**The role of a right fronto-parietal network in cognitive control:
Common activations for “cues-to-attend” and response inhibition.**

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Abstract

Seemingly **distinct** 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 **consisting of two conditions, one with** intermittent unpredictable “cues-to-attend” **and the other without any “cues-to-attend,”** in order to investigate areas involved in inhibition of a prepotent response and top-down attentional control. **Sixteen subjects (6 male, ages ranging from 20 to 30 years) responded to an alternating sequence of letters X and Y and withheld responding when the alternating sequence was broken (e. g., when X followed an X). Cues were rare stimulus font-colour changes which were linked to a simple instruction to attend to the task at hand. We hypothesized that inhibitions and cues, despite requiring quite different responses from subjects, might engage similar top-down attentional control processes and would, thus, share a common network of anatomical substrates. Although inhibitions and cues activated a number of distinct brain regions, a** similar network of right dorsolateral prefrontal and inferior parietal regions was active for **both**. These results suggest that this network, commonly activated for response inhibition, may subserve a more general cognitive control process involved in allocating top-down attentional resources.

Keywords: Top-down control, Cues, right DLPFC.

Much of human behaviour from perception to attentional control is thought to result 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 et al. 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 and 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 and 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 and Owen 2000; Duncan 2001) and the other, that distinct regions of prefrontal cortex execute distinctly different tasks (Goldman-Rakic and 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, Frith et al. 1996; Coull, Frackowiak et al. 1998; Manly, Owen et al. 2003), inhibition (Garavan, Ross et al. 1999; Bunge, Ochsner et al. 2001; Menon,

Adleman et al. 2001), oddball (McCarthy, Luby et al. 1997) and arousal regulation (Kinomura, Larsson et al. 1996; Sturm, de Simone et al. 1999; Sturm and Willmes 2001) all appear to involve strongly right lateralized anatomical networks. Therefore, it may be unwise to assume that different areas of prefrontal cortex 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.

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 et al. 1997). **Others have suggested that there may not, in fact, be a distinction between different executive processes or indeed between executive processes and other types of information representation (Cohen, Braver, and O'Reilly, 1996; Miller and Cohen, 2001).** For example, some authors have suggested that holding items in working memory may involve a similar process to that involved in sustaining attention (Coull, Frith et al. 1996; Awh and Jonides 1998; Coull and Frith 1998). **It has also been argued that the PFC biases activation along certain pathways dependent upon task context (Cohen, Braver, and O'Reilly, 1996).** These authors argue that constructs such as inhibition and memory processes are not, in fact, distinct processes but different expressions of this PFC biasing mechanism. **Although a certain degree of overlap between executive functions cannot be denied, there is also a wealth of evidence to suggest that sub-components of cognitive control are, indeed, distinct entities. Factor analytic studies point to the existence of separable components of executive functioning such as shifting of**

mental set and information “updating and monitoring” (Miyake, Friedman, Emerson, Witzki, Howerter, and Wager, 2000) as well as inhibition in normal control (Chan, 2001) and clinical populations (Burgess, Alderman, Evans, Emslie, and Wilson, 1998). Separate developmental trajectories have also been defined for constructs such as inhibition and selective attention (Booth, Burman, Meyer, Lei, Trommer, Davenport, Li, Parrish, Gitelman, and Mesulam, 2003). It may be the case that diverse cognitive functions share some processing characteristic that is general and super-ordinate, that implements top-down control, and that manifests itself in the activation of a shared cortical network.

As mentioned, 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 (Cohen, Braver, and O'Reilly, 1996); Miller and 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 et al. 2000). **Recent evidence seems to support the former, i.e. selection and enhancement (Egner & Hirsch, 2005). These authors used a Stroop task utilizing face stimuli and associated names to show that during conflict trials, when the name and face did not match, activation in the relevant pathway (associated with either face or name processing, depending on which domain participants were instructed to focus) was amplified rather than activation in the irrelevant pathway inhibited. However, as Nieuwenhuis and Yeung (2005) point out, this may not necessarily**

apply to response inhibition. They suggest that while inhibition of distracters may not be an efficient neural tactic due to the infinite permutations of possible distracters, response inhibition may be more plausible as there is a more limited array of motor responses available to a person at any given time (Nieuwenhuis and Yeung, 2005). In fact Sasaki and coworkers (Sasaki, Gemba & Tsujimoto, 1989; Gemba & Sasaki, 1990) recorded NOGO potentials in the monkey homolog of the cingulate during a GO/NOGO task, which they interpreted as an active inhibition process. Furthermore, upon stimulation of this area, monkeys inhibited their responses in the GO task, supporting the notion of a structure responsible for active inhibition of a motor command. In humans, Burle and colleagues (2004) used a combination of transcranial magnetic stimulation (TMS) and electroencephalographic (EEG) techniques in order to demonstrate active response inhibition in choice reaction time paradigms. In their study, amplification of the “relevant” pathway in the contralateral hemisphere was accompanied by suppression of the irrelevant pathway in the ipsilateral hemisphere. Thus, response inhibition tasks may involve a combination of neural amplification and active inhibition (Burle et al, 2004).

In order to achieve **amplification of relevant neural pathways**, there is a need to maintain task rules and goals in mind. PFC is thought to be involved in the maintenance of task set (Frith and Dolan 1996; MacDonald, Cohen et al. 2000; Garavan, Ross et al. 2002; Ruchow, Grothe et al. 2002). This area is also thought to subserve the *active* inhibition of a prepotent response. Right prefrontal as well as right parietal cortex have

been implicated in this process (Kawashima, Satoh et al. 1996; Konishi, Nakajima et al. 1998; Garavan, Ross et al. 1999; de Zubizaray, Andrew et al. 2000; Braver, Barch et al. 2001; Garavan, Ross et al. 2002; Aron, Fletcher et al. 2003). A recent study, however, has suggested that pre-SMA may be critical for response inhibition and that additional activations, such as the fronto-parietal findings, may be due to supplementary processes such as working memory (Mostofsky, Schafer et al. 2003). **Burle et al (2004) also suggest that the locus of response inhibition may be the SMA.** Since many executive functions such as sustained attention (Wilkins, Shallice et al. 1987; Coull, Frith et al. 1996; Coull, Frackowiak et al. 1998; Sturm, de Simone et al. 1999; Manly, Owen et al. 2003) and inhibition (Kawashima, Satoh et al. 1996; Garavan, Ross et al. 1999; Braver, Barch et al. 2001; Garavan, Ross et al. 2002) appear to 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 or maintenance of task rules and objectives (Passingham and Rowe 2002). **A recent study by Hester and colleagues (2004) utilized an inhibitory paradigm which combined response inhibition demands with differing degrees of working memory load. The authors found an overlapping network of regions subserving working memory and inhibition, suggesting that the common network may reflect increases in top-down attentional control as working memory demands increased. If response inhibition involves a partnership between amplification of relevant and suppression of irrelevant neural pathways, then the question remains as to what neural substrates underlie both of these intertwined processes.**

To address this issue, we utilized a GO/NOGO task with intermittent phasic visual “cues to attend” in order to investigate the neural consequences of “content free” cues (Manly, Davison et al. 2004) on a task of response inhibition. Cues were non-predictive but were linked to an instruction to concentrate on the task at hand and are presumed to engage top-down attentional control processes. We propose that visual cues are not as arousing as auditory alerts, which have been used in previous experiments (Manly, Hawkins et al. 2002; Manly, Davison et al. 2004) and therefore trigger top-down attentional processes more so than bottom-up, arousal-related processes. In fact, a number of studies have used visual warning stimuli without activating arousal-related networks (Weis, Fimm et al. 2000; Coull, Nobre et al. 2001; Thiel, Zilles et al. 2004). 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, Davison et al., 2004). 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, Davison et al., 2004).

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, Ross et al. 1999;

Garavan, Ross et al. 2002; Hester, Murphy et al., 2004). We wished to investigate whether “cues-to-attend” (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. **Although cues and inhibitions share certain characteristics (they are both rare events), we argue that they are relatively distinct cognitive processes, cues themselves requiring no motor-response inhibition. Thus it may be expected that they each engage separate anatomical substrates unless they share another processing characteristic.** We hypothesized that inhibitions would engage a mainly right fronto-parietal network of regions. Furthermore, 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.

METHODS

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. All participants were right-handed, free from neurological disorders, psychiatric

problems or head trauma and were not currently taking any medication. Written consent was obtained from each participant and the university ethics committee granted ethical approval.

Task

Stimuli were presented and responses recorded using E-prime (Psychology Software Tools Inc.). The letters X and Y were presented in alternating sequence at a frequency of 1 Hz. **Stimuli were presented in arial, 120 point size, bold, white font presented against a black background.** Subjects were required to respond by **an identical right hand index finger mouse click** 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. **The timing of the stimulus on-screen presentation time and following blank screen were manipulated (keeping within the 1 Hz time frame)** in an effort to ensure that participants responded correctly (**by withholding the button press**), on average, to 50% of the NOGO events. Stimulus presentation varied **in increments of 100 msec from 600 msec stimulus followed by 400 msec blank screen** to 900/100 msec (also presented 700/300 and 800/200 msec) was tailored to each subject in pre-scan training (**see Figure 1**). Six 315 sec blocks 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-attend” that were **separated from each other by a 19 to 54 sec interval** (average of 28.3 seconds apart). 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 the three blocks (ensuring that cue and inhibitory events did not coincide). The three cue blocks were consecutive and the order of cued versus uncued blocks was counterbalanced across subjects.

fMRI scanning

Scanning was performed on a 1.5 T Siemens scanner. 144 T₁-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 uncued conditions.

Image analysis

Data were analyzed using AFNI (<http://afni.nimh.nih.gov/>) (Cox 1996) software. Images were time-shifted using Fourier interpolation to correct for differences in slice acquisition time, edge-detected by removing any activation outside the brain and 3D motion corrected. Images or individual subjects that displayed excessive motion were excluded from further analysis, as were the first three images in each run. 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' reaction times (RT) slowed significantly for five seconds subsequent to a cue (see Results). For comparative purposes, similar blocks were also defined prior to lures in the un-cued condition (**the blocks that did not contain any "cues-to-attend"**). 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 impulse response functions (IRF) were calculated for correct inhibitions and errors of commission. A non-linear regression program determined the best-fitting gamma-variate function for these IRFs (Cohen, 1997; Ward, Garavan, Ross, Bloom, Cox, and Stein, 1998). The area under the curve of this gamma-variate function was expressed as a percentage of the area under the baseline. These percentage area maps (event-related activation) and percentage change maps (block activation) were then warped into standard Talairach space (Talairach and Tournoux, 1988) and spatially blurred using a 3 mm isotropic rms Gaussian blur. 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 **correct inhibitions in the cued and un-cued condition** with a voxel-wise threshold of $p \leq 0.001$ and a cluster-size criterion of 132 μ l of contiguous significant voxels. These thresholds, determined by Monte Carlo simulations resulted in a 0.05 probability of a significant cluster surviving by chance. **Correct inhibition maps in the cued and un-cued conditions** were then

combined (OR maps wherein a voxel was included if it was significant in either map) 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. All tests were carried out at an alpha level of 0.04 when corrected for multiple comparisons (Keppel 1991).

RESULTS

Performance 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 msec and 369 msec respectively; $t(14) = 3.37$, $p \leq 0.004$).

Correct Inhibition Activation

The combined t-test maps of **inhibitions in the cued and un-cued conditions** contained 18 regions of interest (ROI). These included four regions in the right inferior parietal lobes (IPL), three in the right dorsolateral prefrontal cortex (DLPFC), six areas along the

medial wall, (four in the cingulate cortex, two of which were located in the anterior cingulate cortex (ACC)), and one each in the left insula, parahippocampal gyrus, bilateral thalamus, right superior occipital gyrus and left putamen (see Table 1). Regions in the posterior cingulate and medial frontal gyrus were significantly deactivated during inhibitions. No region was significantly more active for inhibitions in the cued over uncued 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 uncued inhibitions (see Table 1. for significance levels). Two regions in the cingulate were also significantly more deactivated for **inhibitions in the cued relative to inhibitions in the uncued condition.**

 Insert Table 1. here

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. 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 1 and 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.

Insert Figures 1. and 2. here

We then assessed the neuroanatomical similarity of the cues and inhibitions, using the functionally defined ROIs. We 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 1. IPL(1): $t(15) = 1.924$, $p < 0.07$; DLPFC(2): $t(15) = 2.06$, $p < 0.06$). Using the cue ROIs, we examined if these regions were significantly active during **inhibitions in the cued and un-cued conditions**. Two areas, in the IPL and the DLPFC (see ROI (1) in

Figure 2) were significantly active for **inhibitions in the cued condition** (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 **inhibitions in the un-cued condition** (DLPFC(1): $t(15)=3.79$, $p<0.002$; DLPFC(2): $t(15)=2.34$, $p<0.03$). We then compared activation in these ROIs during **inhibitions in the cued and un-cued conditions** revealing no significant difference in the “cue-to-attend” ROIs (although for DLPFC(2) activation was larger yet non-significantly so for **inhibitions in the un-cued condition** $t(14)=-2.043$, $p<0.06$).

Due to the apparent similarity in brain networks activated during inhibitions and cue periods, we carried out a conjunction analysis in order to examine whether there was, indeed, overlap between right prefrontal or parietal regions. Separate t-tests were again carried out for **correct inhibitions in the cued and un-cued conditions**, this time with a voxel-wise threshold of $p \leq 0.01$ and a cluster-size criterion of 138 μl of contiguous significant voxels, again determined by Monte Carlo simulations, resulting in a 0.224 probability ($\sqrt{0.05}$) of a significant cluster surviving by chance in either map. Thus, when the maps are combined together in an AND map (which enables us to examine overlapping voxels between maps) the resulting p value is 0.05 for the AND map. A number of regions were significantly activated both during the cue period and during **correct inhibitions in the un-cued condition** from the conjunction analysis at this threshold; right cuneus, right cerebellar tonsil, right middle frontal gyrus and two regions in right DLPFC (see Figure 3 for DLPFC activations).

Insert Figure 3. here

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 (Konishi, Nakajima et al. 1998; Garavan, Ross et al. 1999; Konishi, Nakajima et al. 1999; Menon, Adelman et al. 2001; Rubia, Russell et al. 2001; Garavan, Ross et al. 2002). 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, Murphy et al., 2004). These activated and deactivated areas may be responsible for the actual inhibition of a prepotent motor response. However, visual “cues-to-attend” also activated a right hemisphere network of anatomical regions. This was observed in the cue-activation map, albeit thresholded at a slightly more liberal level, in the functionally defined region-of-interest analyses and in the conjunction analysis. This suggests that a mainly frontal 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, Larsson et al. 1996; Sturm, de Simone et al. 1999; Sturm and 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, we 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-attend itself.

Instead, we suggest 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 and Shulman 2002). However, in Corbetta’s model “circuit breakers” are bottom-up processes (Corbetta and Shulman 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 temporo-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.

A number of 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, Murphy 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 **inhibitions in the cued and un-cued conditions** and in the conjunction analysis a number of regions were found to overlap, including several regions in right PFC. Right cerebellar and cuneus activations may reflect motor and/or attentional preparation for the up-coming inhibition. Right cuneus has previously been associated with shifting attention spatially and non-spatially as well as shifting between items in long-term memory (Makino, Yokosawa, Takeda, and Kumada, 2004). 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, Schafer et al. 2003). **It is also possible that the cues-to-attend acted as distracters to the task at hand and that this task-irrelevant colour dimension needed to be actively inhibited, resulting in an activation of an inhibitory network during cues themselves. We find this explanation unlikely, however, as performance decrements may be expected with the introduction of distracters in a task. This was not observed in this study. Additionally, subjects were trained before they performed the task in the scanner and were thus accustomed to both the colour change and the associated instruction to attend.**

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, Luby et al. 1997), inhibitory (Garavan, Ross et al. 1999; Bunge, Ochsner et al. 2001; Menon, Adleman et al. 2001), working memory tasks (D'Esposito, Ballard et al. 1998) and tasks involving the ability to sustain attention (Coull, Frith et al. 1996; Coull, Frackowiak et al. 1998; Manly, Owen et al. 2003) or arousal (Kinomura, Larsson et al. 1996; Sturm, de Simone et al. 1999; Sturm and Willmes 2001). **This observation suggests two alternatives; either this diverse array of executive functions are actually manifestations of the same prefrontal control**

process (Cohen, Braver, and O'Reilly, 1996; Miller and Cohen, 2001) or they are indeed separate functions yet have some underlying feature in common.

A number of authors have suggested that there are no distinct entities such as inhibition or working memory, but that these constructs are different expressions of the same frontal lobe control process (Cohen, Braver, and O'Reilly, 1996; Miller and Cohen, 2001). For instance, Cohen and colleagues (Cohen, Braver, and O'Reilly, 1996) suggest that apparent memory impairments and inhibitory problems experienced by schizophrenics in continuous performance tasks may not be due to a progressive failure in separate executive functions *per se*, but may be manifestations of a decay in prefrontally mediated representations, including representations of the task or goal state. Similarly, Kimberg and Farah (1993) argue that impairments in so-called “executive processes” are due to a collapse in stimulus-response associations held in working memory by PFC. However, more recent investigations into frontal lobe functioning and the rise in popularity in imaging techniques have suggested otherwise. Numerous studies have located distinct anatomical networks subserving inhibition (Garavan, Ross et al. 1999; Bunge, Ochsner et al. 2001; Menon, Adleman et al. 2001), working memory (D'Esposito & Postle, 2002) and sustained attention (Manly et al, 2003) to mention but a few. Factor analytic studies have also isolated distinct constructs such as inhibition in both healthy control (Chan, 2001) and clinical groups (Burgess et al, 1998). Differential developmental trajectories have also been suggested for functions such as inhibition and selective attention (Booth et al, 2003).

Therefore, we argue that executive processes are relatively distinct, but are under the influence of a superordinate attentional control mechanism such as the Supervisory Attentional System (Shallice, 1982). Higher levels of attentional control may result in better performance in tasks that tax executive functions differentially (e.g. inhibitory or working memory tasks). Hence the truth may lie somewhere between the two extremes of complete PFC specialization and no specialization of function whatsoever. As witnessed by the Burle et al (2004) experiments, response inhibition may be a combination of active suppression of irrelevant pathways and amplification of relevant ones. Therefore, the overlapping pathways seen for both cues and response inhibition in this paradigm may support such a theory.

Culham and Kanwisher (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 and Kanwisher 2001) which ensures its activation across a wide range of paradigms. 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 and 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 et al. 1999; Postle and D'Esposito 1999; D'Esposito and Postle 2002). The maintenance of task set rules and goals is also thought to involve DLPFC, (Frith and Dolan 1996; Rainer, Asaad and Miller, 1998; Banich, Milham et al. 2000). 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-attend. 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 and 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 **inhibitions in the un-cued condition**

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).

Conclusion

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 **inhibitory events in the un-cued condition**. 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.

FIGURE CAPTIONS

Figure 1: Right hemisphere regions activated by **inhibitions in both the cued and un-cued conditions**. 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 inferior parietal lobes (IPL) and three in the right dorsolateral prefrontal cortex (DLPFC). **Regions 1 and 2 in right IPL and DLPFC respectively displayed a trend towards being active for the cue period as well as for inhibitions in both the cued and un-cued conditions.**

Figure 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.

Figure 3: Right MFG regions activated by both cue periods and **inhibitions in the non-cued condition** (displayed in red) in the conjunction analysis. Areas activated during the cue period are represented in yellow and those activated during **inhibitions in the non-cued condition** in blue.

A: MFG cluster 1 and 3 (centre of mass x, y, z coordinates 48, -15, 39; 45, -16, 29 respectively).

B: MFG cluster 2 (34, -2, 40)

C: MFG cluster 1 and 2.

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

	Brodmann Area	Hemisphere	Volume (μl)	Talairach coordinates (centre of mass)			Significant Difference t(14) Un-cue> cue
				x (RL)	y (AP)	z (IS)	
Frontal lobes							
MFG	9	R	562	47	10	30	**
	9	R	317	49	31	28	
	6	R	164	33	-2	58	
	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	
Subcortical 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	

Table 1.

[†] 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

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Figure 1.

Figure 2.

Figure 3.