of an incorrect response and this can be taken as an index of response conflict. This has been demonstrated in a previous study utilising fMRI and LRP in a study examining response preparation (Dehaene, Naccache, Le Clec, Koechlin, Mueller & Dehaene-Lambertz, 1998). Luu and colleagues (2000) found no evidence of simultaneous priming of the correct and incorrect responses on error trials at all. Neither did subjects report any subjective experience of response conflict on incorrect trials (Luu et al, 2000). However, it has been suggested that the LRP is a limited way in which to measure response conflict in that it measures difference between two responses and not the conflicting activation that they share (Gehring & Fencsik, 2001). Gehring and Fencsik (2001) also point out that this is a measure of pre-response conflict whereas

Botvinick and colleagues' (2001) computational model of response conflict predicts maximum conflict immediately *after* the response.

Carter et al (1998) utilised a continuous performance task (the AX-CPT) in which subjects were required to respond to the target letter X, but only if it was preceded by the letter A. This occurred on most trials (70% of the time), however 20% of the stimuli were designed to produce response conflict by simultaneously activating two competing responses; AY, BX. In the case of AY, the letter A primed the dominant response, to respond to the X following an A which occurred most of the time, but was then followed by a Y which activated the requirement to withhold the response. Similarly with BX, the letter X activated the dominant response, respond to an X, but then the subject had to remember that the previous letter was a B, which activated the requirement to withhold the response. The remaining 10% of stimuli were neutral BY trials. As mentioned, the authors (Carter et al., 1998) found that ACC was active not only during errors, but also on correct trials under situations of increased response conflict. They suggested that ACC is involved in detecting situations in which an error is likely to occur (Carter et al., 1998).

However, there are a number of criticisms that can be levelled at the Carter paper (Carter et al., 1998). Degraded stimuli were used in this task, which may not be optimal stimuli to use in a paradigm such as this as participants may not be aware of whether or not they have made an error. In addition to this, the authors used a confirmatory region of interest (ROI) approach rather than an exploratory analysis, using an ROI taken from a previous AX-CPT study that they had used to investigate WM (Barch et al., 1997). Nonetheless, the study by Carter and colleagues (1998) did

raise the question as to what was happening in these high conflict correct and error trials. This group suggested that response conflict arises prior to a response in correct trials and just after a response in error trials (van Veen & Carter, 2002). These authors have also suggested that ACC detects conflict at the level of responses alone (van Veen, Cohen, Botvinick, Stenger, & Carter, 2001) as it is usually activated only during response incongruities (Milham et al., 2001). This has subsequently been questioned however (Weissman, Giesbrecht, Song, Mangun, & Woldorff, 2003) and some authors have suggested that conflict is detected by ACC only when a participant is aware of levels of conflict (Jonides, Badre, Curtis, Thompson-Schill, & Smith, 2002).

1.2.5 Anatomy of Conflict Monitoring

A number of other studies have subsequently associated ACC with response conflict monitoring (Barch, 1999; 2001; Barch, Braver, Sabb, & Noll, 2000; Botvinick et al., 1999; Botvinick et al., 2001; Carter et al., 2000). Recent studies have suggested that, in fact, error processing and conflict monitoring may indeed be two separate entities and that they may both be located and dissociated along medial PFC (Garavan, Ross, Kaufman, & Stein, 2003; Ullsperger & von Cramon, 2001). These authors have suggested that error detection may take place in more rostral parts of ACC, whereas more dorsal, caudal parts of ACC extending into pre-SMA may be concerned with the detection of response conflict. In fact, Rushworth and colleagues have also made the observation that some studies that have assigned response conflict to the ACC may in some cases have been located in the "human equivalent of the presupplementary motor area" (Rushworth, Hadland, Paus, & Sipila, 2002, pg 2577).

A recent study by Garavan et al (2003) supports the notion of a dissociation between error detection and conflict-monitoring processes along the midline. These authors utilised a mixed block and event-related fMRI design in order to examine midline regions that were specifically sensitive to errors and those that responded to conflict. A GO/NOGO task was employed with varying on-screen duration of stimuli. The shorter a stimulus was on-screen, the faster subjects felt they needed to respond. Faster responding causes increased prepotency to respond, hence making it more difficult to inhibit responding resulting in greater levels of response conflict (Garavan et al., 2003). Therefore sections of the task during which stimuli were on-screen for shorter periods of time were considered high in conflict and those during which stimuli were on-screen for relatively longer amounts of time, low conflict.

Anterior regions of the ACC were sensitive to errors themselves but not to the conflict manipulation, whereas more dorsal regions of the ACC extending into pre-SMA were sensitive to the conflict manipulation and not to errors. In addition, the area in dorsal ACC/ pre-SMA was also tonically active during the high conflict periods. The anterior ACC did not show this pattern. These results suggest that more anterior areas of the ACC are sensitive to errors, whereas more dorsal regions of ACC and pre-SMA may be involved in monitoring for levels of response conflict. Ullsperger and von Cramon (Ullsperger & von Cramon, 2001) used an arrow flanker task in order to separate response-conflict and error processing processes along the midline. These authors found that an area in pre-SMA/ medial Brodmann area 8 was active during conflict, whereas an area in cingulate motor area was more active for errors (Ullsperger & von Cramon, 2001).

Braver et al (2001) suggest that conflict arises under the situation of infrequent responses, "especially in the context of making stereotyped or habitual responses" (page 825). They conducted an fMRI study of a GO/NOGO, target detection and response selection task, which involved 50/50 ratios and also infrequent target conditions. Stimuli were identical in each task. They supposed that low-frequency responses would elicit higher levels of conflict and thus a higher degree of activation in the ACC. This, they assumed would hold true whatever the task. There was some evidence to suggest that a more superior caudal region of the ACC extending into the SMA was activated for low-frequency events, whereas a more rostral inferior region subserved error processing (Braver et al., 2001). Two other studies attempted to separate error and conflict-related processes in a GO/NOGO paradigm (Kiehl et al., 2000; Menon et al., 2001). They too found a dissociation along the midline between these two processes, error-related activity being located in rostral ACC and conflict-related activity in more dorsal ACC. However, the Menon study (Menon et al., 2001) utilised a 50/50 ratio of GOs to NOGOs, which may not be optimal in inducing response conflict. Nevertheless, it is still apparent from these studies that there may indeed be an anatomical separation between these two processes. The area seen in the Ullsperger study (Ullsperger & von Cramon, 2001) during error processing is not as rostral as those seen in the Kiehl (Kiehl et al., 2000), Menon (Menon et al., 2001) and Garavan (Garavan et al., 2003) studies. Ullsperger and von Cramon suggest that this may be due to the emotional valence of errors in the other GO/NOGO tasks as an incorrect response in a flanker task can be corrected but a response to a stimulus that requires an inhibition cannot be corrected (2001).

As mentioned, a number of studies have supported the pre-SMA's involvement in response conflict monitoring in preference to the ACC (Garavan et al., 2003; Hazeltine, Poldrack, & Gabrieli, 2000; Ullsperger & von Cramon, 2001; 2003). A recent review of fMRI studies that attempted to separate conflict and error-related processes found that while error detection appeared to be subserved by the ACC, the focus of conflict-related activations appeared to be in caudal ACC/ pre-SMA (Hester, Fassbender & Garavan, 2004). Single unit recording studies in animals have found no evidence of conflict-related activity in the ACC, although they have been found in supplementary eye field (SEF) (Ito et al., 2003; Schall, Stuphorn, & Brown, 2002; Stuphorn, Taylor, & Schall, 2000). In fact, Stuphorn and colleagues suggest that the SEF may be a node in the supervisory attention system, detecting errors, conflict and the possibility of reinforcement in order to gauge the need for control and influencing cells in the frontal eye field (FEF), which carry out responses (Stuphorn et al., 2000). A study using the flanker task, a paradigm, which has been used on a number of occasions to examine response conflict (Botvinick et al., 1999; van Veen et al., 2001), found activation in pre-SMA/SMA during incongruent blocks of trials but found no activation in the ACC (Hazeltine et al., 2000). Ito et al (2003) also carried out single-cell recordings in monkeys and argue that the ACC is unlikely to be involved in conflict detection as there was no evidence in their study of any conflict-related activity in ACC. However, they do point out that this may not apply to humans because of differences in anatomy. Also, they used a saccade-countermanding task, which allows for only one movement at a time. This may be very different to studies of conflict in humans, as these paradigms often allow for the preparation of multiple responses at once; therefore "conflict between competing bimanual responses may be more common than conflict between competing saccade responses" (p 121).

The pre-SMA, an area in medial PFC that has been described by Picard and Strick (1996) is a likely candidate for the monitoring of response conflict. Pre-SMA has been implicated in higher order motor control such as movement preparation (Hadland, Rushworth, Passingham, Jahanshahi, & Rothwell, 2001), updating of motor plans and motor memory processes (Brass & von Cramon, 2002; Jancke, Himmelbach, Shah, & Zilles, 2000). An area of the pre-SMA, the supplementary eye field (SEF) (Schlag-Rey, Amador, Sanchez, & Schlag, 1997) and in the frontal eye field (FEF) (Connolly, Goodale, Menon, & Munoz, 2002; DeSouza, Menon, & Everling, 2003) is active during preparatory periods in anti-saccade tasks. Activation in pre-SMA has been noted during self-initiated movements. (Deiber, Honda, Ibanez, Sadato, & Hallett, 1999; Hadland et al., 2001) and also when switching between movement sequences (Jancke et al., 2000). Petit et al (Petit, Courtney, Ungerleider, & Haxby, 1998) found activation in pre-SMA during a WM delay and interpreted this activity as reflecting not just preparation of a response but also the selection of a motor response based upon information that has been held in mind. Therefore, it is apparent that pre-SMA is intimately linked with the preparation of motor responses. It follows then, that it is likely to detect conflict that may arise when two competing motor responses are simultaneously active. "The strong interconnections with prefrontal cortex on the one hand and the lateral premotor areas and the SMA on the other could enable this region to monitor for conflicting intentions to act" (Ullsperger & von Cramon, 2001, page 1397)

From the studies reviewed here it seems reasonable that different areas of the ACC react to both errors and response conflict (Garavan et al., 2003). Initially it was

thought that error-related processes were responsible for performance amendment (Gehring et al., 1993; Scheffers et al., 1996) although this has been much disputed (Rodriguez-Fornells et al., 2002; Rollnik et al., 2004). It may be that activation in rostral areas of ACC reflect an emotional response to an error (Leung et al., 2000). It is possible that the stronger the emotional reaction to an error, the more likely subsequent behavioural adjustment will be. Recently it has been suggested that conflict-monitoring processes rather than error detection per se are responsible for behavioural correction (Carter et al., 1998). There may also be a dissociation along the medial wall between error and conflict-related processes, more rostral areas of ACC being involved in an emotional response to errors and more dorsal areas extending into pre-SMA being involved in the detection of the conflict that arises due to the simultaneous activation of two conflicting response tendencies (Garavan et al., 2003; Ullsperger & von Cramon, 2001).

It also appears that the ACC/ pre-SMA seem to have a role in cognitive control. Carter and colleagues (Botvinick et al., 2001; Cohen, Botvinick, & Carter, 2000) would advocate the notion that midline regions detect the occurrence of conflict, which is a sign that an error may be imminent. Once this conflict has been detected, a signal is sent to PFC, which increases attentional control resulting in a reduction in response conflict (Botvinick et al., 2001; Cohen et al., 2000). This is due to a strengthening of the "correct" response pathway and a reduction in activity in the incorrect response pathway. The areas that are involved in the implementation of cognitive control and the manner in which they detect the need for this control and then subsequently enforce it, is a crucial yet unresolved question in cognitive neuroscience. Hence it is interesting to investigate the interactions between the

executive functions reviewed thus far and the allocation of attentional processes in the implementation of cognitive control processes.

1.3 PFC and Attentional Control

As mentioned in the previous section, ACC has been implicated in cognitive control processes. However, there is considerable disagreement as to how the ACC implements this control. ACC has been implicated in attentional processes such as "selection for action" that is, biasing the attentional system toward a target or focus for attention (Pardo, Pardo, Janer, & Raichle, 1990; Posner & DiGirolamo, 1998; Tzourio, Massioui, Crivello, Joliot, Renault & Mazoyer, 1997). A number of authors have noted that the ACC was activated during a variety of cognitive tasks that required some degree of attentional control and concluded that the ACC must be "involved in the selection process between competing processing alternatives on the basis of some pre-existing internal conscious plan" (Pardo et al., 1990, pg 259). Activation in ACC has also been seen to decrease as tasks became more routine or practised and less control is needed (Posner & DiGirolamo, 1998). Problems that can arguably be associated with problems of executive control often result from cingulate lesions and in schizophrenia, which has been associated with abnormalities of the cingulate (Posner & DiGirolamo, 1998). Thus it has been suggested (Posner & DiGirolamo, 1998) that ACC may at least be part of a network that forms supervisory attentional system (Norman & Shallice, 1986).

1.3.1 The Supervisory Attention System

Norman and Shallice (Norman & Shallice, 1986) developed a model of executive control that comprises multiple, overlapping yet separable subsystems of cognitive processing that interact with each other in order to coordinate behaviour to achieve goals. These subsystems are governed by two separate mechanisms. The first system operates by means of contention scheduling, which uses templates or condition-to-action statements to execute familiar or well-learned behaviours. These schema work by inhibiting one another and the schema with the greatest activation is deployed. Once such a schema has been activated it is played out until its end unless it is inhibited by another schema with a higher activation level or by higher-order control. This higher-order control is known as the supervisory attention system. This system intercedes and strengthens or inhibits schema depending upon what is appropriate to a particular situation. The supervisory attention system has access to individual goals and environmental cues whereas the contention-scheduling system merely involves competition between subsystems.

Norman and Shallice (1986) suggest that there are a number of different conditions under which the supervisory attention system is required over basic contention scheduling: during planning or decision making, correcting errors, for novel or not well-learned responses, under conditions which are judged to be difficult or dangerous and when overcoming habitual or automatic responses. Posner and DiGirolamo (1998) also suggest that executive control is not a continuous, on-going process present in all cognitive activity, but can also be employed during parts of a task where contention scheduling is insufficient and these executive functions are necessary

1.3.2 PFC and Cognitive Control

PFC has often been considered to be a candidate for the role of the supervisory attention system. Damage to the PFC has been seen to disrupt higher order behaviour and compromises performance on a number of tasks designed to measure normal executive functioning (Demakis, 2003; Stuss et al., 2000). PFC has often been implicated in the maintenance of representations or task set or rules that define appropriate stimulus-response mappings used in decision making or execution of behaviour (Banich, Milham, Atchley, Cohen, Webb, Wszalek, Kramer, Liang, Barad et al., 2000; Frith & Dolan, 1996; Garavan et al., 2002; MacDonald et al., 2000). ACC along with other midline areas have been believed to be responsible for top-down effects that increase activation in discrete regions that are involved in processing pertinent stimuli (Pardo et al., 1990; Posner & DiGirolamo, 1998). The ACC has been considered to be part of an attention system, which enforces top-down control, or increases "attention to action" by biasing the attentional system toward a target or focus for attention and filtering out distracting, irrelevant stimuli (Pardo et al., 1990; Posner & DiGirolamo, 1998; Tzourio et al., 1997). However, as mentioned, a number of studies have refuted the notion of the ACC actually implementing cognitive control (Banich, Milham, Atchley, Cohen, Webb, Wszalek, Kramer, Liang, Wright et al., 2000; Botvinick et al., 1999; Casey et al., 2000; Milham, Banich, & Barad, 2003; Milham et al., 2001). These authors hypothesise that ACC detects levels of response conflict or situations in which an error is likely to occur. This then signals back to PFC, which adjusts levels of attentional control to suit the situation (Botvinick et al., 2001). This notion will be discussed in more detail. One recent study, however, disputes this in favour of the earlier notion that ACC actually implements control (Markela-Lerenc, Ille, Kaiser, Fiedler, Mundt & Weisbrod, 2004).

1.3.3 DLPFC

Co-activation of DLPFC with midline areas is often seen in tasks that involve response conflict (MacDonald et al., 2000) and in various demanding cognitive tasks (Duncan & Owen, 2000). Hence DLPFC has been implicated in the control of interference and conflict in a number of studies (Carter et al., 2000; Hazeltine et al., 2000; MacDonald et al., 2000; Ullsperger, von Cramon, & Muller, 2002) and is believed to play some role in performance monitoring (Botvinick et al., 2001; Ullsperger et al., 2002). Although various brain regions do appear to have a "short term buffering ability" (Miller, 2000), what sets PFC apart is that it is able to maintain information in the face of distraction (Frith & Dolan, 1996). Studies of neural activity in monkeys have shown that neurons in DLPFC show sustained activity over a delay period between a stimulus and a response based upon that stimulus (Fuster, 1987; Goldman-Rakic, 1994). Lateral PFC has also been implicated in the maintenance of information in mind in humans (D'Esposito, Ballard, Aguirre, & Zarahn, 1998). For this reason, DLPFC has been implicated in WM processes (Smith & Jonides, 2000). DLPFC also has rich connections with other parts of the PFC and the rest of the brain (Fuster, 1997; Miller & Cohen, 2001). It is highly interconnected with association cortex such as parietal lobes (Miller, 2000). DLPFC has also been implicated in response selection in the absence of WM requirements (Hadland et al., 2001). It follows, then, that DLPFC is an important part of a network that implements cognitive control.

1.3.4 The Role of Lateral PFC and ACC in Cognitive Control

Carter and colleagues believe that the ACC serves the function of a "mindless" alarm system, which detects bottom-up signals such as response conflict (Barch et al., 2001;

Barch et al., 2000; Botvinick et al., 1999; Carter et al., 1998) and that this signal is detected by the "thinking" PFC which exercises control (Botvinick et al., 2001; Cohen et al., 2000). A number of authors have suggested that DLPFC and midline areas in conjunction exercise cognitive control, midline areas detecting levels of response conflict then signalling back to DLPFC, which then implements attentional control, resulting in a subsequent reduction in levels of response-conflict detected by midline areas (Botvinick et al., 2001; MacDonald et al., 2000).

Lesion studies have also implicated PFC-midline interactions in the implementation of cognitive control. Gehring and Knight (Gehring & Knight, 2000) noted that damage to lateral PFC did not disrupt the ERN on incorrect trials but increased this ERP waveform on correct trials, so much so, in fact, that the Cz electrode did not significantly differ between errors and correct trials (Gehring & Knight, 2000). Ullsperger and colleagues (2002) also failed to find differences between correct and error ERN responses in patients with lesions of lateral PFC. However, their results suggest an attenuated ERN in error trials and a comparable negativity to controls for correct trials was responsible for the lack of difference between error and correct trials (Ullsperger et al., 2002). Gehring and Knight (2000) also found fewer instances of corrective behaviour (attenuated force of grip response) in the frontal group in comparison to controls. In both of these studies, damage to PFC may have affected the ability to hold representations of the correct response in mind, compromising ACC's capability of distinguishing an erroneous response from a correct one or allowing multiple competing responses to become activated resulting in response conflict, which was then detected by midline regions (Gehring & Knight, 2000; Ullsperger et al, 2002; Rollnik et al., 2004).

The wealth of new evidence does appear to suggest that PFC actually implements cognitive control while midline areas detect situations in which control may be needed. MacDonald and colleagues (2000) found a reduction in Stroop interference was associated with increased levels of activation in left DLPFC. A recent study also found a correlation between bilateral PFC and ACC under conditions of increased response conflict and interpreted this as a cooperative relationship between ACC and prefrontal regions in cognitive control (Badre & Wagner, 2004). Garavan and co-workers (2002) found that activation in a region in left DLPFC was predictive of successful performance in a GO/NOGO task and that midline areas detected errors and levels of response conflict (2003). In order to be a candidate for cognitive control, a region must itself be able, or must interact with regions that are able, to store task rules and goals as well as detected instances in which errors are likely to occur in order to appropriately adjust levels of control. It seems that DLPFC possesses these properties.

From these studies, it appears that DLPFC has an important role to play in the implementation of cognitive control. As mentioned, cognitive control processes can be thought of as akin to the supervisory attention system, which intervenes in cases where automatic routine behaviours are no longer suitable (Norman & Shallice, 1986). This requires a self-driven, endogenous, effortful capacity to engage attentional resources. This internally maintained, endogenous attentional focus can also be maintained over time in situations where external stimuli are not stimulating enough to engage our attentional capacities.

1.3.5 Sustained Attention.

The ability to sustain one's attention during a task is an essential aspect of behaviour. Sustained attention can be thought of as endogenously maintaining attentional focus in situations where there is a lack of external arousal, such as in a boring task (Wilkins, Shallice, & McCarthy, 1987). Early investigations of sustained attention focused on vigilance and vigilance decrements (Mackworth, 1948). This involved very long periods of monitoring and produced highly variable results. More recently, it has been suggested that sustained attentional capacities can be taxed over much shorter time spans (Robertson, Manly, Andrade, Baddeley, & Yiend, 1997). A number of studies have implicated lateral PFC (D'Esposito et al., 1998), usually more localized within the right hemisphere (Lewin, Lee, Wu, Miller, & Duerk, 1996; Manly, Owen, McAvinue, Datta, Lewis & Scott, 2003; Wilkins et al., 1987) in sustaining attention.

1.3.6 Anatomy of sustained attention

Pardo and colleagues (Pardo, Fox, & Raichle, 1991) carried out a PET study of tactile and visual sustained attention. Participants were required to monitor their left or right toe for pauses in ongoing tactile stimulation. Pardo and co-workers (Pardo et al., 1991) found that right DLPFC and superior parietal cortex were active in this condition above rest, irrespective of which toe was being stimulated. In a further condition, subjects were asked to monitor fluctuations in the luminance of a spot of light presented on a monitor and count them. This condition also produced activation in the same right fronto-parietal network as was active for the tactile condition. Lewin and colleagues (Lewin et al., 1996) used a similar paradigm as the visual condition in the Pardo study (Pardo et al., 1991) but utilised fMRI instead of PET. The authors

(Lewin et al., 1996) found similar right-hemisphere activation patterns, but only the right frontal activation reached statistical significance.

However, the studies mentioned above utilised rest as a baseline, which, as mentioned previously (see section 1.4) is not optimal in isolating specific cognitive processes. Coull and co-workers (Coull, Frackowiak, & Frith, 1998) utilised a condition in which subjects monitored for the occurrence of a particular letter in a particular colour. This was contrasted against a baseline during which subjects responded to every stimulus (much fewer stimuli were presented in this condition in order to equate motor responses between the two conditions). Increased activation with time-on-task was noted in the caudate nucleus and posterior cingulate cortex. Decreases in activation as the task progressed were seen in bilateral parietal cortex, right DLPFC and in the thalamus. This finding seems to argue against the right fronto-parietal network being engaged in sustained attention as a decrease in activation was noted in this system with time. However, it may be that this very simple task (subjects performed practically at ceiling for the entire task) encouraged automatic rather than controlled responding. Disengagement of the prefrontal lobes has previously been discussed with regard to automatic responding in that less control is required, causing prefrontal involvement to decrease. Nonetheless, this finding is at odds with the other imaging studies mentioned.

Manly et al (2003) conducted a PET study of sustained attention utlizing the Sustained Attention to Response Test (SART), a task that had been found to be sensitive to traumatic brain injury (TBI) and was related to every day attentional slips of both normal controls and patients with TBI (Robertson et al., 1997). In the SART,

participants are presented with numbers from 1-9 and required to respond to every number except the number 3. Manly et al (2003) utilised both a random and predictable, ascending order presentation (Random SART and Fixed SART respectively) on patients with TBI and normal controls.

The authors (Manly et al., 2003) found that although the Fixed sequence SART was easier than the Random sequence SART, in that the inhibitory event was predictable, it was better able to distinguish between TBIs and controls in terms of errors of commission (Manly et al., 2003). The authors suggested that the Fixed sequence task was more taxing on sustained attentional capacity than the Random SART; Due to lower amounts of exogenous task support subjects need to rely more on internal, endogenous attentional resources or top-down control. Hence, they scanned a number of individuals from the "normal" population while they performed both the Fixed and Random SART. The authors found activation in right DLPFC and superior/ posterior parietal cortex in the Fixed minus Random SART subtraction but found no significant activation in the Random minus Fixed SART subtraction (Manly et al., 2003). This is further evidence for the involvement of right fronto-parietal cortex in sustained attention.

Lesion studies have also implicated right PFC in sustained attention. Wilkins and colleagues (Wilkins et al., 1987) asked patients with damage to the left or right frontal lobes and controls with parietal lobe damage to maintain a count of auditory and tactile stimuli at fast and slow presentation rates. Patients with damage to right PFC performed significantly more poorly at the slow presentation rate (Wilkins et al., 1987). Wilkins and colleagues (Wilkins et al., 1987) suggested that at the faster

presentation rate, there was a higher degree of exogenous stimulation, which engaged attentional processes. However at the slower rate, subjects needed to maintain their own endogenously driven attentional capacities more (Wilkins et al., 1987).

Rueckert and Grafman (1996) found that patients with damage to right PFC were significantly impaired with respect to slowed RT and increased errors of commission or missed targets on three tasks when compared to normal controls; a simple vigilance task, the Continuous Performance Task (CPT) and a monitoring type of task. There was a trend for right frontal patients to be more impaired than left frontal patients but this did not reach significance, except in the CPT. Here right frontal patients were significantly worse than controls and the left frontal group. In addition, right frontal patients showed significant slowing of RT as the task progressed (Rueckert & Grafman, 1996).

Cabeza and Nyberg (2000) in their review of 275 imaging studies of cognitive processes found activation in predominantly right hemisphere fronto-parietal networks in sustained attention and fronto-parietal interactions in sustained attention have also been shown through structural equation modelling of fMRI data in a visual monitoring task (Buchel & Friston, 1997). In a factor analytic study of the Stroop task a right hemisphere fronto-parietal network was identified as most likely subserving vigilance or sustained attention (Peterson et al., 1999). Thus it seems that lesion and imaging studies agree on the importance of right fronto-parietal cortex in self-sustained attention.

1.3.7 Arousal and Alertness

Inherently entangled with sustained attention are processes such as arousal and alertness. Intrinsic alertness and sustained attention involve the internal maintenance of attention and arousal over periods of time. Phasic alertness, however, is the ability to increase ones alertness or attentional resources at a particular point in time in response to external events or exogenous cues such as a warning stimulus. Kinomura and co-workers (Kinomura, Larsson, Gulyas, & Roland, 1996) found activation in midbrain and thalamic structures during a vigilance task over a rest condition and they interpreted their results as supporting the notion of the involvement of these structures in the transition from rest to alert or attentive states. Intrinsic alertness and sustained attention has been found to involve largely right hemisphere fronto-parietal networks (Manly et al., 2003; Sturm et al., 1999; Sturm & Willmes, 2001) mainly irrespective of the modality in which stimuli are presented (Pardo et al., 1991; Weis et al., 2000). Phasic alertness is more controversial. Activations have been found bilaterally (Thiel, Zilles, & Fink, 2004; Weis et al., 2000) and also mainly in left hemisphere (Coull, Nobre, & Frith, 2001) but, as mentioned, have also implicated midbrain and thalamic structures (Kinomura et al., 1996; Sturm et al., 1999; Sturm & Willmes, 2001). To phrase it in simple terms, we can think of phasic alertness as reflecting arousal or alerts states, lasting a short period of time, which are often prompted by externally driven bottom-up processes. This may be driven by midbrian thalamic structures. The maintenance of an intrinsically driven alert state, or sustained attention, can be thought of as top-down preservation of attentiveness or alertness. As this requires conscious effort, it is more often associated with PFC, mainly in the right hemisphere and also with parietal cortex.

1.3.8 Lateralization in PFC

There has been some division in terms of prefrontal lobe function and the anatomical regions that subserve "higher-level" processes. Some researchers believe that regions of PFC can subserve a variety of different types of cognitive processes (Duncan, 2001; Duncan & Owen, 2000), whereas others believe that certain regions are largely specialized to distinct processes (Goldman-Rakic & Leung, 2002). It may be that there is some degree of lateralization in PFC with regard to control processes. Fincham et al (Fincham, Carter, van Veen, Stenger, & Anderson, 2002) used a variation of the Tower of London (TOL) task (a task that is often used to examine planning abilities and is sensitive to prefrontal damage) and trained subjects to work on one step at a time in order to examine problem solving ability at different difficulty levels of the task. The authors suggest that a right fronto-parietal network of regions is involved in WM aspects of the task as activation in this area parametrically increased with difficulty level. Left DLPFC, on the other hand showed an increase in activation during the most difficult level only. The authors argue that this region is involved in the construction of sub-goals and planning of the task (Fincham et al., 2002). Activation in left DLPFC has also been noted during the presentation of infrequently occurring task-irrelevant stimuli (oddball stimuli) and was interpreted as reflecting the implemetation of top-down control in the face of interfering, irrelevant information (Milham et al., 2003).

In an fMRI and PET study of the TOL (Schall et al., 2003), task-difficulty dependent increases in activation were seen in regions of left DLPFC. Left prefrontal lesions were also associated with increased perseverative errors and fewer categories achieved in the WCST (Goldstein et al., 2004) when compared to right prefrontal

lesion, posterior lesion and normal control groups. Maintenance of representations or task goals and rules is thought to be subserved by left PFC. Left DLPFC has previously been implicated in the maintenance of task set (Garavan et al., 2002) or representations (Frith & Dolan, 1996; MacDonald et al., 2000; Ruchsow, Grothe, Spitzer, & Kiefer, 2002) and has been linked to subsequent correction of behaviour (Garavan et al., 2002; MacDonald et al., 2000; Rueckert & Grafman, 1996). Teng (1998) examined the performance of split-brain patients on a task in which two rods were matched according to thickness or length. The aspect that rods were to be matched on changed intermittently and participants were required to change their behaviour appropriately. The left hemisphere performed far better than the right, which appeared to behave more impulsively (Teng, 1998). Rogers et al (Rogers, Sahakian, Hodges, Polkey, Kennard & Robbins, 1998) found that in Parkinson's patients performing a task-switch paradigm, left hemisphere lesions caused greater switch costs than right hemisphere lesions in terms of RT when there was interference between two tasks. Brass and colleagues (Brass & von Cramon, 2002) also found activation in left inferior frontal junction during cues periods in their task and suggested that this region was involved in the selection of task-related rules and the correct stimulus-response associations.

Right frontal areas in conjunction with right parietal cortex have been implicated in many executive functions such as inhibition (Garavan et al., 1999), sustained attention (Manly et al., 2003), WM (D'Esposito et al., 1998) and processes such as arousal (Kinomura et al., 1996; Sturm et al., 1999; Sturm & Willmes, 2001). In fact, some authors have suggested that holding items in working memory may involve a similar process to that involved in sustaining attention (Awh & Jonides, 1998; Coull & Frith,

1998; Coull, Frith, Frackowiak, & Grasby, 1996). Right DLPFC, has also been implicated in monitoring (Rowe, Owen, Johnsrude, & Passingham, 2001). Therefore, it may be unwise to assume that different areas of PFC are highly specialized for any one particular function. The common networks that are activated for a wide variety of cognitive tasks would seem to dictate against this. In addition, Rao and colleagues have demonstrated that those cells that are active during working memory tasks in prefrontal cortex are flexible, adapting to different functions as the requirements of a task change (Rao, Rainer, & Miller, 1997). Therefore, it may be the case that diverse cognitive functions share some processing characteristic that manifests itself in the activation of this shared network for all of these tasks. The challenge then remains to ascertain how these areas interact with each other in the facilitation of cognitive control processes. An additional question is to whether the activation of a common underlying process may explain the reason for activation of similar anatomical networks in a wide variety of cognitive tasks. These are the questions that were addressed by this series of studies.

Imaging is a very effective method of examining the anatomical substrates of such executive functions. In recent years the advent of fMRI has made a huge contribution to human brain mapping. In the following series of studies, fMRI was used to investigate a number of different cognitive processes that have just been discussed. Hence a brief explanation of fMRI will first be provided.

1.4 Functional Magnetic Resonance Imaging

fMRI is a relatively new and very popular imaging technique. However, with the considerable strengths that it brings to the scientific community, it also has weaknesses. These issues must be addressed and acknowledged within any comprehensive body of work utilizing this technique. A brief description of how fMRI works and some of the pros and cons of the method are outlined below.

Much of our bodies are composed of water, which consists of hydrogen and oxygen atoms. In their natural state protons in the nuclei of hydrogen atoms spin randomly. When they are placed within a strong magnetic field, such as in an MRI environment, most of them tend to line up along the magnetic field like compass needles. The protons are then bombarded by short bursts of radio waves of a particular frequency. This knocks the protons out of alignment with the field. As they spin and return to their original spinning positions they emit a particular radio signal of their own, the strength of which depends upon the number of protons in a measured slice of brain. Blood is composed of many different compounds, including oxygenated haemoglobin. As neurons fire, they use energy and thus require oxygen. Hence, oxygenated haemoglobin loses its oxygen and becomes deoxygenated haemoglobin. This causes a surge of new oxygenated blood to flood into that region. fMRI is a measure of the amount of oxygenated blood in a voxel. A voxel is a cube, which has sides of length x, y and z mm, the x, y, z, dimensions being determined before scanning begins. The dimensions can vary depending upon the resolution required by the experimenter. The entire brain is then divided into these voxels, so that activation at each time-point can be seen within each voxel. This is achieved by applying

magnetic gradients across the brain such that the magnetic field is not homogenous over the entire brain. This means that protons at the front of the brain will have a different resonant frequency to those at the back of the brain, for example. Thus, a particular radio frequency can be applied to the brain that reflects the resonant frequency of the protons in one particular slice of brain. In this way, separate slices can be distinguished from front to back (coronal views), from top to bottom (axial views) and from one ear to the other (sagittal views). Hence, one can determine which regions of the brain are active during a certain portion of a task that is which regions are receiving oxygen, through the blood, due to firing of neurons. Thus fMRI is a very indirect measure of neuronal activity.

1.4.1 Pros and Cons Associated with fMRI

fMRI has many positive aspects: it has very good spatial resolution and provides the ability to investigate structures deep within the brain. Additionally, fMRI has a huge advantage over PET in that the number of times that a person can be imaged in fMRI is unlimited since there are no known adverse effects on health associated with this process. This also allows for the scanning of children. Despite these advantages there are also a number of problems associated with the technique. Firstly, fMRI measures are based on blood flow and not directly on neural activation. The neuronal coupling between the haemodynamic response and the neural activity is not precisely known and therefore it is difficult to characterise the shape of the haemodynamic curve. As Fuster (Fuster, 1997) points out, there is "insufficient understanding of the physiological relationships between blood flow, neuron discharge and energy metabolism. Particularly troublesome are the uncertainties concerning the temporal aspects of the correlations between those three variables." (page 186). Fuster (1997)

also points out that neural inhibition is an issue that is not fully understood in imaging as this too presumably requires increased blood flow. What then do deactivations represent? Do they represent a decrease in activity in a certain region relative to baseline or inhibition by another region? These are important issues that need to be addressed as deactivation patterns in the imaging literature are largely ignored and neural inhibition can be just as important in the understanding of brain function as positive activations are.

Additionally, the temporal resolution of these blood flow responses, and hence fMRI, is quite poor; the haemodynamic response may take from 15 to 20 seconds to fully rise and fall. However, the spatial resolution is good and is much better than other imaging techniques such as EEG, which have better temporal resolution. MRI can achieve a structural resolution of 1 or 2 mm. However, in functional imaging this is exasperated by low signal to noise ratios, variability within and between subjects and the rapid acquisition time that is needed in order to capture cognitive processes that are taking place at a relatively fast pace. Natural variations occur not only in the biological systems of the individuals under scrutiny but also in the many variable parameters that are used in collecting and analysing fMRI data. For instance, the spatial resolution of fMRI is somewhat compromised by data processing techniques such as spatial blurring and averaging of statistical maps. Aside from these issues, however fMRI does still have a relatively good spatial resolution. It is for this reason that fMRI and EEG have been recently combined to couple the good temporal resolution of EEG with the good spatial resolution of fMRI (Ullsperger and von Cramon, 2001).

The variability between the sizes and shapes of subjects' heads can also be problematic. In order to allow averaging of activation across subjects each brain is warped into a standardized shape, for example, according to Talairach coordinates (Talairach and Tournoux, 1988). Warping the brain into Talairach (Talairach and Tournoux, 1988) space results in voxels that are 1 X 1 X 1 mm in size. Functional activation is then also warped into this space, once again, causing some of the spatial resolution at the individual level to be slightly compromised. As Fuster (1997) points out there may be diffuseness and variability of activation in neural networks. For this reason, averaging of functional data across subjects may be slightly misleading, as it may result in showing only a relatively small focus of activation in all subjects, which may be the result of much larger networks being averaged together. "The small patches of activation that appear in PET, and even fMRI pictures, may represent artifactitious, statistically constructed foci ("tips of iceberg") within much wider areas or networks that are functionally active but remain largely invisible" (Fuster, 1997, page 187).

1.4.2 Block fMRI design

The first fMRI studies were all block design studies. The temporal resolution of block design studies is intrinsically poor and is not very well suited to measure the timecourses of processes that may occur on the order of seconds or milliseconds (D'Esposito and Postle, 2002). These studies were analysed by using blocks containing the variable of interest and comparable baseline blocks, which were similar in every way to the blocks containing the variable of interest less that particular variable. Experimenters attempted to make the blocks similar with regard to stimuli, responses required and additional variables that may not have been of interest (for

example working memory processes). The logic of "cognitive subtraction" (Posner, 1988) was then applied: This logic assumes that cognitive processes can be added to existing or ongoing cognitive operations without changing or affecting them. Baseline blocks were subtracted from blocks of interest, theoretically resulting in activation associated with only the variable of interest. For example, when investigating a process such as response inhibition, an experimenter using a block design may choose to intersperse blocks with GO and NOGO responses with blocks of purely GO responses. Subtraction of the GO blocks from the GO/NOGO blocks should theoretically result in an activation map for the NOGO events only.

However, this is quite a difficult undertaking and requires very clever and thoughtful design of experiments. If the baseline blocks are not carefully matched to the blocks containing the measure of interest, additional processes may be included in the activation maps resulting in a false activation map for the variable of interest. Also the logic of pure insertion may also be flawed in some cases; the addition of some cognitive tasks may affect ongoing cognitive processes in some cases and these processes are not yet fully understood.

Another potential problem with block designs that can be illustrated using this example of the GO/NOGO task is the contamination of activation maps by error-related processes. The very nature of a GO/NOGO task requires that it will be difficult to withhold responding in the NOGO condition, thus taxing the response inhibition process. However, due to the difficulty of the task, errors are common. Error-related activations will thus also be represented in the activation maps, not just pure inhibitory activations. This is also a problem when comparing the activation

patterns of different groups with different performance differences. For example, many clinical groups that are compared to normal controls often perform more poorly on the imaging tasks than normals. Thus, there will be differential amounts of error-related activation between the two groups, meaning that any differences in brain networks seen between the groups cannot be attributed solely to the variable being measured but may be due to error-related contamination of activation maps (Murphy and Garavan, 2004). This problem can be addressed by tailoring the difficulty of the task to each individual's performance capabilities in order to ensure equal numbers of errors between groups in a between groups comparison.

Another potential problem with block fMRI designs is that they assume that the "transform from neural signal to neuroimaging signal must be linear" (D'Esposito and Postle, 2002, page 170). However, this relationship is not necessarily linear. For example, if a neuron fires, oxygen is needed for this process, therefore blood flow will increase in that particular region. However, as more and more neurons fire, the blood flow increase to a particular brain area must plateau at some point, as there cannot be an infinite increase in blood flow. At levels such as these, for example, the linear relationship between neural activity and blood flow would break down.

Lastly it is extremely difficult or impossible for block designs to disentangle and isolate different components of complex cognitive processes. D'Esposito and Postle (2002) use the example of working memory in the N-back task in order to illustrate this point. The N-back task requires people to keep a stimulus "n" places back in the stimulus stream in mind and compare it to the current stimulus. This involves encoding each stimulus into memory and maintaining it there despite intervening distracting and attentionally significant stimuli, shifting attention back to this event in

memory when the task dictates, comparing the stimulus on screen to this event in memory, utilizing this decision to guide behaviour and subsequently discarding this event in memory in order to prevent it interfering with subsequent events. If an experimenter finds differences between a 3-back condition and a baseline condition which element of these processes or combination thereof is producing the difference? Block designs have extreme problems in trying to answer this question.

However, there are a number of positive features to block fMRI designs. They are much more powerful than event-related designs for example. This is because in a block design there is a greater percentage signal change. Also when correlating the boxcar function with the haemodynamic time series there is ultimately more power due to the greater effect size in block designs. The boxcar function is simply a square wave that is correlated against the time series, which illustrates the ON and OFF periods of the task. Overlapping haemodynamic responses increase the signal, as there is an additive, near linear (see section 1.4.3) relationship between neural responses and haemodynamic responses. In a block design the signal is always "up" because events tend to fall quite close together, whereas in event-related designs the signal rises and falls, as stimuli need to be more widely spaced due to the need for deconvolution techniques (see section 1.4.3).

1.4.3 Event-related design

To overcome some of the problems mentioned above with block fMRI designs new event-related designs were developed. Event-related designs are analogous to ERP analysis techniques in that separate haemodynamic responses or signal changes are calculated for discrete events in the temporal sequence for each voxel in the brain and are then averaged together in order to get a mean response in each voxel of the brain

for each discrete cognitive event. This type of design has many advantages over block designs. Using the example mentioned earlier of measuring response inhibition in a GO/NOGO task it is easy to see the benefits of this design. Response inhibition is best seen when a prepotency to respond has been built up within the experiment. Therefore it is important to have many more GO than NOGO events in a given condition. This is not optimal in a block design, which is more powerful with more events. Also, it is impossible to have a block made up entirely of NOGO events. Obviously there would be no requirement to inhibit responding in such a block, as subjects would simply be required not to respond at all! Event-related fMRI design is perfect for the examination of such cognitive processes as response inhibition and response conflict, however, as many stimuli can be inserted between these critical events, making it more difficult for participants to withhold responding, for example, leading to an increased demand on the response inhibition network. In theory this would result in increased activation. Additionally, it may be that manipulating the ratio of GO to NOGO events in an inhibitory task may fundamentally interfere with the process being studied. For example a ratio of GO to NOGO events of 50:50 may result in response selection being measured than response inhibition *per se*. This process may activate an entirely different network of areas. The result of manipulating the ratio of GO to NOGO responses can clearly be seen in the De Zubicaray GO/NOGO study (2000) (see section 1.1.3).

Although event-related designs can address many of the problems that block designs can experience with the issue of cognitive subtraction, an element of caution in interpretation of the results is still needed as cognitive events rarely if ever occur in isolation. For example, working memory related processes also require attentional and inhibitory processes. Variables such as arousal levels at particular points in time

during the course of a paradigm can also contaminate activation maps. These confounding variables must be considered in the interpretation of any imaging study.

The slow latency of the blood oxygenation level dependant (BOLD) response limited early fMRI studies – in order to examine individual events in a similar manner to that used in EEG studies, events needed to be separated by enough time to allow the haemodynamic response to rise and fully decay. However, later investigations into the properties of overlapping haemodynamic responses suggested that these responses summated in a roughly linear fashion (Boynton, Engel, Glover & Heeger, 1996; Dale and Buckner, 1997), allowing for the separation and analyses of single types of events. At very close presentation rates (less than 1sec) blood flow levels become saturated and not completely additive (Friston et al., 1998). Although this is another issue that limits modern fMRI studies, it is possible to separate events with reasonable accuracy when there is sufficient spacing between the events of interest (about 2 sec). Thus event-related fMRI enables one to examine discreet cognitive events with relative safety and provides excellent spatial resolution with which to determine the anatomical substrates of behaviour.

1.4.4. Mixed block and event-related design

Although separate cognitive events can be examined using event-related analysis techniques, this type of analysis cannot be used to determine tonic brain activity that is sustained activity over a given period of time. This can be activity over the entire experimental paradigm, such as sustained attentional processes, for instance, or over shorter periods of time, for example in task preparation during a cue period. If the experimenter wishes to examine both discreet phasic events whilst also examining

tonic, task-related activation, it is necessary to utilize a mixed block and event related design. A mixed design was utilized in the analysis of all of the studies within this body of work because there was a concern with examining cognitive control processes which involved brain states that were engaged tonically throughout the experimental paradigm as well as phasic activity which occurred upon the presentation of certain stimuli. One study wished to examine tonic activity over the entire task as well as phasic activity linked to specific events within the task. The remaining studies wished to examine sustained activity over a pre-determined period of time within the task in addition to events themselves. Thus, discreet blocks of time were examined in addition to the events themselves. The specific issues related to the analysis of these mixed paradigms will be discussed further in Chapter 2.

Recently, fMRI is frequently combined with other imaging techniques (EEG or transcranial magnetic stimulation (TMS)), which provides further insight into human behaviour. In fact, fMRI is most powerful when examined within the broader framework of lesion studies and data from other imaging techniques. A combination of information from a wide variety of techniques is the wisest course of action when examining the complex questions surrounding human cognition.

Chapter 2

Method

2.1 Subjects

All subjects recruited for the purposes of the following studies were right-handed, were free of neurological disorders, psychiatric problems or head trauma and were not under any medication. Written consent was obtained from each. Aside from one study (Chapter 6) the Institutional Review Board of the Nathan Kline Institute, where the scans were carried out, approved all procedures. For the study in chapter 6, ethical approval was granted by Trinity College Dublin (see Appendices for consent forms).

2.2 Materials

Unless otherwise specified, scanning was performed on a 1.5 Tesla Siemens scanner in which foam padding was used to restrict head movements. T_1-weighted magnetization prepared rapid gradient echo (MPRAGE), sagittal slices were acquired for each subject (slice thickness = 1 mm, field of view = 256 mm) to allow subsequent anatomical localization and spatial normalisation. Functional images were single-shot, T2* weighted, echo planar imaging sequences. TR was always 2000 msec. Stimuli

were presented through an LCD screen, which was mounted on the head coil and was directly in the subjects' line of vision.

2.3 Analysis of functional data.

All images were analyzed using Analysis of Functional Neuroimages (AFNI) software (http://afni.nimh.nih.gov/afni) (Cox, 1996). First, images were time-shifted using Fourier interpolation to correct for differences in slice acquisition time. Since slices were acquired every other slice, odd numbered slices being acquired first followed by evenly numbered slices, they were acquired at subtly different time periods. Thus, all slices were shifted to the time point at which the first slice was acquired. Following this step, spurious activation outside the brain was removed by using an edge detecting technique. This technique essentially creates a mask of the entire area of the brain and superimposes the mask on the brain. Any activation falling outside that mask is set to zero. The images were then corrected for motion in 3 dimensions. Images or individual subjects that displayed excessive motion were excluded from further analysis, as were the first three images in each run.

For blocks of the task a reference (or ideal) time series was created (that is, a series of 0s represented the OFF (or rest) periods during the task and a series of 1s, represented the ON (or task) periods). As all experiments in this body of work were scanned at a TR of 2 sec (one scan of the entire brain was completed every two seconds), each 0 or 1 represented a 2 second time period.. Separate ideals were also made for each type of event in addition to ON and OFF periods. The reference waveforms model the expected haemodynamic response to a task.

The majority of event-related analyses base their activation measure on scaling factors from a multiple linear regression procedure. This is accomplished by solving the equation $\mathbf{Y} = \mathbf{X}\,\boldsymbol{\beta} + \boldsymbol{\varepsilon}$, where $\mathbf{Y}$ is a column vector of the voxels time series data, $\mathbf{X}$ is the design matrix, $\boldsymbol{\beta}$ is a column vector of scaling factors and $\boldsymbol{\varepsilon}$ is a column vector of Gaussian noise terms (Worsley and Friston, 1995). This equation is called the *General Linear Model* (GLM). However, for the events in the studies in this thesis a technique first used by Garavan et al (1999) was utilized, in which the scaling factors are not the basis of the activation measure. By not making any a priori assumptions about the specific shape of the haemodynamic response, this method has the advantage that it can accommodate the differences in haemodynamic shape, both within- and between-subject, that have been reported in the literature (Aguirre, Zarahn & D'Esposito, 1998; Handwerker, Ollinger & D'Esposito, 2004; Neumann, Lohmann, Zysset & von Cramon, 2003). Instead, using deconvolution, this technique performs an estimation of the impulse response function (IRF) for each voxel. Utilizing multiple regression, this procedure calculates the IRF (i.e., the average best-fitting "shape") that follows each event of interest. Using a least-squares multiple regression algorithm, the deconvolution procedure also calculates a scaling value for each regressor (which define the IRF for each voxel) as well as intercept and slope parameters, which can be used to calculate a baseline (i.e., the ongoing mean activity level after excluding the variance due to the events against which events can be measured). The best-fitting haemodynamic shape (as defined by the gamma-variate function above) is then determined for each voxel's IRF by using a non-linear regression algorithm (Ward, Garavan, Ross, Bloom, Cox & Stein, 1998).

After these steps, the estimated haemodynamic shapes were converted into percentage area under the curve scores (%AUC) for each voxel by expressing the area under the haemodynamic curve as a percentage of the area under the baseline. These %AUC represent the activation measure for each voxel. Thus, it is possible to determine activation measures for each variable of interest.

2.3.1 Mixed block and event-related design.

For reasons discussed in Chapter 1, the studies within this body of work utilised a mixed fMRI analysis design. In the study discussed in Chapter 3, I wished to examine sustained attention and task-set maintenance processes, which were engaged throughout the task, as well as error, conflict and inhibitory-related processes, which were active only upon presentation of certain stimuli within the task itself. Therefore, a mixed design allowed for examination of activation throughout the ON period versus the OFF period, as well as activation during the events themselves. Regressors were thus created for events and for blocks of the task. Hence, the columns of the design matrix consisted of both types of reference waveforms, block and event-related, permitting tonic levels of activation and event-related activations to be calculated simultaneously. In other words, block and event-related reference waveforms are both inserted into the deconvolution analysis simultaneously and hence included in the multiple regression analysis resulting in IRFs for events (as discussed above), which are used to calculate percentage area under the curve (%AUC) scores and scaling factors which can be used to determine the percentage change scores (%CS) for blocks. A similar procedure was used in the other studies, except the regressors for the block analyses did not consist of ON periods for the

entire block, but only for certain time periods within a block that were of interest (see individual chapters for a description of the time periods used).

After the %AUC and %CS were calculated for events and blocks, they were warped into standard space. This technique is used due to variability in the shapes and sizes of different subjects' brains and is necessary for averaging and statistical analyses. In this thesis, all brains were warped into Talairach space (Talairach & Tournoux, 1988). Finally, data were blurred using a 3 mm isotropic rms Gaussian blur. This is also a standard technique that is used in the processing of functional imaging data due to variablity across subjects.

After the data had been processed in the above fashion, separate t-tests were carried out against the null hypothesis of no percentage activation change for block and event-related activations in each separate condition (see individual chapters for more detail). This was usually carried out at a voxel-wise threshold of $p \leq 0.001$ (see individual Chapters for variations). A cluster-size criterion, determined by Monte Carlo simulations and depending on the individual parameters of each study (i.e. number of subjects etc) and resulting in a 0.05 probability of a significant cluster surviving by chance was then applied to the data. This ensures that small spurious clusters of active voxels that may be active by chance are not included in the analyses. Finally, maps of similar variables of interest across different conditions were combined (for example all inhibitions or all errors) into one OR map, which resulted in the inclusion of any voxel that was significantly active in any of the individual condition maps. Mean activation in each ROI for each individual subject was then calculated.

These mean activation scores for each ROI for each subject were then subjected to further statistical analyses. Specifics of statistical analyses will be provided in each chapter, however a brief description will be provided here. A number of different analyses were performed including t-tests, ANOVAs and correlational analyses. For example paired comparison t-tests were conducted for activation during events across different conditions, (e.g. inhibitory activation in condition A vs. condition B) in order to examine whether activation significantly differed between conditions in specific brain regions. Repeated measures ANOVAs were carried out for different events between conditions (for example errors in conditions A and B V inhibitions in conditions A and B) in order to examine whether there were differences between different events across conditions. In a number of studies, I was interested in specific dynamics between certain brain regions, namely regions in the PFC and midline areas. To elucidate the possible dynamics between different brain areas in controlling behaviour, correlations were carried out between these areas. If activation in these areas correlated with each other during a certain event, there was a likelihood that these areas were working cooperatively to perform the task at hand. Due to the number of t-tests and correlational analyses that were perfomed during these studies it was necessary to control for multiple comparisons. After carrying out the analyses, the number of tests was counted and were corrected for multiple comparisons using a modified Bonferroni correction (Keppel, 1991), resulting in an alpha level of 0.04. This correction accounted for the number of subjects used and the number of comparisons carried out.

Chapter 3

A Topography of Executive Functions and their Interactions

Abstract

Executive control of behaviour was investigated using fMRI. The Sustained Attention to Response Task (SART), which allows unpredictable and predictable NOGO events to be contrasted, was imaged using a mixed (block and event-related) fMRI design to examine tonic and phasic processes involved in response inhibition, error detection, conflict monitoring and sustained attention. A network of regions, including right ventral PFC, left DLPFC and right inferior parietal cortex, was activated for successful unpredictable inhibitions, while rostral anterior cingulate was implicated in error processing and the pre-SMA in conflict monitoring. Furthermore, the pattern of correlations between left dorsolateral PFC, implicated in task-set maintenance, and the pre-SMA were indicative of a tight coupling between prefrontally mediated control and conflict levels monitored more posteriorly. The results reveal that the executive control of behaviour can be separated into distinct functions performed by discrete cortical regions.

3.1 Introduction

The control over routine, everyday behaviour involves a number of complex executive processes, including the maintenance of current goals, allocation of attentional resources, performance monitoring, inhibition of irrelevant stimuli or responses, detection of errors and the subsequent adjustment of behaviour. Understanding how the brain instantiates these processes and brings them to bear on current task demands in a smooth and dynamic manner remains one of the challenges of cognitive neuroscience as well as a critical challenge for understanding and ultimately reducing human error.

3.1.1 The Present Study

The SART (Robertson et al., 1997) has been shown to both predict the likelihood of such real life errors in normal and brain damaged individuals, but also to be particularly sensitive to the presence of frontally-impacting traumatic injury. In the Random SART the digits 1 to 9 are presented in random order and subjects respond with a mouse click to each digit except 3 to which they must withhold their response. In the Fixed SART the digits are presented in a repeating, ascending order (1, 2, 3,..., 8, 9, 1, 2....) and subjects respond to all digits except 3.

The utilisation of the Fixed SART as a comparison for the Random SART facilitates the investigation of a number of different processes. Both tasks require participants to withhold a motor response to the number 3. However, in the Random SART inhibition of a prepotent motor response is essential as the requirement to inhibit responding is unpredictable whereas in the Fixed SART the need to withhold a response is predictable and may therefore involve response selection rather than

response inhibition *per se*. In the Fixed SART participants are aware that a withhold event is approaching, and as opposed to executing a last minute "urgent" inhibition they are able to prepare a withhold response. We may conclude, then, that a comparison of Random versus Fixed successful inhibitions to NOGO events may isolate response inhibition processes, with the Fixed SART acting as a response-selection and visuo-motor control condition.

Response inhibition may not be the sole function isolated by this comparison, however. The competition between the prepared GO response and the urgent requirement to withhold that prepotent response upon presentation of the NOGO stimulus in a GO/NOGO task has previously been shown to induce response conflict (Braver et al., 2001; Garavan et al., 2003). Response conflict is thought to occur when two conflicting response pathways or tendencies (here, the motor response itself and the need to withhold that response) are activated simultaneously. In addition, Logan's (Logan & Cowan, 1984) race-model, which proposes a "race" between the GO and the NOGO responses upon presentation of a NOGO event, would also support the existence of response conflict in its current definition. Therefore, successful withholds to NOGO stimuli in the Random SART can be expected to involve a degree of response conflict which will presumably be absent from successful withholds in the Fixed SART where individuals will have had time to prepare to withhold their response. Bearing this in mind, we might expect to see activation of regions that monitor for response conflict during successful inhibitions to Random NOGO events as well as regions that are involved in inhibition. From previous studies we may anticipate that right prefrontal areas will be involved in inhibitory processes (Aron et al., 2003; Braver et al., 2001; Casey et al., 1997; Garavan et al., 2002; 1999; Konishi

et al., 1998) whereas areas lying along the medial wall will monitor response conflict (Barch et al., 2000; Botvinick et al., 1999; Braver et al., 2001; Carter et al., 1998; Garavan et al., 2002; Hester, Fassbender & Garavan, 2004; Ullsperger & von Cramon, 2001; van Veen & Carter, 2002; van Veen et al., 2001). We may also expect to see both tonic activation in areas that detect response conflict and activation in areas that combat response conflict by enforcing top-down control.

Activation has previously been observed in the right DLPFC and right superior parietal lobe (SPL) when performing the SART (Manly et al., 2003) and this right hemisphere fronto-parietal network has been implicated in sustained attention (Coull et al., 1998; 1996; Sturm et al., 1999; Wilkins et al., 1987). Error processing, believed to implicate ACC (Kiehl et al., 2000; Menon et al., 2001; Ullsperger & von Cramon, 2001), can be investigated, as commission errors are common in the Random SART. Some of these processes, such as sustained attention, are tonically active throughout the task; in other words, the need to maintain one's endogenously driven attention is constant throughout. These tonic processes are best examined utilizing a block fMRI design. However, other processes such as inhibitory or error-related events are discreet, transitory events and hence require event-related analysis. Consequently, a mixed design (block and event-related) was utilized in order to identify tonically activated areas and areas that were active phasically, for conflict related processes and for both successful and unsuccessful attempts to inhibit responding. It was hypothesized that a right fronto-parietal network would be tonically active reflecting sustained attentional processes and that predominantly right hemisphere fronto-parietal regions would be recruited during successful inhibitions to a NOGO. Midline areas were hypothesized to be involved in error detection and response conflict

monitoring. More specifically, ACC involvement was expected in error detection and pre-SMA in conflict monitoring. Finally, given the proposed dynamics between response conflict and top-down attentional control (Botvinick et al., 2001; Carter et al., 1998; Cohen et al., 2000; Garavan et al., 2002; MacDonald et al., 2000) individual differences among participants were examined in order to evaluate whether or not there was evidence of a relationship between these two processes in the implementation of cognitive control.

3.2 Methods

2.2.1 Subjects

7 males and 14 females with ages ranging from 19 to 37 and a mean age of 26.4 participated in this experiment. Three subjects were subsequently excluded from the analysis due to excessive movement. All participants were Participants were paid for their participation.

2.2.2 Materials

Sustained Attention to Response Task.

A modified version of the SART (Robertson et al., 1997) that consists of a series of numbers from 1 to 9 presented in a random and unpredictable (Random SART) or sequential and predictable (Fixed SART) order was employed (see Figure 3.1). Subjects responded by mouse click to every number except the number 3. Each digit was presented for 250 msecs. In order to minimize response time differences between the Random and Fixed SART a visual response cue of 50 msecs duration with a post-stimulus onset time of 100 msecs, (parameters based on (Manly, Davison, Heutnink,

Galloway, & Robertson, 2000)), was utilized. This response cue, a thickening of the post-stimulus mask, appeared as a "visual blip". Subjects were instructed to respond in time with this response cue and were trained before entering the scanner. The duration of the entire post-stimulus mask varied, (461, 572, 683, 794, 906 or 1017 msec) in order to sample different points in the haemodynamic curve as the NOGO stimulus (the number 3) consistently fell after every ninth digit in the Fixed SART. Post-stimulus duration changed after each full cycle (digits 1 through 9 in the Fixed SART and after each set of nine random digits in the Random SART). A distinct cue to indicate the onset of the next digit was presented during the final 400 msec of all post-stimulus periods (see Figure 3.1.). There were 36 NOGO stimuli in the Fixed SART and 34 in the Random SART. These NOGO stimuli were placed on average twelve seconds apart in the Random SART (ranging from 2 to 30 sec apart). Stimuli were presented and responses recorded using E-prime (Psychology Software Tools Inc.)

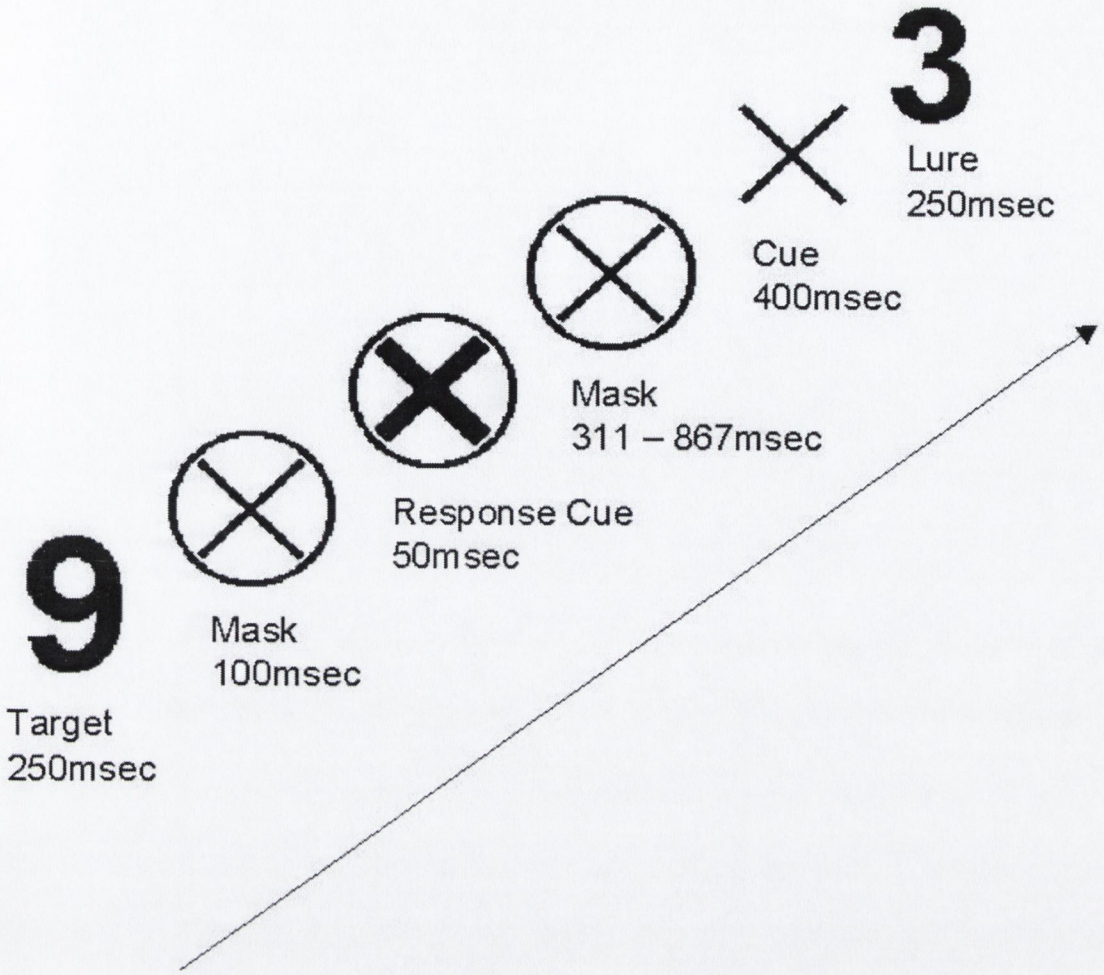


Figure 3.1: An example of one cycle of the Sustained Attention to Response Task (Random) is presented. The variable post-stimulus mask contained a response cue which appeared to participants as a visual "blip" in order to reduce reaction time differences that are typically found between Random and Fixed SART. A predictable pre-stimulus cue was also provided.

fMRI scanning

202 high resolution, T_1-weighted MPRAGE, sagittal slices were acquired for each subject (slice thickness = 1 mm, field of view = 256 mm) to allow subsequent anatomical localization and spatial normalisation. Functional images were single-shot, T2* weighted, echo planar imaging sequences. 22 axial slices (5 mm slice thickness) were acquired for each subject (TR = 2000 msec, TE = 50 msec, flip-angle = 90degrees, 64 mm x 64 mm matrix size, field of view = 256 mm). 305 volumes were

scanned for each run (Fixed and Random SART). Stimuli were presented through an LCD screen, which was mounted on the head coil and was directly in the subjects' line of vision.

3.2.3 Procedure

SART

Stimuli were presented in blocks of 90 to 92 seconds, which alternated with 30 sec rest periods. Five blocks of Fixed SART comprised one run and five blocks of Random SART comprised a second run and run order was counterbalanced across subjects. There were 36 NOGOs in the Fixed and 34 NOGOs in the Random SART of the 326 stimuli in each condition.

2.2.4 Data Analysis

Behavioural analysis

Average percent correct withholds, omission errors, GO and error of commission RTs were obtained for each participant for each condition. Paired comparison t-tests were used in order to compare Fixed and Random SART results, and a 2 (correct inhibition vs. commission error) X 2 (Fixed vs. Random SART) repeated measures ANOVA was carried out on the Fixed and Random RTs for correct responses and errors of commission. Correlational analyses were also conducted between left and right PFC and midline regions.

Image analysis

A mixed regression analysis was employed whereby tonic, task-related activation was calculated as a percentage change score using rest as baseline and separate IRFs were calculated for correct inhibitions and commission errors as discussed in Chapter 2,

resulting in separate %AUC scores for inhibitions and errors.

Separate t-tests against the null hypothesis of no percentage activation change were then performed for Random and Fixed tonic activation and Random and Fixed correct inhibitions with a voxel-wise threshold of $p \leq 0.001$ and a cluster-size criterion of 126 µl of contiguous significant voxels. Fixed and Random tonic activation maps were then combined into OR maps and mean activation was then calculated for each of the resulting functionally defined regions of interest by condition. A similar procedure was employed for the Fixed and Random event-related, correct inhibition map. Differences between the SART conditions in these regions of interest were then tested with paired t-tests.

A slightly different method was used in order to make commission error maps due to the small number of errors in the Fixed SART. Percentage area maps for Fixed and Random SART were combined using weighted averaging (Fixed error activation multiplied by the number of Fixed errors plus Random error activation multiplied by the number of Random errors divided by the total number of errors) before t-testing against zero, resulting in one activation map for Fixed and Random errors combined. A more liberal p value of $p \leq 0.005$ combined with a cluster size criterion of 126 µl of contiguous significant voxels was used for this map, as activations were absent at the level of $p \leq 0.001$. A widespread network of areas was activated for errors, including some areas that were also activated for successful inhibitions. Our previous research has shown that errors of commission on GO/ NOGO tasks often include activated areas seen during successful inhibitions, which we interpret to reflect late,

unsuccessful attempts at inhibition (Garavan et al., 2002). Consequently, areas specific to error-related processes were required to significantly differ in activation from successful inhibitions.

Inter-individual correlations between activated brain regions were performed to determine the degree to which areas underlying executive functions interacted with one another.

3.3 Results

3.3.1 Behavioural Results

Three subjects were excluded from the analysis due to excessive movement. The remaining eighteen subjects (five male, mean age 26.5, range 19-37) had significantly more correct withholds in the Fixed (32.4 ± 5.5) than in the Random SART (24.3± 3.6; $t(17) = 7.6$, $p \leq 0.001$). There were comparable numbers of errors of omission in the two conditions (7.28± 9.22 in the Fixed and 6.83± 9.68 in the Random SART, $t(17) = 0.17$, $p \leq 0.86$). Reaction times are presented in Figure 2.2. Although the commission errors in the Random SART followed a typical pattern for commission errors in GO/ NOGO tasks in that they were significantly faster than response times for GOs (445.9± 97.1 v 374.9± 111.4; $t(16) = 4.121$, $p \leq 0.001$) this was not the case for errors of commission in the Fixed SART in which commission errors and GO response times did not differ (439.7± 113.5 v 431.9± 108.6; $t(15) = 0.350$, $p \leq 0.731$). A 2 (correct inhibition vs. commission error) X 2 (Fixed vs. Random SART) repeated measures ANOVA was carried out on these response times. Performance (correct vs. incorrect) and the interaction were both significant ($F(1,14) = 6.35$, $p \leq .02$; $F(1,14) =$

7.46, $p \leq .02$ respectively).

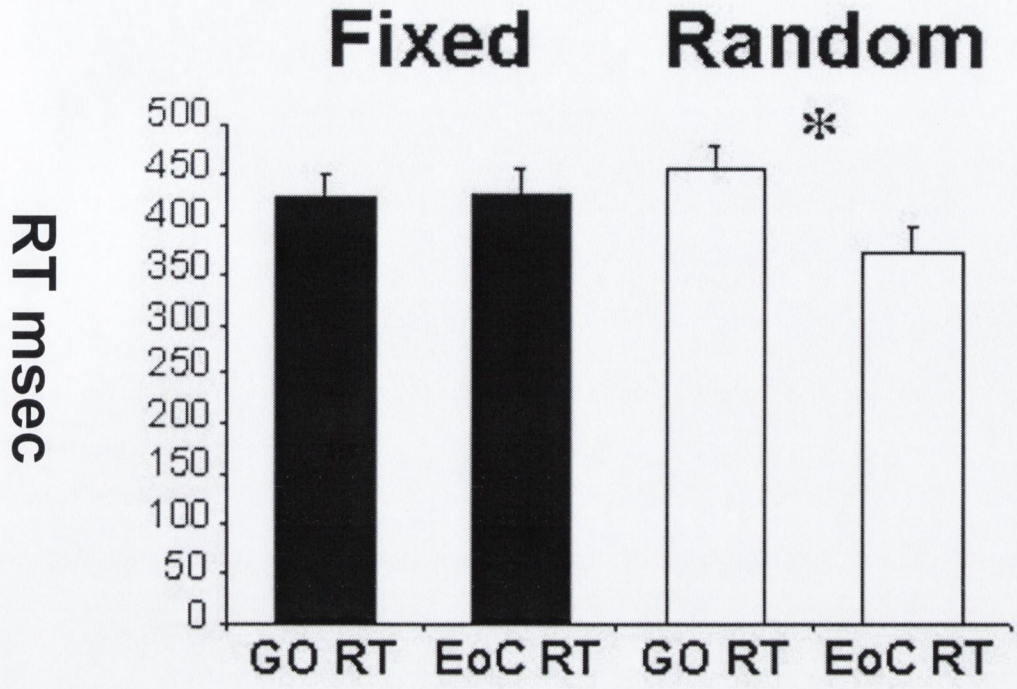


Figure 3.2: GO event reaction times and commission error reaction times (RT) for the Fixed (F) and Random (R) SART, * $p < 0.001$.

3.3.2 fMRI Results

Block Activation

A number of regions, visual, motor and frontoparietal were tonically activated during task performance (see Table 3.1). A subset of these areas were significantly more active for Random compared with Fixed SART and included pre-SMA, left and right putamen, left insula/ inferior frontal gyrus (IFG), left precuneus, left parahippocampal gyrus and left supramarginal gyrus. No area showed significantly greater activation for the Fixed SART (see Figure 3.3).

Table 1.
Tonic Activations for Fixed and Random SART

	Brodmann Area	Hemisphere	Volume (◊l)	Talairach coordinates (centre of mass) x (RL)	y (AP)	z (IS)
Frontal lobes						
Precentral gyrus/MFG	6/9	L	1148	-43	0	32
Primary Motor Cortex	4	L	936	-40	-18	49
Pre-Motor Cortex	6	R	280	46	0	28
Median Wall	6/32	B[a]	1022	-2	-1	49
Frontal Operculum		L[a]	691	-43	8	1
Insula	41/42	R[a*]	824	39	-21	10
Occipital lobes						
Occipital lobe (Cuneus)	17/18/19	B*	15668	-3	-67	6
Inferior Occipital gyrus	17/18/20	R	5762	31	-80	-5
	17/18	L	3853	-30	-89	-5
Lateral Occipital gyrus	19	L	2692	-42	-64	-8
Parietal lobes						
Intraparietal sulcus	7/40	R	592	28	-53	42
		L	629	-30	-46	40
Superior Parietal lobule	7	R*	153	18	-53	62
Inferior Parietal lobule	7	L	610	-33	-61	48
Paracentral lobule	4	R[a*]	385	5	-27	43
Supramarginal gyrus	40	L[a]	181	-42	-39	30
Lingual gyrus		L*	289	-24	-38	-11
Subcortical Regions						
Precuneus	7	L[a*]	1079	-12	-46	47
Putamen		R[a]	762	22	0	7
		L[a]	5238	-21	-8	7
Cerebellum						
Culmen		R	300	6	-55	-20

Note: IFG, inferior frontal gyrus; MFG, middle frontal gyrus; SFG, superior frontal gyrus; L, Left; R, Right; B, Bilateral. For x, y, z coordinates, R, A & S are positive.

[a] signifies that activation was significantly greater in the Random than the Fixed SART.

[b] signifies that activation was significantly greater in the Fixed than the Random SART.

* signifies a deactivation in the Fixed SART

Table 3.1: Tonic activations for the Fixed and Random SART

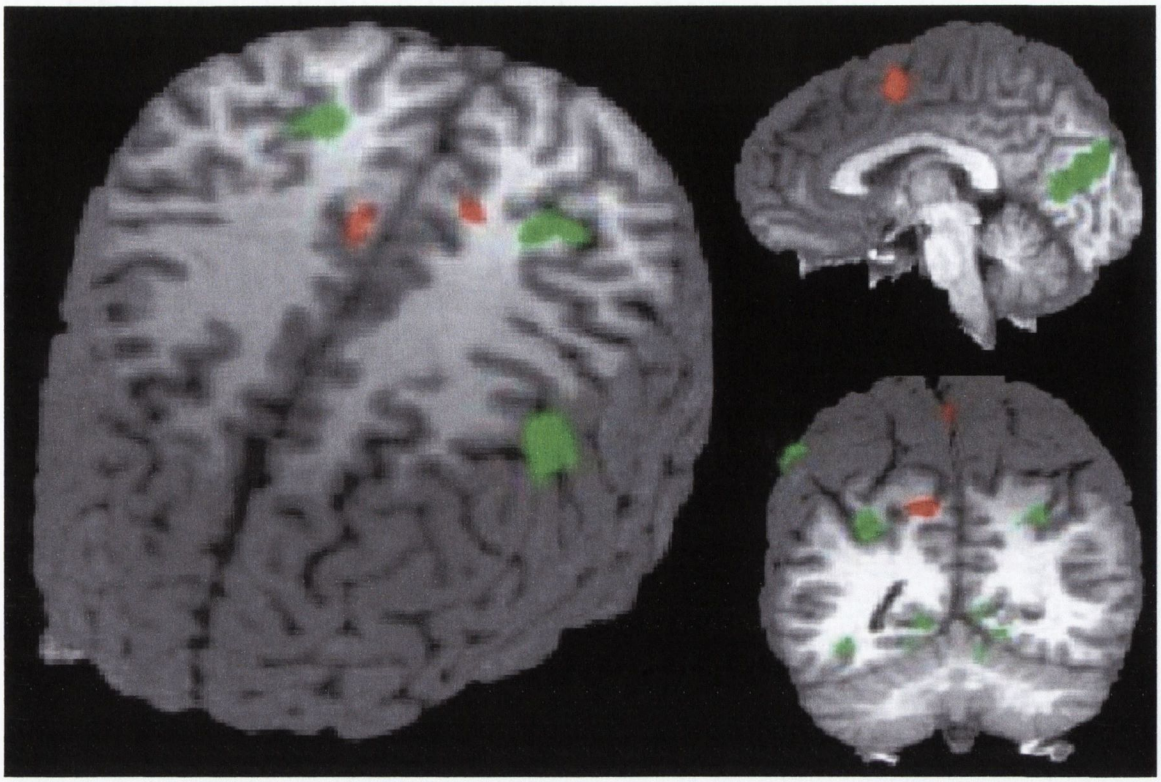


Figure 3.3: Tonic functional activation associated with the Random and both Random and Fixed SART. Areas in red that were significantly more activated for the Random over the Fixed SART included the pre-SMA and the right medial wall. Areas in green that were activated tonically in both the Fixed and Random SART and did not significantly differ between the two conditions included left dorsolateral prefrontal cortex, bilateral inferior parietal cortex and visual areas (bilateral cuneus and left lateral occipital gyrii are shown).

Correct Inhibition Activation

Two distinct networks were seen to underlie correct inhibitions in the Fixed and Random conditions (see Table 3.2). The right ventral frontal cortex, right IPL, left DLPFC and the left putamen were significantly more active during correct inhibitions in the Random condition than in the Fixed condition, whereas the left IFG, right angular gyrus, left insula, and left middle frontal gyrus showed significantly greater activation during correct inhibitions in the Fixed Condition. No area was significantly activated for correct inhibitions in both the Fixed and Random SART suggesting that distinct networks were responsible for withholding a response in the two conditions

(see Figure 3.4).

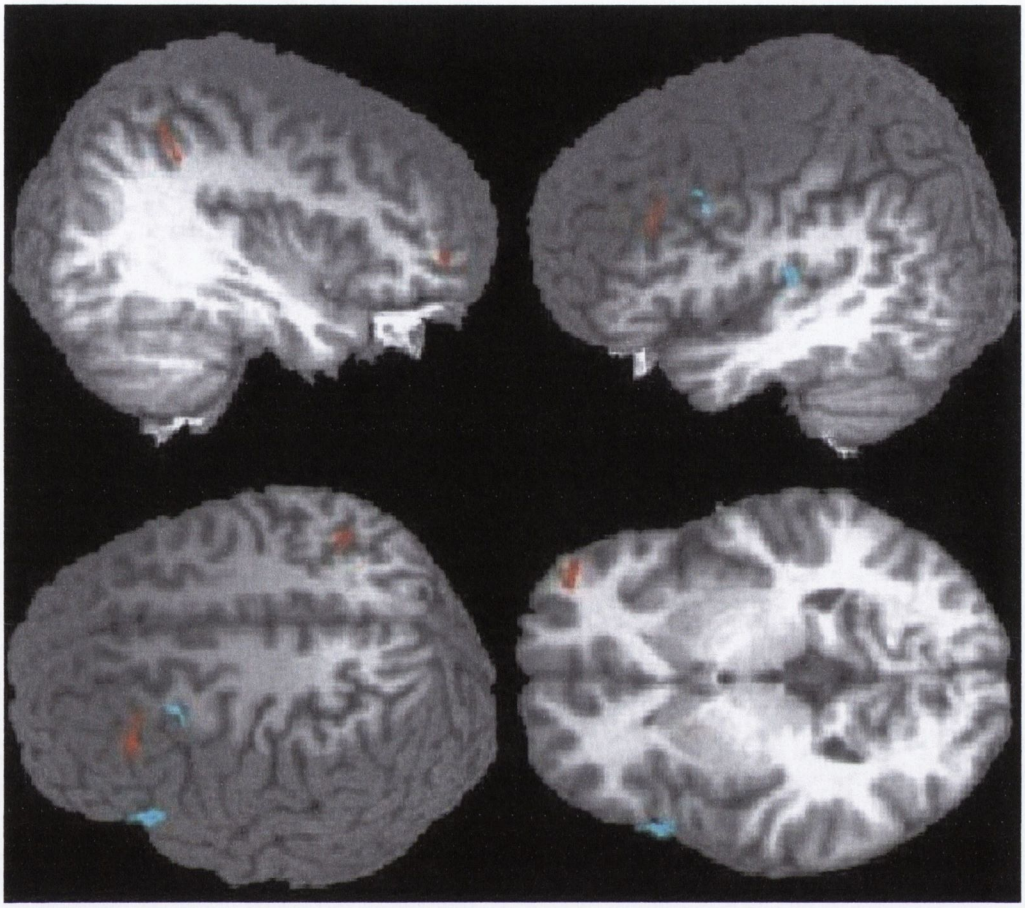


Figure 3.4: Functional activation associated with correct inhibitions for Fixed (blue) and Random (red) SART. Correct inhibitions to unpredictable NOGO events in the Random SART activated right ventral frontal cortex, right inferior parietal cortex and left dorsolateral prefrontal cortex. Correct inhibitions to predictable NOGO events in the Fixed SART activated left middle frontal gyrus, left inferior frontal gyrus and left insula.

Table 2.
Event-Related Activations for Fixed and Random SART

	Brodmann Area	Hemisphere	Volume ((l)	Talairach coordinates (centre of mass) x (RL)	y (AP)	z (IS)
	Activations for Correct Inhibitions					
Frontal lobes						
IFG	45/47	L [b]	340	-52	16	3
IFG/MFG	47/10	R [a]	131	35	49	2
MFG	9	L [a]	136	-42	24	35
Pre-Motor Cortex	6	L [b]	162	-39	8	42
Parietal lobes						
Inferior Parietal lobule	40	R [a]	244	36	-48	44
Angular gyrus	39	R [b]	264	44	-61	31
Postcentral gyrus/Insula	40	L [b]	253	-47	-23	18
Subcortical Regions						
Putamen/Internal Capsule		L [a]	193	-22	11	8
	Activations for Commission Errors					
Frontal lobes						
Anterior Cingulate	32	B	1231	1	25	28
	24/32	R	277	9	35	12
IFG/Insula	47/45	L	1883	-45	19	1
	47	R	285	33	16	-9
	47	R	248	46	16	-1
MFG	9	L	153	-31	20	34
Temporal lobes						
Superior Temporal gyrus	22	L	202	-62	-40	9
Parietal lobes						
Supramarginal gyrus	40	R	1778	47	-43	34
Inferior Parietal lobule	40	L	174	-53	-44	26
	40	L	141	-64	-38	27
Other Regions						
Cingulate	23	L	847	-3	-23	28
Caudate		R	131	30	-40	12

Note: Abbreviations and diacritics are as for Table 1.

Table 3.2: Event-related Activations for Fixed and Random SART

Commission Error Activation

A combined (Fixed and Random) error map was constructed due to the small number of errors, particularly in the Fixed SART. These errors of commission produced widespread cortical activity (see Table 3.2). Activated areas included two regions in ACC and one in posterior cingulate, bilateral inferior frontal gyrus/insula and two left inferior parietal regions (see Figure 3.5.).

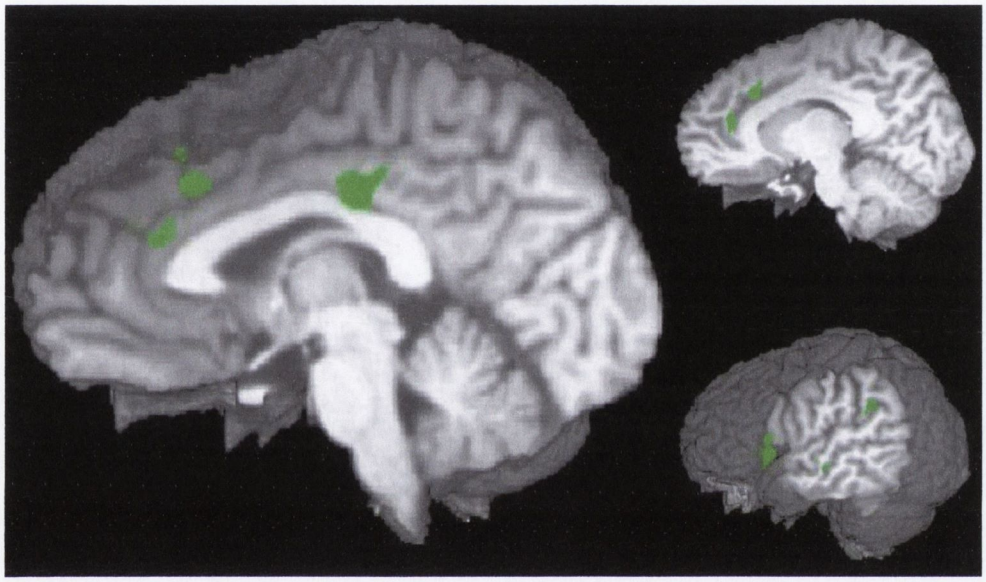


Figure 3.5: Functional activation associated with errors of commission collapsed across the Fixed and Random SART conditions. Areas shown include the anterior and posterior cingulate, left inferior frontal gyrus extending into insula, left inferior parietal lobe and left middle temporal gyrii. Areas are shown in green as this map was derived from Fixed and Random Errors. Due to the small number of errors, Fixed v Random comparisons were not carried out.

Relationship between Tonic and Phasic Activation

We were interested in the interactions between tonic and phasic activation levels and, particularly between areas that might reflect the dynamic between the maintenance of task-set information and levels of response conflict. The tonically activated left DLPFC region is a probable area for subserving the task-set maintenance role (Brass

& von Cramon, 2002; Frith & Dolan, 1996; Garavan et al., 2002; Teng, 1998) while the activated midline areas, particularly the ACC and pre-SMA, were likely to have subserved the conflict monitoring role (Carter et al., 1998; Ullsperger & von Cramon, 2001). Mean activations associated with the Random SART in the following regions were correlated with each other treating subjects as a random effect; the left DLPFC area (precentral gyrus (BA6) extending over the precentral sulcus onto the middle frontal gyrus (BA9)(centre of mass: x=-43, y=0, z=32)) and the pre-SMA region (-2, -1, 49) were both defined by the tonic OR map and the combined error map defined all three ACC regions (1, 25, 28; 9, 35, 12; -3, -23, 28). Only activations in the Random SART were examined, due to the small number of errors in the Fixed SART. A tight coupling was observed between left DLPFC and pre-SMA. Tonic left DLPFC activation correlated positively with tonic pre-SMA activation ($r(18) = 0.7$, $p \leq 0.001$). This coupling was also present when examining phasic activity in these tonically defined ROIs. Hence, for errors of commission, phasic left DLPFC activity correlated with the same pre-SMA region ($r(18) = 0.65$, $p \leq 0.004$). An inverse relationship between these two areas was observed in just one circumstance: Tonic left DLPFC activation correlated negatively with phasic pre-SMA activation for commission errors ($r(18) = -.55$, $p \leq 0.02$). Conversely, neither error-related nor tonic activation in the ACC regions correlated with error-related or tonic activity in the DLPFC or the pre-SMA. Neither were any of these correlations seen between midline areas and the right PFC ROIs.

2.4 Discussion

2.4.1 Neural Network Underlying Response Inhibition.

Two separate networks were activated for correct inhibitions in the Fixed and Random SART. The distinctiveness of these networks was reflected in different patterns of response times for the Random and Fixed SART. Commission errors in the Random SART were significantly faster than GO response times, a common reaction time finding in GO/ NOGO tasks suggestive of insufficient time to inhibit the prepotent GO response (Logan & Cowan, 1984). Conversely, NOGO error response times in the Fixed SART were not significantly different than GO response times, suggesting that errors may have been due to an inattentive default GO response. Therefore, the network of brain regions activated for Random correct inhibitions might be interpreted as being specifically related to response inhibition.

Correct inhibitions to unpredictable NOGO events in the Random SART activated the right ventral PFC, right IPL, left putamen and the left DLPFC. The involvement of prefrontal and parietal areas in response inhibition is very well established (Braver et al., 2001; Garavan et al., 1999; Kawashima et al., 1996; Konishi et al., 1999; Konishi et al., 1998). A role in inhibitory processes has been attributed to the right IPL based on GO/ NOGO (Garavan et al., 1999; Menon et al., 2001; Rubia et al., 2001) tasks, Stroop tasks (Peterson et al., 2002), Stop paradigm tasks (Rubia et al., 2001) and the Simon task (Peterson et al., 2002). Ventral prefrontal involvement in inhibition has also been observed (Garavan et al., 1999; Iversen & Mishkin, 1970). Konishi and colleagues noted right inferior frontal involvement in inhibition irrespective of which hand was used to respond in a GO/ NOGO task (Konishi et al., 1998) and across different types of inhibitory tasks (Konishi et al., 1999). Menon and colleagues (2001)

also found bilateral, but in particular, right hemisphere activation of the inferior frontal sulcus for inhibitory events.

One discrepancy between this task and others that have attempted to measure response inhibition is our finding of left versus right DLPFC involvement in response inhibition (Bunge, Ochsner, Desmond, Glover, & Gabrieli, 2001; Garavan et al., 1999; Menon et al., 2001). One reason for this disparity may be the relatively high verbal demands of the present task. Left DLPFC has been implicated in verbal working memory with a proactive interference component (Jonides et al., 1998). In a further experiment, D'Esposito and colleagues (D'Esposito et al., 1999) found activation in this region during presentation of the probe when it must be compared to the "mnemonic representations of the memory set" (p. 7518). It may be that a similar process takes place in this experiment upon introduction of the NOGO stimulus in that there may be an internal check as to whether the number is part of the GO or NOGO set. Thompson-Schill and colleagues (Thompson-Schill, D'Esposito, Aguirre, & Farah, 1997; Thompson-Schill, D'Esposito, & Kan, 1999) have associated left inferior prefrontal cortex with selection of semantic knowledge in the face of distraction. However, the present GO/NOGO task had a much lower semantic demand requiring the inhibition of a prepotent response tendency and not selection between a number of semantic options.

Another possibility is that observed differences may be due to the use of a consistent stimulus-response mapping in this experiment (i.e., subjects always inhibited to the number 3), whereas others (Bunge et al., 2001; Garavan et al., 2002; 1999) have utilized variable stimulus-response mappings (i. e., the appropriate response must be

chosen for different contexts as it is not unambiguously determined by the stimulus). Variable mapping between the stimulus and the appropriate response may require response selection in which participants must select whether a particular stimulus represents a GO or A NOGO response. This function has been attributed to right DLPFC (Garavan et al., 2002; Rowe et al., 2001) and this may explain why this area was not observed for the consistent mapping inhibition of the present study. If the stimulus-response mappings are variable, mappings need to be maintained in working memory and there may be increased demand on selecting the appropriate mapping. Consequently it may follow that right frontal activations may not be associated with inhibition, *per se*, but with additional processes required at the time of inhibition. Consistent with this reasoning a recent study (Mostofsky et al., 2003) has suggested that right prefrontal involvement may be attributable to task complexities, which require additional processes such as working memory at the point of inhibition. The authors in this study found activation in the pre-SMA alone when a very simple GO/NOGO task was employed but found additional DLPFC activation as task complexity was increased.

In contrast, a mainly left-lateralized network of areas was observed for correct inhibitions to predictable NOGO events in the Fixed SART. Left DLPFC was activated during Fixed correct inhibitions and has previously been implicated in task set maintenance (Frith & Dolan, 1996; Garavan et al., 2002; MacDonald et al., 2000; Ruchsow et al., 2002). A similar area was also activated tonically in the Fixed and Random SART. It may be that this region is involved in tonic task-set maintenance and also reactivates task set just prior to or during the occurrence of the predictable number 3 in the Fixed SART. Consistent with this functional attribution, Brass and

colleagues (Brass & von Cramon, 2002) have recently shown this area to be active during task preparation.

2.4.2 Tonically Activated Executive Functions

An extensive, task-related, tonic activation pattern was observed including visual and motor areas. Of particular interest, however, are those areas that may be associated with executive processing. As mentioned, one particular area of note, the left DLPFC, has previously been implicated in maintenance of representations (Frith & Dolan, 1996; MacDonald et al., 2000; Ruchsow et al., 2002). This same area was observed in a GO/NOGO study after subjects adjusted their behaviour following commission errors and was interpreted as being involved in maintaining/re-establishing task set (Garavan et al., 2002). Consequently, this left DLPFC area, which was significantly active for both the Fixed and the Random SART, as well as for Fixed correct inhibitions, was likely to have been involved in the maintenance of the task set or goals.

The pre-SMA region was seen to be significantly more active for the Random over the Fixed SART. Given this region's involvement in motor preparation (Picard & Strick, 1996; Tanji, 1994), it may be that the increased need for motor preparation in the Random SART, that is the need to be primed to withhold a response, may be responsible for this activation pattern. Another possibility is that the pre-SMA is monitoring for response conflict. This region and more inferior midline regions within the ACC have been implicated in conflict monitoring (Braver et al., 2001; Bunge et al., 2001; Carter et al., 1998; Ullsperger & von Cramon, 2001) and it is reasonable to assume that the Random SART would generate greater amounts of tonic response conflict than the Fixed SART. This latter interpretation is consistent with the pattern

of correlations, discussed below, between the left DLPFC and the pre-SMA. Furthermore, if response conflict is generated by the co-activation of competing motor responses then a role for this structure in conflict monitoring would be consistent with its role in motor preparation (Garavan et al., 2003).

Finally, right parietal and prefrontal areas were anticipated to be tonically active given their established role in sustained attention (Coull et al., 1998; 1996; Sturm et al., 1999; Wilkins et al., 1987). An unexpected but significant deactivation was seen in the right SPL for the Fixed SART and activation was observed in the left IPL and bilateral superior lobules (extending into the IPL in the right hemisphere) and the right IFG in both conditions. Manly et al (2003) found activation in the right DLPFC and right parietal cortex for the Fixed over the Random SART in their PET study whereas, we did not find any activation for the Fixed over the Random SART. The use of a relatively quiet PET environment, an older subject group (mean of 51.86 versus a mean of 26.4 in this study), unvarying stimulus presentation and the absence of a response cue in their study may have been more sensitive than ours to detecting endogenously driven attention.

2.4.3 Conflict Monitoring and Error Processing

Some controversy exists as to whether the ACC is involved in error processing *per se* or rather conflict monitoring (Carter et al., 1998; Kiehl et al., 2000; Ruchsow et al., 2002; Ullsperger & von Cramon, 2001). Carter and colleagues observed activation in the ACC not only during error trials but also during trials involving high amounts of response conflict (Carter et al., 1998). Other evidence suggests that the more rostral region of the ACC may be involved in error detection and the more caudal ACC

extending into the pre-SMA may be involved in response conflict (Braver et al., 2001; Nielson et al., 2002; Ullsperger & von Cramon, 2001; van Veen & Carter, 2002). In the present study a widespread pattern of activity was observed for Fixed and Random errors. These included two regions in the ACC and two left inferior parietal regions. The medial parietal lobes (precuneus) have previously been implicated in error processing (Menon et al., 2001) and the left parietal lobe has also been considered to be a contributor to the P_E (error positivity) (Van Veen & Carter, 2002), a component of error trial ERPs that is thought to reflect error processing. These ACC regions were not activated tonically during task performance. Conversely, an area in the pre-SMA displayed significantly greater tonic activation for the Random SART but did not show a phasic error-related response. Together, these findings suggest that the more rostral area of the ACC is an error processing area and that the more caudal ACC area extending into the pre-SMA serves a response conflict monitoring function (Braver et al., 2001; Kiehl et al., 2000; Menon et al., 2001; Ullsperger & von Cramon, 2001).

3.4.4 PFC and Midline Interactions

Barch and colleagues (2000) predicted a correlation between DLPFC and ACC, under the assumption that conflict monitored by the ACC would trigger recruitment of top-down attentional resources from the DLPFC. In the present study, this relationship was seen between DLPFC and pre-SMA. A positive correlation was also seen between phasic activation of left DLPFC and phasic pre-SMA for errors of commission. We would expect to see this pattern if cognitive control is effected by the detection of high levels of conflict by pre-SMA triggering a rise in top-down control exercised by left DLPFC akin to the model suggested by Botvinick and colleagues (Botvinick et al., 2001). In effect, those subjects who showed the greatest

midline (response-conflict) activation also showed the greatest left DLPFC (top-down control) activation. Consistent with this interpretation, individuals who displayed low tonic levels of top-down control showed increased levels of phasic conflict, monitored by pre-SMA, on error trials. This relationship also supports existing models (Botvinick et al., 1999; Braver et al., 2001; Carter et al., 1998) which posit that cognitive control is achieved by the PFC maintaining representations of task-relevant information and suppressing competing or distracting, task-irrelevant information, thus reducing response conflict as monitored by the ACC, or as in this task, the more caudal part of the ACC extending into the pre-SMA region. Together, these correlations add strong support to the concept of a reciprocal relationship between these two regions (Cohen et al., 2000), the pre-SMA monitoring for conflict and feeding back to DLPFC, which maintains task set and allocates attentional resources.

Interestingly, the inter-regional correlations that have been reported above were not seen between DLPFC and ACC. That this relationship was not observed suggests that the ACC activation observed during error trials may not reflect a conflict-related activation. Instead, one conjecture, in need of further corroborating evidence, is that the ACC activation may reflect emotional (Bush et al., 2000; Luu, et al., 2000; Luu, Tucker, Derryberry, Reed, & Poulsen, 2003; Menon et al., 2001), reward-related processes (Devinsky, Morrell, & Vogt, 1995; Gehring & Willoughby, 2002; Hadland, Rushworth, Gaffan, & Passingham, 2003; Ruchsow et al., 2002) or may be monitoring performance in some other way. In fact, in a recent review paper Schall and colleagues have illustrated that, in monkeys, there has been no evidence of conflict related neural activity in ACC whereas they have seen clear examples of this in pre-SMA (2002). A recent electrophysiological study attempted to dissociate

conflict-related processes and error monitoring in a neurological patient with a lesion of rostral ACC extending into dorsal ACC (Swick & Turken, 2002). The patient displayed a reduction in ERN compared to controls and also displayed lower error-correction rates. However, the stimulus-locked N450 component that was interpreted as reflecting response conflict processes was enhanced. This is suggestive of a dissociation of error and conflict related processes along the midline, with the intact pre-SMA possibly monitoring for response conflict. Finally, Ullsperger and von Cramon provided more evidence of pre-SMA involvement in conflict monitoring in their imaging study of error monitoring using external feedback (2003). In a task in which subjects were highly uncertain about the outcomes of their actions, the authors provided positive, negative and neutral feedback. They postulated that conflict-related activity should occur on high conflict trials irrespective of the type of feedback that was provided (non-informative or negative), whereas activity related to negative feedback should occur only after trials in which participants were provided with informative feedback. They report that the rostral cingulate motor area was activated by negative feedback whereas pre-SMA responded to response conflict. The fact that we found no relationship between ACC and left PFC whereas we did between pre-SMA and PFC is an interesting finding with regard to the ongoing debate as to whether errors themselves or simply levels of response conflict trigger additional recruitment of top-down control as enforced by PFC. In this particular experiment it appears that error-related activity detected by ACC does not directly engage PFC as we found no correlation between these two areas, even during errors. Perhaps this suggests that the characteristic finding of post-error behavioral adjustment (Rabbitt, 1966) can be explained by high levels of conflict-related activity during errors triggering PFC involvement as has been previously suggested by Botvinick and

colleagues (2001).

In summary, the comparison of correct inhibitions to unpredictable NOGO events with inhibitions to predictable NOGO events revealed a discrete number of prefrontal and parietal brain regions implicated in inhibitory control. The rostral area of the ACC and the left parietal lobe displayed a role in error processing, whereas the more dorsal part of the ACC and the pre-SMA appeared to play a role in conflict monitoring. Guided by previous research, we suggest that the parietal and right prefrontal areas were involved in sustained attention while the left DLPFC actively maintained the task set. These results reveal a neuroanatomical fractionation of those executive functions critical for smooth behavioural control. Furthermore, the inter-regional correlations revealed that midline regions and DLPFC work cooperatively in order to complete the task successfully, constantly working in parallel to monitor conflict, maintain task goals and enforce control.

Chapter 4

Prefrontal and Midline Interactions Mediating Behavioural Control.

Abstract

Control of behaviour involves different executive processes. Top-down control is thought to interact with bottom-up demands to facilitate the smooth execution of behaviour. Frontal and midline areas are thought to subserve control processes. In this fMRI study, we utilised a GO/NO-GO task with cued and uncued inhibitory events to investigate the effect of cue-induced levels of top-down control on response conflict detected by midline areas. We found that on a within-subjects, trial-for-trial basis, high levels of top-down control as indexed by left dorsolateral prefrontal activation prior to the NO-GO resulted in lower levels of activation on the NO-GO trial in the pre-SMA. These results suggest a tight coupling between prefrontal and midline regions in the implementation of cognitive control.

4.1 Introduction

Botvinick, Carter, Cohen and colleagues have theorised that PFC and midline areas work together in implementing cognitive control (Botvinick et al., 2001; Cohen et al., 2000). They maintain that the ACC monitors for the conflict produced when two competing response pathways are simultaneously activated and this information feeds back to PFC in order to increase levels of top-down control or selective attention. This leads to a decrease in conflict levels by focusing attention on relevant and away from irrelevant dimensions of a task. Though hypothesised and central to models of cognitive control, prefrontal-midline interactions of this sort have not yet directly been empirically demonstrated. Although MacDonald et al (2000) found an association between higher levels of activation in left DLPFC and reduction in Stroop interference, no neuroanatomical correlates of this reduced interference were reported.

In the previous chapter a between subjects correlation was found between pre-SMA and left DLPFC. In other words participants who showed higher levels of pre-SMA conflict-related activity throughout the task also showed increased amounts of recruited top-down control as indexed by left DLPFC. This effect was also demonstrated when participants made an error; participants who showed increased amounts of activation in the pre-SMA during errors also showed increased levels of activity in left DLPFC. Additionally, those participants that showed increased levels of activity in the left DLPFC throughout the task exhibited lower levels of conflict-related activity in the pre-SMA during actual errors themselves.

In a recent study Badre and Wagner (2004) found similar midline-prefrontal interactions in a working memory task, which manipulated levels of response conflict and refresh and subgoal/integration loads. Activation in ACC and prefrontal areas was positively correlated during response conflict. Badre and Wagner (2004) interpreted this as evidence that these regions are "functionally coupled in the face of elevated response conflict" (page 481). However, the authors averaged over DLPFC areas and over fronto-polar regions so it is not known whether there was an effect of laterality in this study. Although these findings lend strong support to the argument that midline and prefrontal regions work together in concert in order to facilitate cognitive control, it would be more convincing to find this on a within-subjects basis. Consequently, observing control-conflict inter-relationships between cortical areas would progress our understanding of both where and how control processes are instantiated.

4.1.1 The Present Study

These issues were addressed with data from a previous GO/NO-GO study (Hester, Murphy et al., 2004), in which half of the NO-GO events were cued and half were uncued. By examining activity during the preparatory period between the cue and the NO-GO, I sought to identify the mechanisms involved in marshalling top-down attentional control to prepare for the inhibition and, critically, determine how this attentional control affected conflict-related levels of midline activity produced on the NO-GO trial. Response conflict on GO/NO-GO tasks between the prepotent GO responses and the unpredictable requirement to withhold responding upon presentation of the NO-GO stimulus has been suggested in a number of studies in humans (Braver et al., 2001; Garavan et al., 2003; Jones, Cho, Nystrom, Cohen, & Braver, 2002; Nieuwenhuis, Yeung, van den Wildenberg, & Ridderinkhof, 2003) and

primates (Stuphorn et al., 2000). Being interested in the dynamic between PFC (Brass & von Cramon, 2002; Frith & Dolan, 1996; Garavan et al., 2002) and midline areas (Botvinick et al., 1999; Carter et al., 1998; Ullsperger & von Cramon, 2001) associated with behavioural control, the functional analyses focused on cued correct inhibitions (STOPS) and the cue period prior to these correct events. The examination of correct trials only ensured that conflict-related activity was uncontaminated by any other error-specific processes (Garavan et al., 2003).

4.2 Methods

4.2.1 Subjects

5 males and 10 females with ages ranging from 23 to 40 and a mean age of 30 participated in this experiment. All subjects were paid for their participation.

4.2.2 Materials

Task

Participants were required to respond with a button press to a 1 Hz (stimulus was on-screen for 900 msec and was followed by a 100 msec blank screen) series of alternating letters X and Y. Intermittently they were required to inhibit their response when the alternating sequence was broken i.e., when two Xs or two Ys were presented in succession (Garavan et al., 2002). This task is visually simpler than the SART GO/NOGO task. It was decided that it may be beneficial to examine the dynamics between top down control processes and the events themselves in a task such as this which had a less visually complex mask. For the purposes of this task, in which I wished to examine specific events on a trial-for-trial basis, this paradigm was

deemed useful. A cue (the GO stimulus with a line through its middle, e.g., X̶ or Y̶) was presented from 2 to 7 stimuli in advance of half of the NO-GO trials (see Figure 4.1).

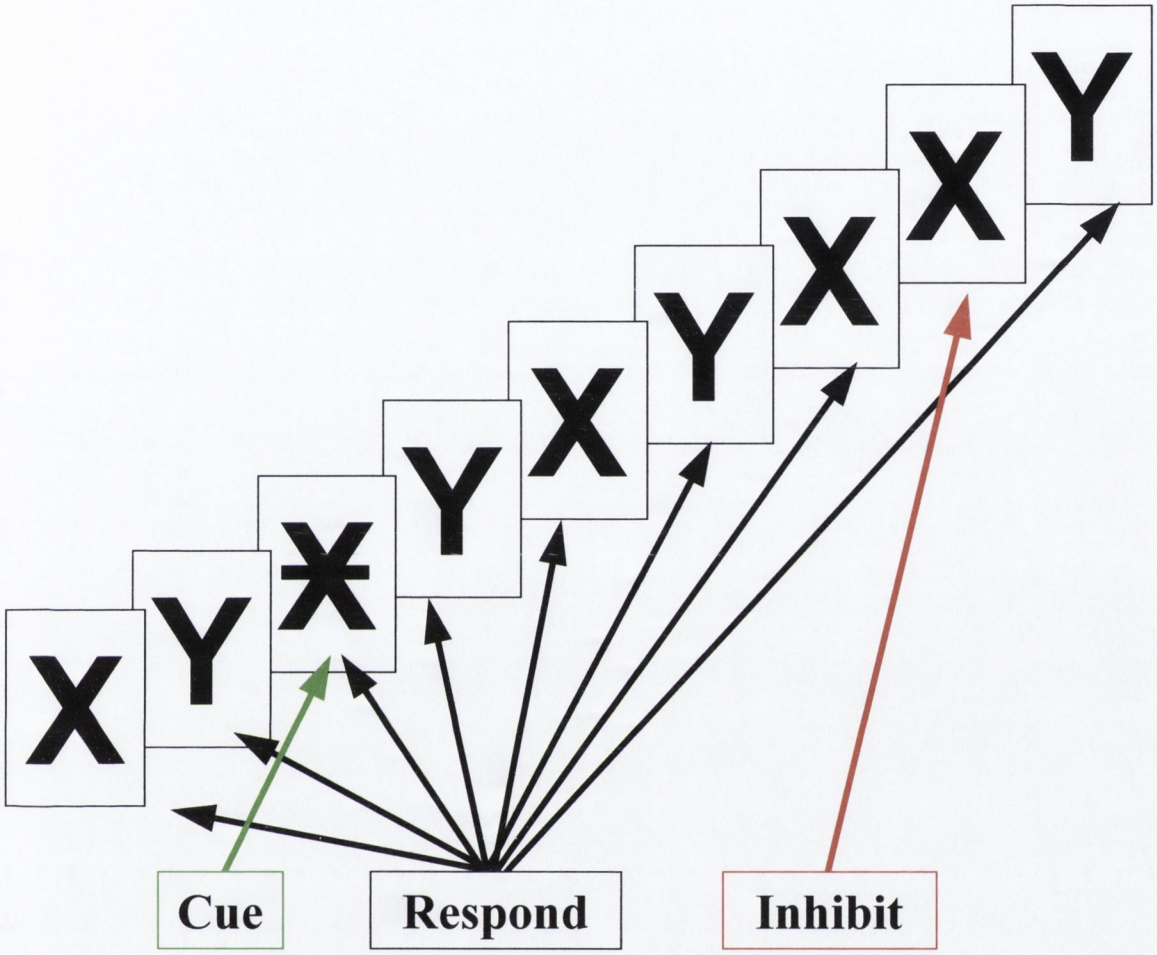


Figure 4.1: A section taken from the XY GO/NOGO task. Participants were required to respond with a button press to each alternating X and Y. When two successive Xs or Ys broke the pattern, participants were required to withhold their response. The red arrow in the figure illustrates an example of this. Either an X or a Y with a line through the middle cued half of these NOGO events. The green arrow in the above figure illustrates an example of this. Stimuli were on-screen for 900 msec followed by a 100 msec blank screen.

fMRI scanning

Contiguous high resolution, T_1-weighted MPRAGE slices were acquired for each subject (slice thickness = 1 mm, field of view = 256 mm) to allow subsequent

anatomical localization and spatial normalisation. Functional images were single-shot, T2* weighted, echo planar imaging sequences. 5 mm slices were acquired for each subject covering the entire brain (TR = 2000 msec, TE = 50 msec, 64 mm x 64 mm matrix size, field of view = 256 mm). Stimuli were presented using an IFIS-SA stimulus-delivery system (MRI Devices Corp., Waukesha, Wisconsin), which was equipped with a 640 x 480 LCD screen, which was mounted on the head coil and was directly in the subjects' line of vision. E-prime (Psychology Software Tools Inc.) presented and recorded participants' responses.

4.2.3 Procedure

GO/NOGO XY Task

Four runs of the XY task were presented to participants, resulting in 40 cued NO-GO, 40 uncued NO-GO and 1096 GO trials. NOGO events fell, on average, 15.75 seconds apart. Cues were interspersed randomly through out the four blocks. All subjects were presented with the same stimulus train.

4.2.4 Data Analysis

Behavioural Analysis

Average percent errors of commission, mean RT for the cue period prior to correct withholds and errors of commission and mean RT for a comparable period prior to the NOGO in the un-cued condition were calculated. Paired comparison t-tests were used in order to compare results from the cued and un-cued conditions.

Image Analysis

A mixed regression analysis was employed whereby cue period activation was

calculated as a percentage change score relative to tonic, task-related activity and four IRFs were calculated for both the cued and uncued inhibitions and commission errors (as Discussed in Chapter 2). Varying the duration of the cue periods (from 2 to 7 seconds) allowed the separation of cue-period activation from the event-related activation. t-tests against the null hypothesis of no percentage activation change were performed for correct inhibitions (STOP) and cue periods with a voxel-wise threshold of $p \leq 0.001$ ($t=4.14$) and a cluster-size criterion of 142μl, which resulted in a 5% probability (corrected) of a cluster surviving by chance.

Subsequent analyses will be restricted to the cued period prior to a correct inhibition and the correct inhibition itself and prefrontal and midline areas given the empirical evidence and theoretical accounts, discussed earlier, of their importance in implementing cognitive control. Thus an intra-individual analysis was performed to examine trial-by-trial interactions in behavioural control. For each subject, activation in the left DLPFC during the cue period was categorized as either high or low based on a split-half comparison of each subject's cue periods. Based on this ranking system the subsequent STOPS were categorized as high or low control STOP events. The multiple regression analysis was repeated with these two new regressors in order to calculate separate high and low control STOP IRFs. To assess the specific importance of left DLPFC in this type of attentional control, identical analyses were performed based on cue-period activation in the right DLPFC. High and low control activation maps were then combined into OR maps mean activation was calculated for each of the resulting functionally defined regions of interest.

4.3 Results

4.3.1 Behavioural Results

Cues improved performance (40% errors without cues, 20% with; $t(14)=4.155$, $p<0.001$) and produced RT slowing during the cue period when measured relative to comparable periods prior to uncued NO-GO trials (370ms vs. 340ms; $t(14)=4.155$, $p<0.001$).

4.3.2 fMRI Results

Cue Activation

A number of areas, including pre-SMA, left and right DLPFC (Figure 4.2), superior parietal cortex, temporal, occipital, insula and fusiform gyri were activated during the cue periods prior to correct withholds.

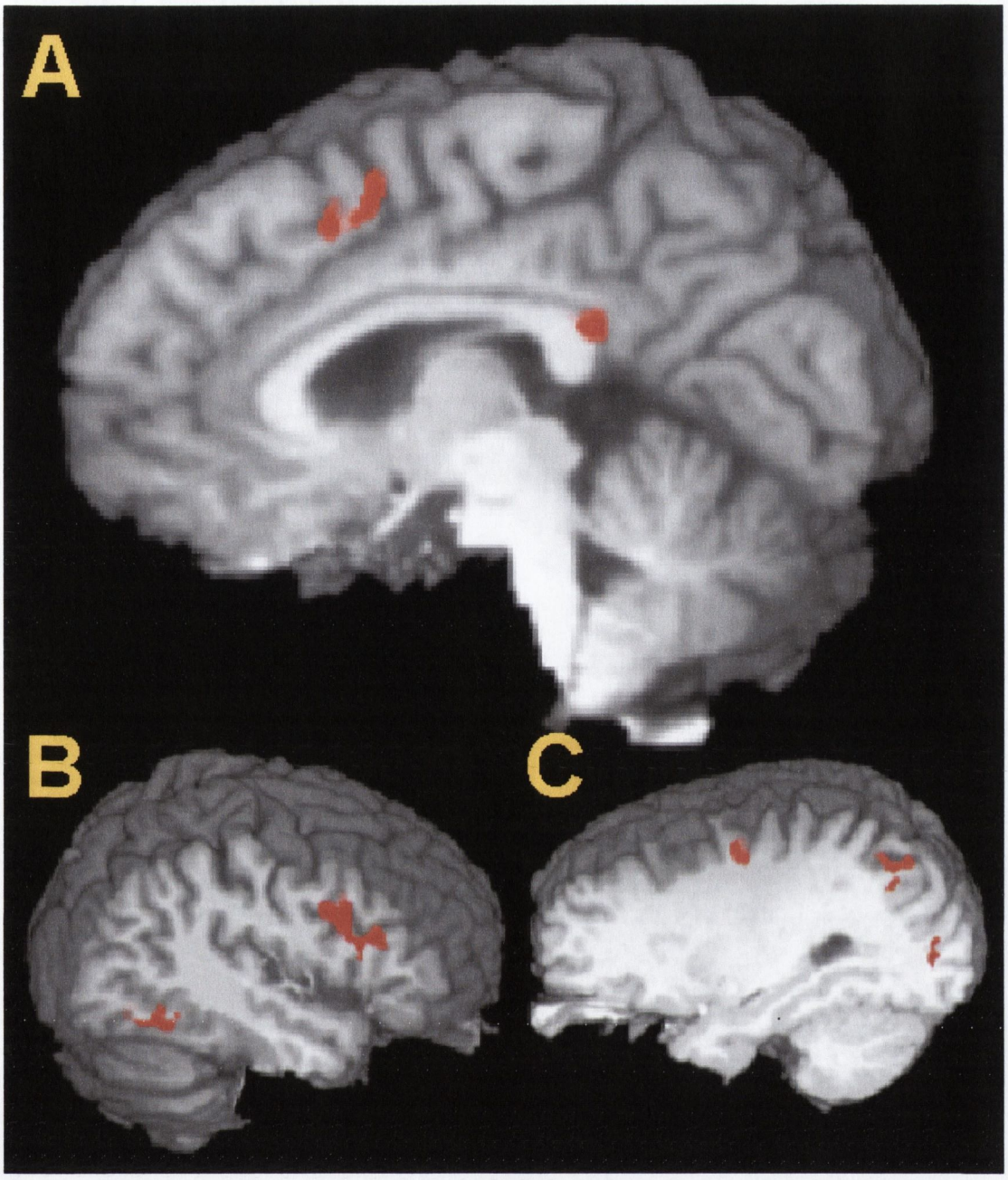


Figure 4.2: Areas activated during cue periods prior to a correct response. Activated areas include pre-SMA (A, Talairach: x = 2, y = 10, z = 46), right (B, 41, 14, 27) and left (C, -28, -7, 48) DLPFC as well as left parietal and occipital and right temporal areas.

Correct Inhibition Activation

The event-related analyses revealed activation in a number of areas including bilateral activation of middle frontal gyrus, inferior parietal lobule, middle temporal gyrus, thalamus and right insula for correct withholds to both cued and uncued NO-GO

events (see Hester, et al., 2004) for full details). ROI analysis, corrected using a modified Bonferroni procedure for multiple comparisons (Keppel, 1991) revealed that activation was greater for cued correct withholds than un-cued correct withholds in a number of regions including middle frontal and parietal regions.

Activation Associated with Left and Right Hemisphere Categorizations

The left hemisphere categorization revealed two midline activations, one in the pre-SMA extending into SMA and one in the SMA proper (Figure 4.3 A(i)). There was significantly lower activation in the pre-SMA for high relative to low control STOPS (0.12 ± 0.05 v 0.07 ± 0.06, respectively; $t(15)= -2.28$, $p<0.04$), the expected pattern if higher levels of control lead to reduced levels of response conflict (Botvinick et al., 2001). The right DLPFC categorization revealed ACC activation (Figure 4.3 B(i)) but this activation did not differ between high and low control STOPS.

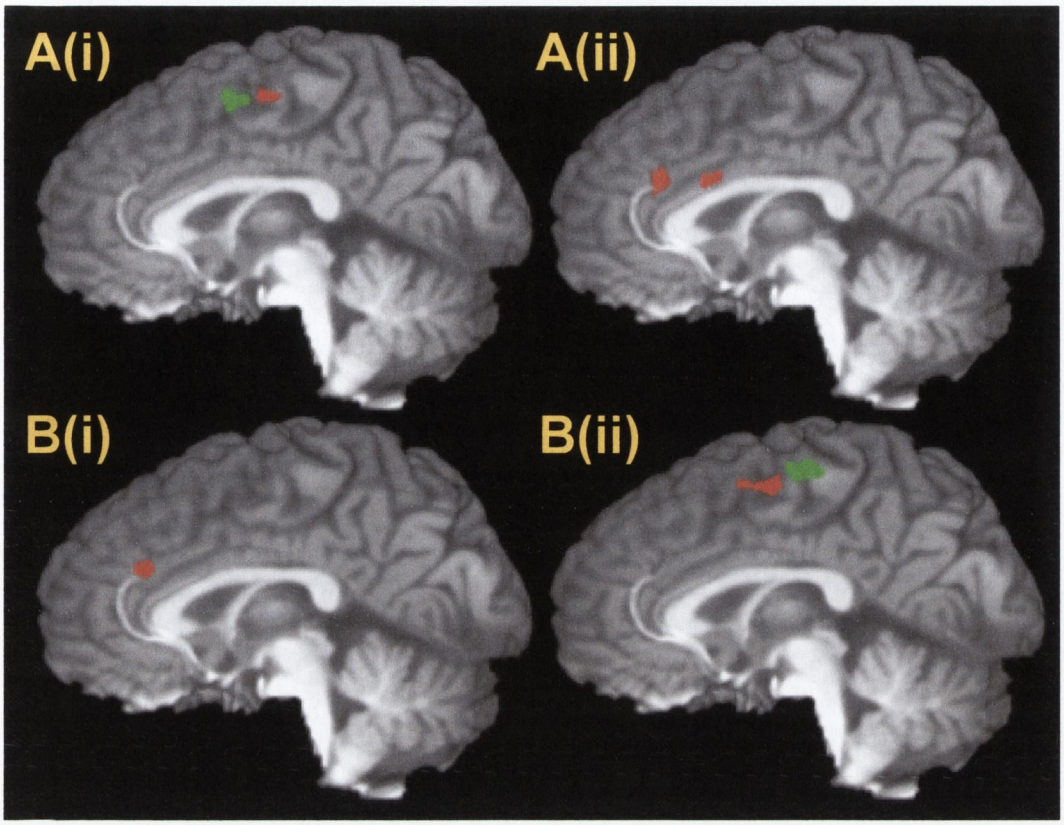


Figure 4.3: Correct inhibition activations from the left DLPFC split (A (i): pre-SMA (0, 1, 58), SMA (1, -11, 59) and (ii): rostral ACC (-2, 30, 28), caudal ACC (1, 13, 26)) and from the right DLPFC split (B (i): ACC (-2, 31, 26) and (ii): rostral SMA (1, -3, 60), caudal SMA (1, -18, 65)). Areas in which activation differed significantly between high and low control conditions are displayed in green.

Although no above threshold activation in the ACC was seen for the left hemisphere split, I was interested in examining any possible relationship between ACC and PFC due to the importance given to the ACC by previous findings and theory (Botvinick, et al, 2001; MacDonald et al, 2000). Thus, the threshold for the STOP activation map was lowered to 0.005, revealing two additional ACC regions (Figure 4.3 Aii). These ACC regions did not differ between low and high control STOPS.

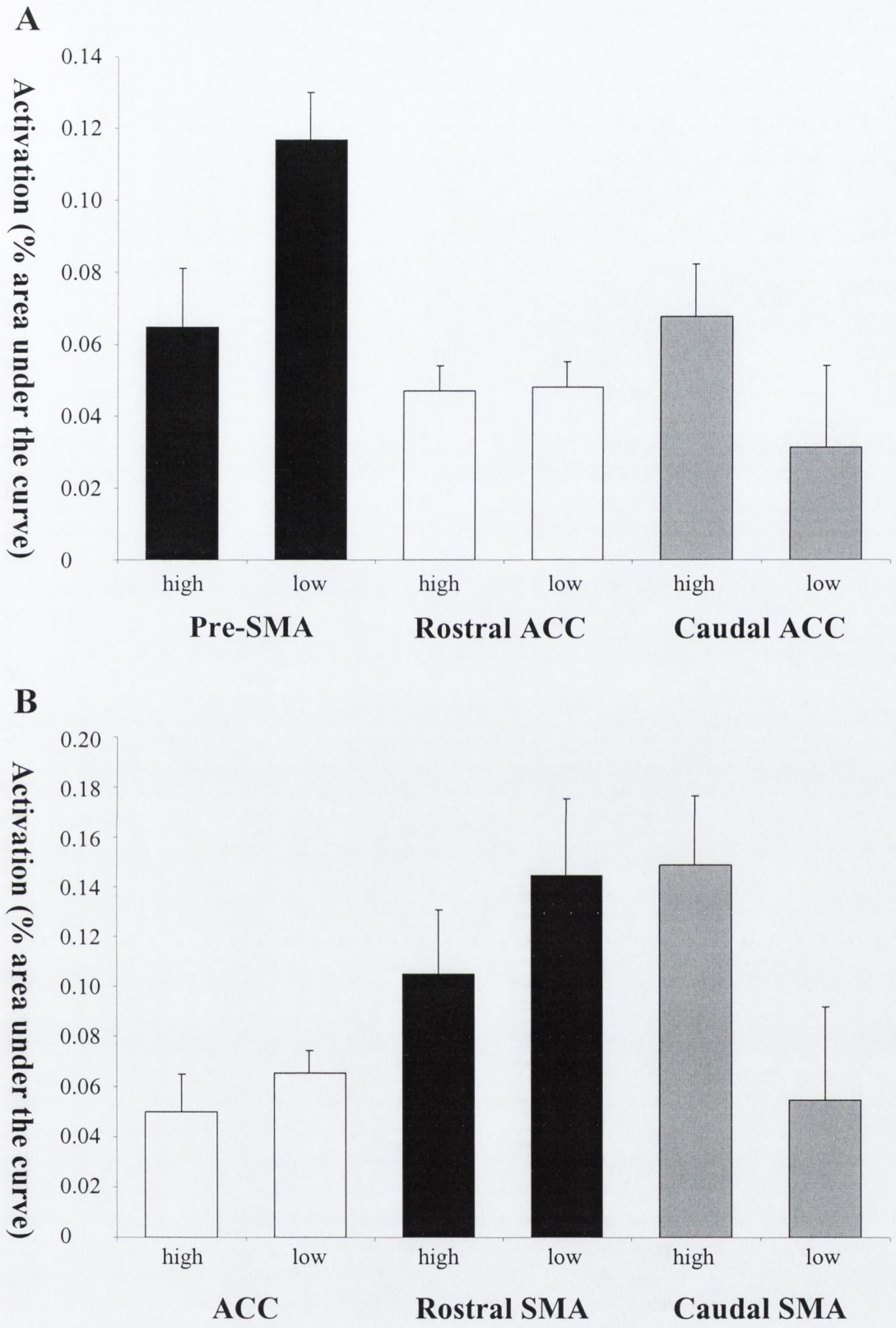


Figure 4.4:
A: Mean activation in pre-SMA and rostral ACC and dorsal ACC for high and low control events as defined by the left DLPFC.
B: Mean activation in ACC and rostral SMA and caudal SMA for high and low control events defined by the right DLPFC.

To test for regional dissociations we combined the two left hemisphere categorization maps. A 2 (high vs. low control) x 2 (pre-SMA vs. ACC) ANOVA was performed for each of the two ACC regions. As shown on Figure 4.4 A, both Region and Region x Control interactions were significant for both ANOVAs (Comparison 3.4 A Rostral ACC: Region $F(1, 14) = 18.98$, $p < 0.001$; Region x Control $F(1, 14) = 4.95$, $p < 0.04$. Comparison 3.4 A Caudal ACC: Region $F(1, 14) = 7.48$, $p < 0.02$; Region x Control $F(1, 14) = 8.5$, $p < 0.01$). Newman-Keuls post-hoc tests revealed that for the first comparison the high-low control effect was present in only the pre-SMA (pre-SMA low V pre-SMA high, $p < 0.006$) and for both comparisons pre-SMA activation in the low control condition was greater than ACC activation in both the low and high control conditions (Rostral ACC: pre-SMA low V ACC low, $p < 0.002$; pre-SMA low V ACC high, $p < 0.004$; Caudal ACC: pre-SMA low V ACC low, $p < 0.007$; pre-SMA low V ACC high, $p < 0.04$).

Lowering the threshold for the right hemisphere split map revealed two additional midline areas, both in SMA, (Figure 4.3 B(ii)). High control STOPS produced significantly greater activation in the more caudal region only (0.15 ± 0.11 v 0.06 ± 0.14 respectively; $t(15)=2.84$, $p<0.01$). As above, we combined the two right hemisphere categorization maps. A 2 (high vs. low control) x 2 (ACC vs. SMA) ANOVA was performed for each of the two SMA regions (Figure 4.4 B). In the more rostral SMA region, there was a main effect of region with the SMA being more active than the ACC (Comparison 4.4 B: $F(1,14)=8.97$, $p<0.01$) but there was no interaction. Conversely, only the Region x Control interaction was significant for the more caudal SMA region (Comparison 4.4 B: $F(1, 14)=11.29$, $p<0.005$) driven by

greater activity in the SMA for high relative to low control STOPS as mentioned above.

4.4 Discussion

These results are indicative of a reciprocal relationship between left DLPFC and pre-SMA in cognitive control in this GO/NO-GO task. This is the first demonstration of these two cortical regions interacting with each other in the implementation of control. In this study this relationship has been demonstrated on a trial-by trial within-subject basis: Trials that were preceded by high control (i.e., high left prefrontal activation) cue periods displayed lower amounts of conflict-related activation than those that were preceded by low control periods. Moreover, this hypothesised pattern of results was observed for the pre-SMA and not the ACC (Botvinick et al., 1999; Cohen et al., 2000), consistent with a conflict-error distinction between these two areas (Hester et al., 2004; Ullsperger & von Cramon, 2001).

I propose that during the cue period increased top-down control in anticipation of the impending NO-GO was implemented by prefrontal cortex and the midline activation reflects increased response conflict during the cue period between the ongoing GO responses and the prepared NO-GO response withhold. That the pre-SMA might reflect the NO-GO motor preparation is, in fact, not inconsistent with a role for this structure in response conflict. If response conflict results from co-activation of competing motor programs then the preparation of the NO-GO response withhold in the presence of the ongoing GO responses may produce conflict between these two motor programs (Garavan et al., 2003).

The maintenance of task goals and rules in working memory is an important aspect of task execution and problem solving. DLPFC has been implicated in these working memory processes and, more specifically, a number of studies have suggested that the maintenance of representations or task set is subserved by left DLPFC (Frith & Dolan, 1996; Garavan et al., 2002; MacDonald et al., 2000; Ruchsow et al., 2002). Similarly, Ruchsow et al (2002) noted left prefrontal activation associated with negative feedback and suggested that it may have reflected an adjustment of rules or strategy following an error. While an association between left DLPFC and task-set maintenance has been previously reported, the left DLPFC region that we observed in this task was quite caudal extending into premotor area suggesting that this area may code for the upcoming motor inhibition (Pochon, Levy, Poline, Crozier, Lehericy & Pillon, 2001; Schubotz & von Cramon, 2002a). Schubotz and von Cramon (2002a, 2002b) have suggested that lateral premotor cortex is involved not only in the execution of complex motor schemes but also in planning to carry them out. In contrast to the inverse relationship between left DLPFC and pre-SMA, greater cue-period right DLPFC activation was associated with greater SMA activity. Perhaps, whereas greater left hemisphere control reduces pre-SMA conflict activity, greater preparation in the right hemisphere, which previous data suggest is a central structure for response inhibition (de Zubicaray et al., 2000; Garavan et al., 1999; Kawashima et al., 1996), yields increased inhibition related activity in the SMA. The pattern of results suggests quite distinct functional roles for the pre-SMA and SMA proper.

In conclusion, these results demonstrate that it is possible to observe the interactions of distinct cortical areas, performing different functions in an interactive, dynamic

way in the service of smooth behavioural control. The results illuminate how top-down, attentional resources that implement cognitive control can influence bottom-up, stimulus driven conflict. Furthermore, it lends more support to the conclusion drawn from the previous chapter, that left DLPFC and pre-SMA, in particular are incolved in this type of cognitive control.

Chapter 5

Functional Anatomy of Task Preparation

Abstract

The present study utilised fMRI and a cued version of a flanker paradigm in order to elucidate the effects of task preparation on subsequent brain activation patterns. A mixed block and event-related design was employed in order to examine activations associated with the cue periods themselves and the cued and un-cued correct responses to incongruent flankers. A number of areas were active during the cues, most notably left DLPFC, which was interpreted as subserving a role in task-set maintenance. Widespread activity was noted for correct responses to incongruent flankers, including bilateral parietal and frontal regions, consistent with previous studies. Activation was increased in these regions for correct responses following cue periods. An overlapping network of regions was also noted for cues and correct responses, suggesting preparation of task-appropriate anatomical regions during the cue period. These results suggest that cue periods allow participants to prime task-relevant areas within the brain and highlight the importance of left DLPFC in top-down control.

5.1 Introduction

Control over behaviour is facilitated by a number of separate yet interacting cognitive functions. The processing and integration of bottom-up sensory information, inhibition of inappropriate task sets and distracting stimuli, detecting situations under which an error in performance may be likely and the subsequent adjustment of levels of available attentional resources or top-down control are all thought to interact with one another in the facilitation of everyday behaviour. One paradigm that has often been used to investigate these processes is the Flanker task in its varying forms. Eriksen and Eriksen first introduced this task in its letter form (Eriksen & Eriksen, 1974) but subsequent studies have used modified versions of this in order to increase interference effects (Botvinick et al., 1999; Casey et al., 2000; Fan, Flombaum, McCandliss, Thomas, & Posner, 2003; Ullsperger & von Cramon, 2001).

The flanker task has been used in a number of studies to examine response conflict. Flanking stimuli in the incongruent condition cause interference in that they trigger an inappropriate motor response. This is co-activated with the correct response triggered by the central stimulus, which is thought to result in response conflict. Accordingly, flanker tasks often find activity in DLPFC and ACC, a network that has been implicated in the detection and resolution of response conflict and the enforcement of top-down attentional control (Badre & Wagner, 2004; Botvinick et al., 2001; MacDonald et al., 2000). Increased amounts of top-down control are thought to decrease levels of response conflict, as activation of the appropriate response channel is thought to be increased due to more efficient allocation of attentional resources (Botvinick et al., 2001).

Left lateral PFC has been implicated in cognitive control in a number of additional studies (Garavan et al., 2002; MacDonald et al., 2000) and in the previous two chapters. Evidence exists that the pre-SMA may also play an important part in monitoring response conflict (Braver et al., 2001; Garavan et al., 2003; Hazeltine et al., 2000; Ullsperger & von Cramon, 2001; Ullsperger & Von Cramon, 2003). Brass and von Cramon (2002) also found left lateral PFC and pre-SMA to be particularly important in task preparation. They suggested that lateral PFC was involved in the "selection of cue-related task rules", whereas pre-SMA implemented "these rules on a higher-order level of motor control" (page 913). Finally, in another GO/NOGO study (Hester et al., 2004) activation in DLPFC and in dorsal ACC/ pre-SMA was seen during task preparation. Activation during a cue period prior to a correct withhold was interpreted as reflecting preparation of task-relevant areas in anticipation of the response (Hester et al., 2004).

5.1.1 The Present Study

In the present study I sought to examine the preparatory activation and top-down attentional control utilising a simple cued and un-cued version of the Eriksen flanker task (Eriksen & Eriksen, 1974). I wished to keep the paradigm as simple and undemanding as possible in order to magnify the effects of increased top-down control during the cue period. Hence we did not use the arrow flanker task (e.g. <<<<<, <<><<) as this can be quite visually complex and demanding. Additionally only two letters were used, one mapped onto a right button, the other onto the left. Activation in left DLPFC and task-relevant areas during the cue period was predicted.

5.2 Methods

5.2.1 Subjects

Subjects were 9 males and 8 females with ages ranging from 18 to 39 (mean age of 28.1). Two female subjects were subsequently excluded from the analyses due to excessive movement (new mean age 27.3). All subjects were paid for their participation. The Institutional Review Board of the Nathan Kline Institute, where the scans were carried out, approved all procedures.

5.2.2 Materials

Flanker Task

Stimuli consisted of 5 letters, the central letter being the one to which subjects were required to respond. Half of the subjects were required to respond with a right button press to the letter S and a left button press to the letter C. The remaining half used the reverse stimulus-response mapping. Congruent stimuli were SSSSS and CCCCC and incongruent stimuli were SSCSS and CCSCC. Stimuli were presented at a frequency of 1Hz, the stimuli being on screen for 500msec followed by a 500msec mask (#####). The paradigm consisted of twelve blocks of, on average, 212 stimuli per block. In six blocks participants were cued to expect an incongruent stimulus. Cues were from 4 to 10 seconds in duration (varying in 2 sec increments) and consisted of a font colour change from white to green. In order to make the onset of an incongruent stimulus completely predictable to allow for maximal contrast with the un-cued condition, the trial immediately preceding presentation of the incongruent trial changed to pink font. Participants were told before every block whether it would be a cued or an un-cued block. Participants were given four training blocks (two cued and

two un-cued) before they entered the scanner. Stimuli were presented and responses recorded using E- prime (Psychology Software Tools Inc.).

fMRI Scanning

For each subject, 202 T^1-weighted sagittal slices were acquired (slice thickness = 1 mm, field of view = 256 mm). Functional images were single-shot, T2* weighted, echo planar imaging sequences. For each subject 22 axial slices (5 mm slice thickness) were acquired (TR = 2000 msec, TE = 50 msec, flip-angle = 90degrees, 64 mm x 64 mm matrix size, field of view = 256 mm) and 667 and 722 volumes were acquired in the cued and un-cued conditions respectively. Stimuli were presented through an LCD screen, which was mounted on the head coil and was directly in the subjects' line of vision.

4.3.2 Procedure

Flanker Task

The paradigm consisted of twelve blocks of, on average, 212 stimuli per block. In six blocks participants were cued to expect an incongruent stimulus. Participants were told before every block whether it would be a cued or an un-cued block. Participants were given four training blocks (two cued and two un-cued) before they entered the scanner.

Incongruent stimuli were separated from each other by at least 20 second periods in order to allow the haemodynamic response to properly decay following each event. 20 cued and 32 un-cued incongruents were presented. Of the 32 un-cued incongruents, 12 were considered "catch" events that fell close together to ensure that participants

did not simply "switch off" and allow their attention to wane in between incongruent trials. These 12 events were subsequently excluded from further analysis (and were censored from the time series analysis). Each block was preceded by a 5 second fixation followed by 5 second screen displaying information as to whether or not there would be a cue in that particular run, and also ended with a 10sec fixation cross.

5.2.4 Data Analysis

Behavioural Analysis

Average percent correct responses to incongruent stimuli, omission errors and RTs to incongruent and congruent stimuli were obtained for each participant in both conditions. Average error RTs were also obtained. Average RTs during the cue period prior to a correct or incorrect response were also calculated, as were RTs during a comparable period prior to a correct or incorrect response in the un-cued condition. Paired comparison t-tests were used in order to compare results in the cued and un-cued conditions. All tests were carried out at an alpha level of 0.04 when corrected for multiple comparisons using a modified Bonferroni correction (Keppel, 1991).

Image analysis

Separate IRFs were calculated for cued correct responses to incongruent stimuli, un-cued correct responses to incongruent stimuli, cued errors to incongruent stimuli, un-cued errors to incongruent stimuli, errors to congruent stimuli in the cued blocks and errors to congruent stimuli in the un-cued blocks. Varying the duration of the cue periods allowed the separation of cue-period activation from the event-related activation. Cue periods prior to correct responses to incongruent stimuli and cue periods prior to errors on response incongruent stimuli were calculated separately.

Comparable periods were also analyzed in the no-cue condition. These were periods of the same length as actual cue periods in the cued condition, prior to correct and incorrect incongruent targets in the un-cued condition. Cue periods and comparable periods in the un-cued condition were calculated as percentage change score over baseline

Separate t-tests against the null hypothesis of no percentage activation change were performed for block and event-related activations with a voxel-wise threshold of $p \leq 0.0001$ and a cluster-size criterion of 57 μl of contiguous significant voxels. Activation maps for cue periods prior to correct and incorrect responses to incongruent stimuli were then combined into OR maps. As the comparable periods in the un-cued block did not show any activation at this threshold they were not included in the OR map. A similar procedure was undertaken for the cued and un-cued correct responses, which resulted in one correct response OR map. Although both errors to incongruent and congruent stimuli were included in the deconvolution analysis in order to control for the variance associated with these events, they were excluded from further analyses, as there were very few such events.

Differences between the conditions in these regions of interest were then tested with paired t-tests. In order to examine whether cues activated task-relevant areas, a combined cue and correct response map was also created and areas of spatial overlap between these two maps identified.

5.3 Results

5.3.1 Behavioural Results

Responses to incongruent flankers overall was significantly slower than responses to congruent stimuli (520.14 v 471.82 msec respectively; $t(15) = 3.93$; $p \leq 0.002$) suggesting that incongruent trials did engender response conflict. Upon examining responses to incongruent flankers and congruent stimuli in the un-cued condition only, responses to incongruents was slower than congruent stimuli, although not significantly so (498.54 ± 94.65 v 468.01 ± 67.04 msec respectively; $t(14) = -1.58$; $p \leq 0.14$). Responses to incongruents were also significantly slower in the cued over the uncued condition (540.27 ± 74.18 v 498.54 ± 94.65 msec; $t(14) = 2.25$; $p \leq 0.04$). The cue was also successful in improving performance; there were significantly more successful responses in the cued compared to the un-cued condition (86.7 ± 10.51% v 76.42 ± 15.4% respectively, $t(14) = 2.66$, $p \leq 0.02$) and response times to congruent stimuli in the cued condition were significantly slower than response times in the un-cued condition (475.96 ± 67.66 v 468.01 ± 67.04 msec respectively; $t(14) = 4.57$, $p \leq 0.001$). There was no significant difference in reaction times in errors to incongruent stimuli or in omission errors in the cued and un-cued conditions (407.58 ± 60.73 v 396.57 ± 58.88 msec, $t(14) = 1.26$, $p \leq 0.23$ and 46 ± 78 v 52 ± 92, $t(14) = -1.53$, $p \leq 0.15$ respectively).

Although there was no significant difference in RT between the cue period preceding a correct response to a target and the cue period preceding an incorrect response to a target (504.77 ± 58.4 v 503.66 ± 65.56 msec respectively; $t(14) = 0.17$, $p \leq 0.87$) the average RT during the cue period preceding a correct target in the cued condition was

significantly slower than a comparable period prior to a correct response in the un-cued condition (504.77 v 467.17 ± 61.57 msec respectively; $t(14) = 6.2$, $p \leq 0.0001$). A number of subjects did not make any errors in either the cued or un-cued condition. For this reason, there are different degrees of freedom between these reported t-tests.

5.3.2 fMRI Results

Cue-Related Activation

Three regions were active for cue periods before correct and incorrect responses to incongruent targets. These were right IPL, right hippocampal gyrus and left DLPFC (see Table 5.1 and Figure 5.1). Activation in these regions was significantly greater for the cue period prior to a correct response than the comparable period in the un-cued condition (see Table 5.1 for levels of significance).

	Brodmann Area	Hemisphere	Volume (μl)	Talairach coordinates (centre of mass) x (RL)	y (AP)	z (IS)	t(14)
Frontal lobes							
MFG	9	L	419	-53	13	28	***
	9	L	111	-39	11	23	**
	9	R	223	35	19	29	***
	9	R	208	39	6	35	***
	6	R	156	23	-6	55	**
PRCG	6	L	239	-41	1	37	***
Parietal lobes							
IPL	40	R	1617	31	-53	46	****
	40	L	280	-34	-52	49	****
IPL	40	L	138	-48	-40	44	***
SPL/precuneus	7	L	409	-22	-60	42	***
Temporal lobes							
PHG	19	R	481	29	-47	-6	**
Other Regions							
Cingulate gyrus	32	R	169	8	22	29	**
		R	127	11	-16	27	*
insula		L	101	-31	19	8	
Insula/claustrum		R	302	30	21	3	

Note: * $p < 0.04$, ** $p < 0.01$, *** $p < 0.001$, **** $p < 0.0001$
Statistical tests refer to pair-wise t-test comparisons between cue periods prior to a correct response v comparable periods in the un-cued condition prior to a correct response.
Abbreviations:
MFG: middle frontal gyrus; PRCG: precentral gyrus; IPL: inferior parietal lobe; SPL: superior parietal lobe; PHG: parahippocampal gyrus.

Table 5.1: Cue-related Activations

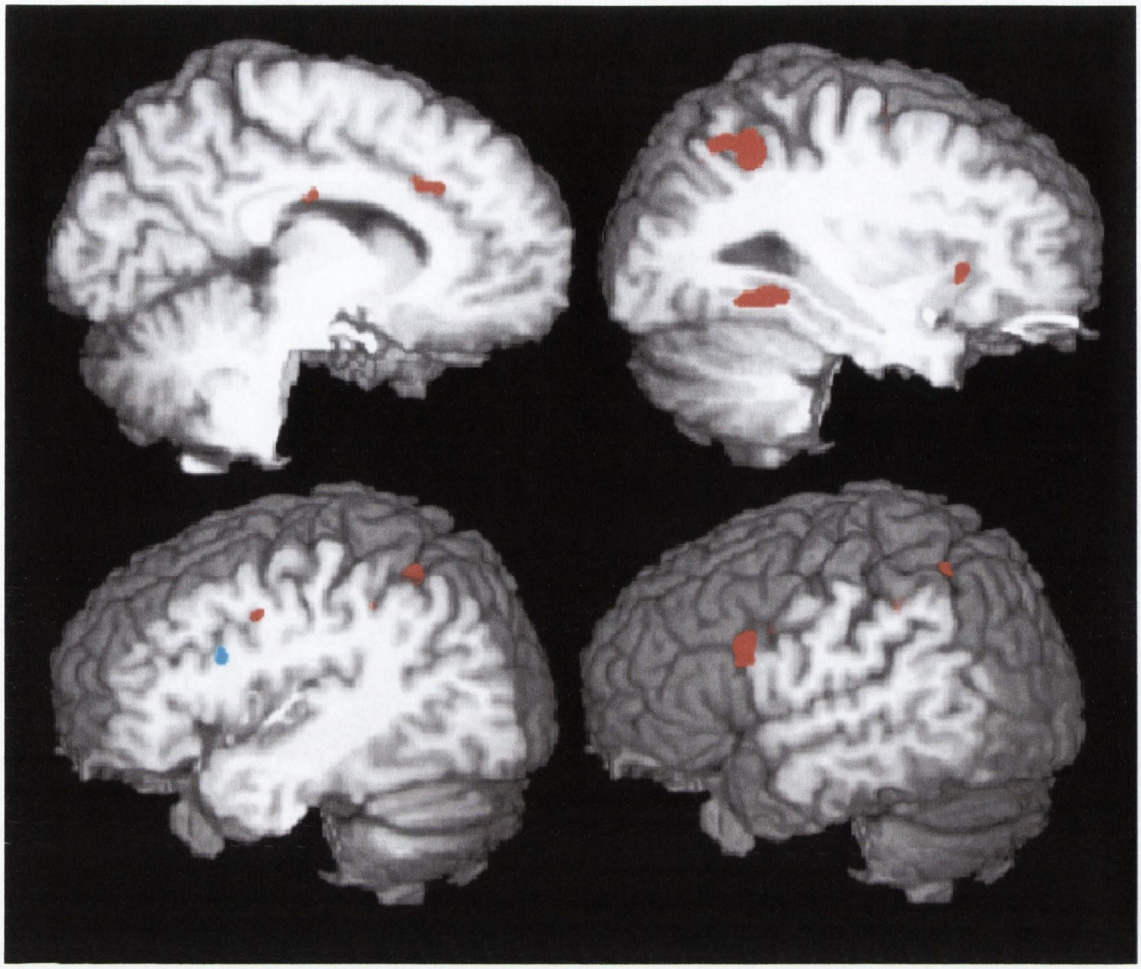


Figure 5.1: Activations during cue periods.
Areas activated included bilateral IPL, parahippocampal gyrus, right insula (top right), two regions in cingulate cortex (top left) and a number of regions in left DLPFC (bottom panels). Areas in red indicate areas that were equally active during cues prior to correct and incorrect responses. One area in left DLPFC was significantly more active during cue periods prior to a correct response. This is represented in blue.

I was interested in examining if any additional areas were active during the cue periods so the threshold was lowered to a less conservative voxel-wide threshold of $p \leq 0.005$ at a cluster size criterion of 100μl, again resulting in a 0.05 probability of any voxel surviving by chance. At this threshold twelve extra clusters were seen (see Table 5.1) including a number of additional left frontal regions, left IPL, two areas in cingulate gyrus and bilateral insula. One region, left middle frontal gyrus (MFG) (BA 9, Talairach coordinates, x = -39, y = 11, z = 23), showed significantly greater

activation for the cued period prior to a correct response than prior to an incorrect response ($t(14) = 2.41$; $p \leq 0.03$), However, this analysis may not be reliable as there were very few errors to targets in the cued condition, hence few preceding cue periods to examine. All regions showed greater activation for the cue period prior to a correct response than for the comparable cue period in the un-cued condition (see Table 5.1 for levels of significance) except the left and right insula, both of which showed a trend in this direction ($t(14) = 2.06$; $p \leq 0.06$ and $t(14) = 1.94$; $p \leq 0.07$, respectively).

Activation during Correct Responses to Targets

Widespread activity was observed for correct responses to targets in the cued and un-cued conditions. These included bilateral IPL, middle frontal gyrus MFG, right superior frontal gyrus (SFG), left postcentral gyrus, bilateral insula, middle temporal gyrus, right supramarginal gyrus and two areas along the medial wall (see Table 5.2 and Figure 5.2). Most of these regions were more active for cued correct responses (see Table 5.2 for levels of significance). These regions included bilateral IPL, MFG, precuneus, an area of MFG extending into pre-SMA, right SFG, parahippocampal gyrus, left postcentral gyrus, fusiform gyrus and middle temporal gyrus. Only one region, left insula, showed the opposite pattern being significantly more active for un-cued correct responses to targets ($t(14) = -2.8$; $p \leq 0.01$).

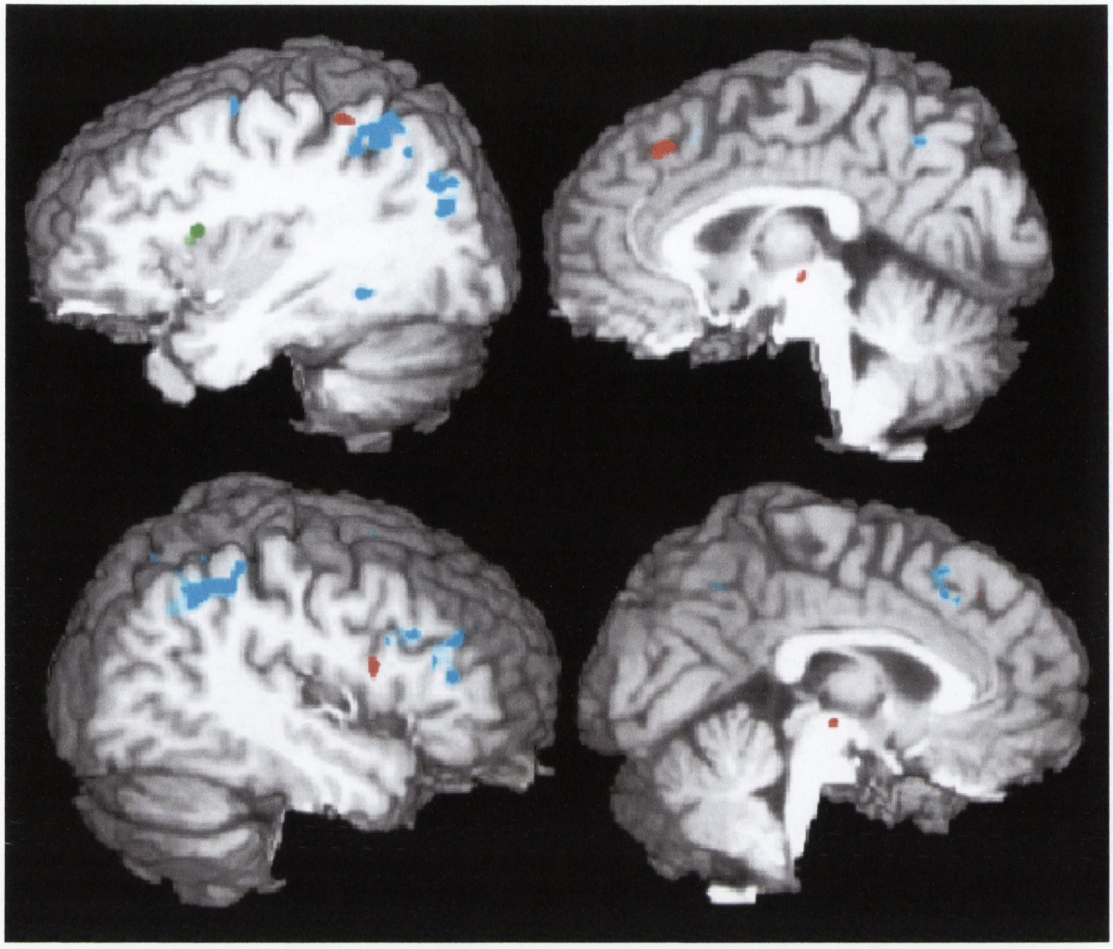


Figure 5.2: Activations during correct responses to incongruent flankers.
Areas activated included left IPL, left motor cortex, left insula (top left), medial PFC, precuneus (top right), right IPL, a number of areas in right DLPFC (bottom left) and a region in pre-SMA (bottom right). Most areas were significantly more active subsequent to a cue period. These regions are represented in blue. Areas in red represent those areas that were equally active in the cued and un-cued condition. Left insula was the only region that was significantly more active during a correct response following no cue. This is represented in green.

	Brodmann Area	Hemisphere	Volume (μl)	Talairach coordinates (centre of mass) x (RL)	y (AP)	z (IS)	t(14)
Frontal lobes							
MFG	9/6	R	2250	29	7	44	***
	9/6	L	1476	-46	5	33	*
	9	R	180	48	14	37	**
	9	R	87	-48	21	32	*
	9	R	80	49	20	23	
	9	L	345	-40	30	27	***
	9	L	103	-32	-3	57	*
	6	R	629	41	32	21	**
IFG	46	L	68	-40	44	18	**
SFG	10	R	62	24	51	9	**
medial wall	8/6	R	172	2	20	43	*
	8	L	148	-3	29	40	
Parietal lobes	40	L	205	-45	-28	45	****
PCG							
IPL	40	R	4671	34	-53	44	***
	40	L	57	-35	-41	53	
IPL/SPL	40/7	L	4489	-36	-56	42	****
SPL		R	101	21	-60	55	
SG	40	R	82	50	-40	31	
Precuneus	7	R	101	9	-60	52	*
	7	R	85	22	-68	37	**
	7	L	393	-10	-62	47	*
	7	B	58	-2	-56	42	*
Temporal lobes							
PHG	37	R	869	29	-45	-7	****
FG	37	L	240	-35	-50	-6	***
MTG	37	L	648	-46	-55	0	****
Other Regions							
insula		R	150	45	8	16	
		L	150	-34	11	12	
Insula/claustrum		R	615	28	17	4	
		L	229	-27	21	3	*
caudate		R	165	10	9	9	
Red nucleus		B	67	-1	-17	-4	

Note: Abbreviations and diacritics are as for Table 1.
Statistical tests refer to pair-wise t-test comparisons between correct responses following cues v correct responses in the un-cued condition.
IFG: inferior frontal gyrus; SFG: superior frontal gyrus; POCG: postcentral gyrus; SG: supramarginal gyrus; FG: fusiform gyrus; MTG: middle temporal gyrus.

Table 5.2: Event-related Activations: Cued and Un-cued Correct Responses to Incongruent Stimuli

Overlap Between Correct Response and Cue-Related Activation Maps

In order to examine whether overlapping regions were activated for cue and correct response maps, the two maps were added together and substantial numbers of overlapping and adjacent activations were identified (see Figure 5.3).

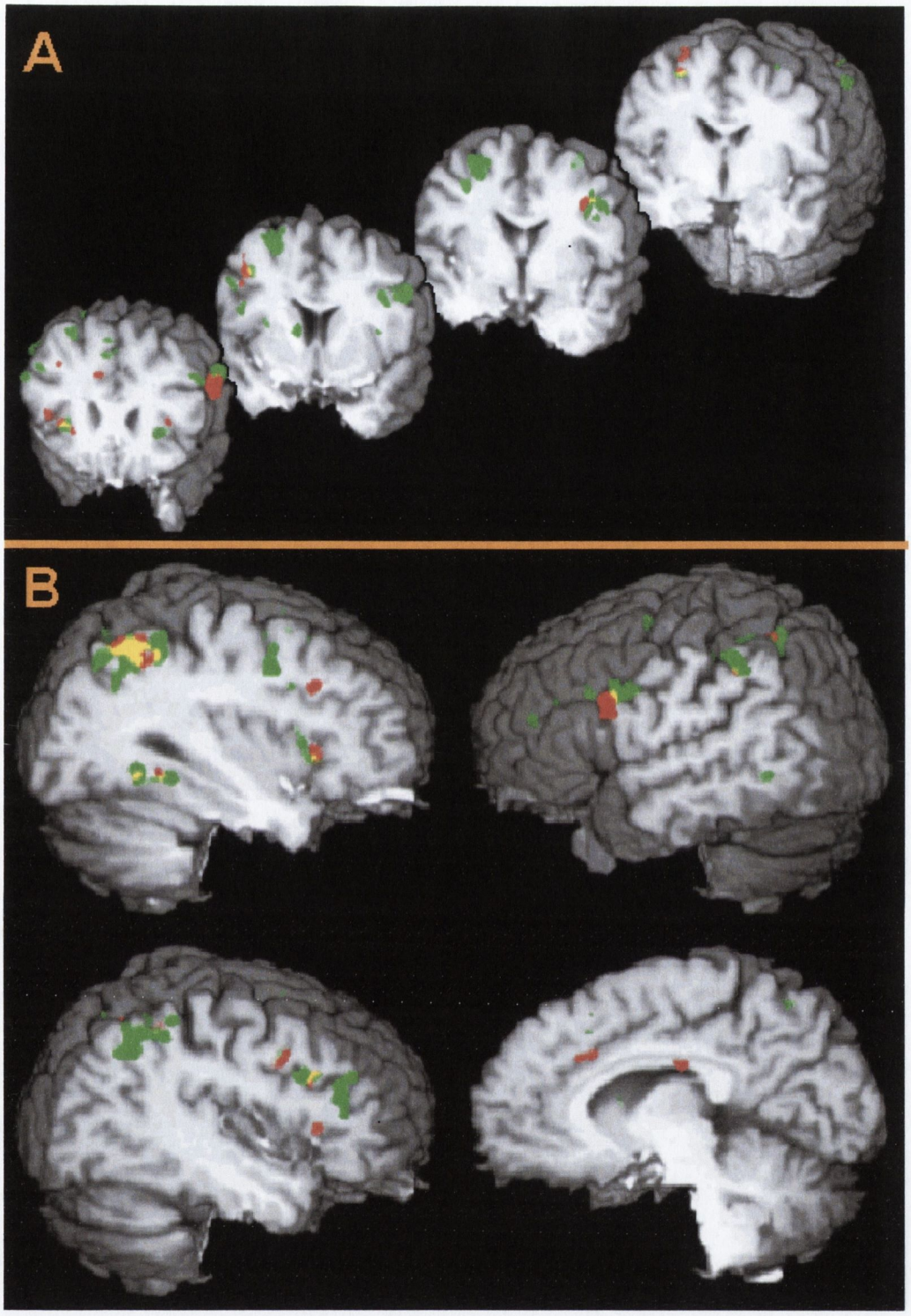


Figure 5.3: Overlap between cue and correct response activations.
Activation for correct responses is represented in green. Activation for cue periods is represented in red. Areas that were significantly active during both cues and correct responses are shown in yellow. These include bilateral DLPFC, right insula and right IPL.

5.4 Discussion

In this task cues succeeded both in significantly improving participants' performance and in slowing reaction times. A number of areas were seen to be active during the cues periods and this activation may represent preparation for the up-coming response. This preparation produced greater event-related activity in the following correct responses to incongruent flankers than when there was no opportunity to prepare for an up-coming incongruent (in the un-cued condition). A degree of overlap between cue and correct response maps suggests that cues activated task-appropriate regions. Left PFC appeared to be particularly important in the preparation of an impending response as activation was predominant here during the cue period and there was some suggestion that this area may have been predictive of a subsequent correct response.

5.4.1 Correct Responses to Incongruent Stimuli

A diffuse pattern of activation was seen for correct responses to incongruent flankers in this task. Activity in bilateral DLPFC (Hazeltine, Bunge, Scanlon, & Gabrieli, 2003; van Veen et al., 2001), right post-central gyrus (Hazeltine et al., 2003), right (van Veen et al., 2001) and left (Hazeltine et al., 2003) IPL and left precuneus (van Veen et al., 2001) has previously been observed in similar flanker paradigms. Activation in right inferior frontal cortex (Hazeltine et al., 2003; 2000), left parietal cortex, SMA and superior parietal cortex (Hazeltine et al., 2000) has been noted during a colour flanker task and overlapping regions in right inferior frontal/ middle frontal, superior frontal cortex and ACC have been noted for both colour and letter style flanker paradigms (Hazeltine et al., 2003). ACC, bilateral frontal, temporal and

right inferior parietal lobe have also been found to be active in arrow flanker tasks (Fan et al., 2003; Ullsperger & von Cramon, 2001). Aside from activity in ACC, these results fit with the broad pattern of activity witnessed in this task during incongruent flankers.

Previous research has attempted to explain the diverging roles of these differing anatomical networks in the performance of a flanker task. Casey and colleagues (2000) utilized different combinations of trial types to dissociate different connected regions that were involved in the completion of their arrow flanker paradigm. ACC and DLPFC were associated with the resolution of conflict. Right hemisphere superior frontal, superior parietal and cerebellar networks were activated during persistent interference and were associated with selective attention. Basal ganglia and insula were associated with violations in the expectancy or probability of events. Decreases in activation were seen in inferior parietal lobe and auditory cortex. This was interpreted as reflecting suppression of activity in "unnecessary" cortical networks (Casey et al., 2000). Aside from the deactivation in inferior parietal lobe, these results are consistent with those found in the present study.

Although slowed reaction times to incongruent stimuli suggested that participants did experience response conflict, activation in ACC was not observed in this task. We did however see activation in medial frontal gyrus in Brodmann area 8, extending into pre-SMA. As noted earlier, a number of authors have found activation in pre-SMA during response conflict (Garavan et al., 2003; Hazeltine et al., 2000; Ullsperger & von Cramon, 2001; 2003). In fact, evidence for a dissociation along the midline for conflict and error-related processes has been found in a number of different fMRI

studies (Garavan et al., 2003; Kiehl et al., 2000; Menon et al., 2001; Ullsperger & von Cramon, 2001). In a previous review of a number of studies that attempted to dissociate error and conflict-related activity in midline areas we have shown that conflict-related activity tends to be associated with more dorsal regions of ACC extending into pre-SMA (Hester, Fassbender, & Garavan, 2004). In line with this theory, we did not observe any significant activation in ACC for correct responses to incongruent stimuli. Unfortunately, there were insufficient errors in this task to examine error-related processes.

5.4.2 Neuroanatomy of Task Preparation

A number of regions, in particular left DLPFC were active during the cue period. DLPFC has been implicated in cognitive control in a number of studies (Botvinick et al., 2001; Carter et al., 2000; Ullsperger et al., 2002). Left DLPFC in particular has been implicated in control processes (Hazeltine et al., 2000; MacDonald et al., 2000). MacDonald and colleagues (2000) found that increased levels of top-down control as exercised by left DLPFC resulted in a reduction in Stroop interference. This area has been associated with the maintenance of task representations (Frith & Dolan, 1996; MacDonald et al., 2000; Ruchsow et al., 2002). It has also been linked to behavioural correction (Garavan et al., 2002; MacDonald et al., 2000; Rueckert & Grafman, 1996). In fact, in the present study there was evidence that activation in an area of DLPFC was associated with subsequent correct performance. This is supportive of the notion that this region is involved in the top-down allocation of attentional resources or the storage of task goals and rules. A stronger representation of these rules should facilitate appropriate responding. In fact, these two notions may be inter-dependent;

knowing how and when to exercise top-down control may be dependent upon stored task goals.

A wide range of other activations was also noted at a lower threshold. It has previously been suggested that areas activated during a cue period reflect preparation of relevant areas needed to perform that particular task (Brass & von Cramon, 2002). Hester et al (2004) also found that cues activated regions that were subsequently required for successful inhibitions in a GO/NOGO task. In this task we also noted a similar activation pattern between cues and subsequent correct responses to targets (see Figure 5.4). It may be that task-relevant areas are being primed during the cue period. Consistent with this, activation was noted in left premotor and motor areas during the cue period, which may reflect motor preparation for the upcoming response (responses were always made with the right hand, albeit with different fingers of the right hand).

The opportunity to prepare for an up-coming incongruent event also resulted in increased amounts of activation during the subsequent response. This lends further support to the notion that the cue allows participants to prime areas needed for the task. The only area that was more active during un-cued correct responses to incongruents was left insula. This activation may reflect an arousal response to an unexpected incongruent event.

5.4.3 Prefrontal and Midline Interactions

Responses to incongruent flankers subsequent to a cue were significantly slowed when compared to responses to un-cued incongruent targets. This suggests one of two

things; that cues did engage top-down attentional processes and slowed responding or that cues primed both responses (left and right finger responses) simultaneously, thereby increasing levels of response conflict and slowing RT. It has previously been demonstrated that patterns of rapid responding result in increased levels of response conflict (Garavan et al., 2003); therefore it may be facilitative to respond slowly. However, it would also be predicted that increased levels of top-down control should strengthen activation in the "appropriate" pathway (Botvinick et al., 2001), resulting in faster responding.

In this task it is difficult to say what is happening because the cue did not inform the participant as to which response should be primed. In fact, contrary to our hypothesis there was significantly greater activation in pre-SMA during cued correct responses to incongruent flankers than during un-cued correct responses to incongruents. There was no significant difference in activation in medial Brodmann area 8 during these two events. As left DLPFC has been implicated in task set maintenance in a number of studies (Frith & Dolan, 1996; Garavan et al., 2002) and because a relationship between this region and pre-SMA during conditions of increased response conflict was noted in the previous chapters, activation in these areas during the cue period prior to a correct response and a comparable un-cued period and also during the subsequent correct response was plotted in order to gain a clearer understanding of what was occurring in these cortical regions in this task (see Figure 5.4).

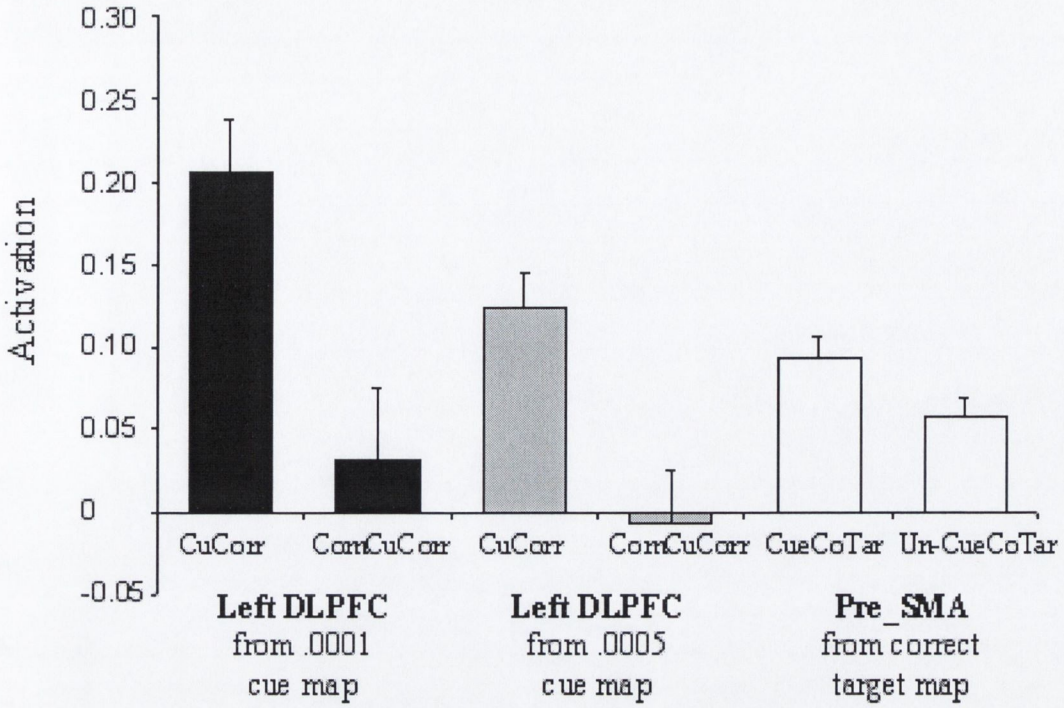


Figure 5.4: Activations in two areas of left DLPFC and pre-SMA.
The black bars represent the DLPFC activation from the 0.0001 cue activation map. This region showed a trend in the direction of greater activation for cue periods prior to a correct response. The grey bars represent the smaller activation focus from the 0.0005 cue activation map. This region predicted success in responses to targets. The pre-SMA region was taken from the correct response activation map.
Activation in both DLPFC regions is represented by a percentage change score, whereas activation in pre-SMA is represented by a percentage area under the curve score.
Cucorr: Activation during a cue period prior to a correct response.
ComCuCorr: Activation during a comparable period in the un-cued condition prior to a correct response.
CueCoTar: Activation during a correct response to an incongruent flanker following a cue.
Un-CueCoTar: Activation during a correct response to an incongruent flanker following no cue.

Although cue activation represents a percentage change score and activation during correct targets represents a percentage area under the curve score, precluding any specific quantitative comparisons, certain observations can be made from the graph. Firstly we can see that activation in left DLPFC is greater for the cue period than during a comparable un-cued period. We can also see that activation in pre-SMA during cued correct responses is greater than activation during un-cued correct

responses. There are two possible explanations for this. The first is that the cue does, in fact, cause increased amounts of response conflict due to a priming of two conflicting responses. This suggestion has previously been made; pre-SMA/midline activity during an unpredictive cue period was interpreted as reflecting response conflict due to the simultaneous priming of two conflicting responses (the GO and NOGO response) in a GO/NOGO task (Hester et al., 2004).

There is an alternative explanation, however. Activity over the entire brain was increased during the cue period. It may be that this increase in general levels of activation in the brain caused activity in midline regions to be relatively increased. Closer observation of the graph in Figure 5.5 reveals that activity in pre-SMA is reduced in comparison to activation in the left DLPFC in the cued condition but is increased relative to activity in this region during the un-cued condition. This is the pattern that we would expect to see if increased levels of cognitive control as implemented by PFC caused a reduction in levels of conflict as measured by midline regions (Botvinick et al., 2001). However, this explanation is post-hoc and extremely speculative. Therefore, no concrete conclusions can be drawn about midline-prefrontal interactions in this particular experiment.

In conclusion, a broad network of cortical areas, largely consistent with previous studies, was active during correct responses to incongruent flankers in this task. Activation in pre-SMA was noted as opposed to ACC, however. A number of similar cortical regions were also seen to be active during the cues themselves. This may reflect priming of cortical areas in preparation for the upcoming response. Left DLPFC activation was particularly noted during the cue period and also during correct responses to incongruent targets themselves. Consequently this area may be

involved in exercising top-down control under situations in which there is a need for additional attentional resources.

Chapter 6

The Role of a Right Fronto-Parietal Anatomical Network in Cognitive Control

Abstract

Seemingly diverse cognitive tasks often activate similar anatomical networks. For example, right fronto-parietal cortex is active across a wide variety of paradigms suggesting that these regions may subserve a general cognitive function. We utilized fMRI and a GO/NOGO task with intermittent unpredictive "cues-to-action" in order to investigate areas involved in inhibition of a prepotent response and top-down attentional control. A similar network of right dorsolateral prefrontal and inferior parietal regions were active for cues and inhibitions. Inhibitions in the un-cued condition also activated additional right fronto-parietal regions. These results suggest that this network is involved in general cognitive control processes through the allocation of top-down attentional resources.

6.1 Introduction

Human behaviour results from an interaction between top-down and bottom-up processes (Miller, 1999). Top-down processes are synthesized by experience and the cortical connections that underlie these processes are constantly changing, being strengthened or broken depending on changing contingencies and experience. They are guided by stored rules and knowledge. The prefrontal lobes are generally considered to be involved in top-down attentional processes (Coull, Frith, Buchel, & Nobre, 2000). Bottom-up processes are sensory-driven and automatic, for example orienting towards an unexpected sound or movement in the environment, and are subserved by well-established cortical pathways that connect stimulus and response (Miller & Cohen, 2001). This allows automatic behaviours to be executed quickly and without attentional control, freeing the system for additional processing that may be needed. Top-down processes are thought to be important for intervening and interrupting bottom-up processes in situations where it is maladaptive or unsuitable for these behaviours to be completed (Norman & Shallice, 1986).

There are two broad schools of thought on how the frontal lobes exercise control, one, which suggests that regions within the frontal lobes serve a variety of differing functions (Duncan, 2001; Duncan & Owen, 2000) and the other, that distinct regions of prefrontal cortex execute distinctly different tasks (Goldman-Rakic & Leung, 2002). Despite the evidence for a certain degree of differentiation in the frontal lobes, it is interesting to note that many seemingly diverse cognitive functions have anatomical networks in common. Sustained attention (Coull et al., 1998; Coull et al., 1996; Manly et al., 2003; Sturm et al., 1999; Wilkins et al., 1987), inhibition (Braver et al., 2001; Bunge et al., 2001; Garavan et al., 2002; Garavan et al., 1999;

Kawashima et al., 1996; Menon et al., 2001), oddball (McCarthy, Luby, Gore, & Goldman-Rakic, 1997) and arousal regulation (Kinomura et al., 1996; Sturm et al., 1999; Sturm & Willmes, 2001) all appear to involve strongly right lateralized anatomical networks. Therefore, it may be an over-simplification to assume that different areas of prefrontal cortex are highly specialized for any one particular function. It may be that diverse cognitive functions share some process, which results in the activation of common anatomical networks of regions among these executive functions. In this chapter, it is proposed that this super-ordinate process is attentional top-down control.

A number of authors have suggested that PFC enforces top-down control by biasing attention toward important features in the environment, leading to a decrease in activation in irrelevant, distracting channels, which may otherwise compete for attentional resources (Miller & Cohen, 2001). This could be achieved either by a simple selection and enhancement of the salient item over all other distracters, or an active inhibition of distracting, non-selected items (Rowe, Toni, Josephs, Frackowiak, & Passingham, 2000). As mentioned previously, in order to achieve this, there is a need to maintain task rules and goals in mind, which is thought to be implemented by PFC (Frith & Dolan, 1996; Garavan et al., 2002; MacDonald et al., 2000; Ruchsow et al., 2002). PFC, in particular right PFC in conjunction with right parietal lobe (Aron et al., 2003; Braver et al., 2001; de Zubicaray et al., 2000; Garavan et al., 2002; Garavan et al., 1999; Kawashima et al., 1996; Konishi et al., 1998) have also been implicated in the inhibition of a prepotent response. A recent study, however has suggested that pre-SMA may be critical for response inhibition and that additional areas that are seen in many inhibitory tasks are due to supplementary processes such as WM (Mostofsky et al., 2003). Since many executive functions such as sustained attention and

inhibition (Braver et al., 2001; Garavan et al., 2002; Garavan et al., 1999; Kawashima et al., 1996) appear to be activate cortical networks comprised of largely right prefrontal, particularly DLPFC, and parietal regions, it remains unresolved whether these patterns of activation reflect the processes themselves (e.g., inhibition) or represent more general cognitive control processes such as monitoring, attentional selection (Passingham & Rowe, 2002) or maintenance of task rules and objectives (Passingham & Rowe, 2002).

6.1.1 The Present Study

To address this issue, we utilized a GO/NOGO task, similar to the task utilized in Chapter 4, with intermittent phasic visual "cues to action" in order to investigate the neural consequences of "content free" cues (Manly, Davison, Gaynord, , in 2004) on a task of response inhibition. Cues were non-predictive but were linked to an instruction to concentrate to the task at hand and are presumed to engage top-down attentional control processes. It is proposed that visual cues are not as arousing as auditory alerts, which have been used in previous experiments (Manly et al., 2004; Manly, Hawkins, Evans, Woldt, & Robertson, 2002) and therefore trigger top-down attentional processes more so than bottom-up, arousal-related processes. Auditory cues have been used as a "wake up" stimulus in order to aid TBI patients during certain tasks (Robertson, Mattingley, Rorden, and Driver, 1998). Phasic alerting by relevant auditory external events is thought to depend on ascending thalamic-mesencephalic projections (Robertson et al, 1998). In fact, a number of studies have used visual warning stimuli without activating arousal-related networks (Coull et al., 2001; Thiel et al., 2004; Weis et al., 2000). Unpredictable, non-predictive auditory alerts, when linked with an instruction to concentrate on one's performance in a task, have been

shown to improve performance of both healthy and neurologically damaged individuals in terms of errors of commission in a GO/NOGO task (Manly et al., in press). The authors suggest that these phasic interruptions momentarily disengage ongoing performance of a task and allow for an adjustment or re-evaluation of goals, which may have been difficult to do when the system was otherwise engaged in activity. Therefore, periodic interruptions may disturb automatic patterns of response production, allowing for the engagement of more controlled, top-down regulation of behaviour, resulting in improved performance (Manly et al., in press).

In this study, we used a GO/NOGO task, which has been shown on a number of occasions to engage systems responsible for response inhibition (Garavan et al., 2002; 1999; Hester, Murphy et al., 2004). I wished to investigate whether "cues-to-action" (theoretically engaging processes involved in the maintenance of task set and top-down attentional control mechanisms) would activate similar networks of areas as those involved in the actual inhibitions themselves. It was hypothesized that inhibitions would engage a mainly right fronto-parietal network of regions. Additionally, if this right hemisphere network reflects top-down attentional control processes as opposed to inhibitory processes *per* se, it may be reflected in activation in this network during the cue periods themselves. Such a finding may clarify the role of these regions in response inhibition or top-down attentional control processes.

6.2 Methods

6.2.1 Subjects

Six male and eleven female subjects with ages ranging from 20 to 30 and a mean age

of 23.8 participated in this experiment. One female subject was excluded from the study due to very poor performance on the task on the day of scanning, as she was feeling unwell and one male was excluded due to excessive movement resulting in a new mean age of 23.7. Written consent was obtained from each participant and the university ethics committee granted ethical approval.

6.2.2 Materials

Task

Stimuli were presented and responses recorded using E-prime (Psychology Software Tools Inc.). A similar XY task as in Chapter 3 was used. The letters X and Y were presented in alternating sequence at a frequency of 1 Hz. Subjects were required to respond by button press to each letter appearing on screen, but were required to inhibit their response when the alternating sequence was broken. That is, when either two of the same letter were presented in succession, subjects were required to withhold their response to the second letter in the sequence. Stimulus presentation, which varied from 600/400 to 900/100 msec (stimulus presentation followed by a blank screen), was tailored to each subject in pre-scan training in an effort to ensure that participants responded correctly, on average, to 50% of the NOGO events. On occasion, a "cue-to-action" was presented. The cues consisted of two consecutive stimuli appearing in a pink font, rather than the white font used for all other stimuli. During pre-scan training subjects were instructed that the cues were presented in order to make them re-engage with the task. The phasic cues, which were not predictive of an up-coming NOGO, were pseudo-randomly scattered throughout cue blocks (ensuring that cue and inhibitory events did not coincide).

fMRI scanning

144 T_1-weighted sagittal slices were acquired for each subject (slice thickness = 1 mm, field of view = 250 mm). Functional images were single-shot, T2* weighted, echo planar imaging sequences. 20 sagittal slices (7 mm slice thickness) were acquired for each subject (TR = 2000 msec, flip-angle = 90 degrees, 128 mm x 128 mm matrix size, field of view = 240 mm). 168 volumes were scanned for each separate block in both the cued and un-cued conditions. Stimuli were projected onto a screen at the foot of the scanner and subjects viewed the screen with the aid mirrors that were mounted on the head coil, directly in their line of vision.

6.2.3 Procedure

GO/NOGO XY task

Six 315 sec blocks of the XY task were presented to subjects, 120 of the 1890 stimuli being NOGO events. NOGO events fell, on average, 13.2 sec apart. Three of the six blocks contained ten visual phasic "cues-to-action" that were presented from 19 to 54 sec apart (average of 28.3 sec apart). The three cue blocks were consecutive and the order of cued versus un-cued blocks was counterbalanced across subjects.

6.2.4 Data Analysis

Behavioural Analysis

Average percent correct withholds, omission errors, GO and error of commission RTs were obtained for each subject for each condition. Average pre and post-cue RTs were also recorded (5 events prior to and after a cue were averaged). Paired comparison t-tests were used in order to compare results from the cued and un-cued conditions. All

tests were carried out at an alpha level of 0.04 when corrected for multiple comparisons (Keppel, 1991).

Image analysis

A mixed regression analysis was employed whereby cue periods were calculated as a percentage change score using on-going task-related activation as baseline. These mini-blocks were defined based on the behavioural data, which showed that participants' RT slowed significantly for five seconds subsequent to a cue (see 6.3 Results). For comparative purposes, similar blocks were also defined prior to lures in the un-cued condition. These blocks were of similar duration and in similar locations in the time series to the cued blocks, but defined periods in the stimulus train where there were no actual cues. Separate IRFs were calculated for correct inhibitions and errors of commission. Although an error regressor was included in the deconvolution, further analysis was limited to correct inhibitions and block activations only as we were specifically interested in comparing activation patterns for cues and inhibitory control.

Separate t-tests against the null hypothesis of no percentage activation change were then performed for cued and un-cued mini-block activation and cued and un-cued correct inhibitions with a voxel-wise threshold of $p \leq 0.001$ and a cluster-size criterion of 132 μl of contiguous significant voxels. Cued and un-cued correct inhibition maps were then combined and mean activation calculated for each of the resulting functionally defined regions of interest by condition. There were no significant activations in the un-cued mini-block map, so block analyses were confined to the cued mini-block map.

6.3 Results

6.3.1 Behavioural Results

Subjects achieved on average 65.11% correct inhibitions in the condition with cues and 68.22% in the condition without cues but this difference was not significant ($t(14)= -0.68$, $p \leq 0.5$). Although the average response times were slower in the cued condition (370 msec) than in the un-cued condition (361 msec), this difference did not reach significance ($t(14)= -0.77$, $p \leq 0.5$). However, there was a significant slowing of RTs around the cue event, with post-cue RTs (five events following a cue) being longer than pre-cue RTs (five events preceding a cue) (388.67 ± 56.34 msec and 369.4 ± 58.62 msec respectively; $t(14)= 3.37$, $p \leq 0.004$). There was no significant difference between omission errors or error RTs in the cued and un-cued conditions (omission errors: 3.73 ± 4.15 v 4.87 ± 3.38 respectively; $t(14)= -1.03$, $p \leq 0.3$; error RT: 309.4 ± 51.56 v 322.3 ± 84.7 msec respectively; $t(14)= -0.83$, $p \leq 0.4$). As is normally the case with commission errors in GO/NOGO tasks, error RTs were significantly faster than GO RTs in both the cued and un-cued conditions (Cued condition: 309.4 v 370.27 ± 55.63 msec respectively; $t(14)= -4.64$, $p \leq 0.0001$; Un-cued condition: 322.32 ± 84.7 v 361.3 ± 54.97 msec respectively; $t(14)= -2.48$, $p \leq 0.03$).

6.3.2 fMRI Results

Correct Inhibition Activation

The combined cued and un-cued inhibition t-test maps contained 18 ROIs. These included four regions in the right IPL, three in the right DLPFC (see Figure 6.1), six areas along the medial wall, (four in the cingulate cortex, two of which were located

in the ACC), and one each in the left insula, parahippocampal gyrus, bilateral thalamus, right superior occipital gyrus and left putamen (see Table 6.1). Regions in the posterior cingulate and medial frontal gyrus were significantly deactivated during inhibitions. No region was significantly more active for cued over un-cued inhibitions but there were several that showed the opposite pattern. Regions in the DLPFC, right IPL, left insula and left putamen were all significantly more active for un-cued inhibitions (see Table 6.1 for significance levels). Two regions in the cingulate were also significantly more deactivated for cued inhibitions relative to un-cued inhibitions.

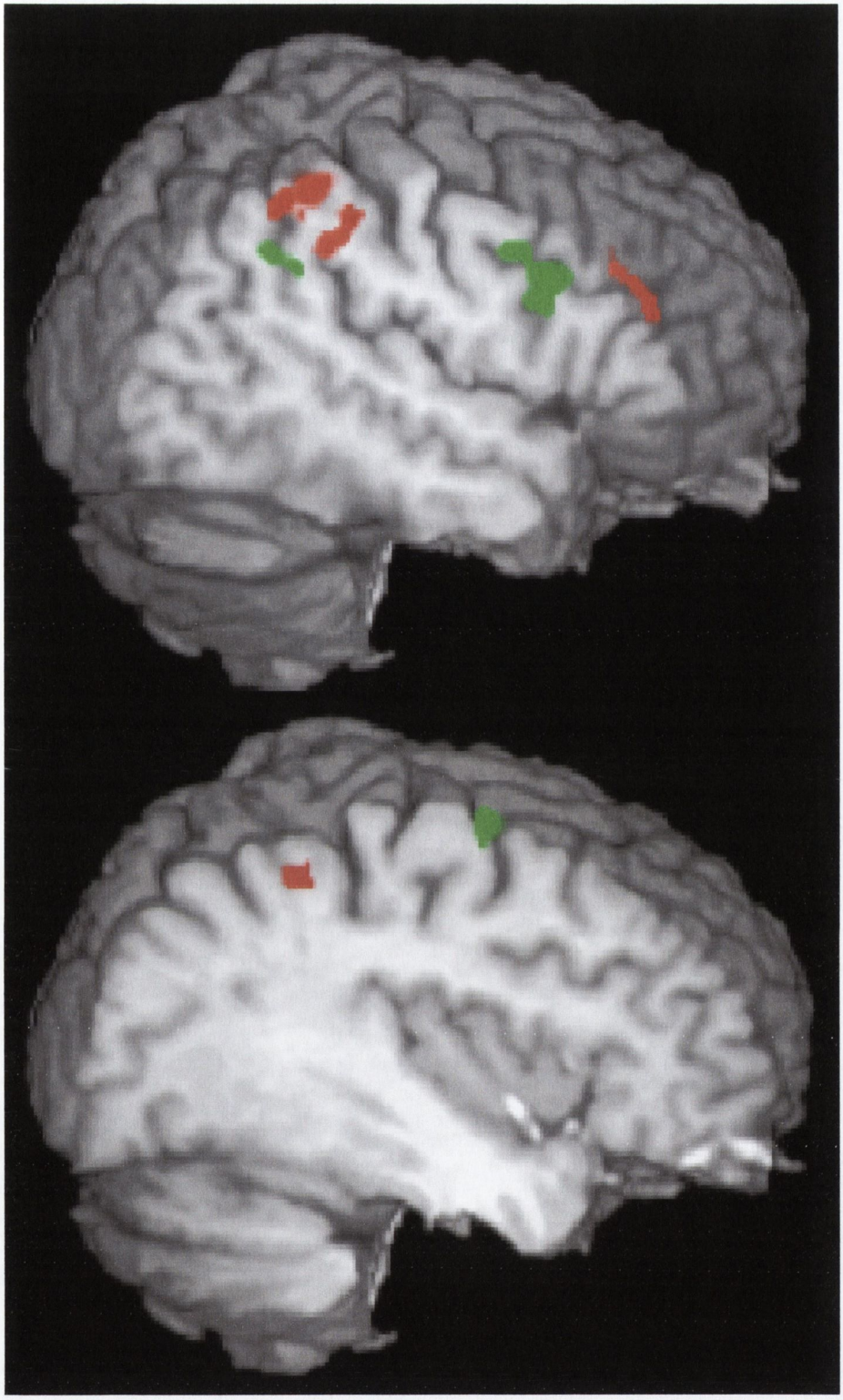


Figure 6.1: Right hemisphere regions activated by both cued and un-cued inhibitions. Areas in red are those regions that were active for inhibitions in both cued and un-cued conditions. Areas in green represent those regions that were significantly more active for inhibitions in the non-cued condition. Areas that were active included four regions in the right IPL and three in the right DLPFC.

Event-related Activations: Cued and Un-cued Correct Inhibitions

	Brodmann Area	Hemisphere	Volume (μl)	Talairach coordinates (centre of mass) x (RL)	y (AP)	z (IS)	Significant Difference t(14) Un-cue> cue
Frontal lobes							
MFG	9	R	562	47	10	30	**
	9	R	317	49	31	28	
	6	R	164	33	-2	58	
medial wall†	10	B	331	3	49	3	
	10	B	215	4	48	-8	
Parietal lobes							
IPL	40	R	1108	42	-41	48	
	40	R	288	46	-34	40	
	40	R	187	5	-24	25	**
SG		R	181	47	-47	35	****
Temporal lobes							
PG	35/36	L	227	-24	-36	-8	
Occipital lobes							
SOG	19	R	165	39	-77	28	
Other Regions							
ACC	32	B	489	1	34	-6	
		B	169	-3	-6	24	**
insula	24	L	166	-40	-	12	*
cingulate†	13	L	155	-8	-56	26	
	31	L	132	-8	-42	28	**
thalamus		B	145	3	-8	13	
putamen		L	138	-25	0	19	***

† Signifies a deactivation

* $p < 0.04$, ** $p < 0.01$, ***$p < 0.001$, ****$p < 0.0001$

Abbreviations: MFG: middle frontal gyrus; IPL: inferior parietal lobe; SG: supramarginal gyrus; PG: parahippocampal gyrus; SOG: superior occipital gyrus; ACC: anterior cingulate cortex

Table 6.1: Event-related Activations: Cued and Un-cued Correct Inhibitions

Activation during Cue Periods

The combined cue map contained 5 ROIs. These were mainly in visual areas including left middle occipital gyrus, right precuneus, right cuneus/ precuneus, right lingual gyrus and one area in left insula.

To further explore any similarity in the neuroanatomy underlying cues and inhibitions, we lowered the threshold of the cue map to 0.005 and used the same cluster size criterion. A number of additional activation areas were revealed, primarily in visual association and bilateral cerebellum (culmen and cerebellar tonsil) regions, although a number of mainly right hemisphere activation clusters were observed in the superior temporal gyrus, paracentral lobule, and precentral gyrus (see Table 6.2 for a complete list of areas activated). Three additional clusters in the right frontal and right parietal regions were also revealed. Of these regions, two clusters in the DLPFC and one in the IPL were of particular interest due to their proximity to regions activated for inhibitions (see Figures 6.1 and 6.2). The respective centers of mass for the two DLPFC cue activations fell 10.3 mm and 14.2 mm from the centers of mass of the nearest inhibitory activations. Similarly, the IPL region fell 9.3 mm from the center of mass of the nearest inhibition-related IPL region.

	Brodmann Area	Hemisphere	Volume (μl)	Talairach coordinates (centre of mass) x (RL)	y (AP)	z (IS)
Frontal lobes						
MFG	9	R	189	47	15	39
	9	R	149	39	6	41
		R	182	19	49	6
Paracentral Lobule		R	145	14	-36	55
Parietal lobes						
Lingual Gyrus		R	893	13	-77	0
		L	250	-19	-80	-7
POCG/IPL		R	288	36	-34	49
Temporal lobes						
STG	21	R	286	64	-15	-2
FG		L	245	-42	-71	-12
Occipital lobes						
MOG		L	757	-25	-86	12
		L	456	-41	-75	1
Cuneus	18	R	327	16	-73	20
	18	L	194	-13	-92	23
		R	253	13	-86	10
	30	R	132	7	-66	10
	23	L	277	-8	-69	14
Other cortical areas						
insula		L	401	-44	20	12
Post. Cingulate	30	R	234	23	-57	8
Precuneus		L	3878	9	-68	45
		L	177	-11	67	47
Cerebellum						
Cereb. Tonsil		L	438	-22	-66	-35
		R	274	33	-59	-38
Culmen		L	156	-9	-41	-21
		L	144	-11	-65	-9

Abbreviations: same as Table 5.1. Also POCG: postcentral gyrus; MOG: middle occipital gyrus; FG: fusiform gyrus; STG: superior temporal gyrus; Post.: posterior; Cereb.: cerebellar

Table 6.2: Block Activations: Cues at p = 0.005.

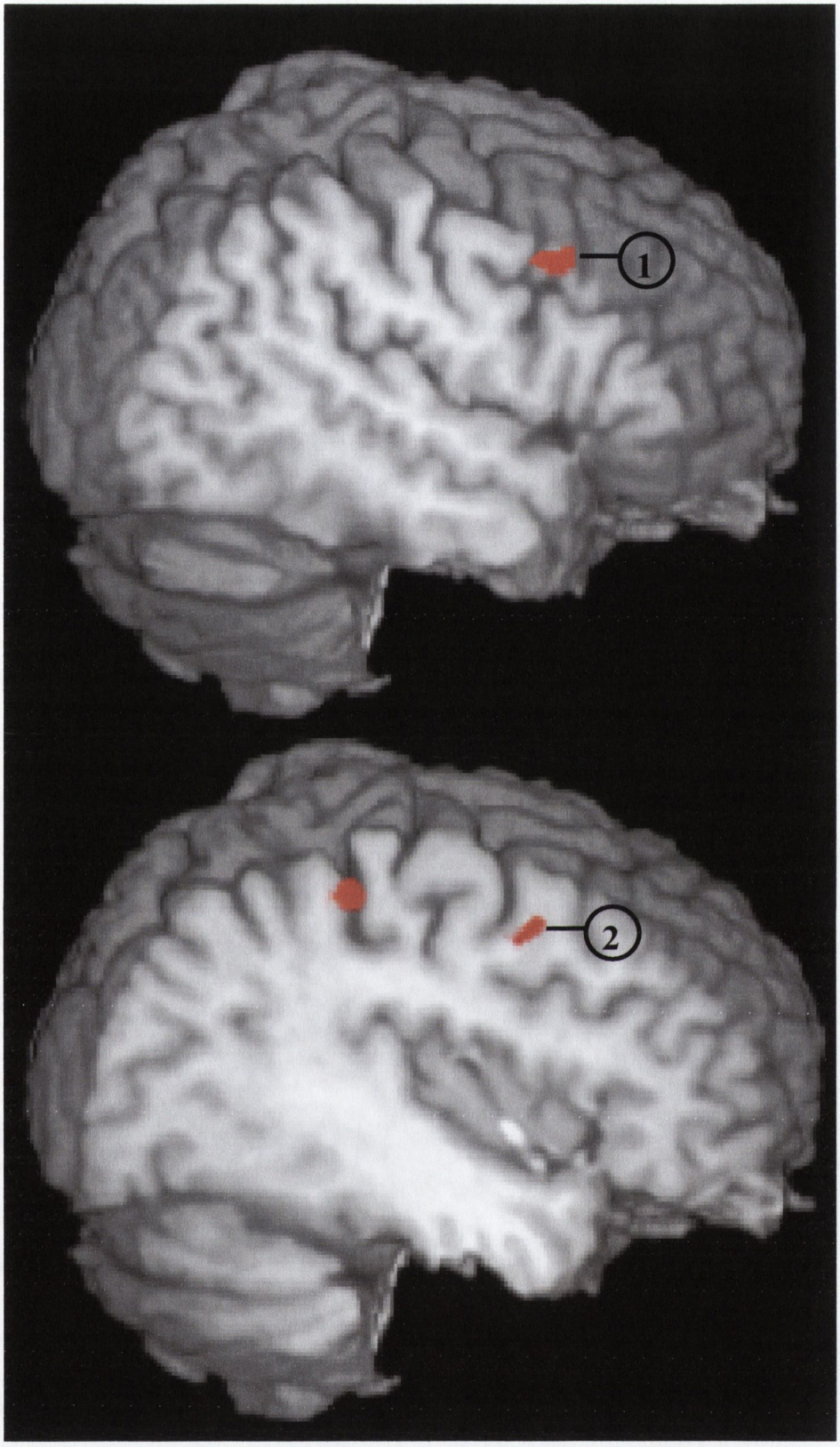


Figure 6.2: Right hemisphere regions that were active during the cues. These regions included two areas in right DLPFC and one in right IPL. Numbers 1 and 2 indicate the two areas in DLPFC.

The final analysis assessed the neuroanatomical similarity of the cues and inhibitions, using the functionally defined ROIs. I tested for significant activation in right hemisphere fronto-parietal regions during the cues themselves in ROIs that were defined by the inhibitory OR map and for activation during inhibitions in ROIs defined by the cue map. None of the inhibitory ROIs were significantly active for the cues themselves but two areas fell just outside the level of significance, one in the IPL and right DLPFC regions (See Figure 6.2 IPL: $t(15)= 1.924$, $p< 0.07$; DLPFC(1): $t(15)= 2.06$, $p< 0.06$). Using the cue ROIs, I examined if these regions were significantly active during cued and un-cued inhibitions. Two areas, in the IPL and the DLPFC (see ROI (1) in Figure 6.2) were significantly active for cued inhibitions (DLPFC: $t(15)= 2.42$, $p< 0.03$; IPL: $t(15)= 2.43$, $p< 0.03$) while both dorsolateral ROIs were significantly active for the un-cued inhibitions (DLPFC(1): $t(15)= 3.79$, $p< 0.002$; DLPFC(2): $t(15)= 2.34$, $p< 0.03$). Activation in these ROIs was then compared during cued and un-cued inhibitions revealing no significant difference in the "cue-to-action" ROIs (although for DLPFC(2) activation was larger yet non-significantly so for non-alerted inhibitions $t(14) = -2.043$, $p< 0.06$).

6.4 Discussion

A mostly right hemisphere network of regions was active for correct inhibitions irrespective of the cueing condition. The network included activation in the right occipital, prefrontal and parietal regions, left putamen, cingulate and insula, and bilateral thalamus, which is consistent with a number of previous studies of response inhibition (Garavan et al., 2002; 1999; Konishi et al., 1999; Konishi et al., 1998; Menon et al., 2001; Rubia et al., 2001). Significant deactivations were also observed

in posterior cingulate and medial frontal gyrus. Significant deactivation in medial frontal gyrus and posterior cingulate cortex has previously been shown to be functionally relevant having been associated with successful task performance in a similar GO/NOGO task (Hester et al., 2004). These activated and deactivated areas may be responsible for the actual inhibition of a prepotent motor response. However, visual "cues-to-action" also activated a right hemisphere fronto-parietal network of anatomical regions. This was observed in both the cue-activation map, albeit thresholded at a slightly more liberal level, and in the functionally defined ROI analyses. This suggests that the fronto-parietal subset of this network of regions may subserve a common process shared by both the inhibition of a prepotent response and the cues themselves. Despite the lack of an effect of the cues on performance, fewer cortical areas were involved in behavioural inhibition in those conditions that contained the cues. That is, two additional areas in right DLPFC and one in right IPL were activated for inhibitions in the un-cued condition. The implications of these results for understanding the role of right fronto-parietal cortex in inhibitory control will be addressed below.

Midbrain-thalamic or brainstem networks have previously been associated with arousal in a number of studies in different modalities (Kinomura et al., 1996; Sturm et al., 1999; Sturm & Willmes, 2001). The absence of significant cue-related activity in these areas during the current study argues against the right-hemisphere activation reflecting solely an arousal response. Additionally, I suggest that levels of arousal may already have been at ceiling in this task due to the fact that task difficulty was tailored to each individual to ensure high error-rates. This may also explain the absence of differences in performance between the cued and un-cued condition even

though there was significant slowing around the cue-to-action itself.

Instead, I propose that this right hemisphere network of regions is activated by top-down attentional, rather than by bottom-up stimulus-driven, processes. It is possible that cues act as "circuit breakers", interrupting automatic control of task performance to allow the re-establishment of top-down attentional control to take place (Corbetta & Shulman, 2002). However, in Corbetta's model "circuit breakers" are bottom-up processes (2002). These authors believe that top-down or goal driven processes are subserved by a dorsal fronto-parietal network including frontal eye fields and intraparietal sulcus, whereas bottom-up, stimulus-driven processes are subserved by a mainly right hemisphere network including ventral frontal cortex and the tempero-parietal junction. In this model the bottom-up anatomical network acts as a "circuit breaking alerting system" when external salient events are detected. The functional anatomy of the cues in the present study most likely reflects the fact that these cues, rather than being inherently arousing, were tied to an instruction to engage attentional processes and thus resulted in top-down interruptions in ongoing behavioral patterns.

Two possible explanations for why cues and inhibitions activate common neural regions suggest themselves. First, these regions may be required for inhibition and their activation during cue events reflects preparation for an imminent inhibition. Hester and colleagues (Hester et al., 2004) have previously found that cues that informed subjects that a target was imminent activated brain areas that were subsequently required for the inhibitory event itself. It is possible that in this study, cues, though non-predictive, induced a top-down control signal, which caused task-related areas to be prepared in readiness for a target. Areas active during cue events

were also found to be in close spatial proximity to regions active for both cued and un-cued inhibitions. However, a recent study has suggested that lateral and inferior frontal and parietal regions that are commonly found to be active during inhibitions are not necessarily involved in the process of inhibition itself but may be due to additional processes such as working memory that are often called upon in inhibitory tasks (Mostofsky et al., 2003).

An alternative explanation is that activation of fronto-parietal regions for both cues and inhibitions reflects a common underlying control or attentional process. Many diverse cognitive tasks produce activation of a right hemisphere fronto-parietal network, including oddball (McCarthy et al., 1997), inhibitory (Bunge et al., 2001; Garavan et al., 1999; Menon et al., 2001), working memory tasks (D'Esposito et al., 1998) and tasks involving the ability to sustain attention (Coull et al., 1998; Coull et al., 1996; Manly et al., 2003) or arousal (Kinomura et al., 1996; Sturm et al., 1999; Sturm & Willmes, 2001). Culham and Kanwischer (2001) suggest a number of reasons why parietal cortex is active in such a wide range of seemingly diverse cognitive tasks, including that parietal cortex may simply be an "association cortex" in which separate functions come together. This has been suggested due to the parietal lobes' activation during multifaceted and multi-modal responses. Alternatively, it may be that the parietal lobes perform a very general function such as attention (Culham & Kanwisher, 2001), which ensures its activation across a wide range of paradigms. Neurons in lateral intraparietal area have been found to be active during fixation, free gaze and pursuit-related activity (Ben Hamed, Duhamel, Bremmer, and Graf, 2002; Bremmer, Distler, and Hoffmann, 1997) and activity here has been shown to be dependent on the position of the eyes in the orbits (Ben Hamed et al, 2002). It has

been suggested that this region may be involved in the direction of attention linked to eye movements (Ben Hamed et al, 2002; Bremmer et al, 1997). Similarly, it has also previously been suggested that right parietal cortex may be involved in some "fundamental low-level attentional process .... that acts as a lowest common denominator for many types of cognitive processes" (Coull & Frith, 1998).

Petrides (1994) has suggested that ventral prefrontal areas are involved in receiving information from posterior association areas and subsequently storing and organizing them, whereas DLPFC is involved in monitoring and manipulating information in working memory. A number of subsequent studies have suggested that although DLPFC and ventral PFC are both engaged in working memory maintenance trials, DLPFC is recruited to an additional extent when manipulation of information in WM is needed (D'Esposito & Postle, 2002; D'Esposito et al., 1999; Postle & D'Esposito, 1999). The maintenance of task set rules and goals is also thought to involve DLPFC, (Banich et al., 2000; Frith & Dolan, 1996). Frith and Dolan (1996) have suggested that the DLPFC may act as the central executive whereas posterior association areas may act as the slave systems components of memory.

In this task we observed activation of right DLPFC and right IPL during both inhibitions and cues-to-action. These functions, along with the diverse array of paradigms that have previously identified activation of a right hemisphere fronto-parietal network, require top-down modulation and monitoring of attentional resources: even the arousal network, which is thought of as a bottom-up process, is thought to be mediated by prefrontal cortex in a top-down fashion (Posner & Petersen, 1990). It may be, then, that the right fronto-parietal network is involved in the

allocation of top-down or attentional resources when they are required during behaviour and may also be involved in monitoring for situations in which this control needs to be implemented. Consequently, the additional right hemisphere fronto-parietal regions recruited during un-cued inhibitions may reflect the need for the allocation of extra attentional resources under conditions of low levels of top-down control (in the un-cued conditions).

To conclude, there were a number of different regions that were activated irrespective of whether inhibitions were made in the cued condition or in the un-cued condition; two areas in inferior parietal lobe and one in middle frontal gyrus in Brodmann area 9. A right fronto-parietal network was also active for the cues themselves possibly reflecting a mechanism for top-down attentional engagement in right DLPFC and IPL. Although there were no behavioural differences between cued and un-cued conditions, additional right fronto-parietal regions were active when subjects withheld their responses to un-cued inhibitory events. This may have reflected increased recruitment of cortical areas in order to boost levels of top-down control in order to successfully inhibit responding. These results suggest that right fronto-parietal cortex may be involved in allocating top-down attentional resources in a variety of cognitive tasks and may explain why this network of anatomical regions is consistently seen to be active during many different cognitive paradigms.

Chapter 7

General Discussion

The four experiments conducted within this thesis provide insight into a number of different executive functions, their anatomical localization within the brain and also the dynamic relationship between these cognitive functions and thus the brain regions associated with them in the facilitation of complex human behaviour. Functions such as the ability to sustain attentional focus or levels of arousal, detect errors or the situations under which an individual is in danger of making an error, inhibit inappropriate responses in favour of the correct ones and ultimately the ability to implement some degree of control over all these processes are critical to normal human functioning. A comprehensive knowledge of such cognitive networks is also important in rehabilitation of individuals with compromised behaviour and brain insult.

In Chapter 3 a range of different executive functions were examined. These functions included sustained attention, response inhibition, error detection, response conflict

and task-set maintenance. The analysis of both tonic and phasic activations facilitated the examination of both discreet events, such as the moment of inhibiting a response, or detecting errors or response conflict and processes that were engaged throughout sections of the task, such as task-set maintenance, sustaining attentional focus and again, conditions under which there were more sustained levels of response conflict. This type of analysis is particularly effective in the examination of on-going executive functions and their interplay during a cognitive paradigm. Correlational analyses can then aid in the examination of how different brain regions interact and depend upon one another during a task.

In this chapter, it was concluded that a right fronto-parietal network, in conjunction with left DLPFC was responsible for the inhibition of a prepotent motor response. A right hemisphere network underlying response inhibition has been suggested by a number of authors (Garavan et al., 1999; Menon et al., 2001; Rubia et al., 2001). However, in this SART study left DLPFC was also active for inhibitions. This may have been due to the particular demands of the task or, alternatively may argue against right hemisphere dominance in response inhibition. Rostral ACC was implicated in the detection of errors, possibly reflecting an emotional response to an error (Bush et al., 2000; Falkenstein et al., 2000; Leung et al., 2000). Pre-SMA was seen to be active during situations of response conflict, both phasically during errors and also tonically under situations of increased response conflict in line with a number of previous studies (Garavan et al., 2003; Ullsperger & von Cramon, 2001). Parietal and right prefrontal regions were thought to be involved in sustained attention (Coull et al., 1998; Coull et al., 1996; Sturm et al., 1999; Wilkins et al., 1987) and left DLPFC was thought to be involved in the maintenance of representations or task-set

maintenance (Brass & von Cramon, 2002, 2004; Frith & Dolan, 1996; Garavan et al., 2002; MacDonald et al., 2000; Ruchsow et al., 2002). Furthermore, correlational analyses also suggested that left DLPFC and pre-SMA worked in conjunction in order to implement cognitive control, pre-SMA detecting situations under which an error may be likely to occur, relaying back to left DLPFC, which subsequently adjusted levels of top-down attentional control in order to accommodate this information in line with previous theories on cognitive control and response-conflict monitoring (Botvinick et al., 2001).

In Chapter 3 between-subjects correlations suggested that left DLPFC was associated with pre-SMA in the implementation of cognitive control. These prefrontal-midline interactions were further explored in Chapter 4. On this occasion, however, this relationship was examined on a within-subjects, trial-by-trial basis. Only correct responses were examined in this experiment in order to exclude the additional processes associated with the actual detection of errors themselves. "High control" cue periods, that is, cue periods during which there were larger amounts of activation in left DLPFC, were followed by trials in which lower amounts of response conflict were experienced, as detected by pre-SMA. "Low control" cue periods resulted in increased subsequent levels of activation in the pre-SMA. This pattern was not seen in right DLPFC or ACC. This adds further support to the notion that left DLPFC and pre-SMA are involved in cognitive control.

From these three experiments we can conclude that pre-SMA is a likely candidate for the detection of response conflict. This information is then transferred to PFC, probably left DLPFC, which subsequently appraises the need for elevated or reduced

levels of attention and implements this control (see Figure 7.1).

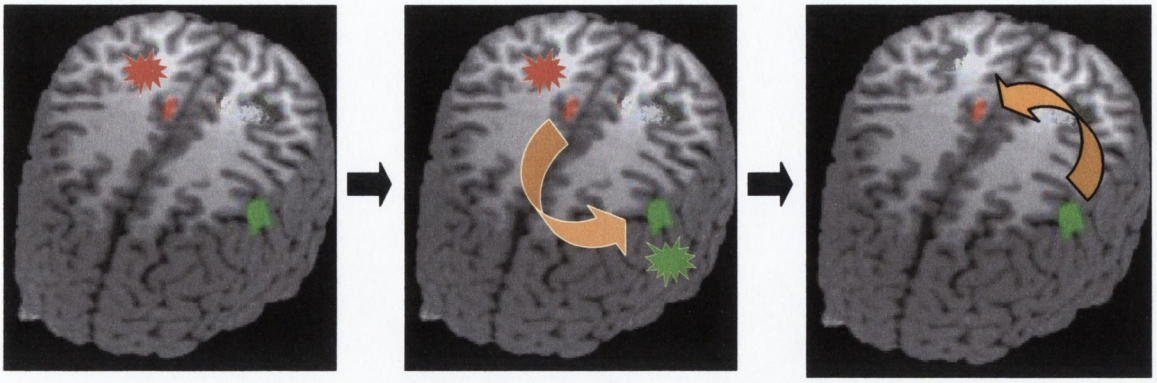


Figure 7.1: Midline-prefrontal interactions in cognitive control.

From the previous research and the evidence drawn from this thesis, this model of cognitive control is proposed. Pre-SMA is proposed to detect levels of response conflict (shown in red). This conflict signal is then relayed to left DLPFC (in green), which enforces greater levels of top-down control, causing levels of response conflict to subsequently be reduced.

In Chapter 5 I discuss an experiment that was designed in order to further examine the importance of left DLPFC in top-down control and to investigate the effect of task preparation on subsequent brain activation patterns. The relationship between left DLPFC and pre-SMA was also hoped to be examined further with this task. Flanker tasks have been found to produce conflict in a number of different studies (Fan et al., 2003; Ullsperger & von Cramon, 2001; van Veen et al., 2001). Therefore a flanker task with intermittent cues was utlised to manipulate both top-down control and response-conflict levels. Additionally, in the design of this task, particular care was taken to separate events by at least 20 seconds in order to allow the haemodynamic response to rise and fall, and thus gain a clearer activation map associated with these events. Bilateral prefrontal and parietal regions consistent with the findings of previous flanker paradigms (Fan et al., 2003; Hazeltine et al., 2000; Ullsperger & von Cramon, 2001; van Veen et al., 2001) were noted during incongruent events. A

similar network of cortical regions was also active during the cues themselves, possibly reflecting the priming of up-coming responses (Hester et al., 2004). This network included right insula, bilateral DLPFC, and bilateral but predominantly right IPL. A number of authors have previously suggested that areas active during a cue period reflect preparatory activation of relevant cortical areas in anticipation of a certain response (Brass & von Cramon, 2002; Hester et al., 2004). We suggest that, in this study task-relevant areas were primed during the cue period. Consistent with this notion, increased activation was noted during correct responses to incongruent flankers in task-relevant areas following the presentation of a cue.

Unfortunately, it was a little unclear as to whether cue periods themselves engendered levels of response conflict, as activity in pre-SMA was greater during cued correct responses to incongruent flankers than during un-cued correct responses when cognitive control should have been reduced. However from the evidence of previous research (MacDonald et al., 2000; Ullsperger & von Cramon, 2001) as well as the other experiments conducted within this thesis it is likely that the patterns of activation that were seen here, once again reflect a cooperative relationship between left DLPFC and pre-SMA in cognitive control. As mentioned, activation over the entire brain was increased during the cue period, which may have raised the baseline levels of activity, hence giving an artificial picture of what was occurring within the pre-SMA. In fact, when examining the pattern of activation in left DLPFC and pre-SMA during cued and un-cued periods and the incongruent events that immediately followed these periods, activity in pre-SMA during a cued correct response to an incongruent flanker was reduced in comparison to activation in left DLPFC during the previous cue period but was increased during an un-cued correct response in

comparison to the preceding period containing no cue. However, this is a very post-hoc analysis of the results, therefore this experiment, although providing insight into areas involved in top-down control and preparation of an impending response, may not, in fact shed much light on the dynamics between midline regions and PFC in cognitive control.

As mentioned previously in Chapter 3, right hemisphere prefrontal-parietal network was proposed to be involved in both the inhibition of a prepotent response and the sustaining of attentional focus over time. This theme was further investigated in the final study in this thesis. In Chapter 6, the observation was made that similar anatomical regions, namely right frontal and parietal cortex, subserve a number of differing executive functions. Additionally, it was recently suggested that many regions that have been associated with response inhibition might, in fact, reflect additional processes involved in performing such tasks (Mostofsky et al., 2003). It was thus hypothesised that this right hemisphere network may also be involved in a more general way in the implementation of cognitive control. A cued GO/NOGO paradigm was utilised and it transpired that a very similar network of right hemisphere frontal and parietal regions was active during both cues and the inhibitions themselves. This was interpreted as evidence to suggest that similar control processes were involved during cues and inhibitions.

Thus, the results from this thesis seem to implicate a number of different anatomical regions in cognitive control processes, depending on the type of task, and possibly the type of situation under which control is needed. Why is it that under situations of response conflict left DLPFC seems to be involved in enforcing control, whereas in a

wide variety of cognitive tasks, right DLPFC seems to be involved? Left DLPFC has been associated with task-set maintenance on a number of different occasions (Brass & von Cramon, 2002, 2004; Frith & Dolan, 1996; Garavan et al., 2002; MacDonald et al., 2000; Ruchsow et al., 2002). It may be that under situations of response conflict, when two different response possibilities are activated, the goal of the task must be refreshed in order to aid in the decision as to which response is the most appropriate.

It may be that right PFC, on the other hand, possibly in association with right parietal cortex may adjust control under situations of changing task contingencies. This region may be more flexible, adapting control from moment to moment, for example, when an urgent inhibition is required or an oddball stimulus is presented, upsetting the established pattern of responding or the expectation about the stimulus train. Brass and colleagues (Brass & von Cramon, 2004) have suggested that left PFC may be responsible for "activating a general task representation", whereas right PFC "seems to be related to the selective retrieval of the relevant task set when interference arises from a non-relevant task set" (page 618). Alternatively it may be that left PFC maintains task goals and rules, whereas right PFC implements this control in line with the task representations stored in left PFC.

These ideas are speculative, however and it is beyond the scope of this work to elucidate the separate roles of left and right PFC. However, it seems clear that bilateral PFC is involved in implementing cognitive control. Pre-SMA is likely to detect situations in which errors are likely to occur, signalling PFC for the need for increased control, if needed and ACC may be involved in registering an emotional reaction to errors themselves. A better understanding of the interaction of different

brain networks such as these, in the facilitation of behaviour is particularly important, not only to help clarify the elusive topic of how activity in anatomical brain regions translate to actual complex human behaviour, but also in order to better understand what happens when these networks break down, such as in the case of brain insult or clinical disorders.

A comprehensive knowledge and understanding of how the brain instantiates behaviour normally can aid in rehabilitation of individuals suffering from such disorders. Problems with executive control of behaviour have been implicated in a number of disorders. ADHD has been associated with problems with inhibition and sustained attention (Barkley, 1997; Cairney et al, 2001; Casey et al, 1997). Smaller volumes have been found in PFC in children with ADHD (Castellanos, Giedd, Marsh, Hamburger, Vaituzis, Dickstein, Sarfatti, Vauss, Snell, Lange, Kaysen, Krain, Ritchie, Rajapakse, and Rapoport, 1996; Durston, Hulshoff Pol, Schnack, Buitelaar, Steenhuis, Minderaa, Kahn, and van, 2004; Kates, Frederikse, Mostofsky, Folley, Cooper, Mazur-Hopkins, Kofman, Singer, Denckla, Pearlson, and Kaufmann, 2002; Mostofsky, Cooper, Kates, Denckla, and Kaufmann, 2002), particularly in the right hemisphere (Filipek, Semrud-Clikeman, Steingard, Renshaw, Kennedy, and Biederman, 1997; Hill, Yeo, Campbell, Hart, Vigil, and Brooks, 2003; Yeo, Hill, Campbell, Vigil, Petropoulos, Hart, Zamora, and Brooks, 2003). ADHD has been associated with a right hemisphere deficit in behavioral (Carter et al, 1995), fMRI (Rubia et al, 1999; Vaidya et al, 1998) and EEG studies (Pliszka et al, 2000; Steger, Imhof, Steinhausen, and Brandeis, 2000). Reduced activity in ACC and midline regions has been found for ADHD compared to control subjects in a delay paradigm (Rubia et al 1999), Stop paradigm (Rubia et al, 1999), counting Stroop task (Bush et

al, 1999) and in a study of decision making (Ernst, Kimes, London, Matochik, Eldreth, Tata, Contoreggi, Leff, and Bolla, 2003), which may suggests a possibility for differences in error processing or conflict monitoring in individuals with ADHD.

Problems with inhibition have been implicated in conditions such as OCD (Enright & Beech, 1993) and Tourettes syndrome (Peterson et al., 1998) as well. OCD has also been linked to problems with action monitoring; hyperactivity in midline areas has been noted during both error processing (Gehring, Himle, and Nisenson, 2000b; Ursu, Stenger, Shear, Jones, and Carter, 2003) and conflict monitoring (Maltby, Tolin, Worhunsky, and Kiehl, 2005; Ursu, Stenger, Shear, Jones, and Carter, 03) and has been correlated with OCD symptom severity (Maltby, Tolin, Worhunsky, and Kiehl, 2005; Ursu et al, 2003). An overactive monitoring system may cause individuals with OCD to perpetually feel that an error is either likely to or already has occurred, resulting in excessive checking behaviour and constant worrying. Clinical disorders such as schizophrenia which involve dysfunction of ACC have also been associated with problems in monitoring and responding to errors (Alain, McNeely, He, Christensen, & West, 2002; Holcomb, 2004). Faulty error processing systems may lead individuals to misjudge or exaggerate the implications of erroneous actions.

Finally, anterior cingulate hypoactivity has been observed in cocaine, (Kaufman, Ross, Stein, and Garavan, 2003), opiate (Forman, Dougherty, Casey, Siegle, Braver, Barch, Stenger, Wick-Hull, Pisarov, and Lorensen, 2004) and marijuana users (Eldreth, Matochik, Cadet, and Bolla, 2004). This hypoactivity may play a part in addiction, perhaps meaning that although individuals realise that their behaviour is maladaptive they are unable to amend it, or they do not appreciate the full

implications of their actions. If we glean a better understanding of how networks behave in the "normal" human brain may help us to elucidate what happens when these networks break down. We may then be able to teach individuals alternative strategies in order to deal with the compromised function of these networks or alternatively provide drugs that boost or stabilise activity in compromised brain areas.

Appendices

Consent Forms

- Trintity College Dublin Consent Form
- Nathan-Kline Institute Scanning Consent Form
- James' Hospital and Trinity College Dublin Consent Form

Psychology Department

CONSENT FORM

I hereby consent to participate in research carried out by researchers in the Psychology Department. I understand that I may withdraw my participation at any time, including at any time during a study. I understand that the data obtained through my participation are confidential and anonymous. They will be used only for the purposes of research. I will be informed of the general nature of the study before participating, and an explanation of the aims of the study will be provided after I have completed my participation, at which time any further questions will be discussed.

I understand that I will not be requested to do anything that would be detrimental to a person's well-being, under normal circumstances. I understand that I will receive credits for my participation. I confirm that I am over 18 years of age, of sound mind, and thus capable of giving my consent.

Signed _____ Date: _____ 2002

Witness _____

NATHAN S. KLINE INSTITUTE FOR PSYCHIATRIC RESEARCH (NKI)

INFORMED CONSENT TO PARTICIPATE IN RESEARCH INVOLVING MAGNETIC RESONANCE IMAGING (MRI) USING THE 1.5 TESLA MRI SYSTEM

You are being asked to volunteer to be a subject in a research study. This form is designed to provide information about this study which you should know and understand, as well as to answer any questions.

Participant Name: _____ **Participant ID:** _____

Project Director:	**John J. Foxe, Ph.D.**	**Phone: 845-398-6555**
Co-Investigators:	Glenn Wylie, D.Phil.	(845) 398-6555
	Antigona Martinez, Ph.D.	(845) 398-5497
	Marina Shpaner	(845) 398-6538
	Jeannette Piesco	(845) 398-6538
	Manual Gomez	(845) 398-6538

TITLE OF RESEARCH STUDY: ***Inhibitory Control in a Go-NoGo task***

Your participation will involve this many visits: 1

Each of these visits will take the following amount of time: 2 hours

The total duration of your participation will be this amount of time: 2 hours

THE PURPOSE OF THIS RESEARCH IS: to study one of the important ways by which our brain controls our behavior. Often, it is important for us to not respond to something that happens in the environment - that is, we might wish to ignore certain kinds of things that may occur. We are interested in the brain mechanisms that allow us to suppress or ignore responses to such occurrences.

THE FOLLOWING PROCEDURES WILL BE INVOLVED:

MRI scanning makes pictures of your brain. During the scanning session, you will lie down quietly on a bed, and the bed will slide into the scanner. Once you are inside the scanner, it will start to take the pictures. For some experiments, pictures of the brain are not actually taken, but other information about the brain's structure and/or function are measured by the scanner.

We will first take a picture of your brain and then we will proceed by presenting a series of stimuli that you will be asked to categorize in one of two ways. This series will last about 10 minutes. After each series, you will be asked if you wish to continue. If you wish to stop, you will have the option to return for another visit to finish. Remember that you can ask to stop at any time.

While the scanner is working, you may hear noises, like knocking or beeping sounds. We will give you ear-plugs or earphones to reduce the noise to a more comfortable level. While you are in the scanner, you can talk to the person who is running the scanner, and if you ask, they can stop the scan.

THE POTENTIAL RISKS OR DISCOMFORTS TO YOU ARE:

This MRI scanner is a research device. The safety of this scanner has been reviewed and its use in this study has been judged not to be associated with significant risk. There are no known risks associated with this kind of MRI scanning. The magnet in the scanner can cause electronic devices like pacemakers, beepers, and watches to malfunction, and some metal objects can be pulled into the

magnet. If you have an electronic device (like a pacemaker) on your body, or implanted in your body, there is a risk that it may stop working. If you have iron or steel on or in your body (except teeth fillings), there is a risk that the metal may move or be dislodged. We will ask you a series of questions before the scan to make sure you do not have any metal on or in your body, and we will ask you to take off metallic objects you may be wearing (such as a watch or jewelry). If you have iron or steel in your body that cannot be removed, you cannot have the scan.

The long-term effects of being placed in a magnet of this strength are unknown, but you should be aware that there have been no reports of any ill long-term effects caused by magnets of the same and even higher strength here or elsewhere. Also, although there are no known risks associated with pregnancy, we will not scan someone who is pregnant; so you should understand that if you are a woman in her child-bearing years, your consent to participate indicates that you believe you are not pregnant, and pregnancy testing will be used to assure that you are not pregnant.

Some people have reported sensations during the MRI scan, such as "tingling" or "twitching", which are caused by changes in the magnetic field that can stimulate nerves in your body. If you experience sensations and feel that these are uncomfortable, you can tell the operator and stop the scan. Rarely some people have experienced painful sensations, and if you do we will stop the scan immediately. Despite these experiences, no one has ever had sensations from the scan that did not stop as soon as the scanning stopped. After you finish the session and leave the scanner, the operator will ask you questions about whether you had any sensations or other experiences.

In some experiments, you may be asked to perform tasks while you are in the scanner. These tasks involve different activities, such as listening to sounds, making decisions, and/or pressing buttons. Sometimes these tasks can be tiring or frustrating.

THERAPEUTIC OBJECTIVES: This research study will give you no direct benefits. While sometimes MRI scans are done for clinical purposes, the scans you will receive are being done for research purposes. Since these scans are not designed for clinical reading, your scans will not receive a clinical interpretation. It is hoped, however, that the knowledge gained will be of benefit to others in the future.

THE POTENTIAL BENEFITS TO YOU OR TO OTHERS ARE: By participating in this research, new methods for gaining information about the brain can be obtained. These methods may be used in research studies of mental illnesses to enhance our understanding of the causes and treatments for these disorders.

IF YOU DO NOT PARTICIPATE IN THIS RESEARCH, YOU MAY RECEIVE THE FOLLOWING ALTERNATIVE TREATMENT(S): Since this is not a treatment research study, there are no alternative treatments.

CONFIDENTIALITY: Should you consent to participate in this research, your identity will be kept confidential within the following limits. If research drugs and/or devices subject to U.S. Food and Drug Administration (FDA) regulations are involved, it may be necessary for this consent form and other medical records to be reviewed by representatives of the FDA and the agency providing the test substance and/or the Sponsor of the study. A copy of this informed consent may also be sent to the Director of Quality Assurance at Rockland Psychiatric Center for monitoring purposes. Under state law, certain legal advocacy organizations (groups that support subjects' rights) have authority to obtain confidential subject records. We could be required to give copies of your study records to one of these organizations if they request these. However, they would not be allowed to reveal your identifying information to anyone else without your permission. All research information obtained from you will not be identified with your name; we will use only a coded number and/or your initials. All data will be kept in locked cabinets, and any publications resulting from this study will not identify you.

TERMINATION OF YOUR PARTICIPATION: Your decision to take part in this study is voluntary. You have the right to decide not to participate. Should you agree to participate in this research, you may change your mind at any time and withdraw from the study. If you choose not to participate, there will be no penalty or loss of benefit to which you would otherwise be entitled. The Project Director may withdraw you from the study without your consent at any time if: he believes it is

in your best interest; you significantly fail to follow study directions and procedures; there are unexpected or serious side effects.

MEDICAL COMPENSATION FOR RESEARCH-RELATED INJURIES: Federal and New York State regulations require that we inform you about our institution's policy with regard to compensation and payment for treatment of research-related injuries. All forms of medical diagnosis and treatment – whether routine or experimental – involve some risk of injury. In the event that you experience an injury at The Nathan Kline Institute as a direct result of participating in this research the facility will provide emergency medical care within its capabilities, arrange such other emergency medical care as may be necessary and assist you in arranging follow up care. Neither the facility nor Nathan Kline Institute, nor The Research Foundation for Mental Hygiene, Inc. make any commitment to pay for medical care, nor do they have programs to provide you with financial compensation for such injury

By agreeing to participate in this research and signing this consent form, you do not waive any legal rights nor do you release the research staff, The Nathan Kline Institute, or the Research Foundation for Mental Hygiene, Inc. from liability for negligence.

PAYMENT FOR YOUR PARTICIPATION: You will be paid at a rate of $10/hour for participating in this study, and there will be no costs to you to participate.

GENERAL CONDITIONS AND OTHER INFORMATION:

1. You will be told of any new findings that may influence your willingness to continue to participate in this research. Your participation is this study may be terminated by the Project Director if in his/her judgment it is inadvisable for you to continue.
2. If you would like to discuss **your rights as a research subject and/or your participation in this study** with an institutional representative who is not part of this study, you may **contact Erna Ostrom, NKI/RPC IRB Coordinator at (845) 398-5493 or Carol Roth, NKI/RPC IRB Director at (845) 398-5492.**
3. If you have any **questions about this research during the study**, or if you experience a research-related injury at any time during this study, you may call **Dr. Foxe at 845-398-6547.**
4. A copy of this consent form will be given to you, and a copy will be kept at in a locked file in the office of the researchers.

I voluntarily consent to participate in the research study described above.

_____

Print Subject Name

_____ _____

Subject Signature Date

I believe that this consent is freely given, by a subject with sufficient capacity to consent, who has been given all information deemed necessary by the Institutional Review Board or requested by the subject.

_____

Print Name of Person Obtaining Consent

_____ _____

Signature of Person Obtaining Consent Date

INFORMATION SHEET

Cognitive and Motor Function in Adults with Attention Deficit Hyperactivity Disorder: An examination using functional magnetic resonance imaging (fMRI)[1]

Research Team: Professors Michael Gill, Michael Fitzgerald, Ian Robertson and Drs. Aiveen Kirley, Hugh Garavan and Mark Bellgrove, Trinity College Dublin

Attention Deficit Hyperactivity Disorder (ADHD) is a disorder of childhood that is characterized by deficits in attention, inhibition and hyperactivity. In 30-60% of cases, ADHD persists into young adulthood, placing sufferers at an increased risk for social disadvantage including unemployment, drug abuse and alcoholism. Understanding ADHD in young adulthood is therefore vitally important for both the scientific and the general community.

The purpose of this study is to tell us whether young adults with ADHD are activating the same areas of the brain as adults who do not have ADHD, when they are performing certain tasks. One way that we can investigate this question is by asking people to perform tasks while they are lying in an **MRI** machine that takes rapid pictures of the brain. We are therefore in need of a **group of healthy young adults** without ADHD who can act as a comparison group for our young adults with ADHD. If young adults with ADHD are not activating the same areas of the brain as healthy controls then this provides us with important information about how the brain may be affected in ADHD.

Magnetic Resonance Imaging, or **MRI**, is a technique that uses very powerful magnets to obtain pictures of human tissue and of human blood flow (blood flow in the brain tells us which parts of the brain are currently active). You should understand that the MRI is conducted for research purposes only and is not the type used for diagnostic purposes, clinical evaluation, or treatment. It will not be systematically reviewed for abnormalities. However, occasionally, an incidental finding on the MRI will show what could be an abnormal finding. Should this occur and you need another type of MRI that is diagnostic, or another exam to be used as a basis for diagnosis and treatment, you will be referred to the appropriate consultant(s) for such exams.

The MRI machine that will be used in this study is the 1.5 Tesla (a measure of magnetic strength) machine in St James' Hospital Dublin. You will be asked to perform an attention task , that you will have already practiced with one of the researchers. The purpose of the MR scanning is to determine which brain regions are involved as you perform the task. Upon entering the MRI facility you will be fitted with a helmet and headphones. The helmet is to prevent excessive head movements that may interfere with the imaging, while the headphones are to minimize any adverse effects of the loud noise generated by the MRI machine. The noise generated by the machine can be very loud and can result in a temporary decrease in the ability to hear quiet sounds. Sometimes, there may be some discomfort associated with lying in the scanner for 1 to 1 ½ hours, and in having ones head movements restrained. It has been reported that in about one in a million scans, the radio frequency waves used in the exam has caused minor burns.

It is important to realize that there are **virtually no risks associated with MRI**. Importantly, MRI uses a magnetic field and there is no radiation involved. On occasion a person may experience claustrophobia. To safeguard against any adverse reactions that you may

[1] Scanning for the study outlined in Chapter 5 was covered under the ethical approval of an on-going departmental study into ADHD. Participants were covered under the umbrella of normal controls within this study.

experience while in the scanner, you will be given a button whilst in the scanner, that you need only push to be immediately withdrawn from the scanner. It is important to realize that you can be withdrawn from the study at any point in time.

If you agree to being involved in the study, then a member of the research team would come and visit with you in your home prior to scanning to tell you more about the project and to give you practice on the task, so that you feel as comfortable and as confident as possible while in the scanner. Any costs associated with your travel to St James' Hospital for the scanning will be covered by the project.

If, at any time, you have any questions regarding this research, please feel free to contact Dr Garavan on 01 608 3910.

CONSENT FORM

Title of Project:

Cognitive and Motor Function in Adults with Attention Deficit Hyperactivity Disorder: An examination using functional magnetic resonance imaging (fMRI)

Information about the Project:

Attention Deficit Hyperactivity Disorder (ADHD) is a disorder of childhood that is characterized by deficits in attention, inhibition and hyperactivity. In 30-60% of cases, ADHD persists into young adulthood, placing sufferers at an increased risk for social disadvantage including unemployment, drug abuse and alcoholism. Understanding ADHD in young adulthood is therefore vitally important for both the scientific community and the community, in general.

The purpose of this study is to tell us whether young adults with ADHD are activating the same areas of the brain as adults who do not have ADHD, when they are performing certain tasks. One way that we can investigate this question is by asking people to perform tasks while they are lying in an **MRI** machine that takes rapid pictures of the brain. We are therefore in need of a **group of healthy young adults** without ADHD who can act as a comparison group for our young adults with ADHD. If young adults with ADHD are not activating the same areas of the brain as healthy controls then this provides us with important information about how the brain may be affected in ADHD.

You are being asked to participate in our MRI study of attention and motor function (e.g., motor coordination) in ADHD. The study will involve you coming to the MRI facility located at St James' Hospital Dublin. The scanning will take between 1 and 1 ½ hours. All costs associated with your travel to and from the Hospital will be met by the research project.

The risks associated with MRI have been outlined in the attached information sheet. If at any time during the research you wish to withdraw from the study then you may. All information gathered during the course of this research is available to you upon request and is held in the strictest confidence.

If you are happy to be involved in this study, then please complete this consent form and make it available to the researchers at the time of their visit. You **do not need** to return this consent form in the mail.

By providing my consent I agree that:

I have been informed of the discomforts and risks which I may reasonably expect to experience as part of this study. When used on appropriately qualified individuals, MRI presents virtually no risk. There will be no exposure to x-rays or radioactivity in this study. I understand that the radio frequency waves used in this exam has produced burns in about one in a million exams (most of those minor). I understand that noise produced by this exam could be very loud, and that I will wear earplugs to prevent damage to their hearing. Even with earplugs, the noise produced by the exam may produce temporary threshold shifts (i.e., decreased ability to hear quiet sounds). I may experience some discomfort from lying in the scanner for 1 to 1.5. I may experience some signs of claustrophobia (fear of being closed in a tight space). Some tight sensations may occur from having my head restrained to prevent movement. I will also be asked to perform some tasks that I have performed on previous occasions, and should not therefore cause undue distress.

I have been informed that other risks of injury due to MRI include damage to implanted electronic devices (such as pacemakers), hemorrhage if aneurysm clips are present and trauma if ferrous metal objects are brought too close to the scanner. However, these risks are minimal in a properly administered site. **I do not have any of these items in my body.**

Participant's Consent: I agree to (insert name).....participate in the above research that will involve completing a range of tasks while in an MRI scanner located at St James' Hospital Dublin.

Participant's Signature:.....

Date:.....

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