Neural and Psychological Mechanisms of Interference Control

by

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To my father, who passed onto me a scientific mind.

To my mother, whose unrelenting positive support gave me confidence.

To my brother, my role model.

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Abstract

Interference control is the ability to select relevant information while filtering out irrelevant distracting information. Theories of interference control differ regarding whether a single system of control acts upon multiple representations, or whether dissociable forms of control exist. Moreover, it is unclear whether control relies on the facilitation of relevant information, inhibition of irrelevant information, or both. Here, we combine cognitive psychology, functional neuromaging, and meta-analytic techniques to examine the neural and psychological mechanisms of interference control. We find common control-related activation in the dorsolateral prefrontal cortex across perceptual, memorial, and response selection. However, control networks in more posterior regions of the brain differentiate by the kinds of representations that control acts upon. We suggest that the frontal eye fields and superior parietal lobule may be most closely linked to selective attention mechanisms that underlie perceptual selection, but that these regions may also be recruited to select upon competing memorial and response representations. Interference control processes acting upon competing memories preferentially recruit left ventrolateral prefrontal cortex, which shows enhanced functional connectivity with the medial temporal lobe when selection

demands are increased. Finally, response selection processes may engage the premotor cortex, and all forms of selection may be dissociable from inhibition processes that act just before motor execution. We demonstrate that at least in the perceptual domain, control processes act by a combination of facilitation of relevant information and inhibition of irrelevant information, and that inhibition can affect processing at least several seconds into the future. The role of inhibition in memory remains less clear. Our results suggest that common goal-related information stored in the dorsolateral prefrontal cortex biases processing in dissociable posterior networks responsible for different kinds of information. Hence, both common and dissociable neural and psychological mechanisms underlie interference control.

Chapter 1

Introduction

Consider the following situations:

- Faced with interesting scenery and several other motorists, a driver determines where to deploy her attention.
- Having scheduled multiple lunch arrangements, a student attempts to recall whether they are having lunch with a friend today or the next day.
- A diner chooses an entrée from a list of many delectable items.

All of these situations require selection. Oftentimes, selection proceeds automatically and we hardly notice it. What makes these cases interesting is that selection is effortful due to the presence of salient competing information. In these situations, control is required to select relevant information amongst irrelevant competitors. How is such control achieved? This is a question that has been of interest since the inception of experimental psychology.

The study of cognitive control has largely centered around tasks that require effortful discipline over automatic behaviors. Consider the classic Stroop task (Stroop, 1935). In this task, subjects are presented with colored words. Subjects

are instructed to refrain from their automatic tendency to read the words, and instead name the color that the words are printed in. In conditions where the word and the color match (e.g. the word “red” printed in red), there is little control needed since there is no conflict present. However, when the word and the color mismatch (e.g. the word “red” printed in green), control must be called upon in order to make the appropriate response in the face of conflicting color and word representations. Careful dissection of this task reveals that there are multiple routes towards successful performance. For one, attentional processes may be drawn upon to emphasize the color aspect of the input and/or attenuate the word input. Alternatively, both inputs may be perceived, yet control may allow only the color input to elicit its semantic representation. In the case that both the color and word activate their semantic representations, one might excite only the stimulus-response mapping for the color representation and/or suppress the stimulus-response mapping of the word. Finally, if the wrong response has been selected, this response may be withdrawn in favor of the correct response. Hence, even in this simple task, appropriate control can be achieved in several ways.

What the opening examples and the Stroop task illustrate is that effortful selection can occur on several levels of representation. These levels range from sensory inputs, to memories, to motor outputs. Clearly there are varied forms of information to be selected. What is unclear is whether the act of selecting among different sorts of information varies, as well, or whether a single governing

system of control is responsible for selecting amongst information of all kinds. In other words, is there a single control process or might control processes be distinguished in some meaningful way? Of further interest are the computational mechanisms by which control is achieved. For instance, is it the case that effortful selection proceeds via highlighting relevant information, attenuating irrelevant information, or both? Answers to these questions are central to our understanding of cognition.

Here, we will use the term “interference control” or “interference-resolution” to describe selection in the face of competing information. Historically, the term “inhibition” has been used in a synonymous way. However, this term presupposes the mechanism by which control is achieved: namely, the down-regulation of competing information. Although this account has intuitive appeal, empirical support for inhibition acting at a cognitive level is scarce (see MacLeod et al., 2003 for a review). Hence, recognizing that the mechanisms of control remain largely unclear, we restrict our use of term “inhibition” to cases where there is good reason to suspect that inhibition is truly at work, and use theory neutral terms otherwise.

1.1 Theories of Interference Control

Popular accounts of interference control are mixed regarding whether interference control is subserved by a single process, or a collection of

processes. In addition to variations in process distinctions, these accounts vary in the mechanisms underlying interference control.

1.1.1 Unitary Theories

1.1.1.1 Hasher, Zacks, and May, 1999 – Inhibition: Access, Deletion, and Restraint

Hasher, Zacks, and May (1999) hypothesized that inhibition is the critical component to interference control. These authors reasoned that inhibition performed three functions in the service of goal-directed behaviors. First, inhibition serves to prevent irrelevant information from capturing attention (access). Second, inhibition removes irrelevant information from mind (deletion). Third, inhibition prevents habitual responses from being produced, allowing less prepotent responses to be made (restraint). Hasher, Zacks, and May (1999) argued that the access and deletion functions of inhibition preserve the contents of memory so that only goal-relevant information is maintained. Deficits in either of these functions increase “mental clutter”, producing problems during retrieval. The authors applied this reasoning to memory declines in old age explaining that inhibitory declines with age produce more information to sift through in working memory leading to less efficient retrieval operations.

1.1.1.2 Kane et al., 2001 – Controlled Attention

Similar to Hasher, Zacks, and May (1999), Kane and colleagues (2001) theorized that interference control depends upon a single process. However, rather than highlighting inhibition as the mechanism that enables interference control, these authors argued that differences in interference control result from differences in controlled attention. By the controlled attention account, irrelevant information is shielded from memory by focusing attention on goal-relevant information. Outside of focal attention, irrelevant information fades away. Hence, this account does not endorse active inhibition as the mechanism underlying interference control, but rather excitation of relevant information. Irrelevant information need not be inhibited per se, rather it needs to not be maintained. These authors further speculated that if inhibition exists, it is the result of active maintenance that blocks distracting information. Therefore, inhibition may be a by-product of directing attention towards relevant information, rather than an active process focused upon suppressing irrelevant information.

1.1.1.3 MacLeod et al., 2003 – Episodic Retrieval

Both the inhibition and controlled attention accounts of interference control highlight the need to maintain goal-relevant information. Failures to maintain relevant information or filter out irrelevant information cause performance decrements observed in interference tasks. By contrast, MacLeod and colleagues (2003) focused on retrieval as the locus of performance decrements in interference tasks. These authors argued that interference tasks elicit automatic retrievals of conflicting information since multiple sources of

information compete for representation. The resolution of this retrieval-related conflict is a demanding operation, which causes decreases in performance. Furthermore, these authors favored an inhibition-free interpretation of interference control, pointing out that choosing among competing alternatives does not necessitate inhibiting one of them.

1.1.1.4 Braver, et al., 2007 – Proactive versus Reactive Control

The episodic retrieval account of interference control is clearly at odds with the inhibition account in that the episodic retrieval account sees no role for inhibition. At first blush, the episodic retrieval account may also seem incompatible with the controlled attention view since the controlled attention view highlights maintenance operations as the heart of interference control, whereas the episodic retrieval account focuses on retrieval. Work by Braver and colleagues (2007) demonstrates that these two accounts need not be mutually exclusive, however. By Braver et al. (2007), interference control can either be realized proactively, as in the careful maintenance of goals or goal-relevant information in the face of distraction. Alternatively, interference control can proceed reactively. In this case, a target stimulus is allowed to retrieve associated details, both relevant and irrelevant. After these details have been retrieved, control processes may select the appropriate information. Hence, this reactive form of control may have its locus at retrieval. Braver et al. (2007) showed that subjects differ in the degree to which they favor a proactive or reactive strategy, and that these differences were related to differences in fluid intelligence. However, both

strategies recruited similar neural correlates, suggesting that the same control processes operated for both proactive and reactive control, but at different points in time. Hence, it is possible that both the controlled attention view and episodic retrieval account are correct, and variations in task and subject strategy may favor one or the other at a given time.

1.1.1.5 Neural Instantiation of Single Process Theories – Biased Competition Models

If a single form of interference control acts upon multiple representations (e.g. percepts, memories, responses), how might control be instantiated in the brain? Several accounts have posited that a similar network of top-down control produces biasing signals that resolve competition at various levels of processing (Desimone and Duncan, 1995; Kastner and Ungerleider, 2000; Miller and Cohen, 2001). Top-down control is thought to originate from prefrontal cortex (PFC) and posterior parietal cortex (PPC) and modulate neural activity in representational cortex such as visual cortex for percepts, temporal cortex for memories, and motor cortex for responses. These control signals may act to highlight relevant information (Kastner et al., 1999; Egner and Hirsch, 2005), similar to the controlled attention account, or dampen irrelevant information (Tootell et al., 1998; Muller and Ebeling, 2008), similar to the inhibition account. Moreover, control can act at different points in time. Top-down biasing of visual cortex has been demonstrated during prepatory periods as subjects await a stimulus at a particular location (Kastner et al., 1999), supporting a proactive form of control.

Additionally, control signals from PFC are ramped up following high conflict situations (Kerns et al., 2004), reflecting a reactive form of control.

1.1.2 Multi-process Theories

Although parsimonious in their explanation of interference control, unitary theories face several challenges. For starters, measures of interference control often show near-zero correlations with one another (Kramer et al., 1994; Shilling et al., 2002). Such poor consistency among interference measures casts doubt on the claim that they tap the same fundamental ability. In addition, some patient populations demonstrate difficulties with some tasks involving interference control, but not others, suggesting a deficit in a specific form of interference control (e.g. Nigg, 2000; 2001). As a result, some theorists have suggested that interference control processes form a family of functions.

1.1.2.1 Nigg, 2000 – Interference Control, Cognitive Inhibition, and Behavioral Inhibition

Nigg (2000) hypothesized a taxonomy of interference control processes similar to the inhibition account of Hasher, May, and Zacks (1999). He distinguished four types of effortful control: 1) interference control prevents interference due to resource or stimulus competition; 2) cognitive inhibition suppresses unwanted thoughts to protect working memory; 3) behavioral inhibition suppresses inappropriate responses; and 4) oculomotor inhibition provides control over reflexive saccades. Nigg's interference control is similar to access in the Hasher,

Zacks, and May (1999) framework: cognitive inhibition is similar to deletion, and behavioral inhibition and oculomotor control map onto the restraint function. Like Hasher, Zacks, and May (1999), Nigg (2000) endorsed the position that control is achieved via inhibition. However, whereas Hasher, Zacks, and May (1999) spoke of inhibition as a single process that performs multiple functions, Nigg (2000) admitted uncertainty regarding whether each function was performed by a separable system. In his framework, Nigg (2000) hypothesized partially overlapping, but partially distinct neural correlates for each process and recognized that much work was needed to investigate these speculations.

Other authors have proposed taxonomies of interference control processes, but each of these map more or less onto the same framework proposed by Nigg (2000) (e.g. Dempster, 1993; Harnishfeger, 1995). Hence, several researchers have converged on the idea that interference control processes may be parsed by stages of processing. Therefore, the critical test to determine between unitary and multi-process theories may be to examine whether there are distinguishable interference control processes related to encoding perceptual material, maintaining information in memory, selecting among responses, and executing responses. There has been little work addressed at examining these distinctions, and as a result, multi-process theories of interference control rely largely upon conceptual distinctions rather than empirical support (Friedman and Miyake, 2004). Hence, there is a need for careful examination of distinctions among interference control processes.

1.2 Present Work

In the following chapters, I present 6 studies aimed at enhancing our understanding of interference control. Chapter 2 describes a meta-analysis of neuroimaging work that serves to summarize the extant neuroimaging data on interference control, as way as lay the groundwork for further studies. Chapter 3 focuses on a specific form of interference: interference from previously relevant, but no longer relevant memories (proactive interference). There we use event-related functional magnetic resonance imaging (fMRI) to examine the neural correlates of proactive interference and the mechanisms that are involved in its resolution. Chapter 4 describes the use of additive factors logic in a behavioral study to distinguish control processes related to proactive interference from those related to responses. Chapters 5 and 7 contrast the neural correlates of proactive interference-resolution with those involving selective attention to inputs. Chapter 5 examines these processes during retrieval, whereas Chapter 7 investigates their operation during encoding and maintenance. Chapter 6 examines control over attention more closely, testing whether control processes of selective attention use an inhibitory mechanism.

Chapter 2

Interference-Resolution: Insights from a Meta-Analysis of Neuroimaging Tasks

The need to select information among competing alternatives is ubiquitous. Oftentimes, successful cognition depends upon the ability to focus resources on goal-relevant information while filtering out or inhibiting irrelevant information. How selective attention operates, and whether and how irrelevant information is inhibited or otherwise filtered out has been a major focus of research since the inception of experimental psychology. For the past 15 years, cognitive neuroscientists have used neuroimaging to uncover the brain mechanisms underlying processes responsible for handling irrelevant information. Much of this research has used variants of classic cognitive interference-resolution tasks, each different in its superficial characteristics but sharing the common requirement to resolve conflict. What have we learned from this large corpus of data?

Examining the multitude of studies focusing on interference-resolution tells an extremely varied story. Figure 1a shows a plot of the peaks of activation of forty-seven studies which purport to examine interference-resolution (see the studies listed in Table 2.1). Ostensibly, there appears to be little consistency in these data. Several factors may be contributing to the massive inter-study variance.

First, Figure 2.1a includes activations from different tasks, subjects, equipment, scanning parameters, and statistical analyses. If we constrain our focus to just one task, however, the activations do not appear to be much more consistent. Figure 2.1b shows the activations arising just from the Stroop task (Stroop, 1935), and these do not appear any more orderly. Indeed, the variability among the reported peaks across all interference-resolution tasks corroborates behavioral findings that correlations in performance among different interference-resolution tasks are low (Kramer, Humphrey, Larish, Logan, & Strayer, 1994; Shilling, Chetwynd, & Rabbitt, 2002). Indeed, even simple changes in task parameters appear to produce very different results (e.g. de Zubicaray, Andrew, Zelaya, Williams, & Dumanoir, 2000; MacLeod, 1991). It seems clear that understanding interference-resolution will take deeper analytic methods that interrogate possible strategic and mechanistic differences. Some researchers have attempted to examine the neural signatures of various interference-resolution tasks within the same subjects to uncover whether any consistency can be found (Fan, Flombaum, McCandliss, Thomas, & Posner, 2003; Liu, Banich, Jacobson, & Tanabe, 2004; Peterson et al., 2002; Wager et al., 2005). These efforts have revealed that activations in different tasks overlap in a number of regions, but that there are also regions unique to one task or another. What underlies these commonalities and differences?

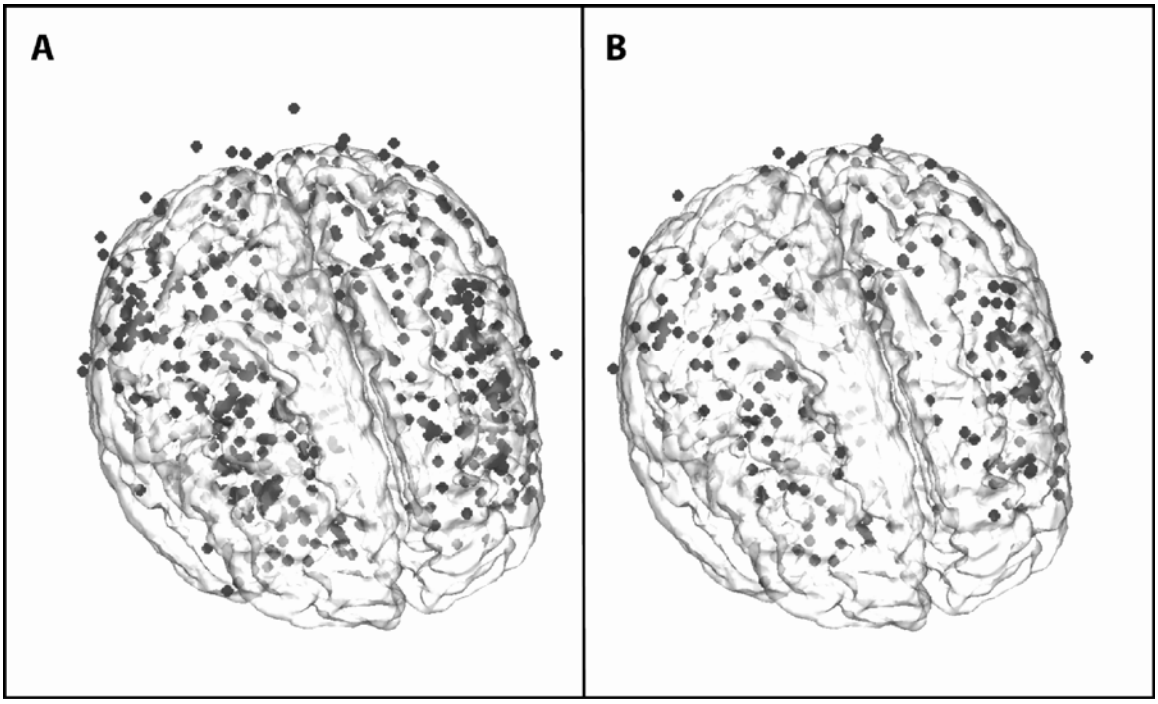

Figure 2.1. Peak Plot. A) Peaks from the 47 studies included in the meta-analysis plotted in a single brain. B) Peaks from the studies using the Stroop task.[1]

At this point, there have been a sufficient number of studies of interference-resolution to begin to answer these questions. Here, we attempt to sift through the inter-study variance in the interference-resolution literature and pick out the consistencies among studies and tasks. In addition to trying to uncover the neural basis of interference-resolution, we shall also consider why variations in

[1] It is clear from this figure that certain peaks seem to lie outside of the canonical brain (avg152T1.img; SPM, Wellcome Department of Cognitive Neurology, http://www.fil.ion.ucl.ac.uk/spm/). In order to plot all of the reported peaks into a single brain, coordinates that were reported in Talairach space were converted to MNI space (http://www.mrc-cbu.cam.ac.uk/Imaging/). It is possible that either there are some imperfections with the transformation tool or that some authors incorrectly reported that their coordinates were in Talairach space when they were actually in MNI space, causing the transformation to move these peaks outside of the canonical brain.

tasks and task parameters may lead to separable patterns of neural activation. Although the meta-analytic methods used here preclude us from drawing strong conclusions about interference-resolution (because they rely on reported peak coordinates from previous studies), they allow us to begin to form hypotheses that further investigations can either confirm or deny (e.g. Fox, Laird, & Lancaster, 2005).

2.1 Methods

2.1.1 Study Selection

For our analyses we included 6 tasks that have been prominent in the interference-resolution literature: the go/no-go task, flanker task, Stroop task, stimulus-response compatibility task, Simon task, and stop-signal task (all described below). Studies were included only if they reported peaks of activation in standardized coordinate space (Talairach or MNI). Notably absent are tasks that examine the resolution of proactive interference (e.g. Jonides, Smith, Marshuetz, Koeppe, & Reuter-Lorenz, 1998) since a review of these data has already been published (Jonides & Nee, 2006). Furthermore, we do not include the anti-saccade task in this mix because models of this task are already at the single-unit level, and our coarse techniques of analysis would be unable to inform this literature further (Munoz & Everling, 2004). We included neuroimaging studies that used either PET or fMRI between 1990 and 2005 that examined normal, healthy, young adults.[2] Although we recognize that there may be

[2] Several studies included also looked at patient, younger, or older populations. Data included in our analyses consisted only of those data extracted from normal, healthy young adults.

differences between blocked and event-related designs in terms of neural activations, there were insufficient studies to examine each separately. Therefore, we have combined both types of designs in our analyses. Forty-seven studies met our criteria and are listed in Table 2.1. When possible, we restricted our analyses to correct trials only.

2.1.2 Tasks

Go/No-Go. In the go/no-go (GNG) task, subjects are required to respond to one stimulus (the letter “Y” for example), but withhold a response to another stimulus (“X”). Responses are labeled “go” trials, while trials on which a response is to be withheld are called “no-go” trials. It has been argued that as the number of “go” trials preceding a “no-go” trial increases, a greater prepotent tendency to respond is formed (de Zubicaray et al., 2000; Durston, Thomas, Worden, Yang, & Casey, 2002; Durston et al., 2002; Rubia et al., 2001). This prepotent response must be resolved in order to perform properly on “no-go” trials. Our analyses included contrasts of no-go versus go responses.

Flanker. The flanker task requires a subject to attend to a centrally fixated stimulus while ignoring flanking stimuli (Eriksen & Eriksen, 1974). In a paradigmatic case, the central stimulus can be a letter (“H”, for example), which subjects learn to associate with a given response (say, a left keypress). Flanking stimuli can be of 3 types. First, the flankers can be identical to the imperative stimulus. In this case, both the relevant and irrelevant stimuli are consistent

(HHH). We will refer to this trial-type as “identical.” Flankers can also be different from the central stimulus (“S”, for instance), but participants are instructed to map these stimuli onto the same (say, left) response as the target stimulus (SHS). This trial-type is called “congruent.” Finally, stimuli can differ not only in form from the relevant stimulus, but also in response pairing (“G” mapped onto a right keypress). This is what we call an “incongruent” trial (GHG). Thus, on identical trials, no conflict is present. On congruent trials, there is stimulus conflict but not response conflict, and on incongruent trials there is stimulus as well as response conflict (Kornblum, Stevens, Whipple, & Requin, 1999; van Veen, Cohen, Botvinick, Stenger, & Carter, 2001; Zhang, Zhang, & Kornblum, 1999). Our analyses included both contrasts of incongruent versus congruent responses and incongruent versus identical responses. There were insufficient studies to tease these two contrasts apart. Additionally, there was an insufficient use of neutral conditions (i.e. flanking stimuli that map onto no response), to include as a point of comparison.

Stimulus-Response Compatibility. In the stimulus-response compatibility (SRC) paradigm, a subject is required to switch between two stimulus-response mappings. One mapping, referred to as “compatible”, is directly suggested by the stimulus. For example, a typical SRC task might employ arrows as stimuli in which case a “compatible” mapping might be a left keypress to an arrow pointing left and right keypress to an arrow pointing right. An “incompatible” mapping would require a left keypress to a rightward pointing arrow and a right keypress

to a leftward pointing arrow. Thus, in the “incompatible” condition, a prepotent response that is suggested by the stimulus and developed by previous “compatible” responses must be overcome. Our analyses included incompatible minus compatible contrasts.

Stroop. In the Stroop task, subjects must identify the hue in which a word is printed while ignoring the referent of the word. There are three basic types of trials in a typical Stroop task: incongruent, congruent, and neutral. On congruent trials, both the color of the word and the word’s referent elicit the same response (for example, the word “red” printed in red ink). On incongruent trials, the color and referent of the word elicit different responses (the word “green” printed in red ink). Neutral trials may be of several types, but for all neutral trials the referent of the stimulus does not provide a competing response to the hue (for example, a series of X’s printed in red, or the word “LOT” printed in red). Our analyses included both incongruent minus congruent and incongruent minus neutral contrasts.

Simon. The Simon task is similar to the Stroop task, except that the irrelevant stimulus dimension is spatial. For example, in a paradigmatic Simon task, a relevant stimulus is presented at various spatial locations. The stimulus (say, a colored circle) might appear either to the right or left of fixation. The circle is mapped onto a left or right response (e.g. red-left, blue-right), and subjects must respond to the stimulus while ignoring the potentially distracting spatial

placement of the stimulus. It has been found that when the location of the stimulus is incompatible with the response it elicits (a red circle presented to the right of fixation), reaction times are slower than if the location is compatible with the response. This is due to the resolution of interference caused by the irrelevant spatial dimension of the stimulus. We included incompatible minus compatible contrasts in our analyses.

Stop-signal. The stop-signal task requires a subject to cease executing a readied response. In a typical stop-signal task, a subject is required to respond to a stimulus, but withhold the response if a tone is heard. Varying the onset of the tone relative to the response can affect the error-rates (responses not withheld) and thus the demands on conflict-resolution processes. Our analyses include stop versus go responses.

2.1.3 Density Analysis

We used a data-driven approach to discovering which regions of the brain were most consistently reported in the corpus of studies. To this end, we employed a density analysis technique, which has been successfully used in other meta-analyses (Wager, Jonides, & Reading, 2004; Wager, Phan, Liberzon, & Taylor, 2003) and is similar to other voxel-based methods (Fox et al., 2005; Laird et al., 2005). The density technique is similar to the Activation Likelihood Estimate (ALE) method used in some other meta-analyses (Turkeltaub, Eden, Jones, & Zeffiro, 2002), with one distinction. The density technique examines the spatial

consistency among reported peaks and locates brain voxels in which the density of reported peaks exceeds what would be expected by chance. The ALE method assesses the probability that at least one activation peak fell within that voxel by assessing the union of probability values across individual peaks. Though the methods give very similar results, we test the null hypothesis that the spatial distribution of peaks is random, whereas the ALE method tests the null hypothesis that no studies activated a particular voxel.

The density analysis was conducted as follows. We first converted all Talairach peaks into MNI space in order to have all the data mapped into a common stereotactic space (http://www.mrc-cbu.cam.ac.uk/Imaging/). Next, we plotted all of the peaks reported in each study onto a canonical brain (avg152T1.img; SPM, Wellcome Department of Cognitive Neurology, http://www.fil.ion.ucl.ac.uk/spm/). We included only positive activations since deactivations are inconsistently reported and difficult to interpret (Phan, Wager, Taylor, & Liberzon, 2002; Wager et al., 2003). We then calculated a peak density estimate for each of the 2 x 2 x 2 mm voxels in the brain; this was defined as the number of the *n* peaks in the analysis contained within a sphere of 10 to 20 mm (depending on analysis, described below) surrounding that voxel, divided by the volume of the sphere. Thus, the units of density reported are peaks per cubic mm of brain tissue. In order to determine a density distribution for the null hypothesis, we conducted a Monte Carlo simulation with 5000 iterations per analysis, assuming no systematic spatial organization of the voxels. For each iteration, *n* points corresponding to

the *n* reported peaks were distributed randomly throughout the gray and white matter of the brain (excluding ventricles and sinus spaces). White matter was included because many reported peaks fall within white matter near white/gray matter boundaries.[3] The density-estimate map across the brain for the peaks as actually reported in the literature was then compared to this null distribution using a significance threshold of the 95th percentile of the null distribution ($p < 0.05$, brain-wise, one-tailed). The test statistic is the density of reported peaks in the local area around the voxel being tested, and the Monte Carlo simulation provides p-values that reflect how (un)likely it is to obtain the observed density if peaks were actually randomly (uniformly) distributed throughout the brain. A low p-value would indicate that the null-hypothesis uniform distribution of peaks is unlikely to result in a cluster as dense as the one observed. If the density-estimate of a given voxel was significantly greater than what would be expected by the simulated null distribution, we took this voxel to be active for that particular analysis.[4]

[3] We acknowledge that although some reported peaks fall within white matter, or gray matter/white matter boundaries, peaks are more likely to fall within gray matter. Therefore, it may not be appropriate to distribute simulated peaks uniformly across gray and white matter. However, the assumption of uniform distribution across gray and white matter greatly simplifies the analysis. Some studies do report peaks relatively deep in white matter, whether due to spatial imprecision or neuro-vascular translation in the BOLD effect or some other factors. The inclusion of white matter makes the tests here slightly less conservative than they would be if we included only some white matter (near gray-matter structures, for example) or only gray matter, but the difference is relatively small. Indeed, analyses that excluded white matter produced very similar results (as did simulations that increased the number of Monte Carlo simulations to 10000). Therefore, we deem that this method offers a reasonable approximation.

[4] We realize that using peaks ignores the volume and significance level of activation. Additionally, our resolution is limited by the density radius and the nonconformity of peaks may derive from variations in smoothing function images. As a result, we merely propose hypotheses from our data rather than drawing conclusion. However, we point out that this technique and techniques similar have provided useful results in several published studies (e.g. Phan et al., 2002; Turkeltaub et al., 2002; Wager et al., 2004; Wager et al., 2003).

Active voxels were grouped into contiguous voxels using SPM2's contiguity assessment procedures (spm_cluster.m; Wellcome Department of Cognitive Neurology), i.e., if voxels share at least one vertex, they are considered to be part of the same contiguous region. The resulting clusters are reported in Table 2. Localization of these clusters was performed by first converting the clusters back into Talairach space (http://www.mrc-cbu.cam.ac.uk/Imaging/) and then consulting a standard brain atlas (Talairach & Tournoux, 1988).

We performed a separate density analysis for each interference contrast: go/no-go, flanker, SRC, and Stroop. Due to the small number of studies that investigated the Simon and stop-signal tasks, we were unable to perform a density analysis on these tasks. Additionally, we performed a density analysis on all of the studies taken together. For the individual studies, a density sphere of radius 20-mm was used. We used a larger sphere for these analyses because few studies and therefore few coordinates were available for each of these tasks. For the analysis that combined all tasks, we used a smaller region of 10-mm radius, consistent with the size used in previous such meta-analyses (Wager et al., 2003).

2.2 Results

The density analysis performed on the combination of all the tasks produced significant clusters bilaterally in the dorsolateral prefrontal cortex (DLPFC), inferior frontal gyrus (IFG), anterior cingulate cortex (ACC), and posterior parietal cortex (PPC) (Figure 2.2). Table 2.2 summarizes the results.

2.2.1 Individual Task Analyses

Density analyses performed on each task individually by and large revealed a subset of the combination of all tasks analysis (Table 2.2; Figure 2.3).

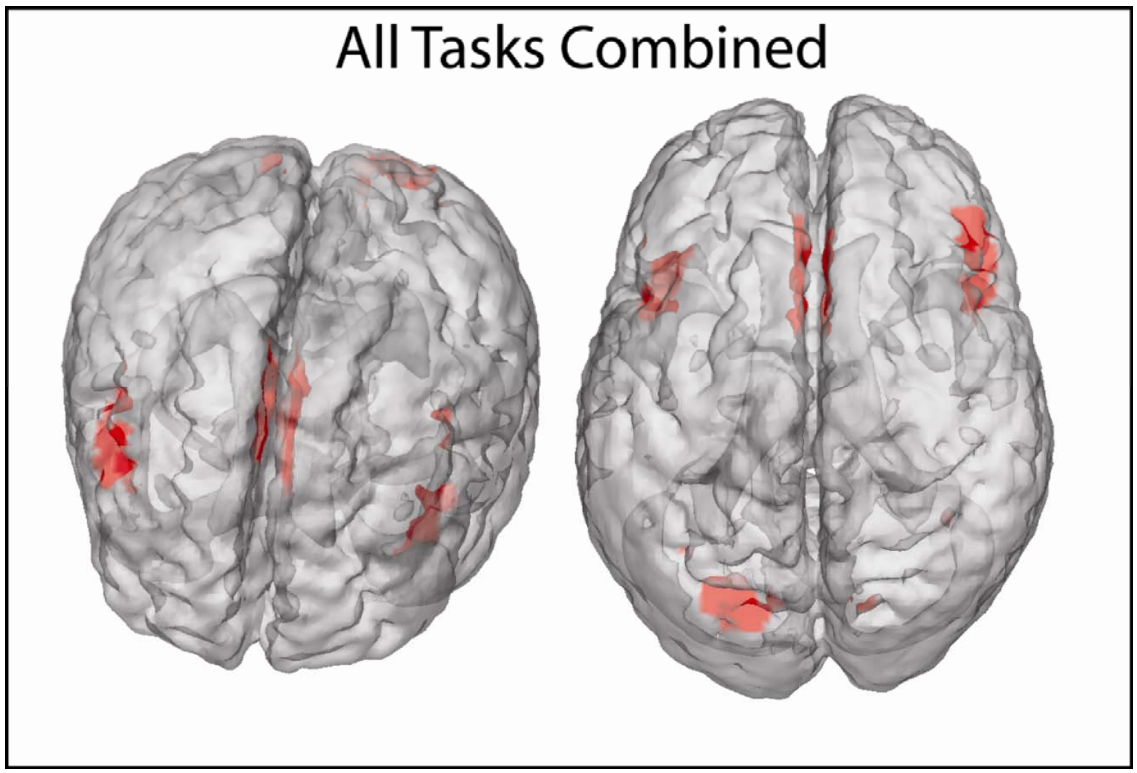

Figure 2.2. All Tasks Combined. Results of a peak density analysis performed on all of the 47 studies included. Regions are reported in Table 2.2.

2.2.1.1 Go/No-Go

For the go/no-go task, the most prominent cluster was in right dorsolateral prefrontal cortex, extending inferiorly into the right inferior frontal gyrus and insula. There were also significant clusters in left dorsolateral prefrontal cortex,

anterior cingulate, and right posterior parietal cortex, but these were smaller in extent. There were also small clusters in right occipital cortex.

2.2.1.2 Flanker

The flanker task produced a significant cluster in right dorsolateral prefrontal cortex. Another smaller cluster was found in the right insula, but the extent of the inferior cluster was not nearly the size of the one found in the go/no-go task.

2.2.1.3 Stimulus-Response Compatibility

The SRC task produced reliable clusters most prominently in bilateral posterior parietal cortex, but primarily right lateralized. Clusters were also found in left supplementary motor area and premotor cortex, as well as in the anterior cingulate cortex.

2.2.1.4 Stroop

Clusters from the Stroop task were primarily left lateralized. There was a large cluster in left dorsolateral prefrontal cortex that extended inferiorly to the insula. Additionally, we found a very large cluster in medial frontal cortex including the anterior cingulate. To a lesser extent there was also a cluster in left posterior parietal cortex. There were also clusters in right dorsolateral prefrontal and posterior parietal cortices, but these clusters were much smaller in extent than the ones found in the left hemisphere. Finally, there was also a small cluster in the thalamus.

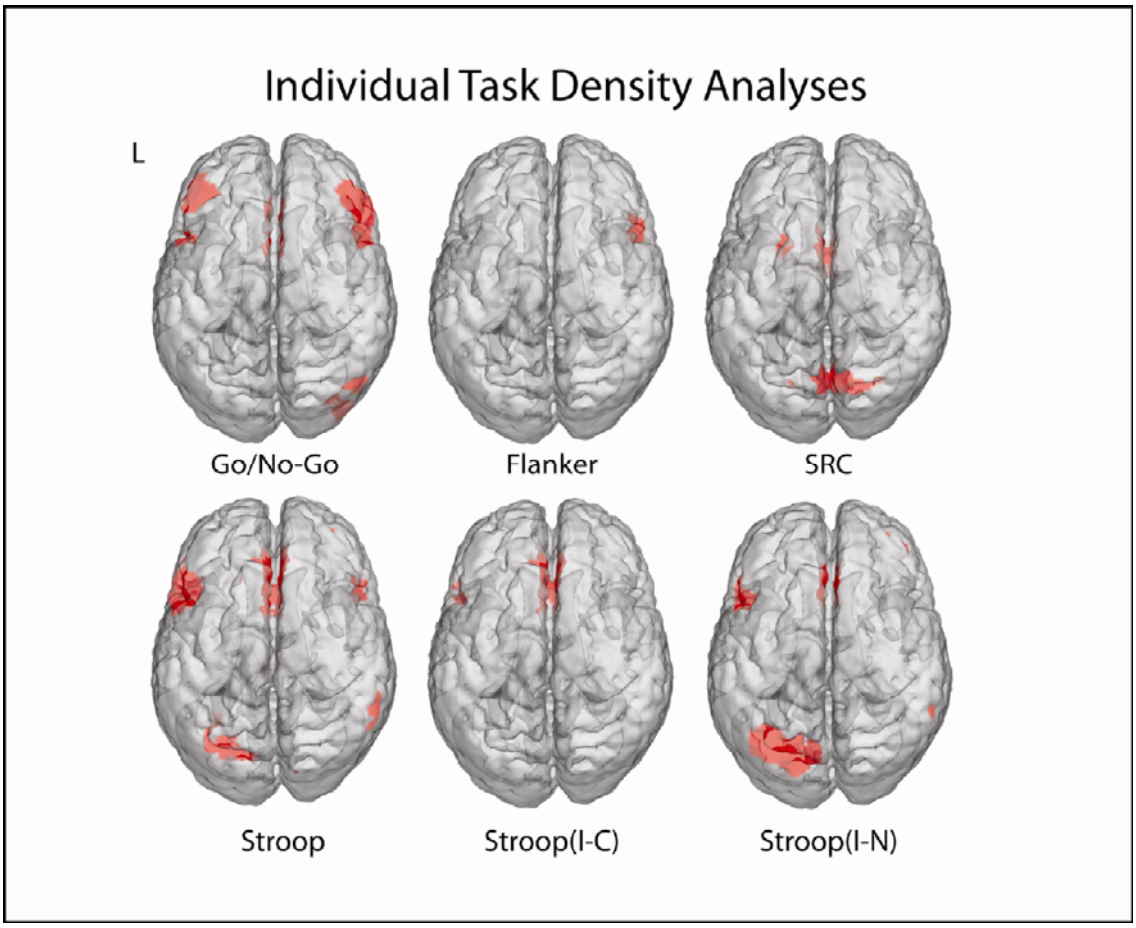

Figure 2.3. Individual Task Density Analyses. Results of peak density analyses performed separately on the go/no-go, flanker, stimulus-response compatibility, and Stroop tasks. Also included are separate density analyses performed on studies investigating the incongruent versus neutral Stroop contrast and the incongruent versus congruent Stroop contrast.

2.3 Discussion

Despite the seemingly random scatter of activation pictured in Figure 1, our density analysis yielded reliable clusters of activation in many areas that have often been implicated in interference-resolution. This network of regions may

therefore be involved in interference-resolution in general. However, a look at our individual task-analyses reveals that each task reliably activates a subset of these regions. Understanding why each task loads differentially on a distinct subset of regions may be the key to understanding how the brain resolves conflict.

Each task included in this study relies on different methods for inducing cognitive conflict. It is likely that these different forms of conflict act upon different neural mechanisms. For instance, mechanisms that filter out distracting visual information may be useful in the flanker, Stroop, and Simon tasks where conflict is produced by competing irrelevant stimuli, but these same mechanisms would not be relevant for the go/no-go task, in which there are no visual distractors. Therefore, examining the differences in the kinds of conflict each task produces and differences in the neural activations that accompany each kind of conflict-resolution may shed light on the neural mechanisms underlying interference-resolution.

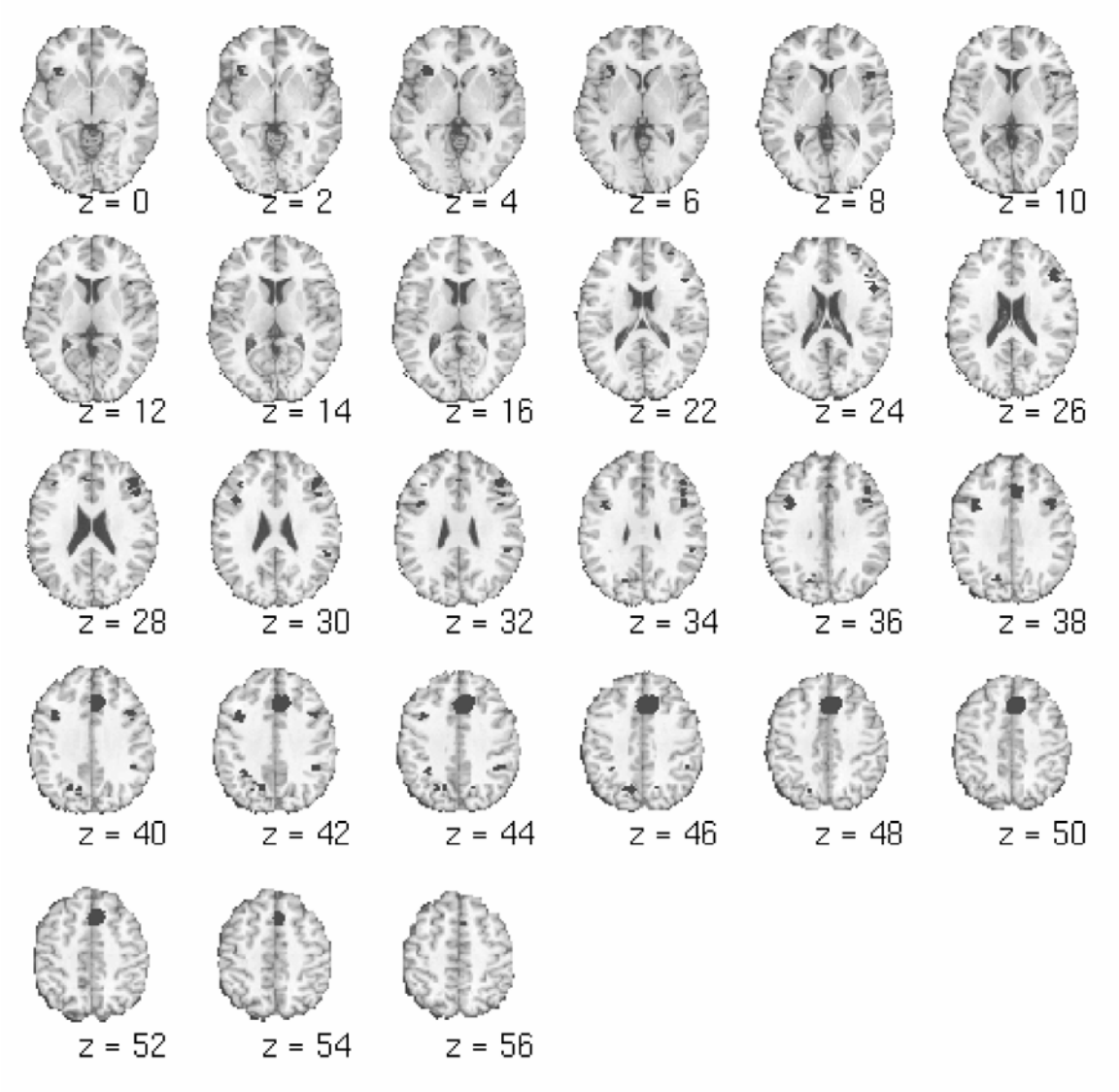

Figure 2.4. All Tasks Combined Slices. Slice renderings of the peak density analysis performed on all of the 47 studies included.

2.3.1 Go/No-Go and Stop-signal

It is clear that the go/no-go task induces conflict in mechanisms responsible for selecting and executing an appropriate response. As some authors have argued, response-selection and response-execution may be distinguishable stages of processing (Rubia et al., 2001; Rubia, Smith, Brammer, & Taylor, 2003).

Therefore, when subjects attempt to overcome the prepotent tendency to respond in the go/no-go task, they may accomplish this either by biasing decision processes towards selecting the appropriate response, or by restraining an inappropriate response from being executed and later selecting the appropriate response. In the former case, interference-resolution acts upon response-selection and in the latter, it acts upon response-execution. At which stage conflict is resolved is likely influenced by the experimental parameters. For instance, as the proportion of “go” to “no-go” trials increases, a greater prepotency to respond is formed which may heavily bias response-selection processes in favor of responding, therefore making a subject more reliant upon mechanisms of restraint acting upon response-execution (de Zubicaray et al., 2000; Garavan, Ross, & Stein, 1999). It is likely also that speeded responding would produce a similar effect. Although changes in task parameters would be interesting to explore, we have an insufficient number of studies exploring the go/no-go task to warrant meta-analytic techniques. Therefore, for specifics on how the neural mechanisms underlying interference-resolution change as task parameters differ, we rely on single studies.

By far the most reliable activation we found in the go/no-go task was in right frontal cortex, including dorsolateral prefrontal cortex and inferior frontal regions. Somewhat speculatively, we can tease apart what parts of this activation may be due to response-selection and what may be due to response-execution. One approach is to examine what neural changes occur as the go/no-go task

becomes more or less difficult. Presumably, by the logic we have presented, increased difficulty caused by an increased prepotency to respond requires a greater contribution of resolution mechanisms acting upon response-execution. Several studies examining this have reported that activation in the right inferior frontal gyrus increases with increased task difficulty (Durston et al., 2002; Durston et al., 2002; Garavan et al., 1999). Another study which parametrically varied the number of no-go trials found that as the number of no-go trials increased, reaction times increased and errors decreased, suggesting a shift toward more controlled responding (de Zubicaray et al., 2000). This shift in response style was accompanied by an increase in right dorsolateral prefrontal cortex. Taken together, it appears that in the go/no-go task, right inferior frontal gyrus activation underlies resolution during response-execution, whereas right dorsolateral prefrontal cortex activation accompanies more controlled resolution, perhaps during the selection of a response.

Although our reasoning is somewhat speculative, it corroborates well the literature concerning the stop-signal task. In the stop-signal task, the subject must restrain a response when a stop-signal occurs, therefore relying solely upon mechanisms that resolve conflict during the execution of a response. Indeed, neuroimaging studies that have examined the stop-signal task have implicated the right inferior frontal gyrus for this kind of interference-resolution (Rubia et al., 2001; Rubia et al., 2003). Even stronger evidence for this case is made by lesion evidence. It has been found that as the size of a lesion in the right inferior frontal

gyrus increases, performance in the stop-signal task gets poorer, therefore implicating the right inferior frontal gyrus as a region that is vital to the resolution of conflict during response-execution (Aron, Fletcher, Bullmore, Sahakian, & Robbins, 2003; Aron, Robbins, & Poldrack, 2004). Although we had an insufficient number of stop-signal studies to examine this task separately, the combination of neuroimaging and lesion evidence appears to provide strong support for the notion that the right inferior frontal gyrus is heavily involved in resolving conflict due to response-execution.

2.3.2 Flanker

Our examination of the flanker task revealed significant clusters in right dorsolateral prefrontal cortex and right insula. Notably, these areas overlapped with the frontal areas activated by the go/no-go task, suggesting that these regions may underlie common mechanisms (Figure 2.5) (Wager et al., 2005). What might these mechanisms be? As we described above, the flanker task can involve stimulus conflict, when the distractor stimuli and target stimuli do not match, and response conflict, when the distractor stimuli are mapped onto a different response from the target stimuli. Since the go/no-go task does not include stimulus conflict, the overlapping activations most likely result from response conflict. However, in our discussion of the go/no-go task, we delineated two forms of response conflict: response-selection conflict and response-execution conflict. Furthermore, we implicated right dorsolateral prefrontal cortex activation with resolution of response-selection conflict and right inferior frontal

activation with the resolution of conflict during response-execution. Do these implications match up with the flanker data?

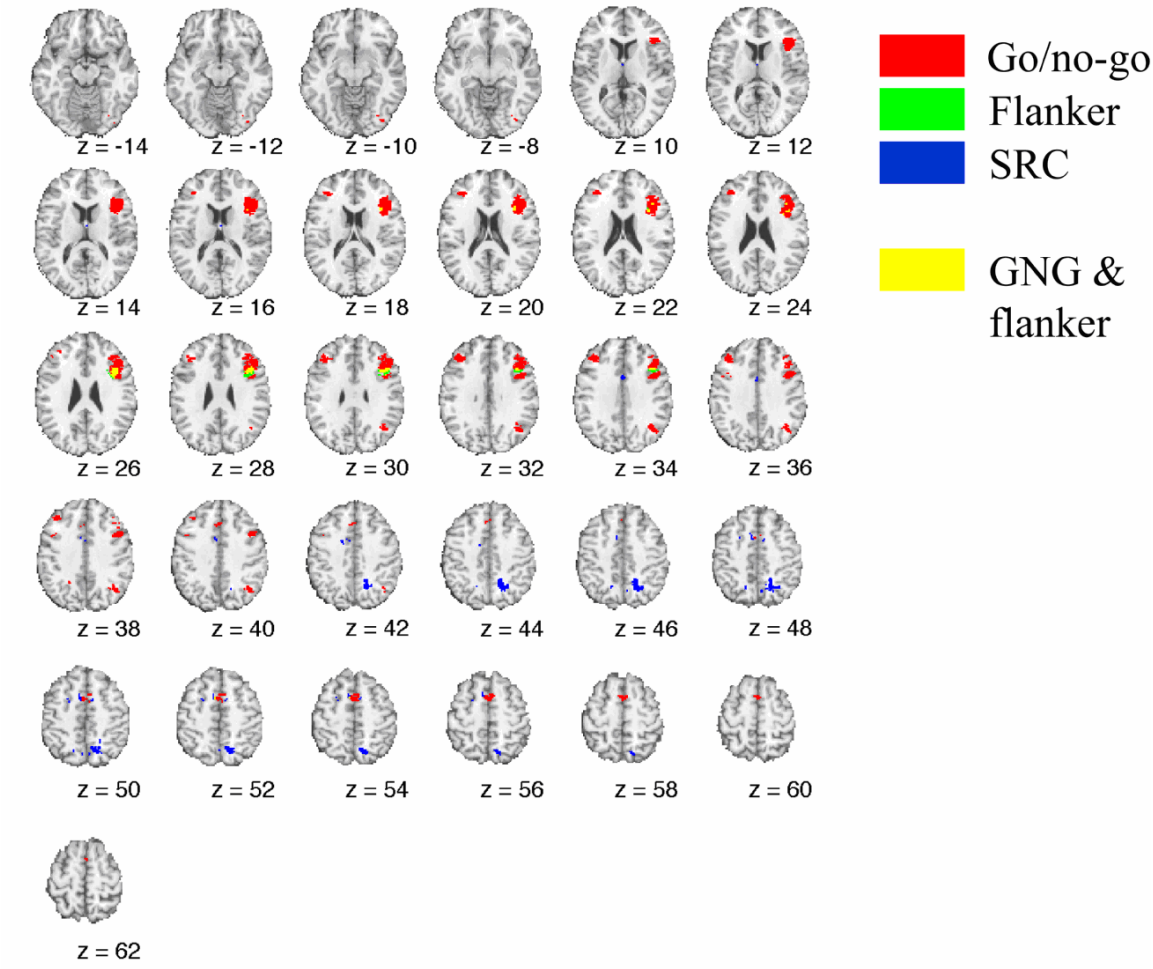

Figure 2.5. GNG, Flanker, SRC Slice Renderings. Slice renderings showing the results of the peak density analyses performed on the go/no-go (red), flanker (green), and SRC (blue) tasks. Activation overlap between the go/no-go and flanker tasks is depicted in yellow.

The overlap in right dorsolateral prefrontal cortex appears to be concordant with the idea that right dorsolateral prefrontal cortex is involved in interference-resolution during response-selection. Incongruent flankers bias response-

selection processes against the appropriate response, therefore requiring resolution processes to overcome this bias. Therefore, in both the flanker and go/no-go tasks, there is a need to select against a bias toward an inappropriate response. However, the low error rates typically found in the flanker task suggest that there is little need to restrain a response during response-execution. Therefore, the inferior frontal overlap appears to be somewhat puzzling.

Whereas the go/no-go task produced a cluster that incorporated both the right inferior frontal gyrus and insula, the inferior frontal cluster in the flanker task was found exclusively in the insula. We did not distinguish the right inferior frontal gyrus from the insula in our earlier discussion, mainly because the role of the insula in cognitive tasks remains unclear. One study that compared the go/no-go, flanker, and SRC tasks in the same subjects found common anterior insula activation among the tasks, activation which correlated with behavioral performance (Wager et al., 2005). These authors argued that since all three tasks have resolution processes acting upon response-selection in common, the insula is involved somehow in response-selection processes. If this is the case, then the common insula activation we find in our meta-analysis is orderly in that it may reflect common mechanisms of response-selection in the go/no-go and flanker tasks. However, other authors have argued that the anterior insula is involved in the restraining of inappropriate responses (Garavan et al., 1999). If this is the case, then the insula cluster found here is somewhat problematic.

A closer look into our flanker studies reveals that one study used a speeded flanker task which produced nearly chance accuracy on incongruent trials (Ullsperger & von Cramon, 2001). The difficulty of this task may have shifted resolution processes to response-execution, consistent with our logic for the go/no-go task. Indeed, 11 of the 14 inferior frontal peaks found in our flanker analysis were contributed by this study alone. Therefore, if the inferior frontal region shared by the go/no-go and flanker tasks really does reflect resolution processes acting upon response-execution, then our flanker result appears to be compatible with this account.

2.3.3 Stimulus-Response Compatibility

The SRC task is similar to the go/no-go task in that subjects must overcome a prepotent tendency to respond inappropriately in order to perform the task correctly. However, the prepotency in the two tasks is somewhat different. In the go/no-go task, the prepotent tendency to respond is due to the immediately preceding context. In other words, a subject has responded to several “go” trials and is therefore likely to respond. In the SRC task, however, the prepotency to respond inappropriately is not due to the immediately preceding context, but rather due to the subject’s familiarity with the stimulus in general. For example, it is more natural, based upon previously learned responses, to respond to a left arrow with a left response. However, on incompatible trials, subjects must overcome this learned tendency to respond appropriately. Put another way, one major difference between the go/no-go and SRC tasks is a difference in time-

scale: in one, a response has been learned due to an immediately preceding context; in the other, a response has been learned over the course of a lifetime. As our data illustrate, these differences result in very different neural patterns. In contrast to the go/no-go and flanker tasks which produced predominately frontal activation, the bulk of the activation in the SRC task was in parietal cortex. The largest cluster was in left posterior parietal cortex which included the intraparietal sulcus. Additional clusters were found in the anterior cingulate and premotor/supplementary motor area.

We can contrast the go/no-go and flanker tasks with the SRC task to help understand these differences. Let us begin with what is in common between them. Although a study comparing the go/no-go, flanker, and SRC tasks in the same subjects found several neural regions in common to both (Wager et al., 2005), the only overlap we found was between the go/no-go and SRC task in left premotor cortex. This region has been implicated in response-selection (Iacoboni, Woods, & Mazziotta, 1998), and rTMS performed on this region impairs performance on incompatible trials (Praamstra, Kleine, & Schnitzler, 1999). Therefore, the SRC task may have some component of interference-resolution during response-selection in common with the go/no-go task.
What is interesting about the neural pattern of results found for the SRC task is that the areas implicated are exactly those regions implicated in a meta-analysis of switching-attention (Wager et al., 2004). Indeed, a study that directly compared the SRC task with a switching task found close parallels between the

neural signatures of the two tasks (Sylvester et al., 2003). One possibility is that interference-resolution in the SRC task is very similar to switching. On incompatible trials, the prepotent response may automatically be elicited and subjects may need to switch their response-set to activate the appropriate response. An alternative, but similar proposal is that activation for both switching and the SRC task indicates the need to select among competing stimulus-response associations. However, further testing will be needed to verify whether the type of resolution involved in the SRC task is truly more akin to switching than the resolution involved in the go/no-go and flanker tasks.

2.3.4 Stroop

Like the flanker task, the Stroop task involves filtering out distracting irrelevant information that can compete with the appropriate response. However, unlike the flanker task, in which the distractors are adjacent to the imperative stimulus, in the Stroop task, the target and distractor are different attributes of the same object. Additionally, due to the automatic nature of reading the distracting material, an incorrect response is highly prepotent on incongruent trials. Therefore, in the Stroop task there appears to be a greater demand for selective attention to filter out the distracting information.

In the event that selective attention fails to filter out the irrelevant information completely, it is likely that the irrelevant information will bias toward the inappropriate response. How interference-resolution proceeds in this case

depends on the specifics of the paradigm. It has been argued that the verbal-response Stroop task is very different from a manual-response Stroop task, due to the verbal task having an automatic mapping of stimulus to response, whereas the manual case has an arbitrary mapping (MacLeod, 1991). Due to the movement involved in verbal responses, neuroimaging has by and large relied on manual responses. A manual response version of the Stroop task most likely relies upon response-selection because the subject is required to select among the arbitrary mappings provided by the experimenter. In this case, as with the go/no-go, flanker, and SRC tasks, resolution mechanisms must act upon response-selection to favor the correct response in the face of strong competition.

Overall, the Stroop task is similar to the other tasks studied here in its reliance on interference-resolution acting upon response-selection. However, it differs from the other tasks in its greater need for selective attention. Additionally, of the tasks studied here, the Stroop task is the most verbal in nature. Beginning with what is common, the Stroop task overlaps with the go/no-go and flanker tasks in right dorsolateral prefrontal cortex, and with the SRC task in left premotor/supplementary motor area. Consonant with the idea that the Stroop task shares response-selection components with these tasks, all of these regions have been implicated in the resolution of interference during response-selection (Bunge, Hazeltine, Scanlon, Rosen, & Gabrieli, 2002; Durston et al., 2002; Iacoboni et al., 1998; Praamstra et al., 1999). Additionally, the Stroop task

overlaps both the go/no-go and SRC tasks in the anterior cingulate cortex. This region has been the subject of much debate, mostly centered around its function as a monitor involved in the resolution of response conflict (e.g. Botvinick, Braver, Barch, Carter, & Cohen, 2001). Once again, this is compatible with the notion that the Stroop task shares response-selection components with the other tasks.

Although we failed to find significant overlap, there was a close correspondence in left posterior parietal cortex (BA 7) between the Stroop task (-22, -64, 46) and the SRC task (-16, -62, 48). Both tasks share the need to overcome an overly learned prepotent response: in the SRC task the tendency to respond left to a left pointing arrow and in the Stroop task the tendency to read written words. Earlier, we speculated that resolution in the SRC task may be similar to switching from the prepotent response set to the appropriate response set, or selecting among stimulus-response associations. It is worth noting that regions that are highly related to switching according to a meta-analysis of switching tasks (premotor cortex, intraparietal sulcus, and the anterior cingulate) are present in the Stroop analysis as they are in the SRC analysis (Wager et al., 2004). Therefore, the Stroop and SRC tasks may share the same sort of switch or stimulus-response association-related interference-resolution.

Other authors have also speculated that the Stroop task shares mechanisms with switching tasks (Brass, Derrfuss, Forstmann, & von Cramon, 2005; Derrfuss,

Brass, Neumann, & von Cramon, 2005). These authors propose that both tasks share the need for updating task representations. Based upon a meta-analysis of Stroop and switching tasks, these authors proposed that a region in left frontal cortex termed the inferior frontal junction may mediate this function (Derrfuss et al., 2005). In accordance with this claim, we found a large left frontal cluster in our Stroop analysis which overlapped with this proposed region. We might also expect to find similar activation in the SRC task which would ostensibly require the same task-representation updating function. However, we did not find reliable clusters in this region in our SRC analyses although it is possible that this result is due to insufficient power. Perhaps more puzzling is the finding that a separate meta-analysis of 31 switching studies also failed to find reliable clusters in the left inferior frontal junction (Wager et al., 2004), although these authors did find a large left dorsolateral prefrontal region that was more anterior to the inferior frontal junction at a reduced threshold. Further examination is required to provide consensus regarding the role of the inferior frontal junction and its relation to the Stroop and switching tasks.

In contrast to the other tasks studied here, the Stroop task is highly left lateralized, most prominently in left dorsolateral prefrontal cortex and inferior frontal regions. Part of this lateralization may be due to the strongly verbal nature of the Stroop task. Indeed, some authors have implicated left inferior frontal regions in the resolution of verbal conflict (Jonides & Nee, 2006; Jonides et al., 1998; Leung, Skudlarski, Gatenby, Peterson, & Gore, 2000). Some of the

lateralization may also be due to the greater need for selective attention processes involved in filtering out strongly competitive irrelevant information. Consonant with this idea, one study examined differences during a preparatory period preceding either the Stroop task, or the reverse Stroop task where subjects make the easier response of responding to the word rather than the color (MacDonald, Cohen, Stenger, & Carter, 2000). These authors found greater left dorsolateral prefrontal cortex activation for the Stroop task relative to the reverse Stroop task. If we believe that the selective attention demands are greater for the more difficult task, then it follows that left dorsolateral prefrontal cortex may be engaged in preparation for high demands on selective attention. However, this version of the Stroop task involved switching between Stroop and reverse Stroop and produced an abnormally large reverse-Stroop effect, so any conclusions must be drawn with caution.

Perhaps better evidence regarding the involvement of left dorsolateral prefrontal cortex in selective attention comes from several studies that examined differences when competing stimuli are response-eligible versus response-ineligible (Liu, Banich, Jacobson, & Tanabe, 2006; Milham & Banich, 2005; Milham, Banich, & Barad, 2003; Milham et al., 2001). In these studies, subjects learned a mapping of some colors to response keys. These were response-eligible colors. Contrasting with these colors were other colors that did not have mapped responses. Since these items were not available for response, they were response-ineligible. Importantly, when used as distracting words, response-

eligible words caused both stimulus and response conflict on incongruent trials, while response-ineligible words caused only stimulus conflict. Therefore, examining neural responses to response-ineligible trials compared to neutral trials isolates processes involved in resolving stimulus conflict. Indeed, several studies examining this paradigm have found left dorsolateral prefrontal cortex related to resolving stimulus conflict (Liu et al., 2006; Milham & Banich, 2005; Milham et al., 2003; Milham et al., 2001). This lends support to the idea that left dorsolateral prefrontal cortex is involved in selective attention.

Unlike our other tasks, we included both incongruent versus congruent and incongruent versus neutral peaks in our analyses in that there were many studies that examined each contrast. Since we had sufficient data, we also explored whether the incongruent versus congruent contrast differed from the incongruent versus neutral contrast as some authors have reported (Bench et al., 1993; Carter, Mintun, & Cohen, 1995; Taylor, Kornblum, Lauber, Minoshima, & Koeppe, 1997). Indeed, there were significant differences (Figure 2.3, 2.6). The incongruent minus neutral contrast exhibited far greater left dorsolateral prefrontal cortex and left posterior parietal activation, whereas the incongruent versus congruent contrast revealed larger anterior cingulate activation. What this must mean is that congruent trials produce greater activation in left dorsolateral prefrontal and posterior parietal cortex than neutral trials and less activation in the anterior cingulate than neutral trials.

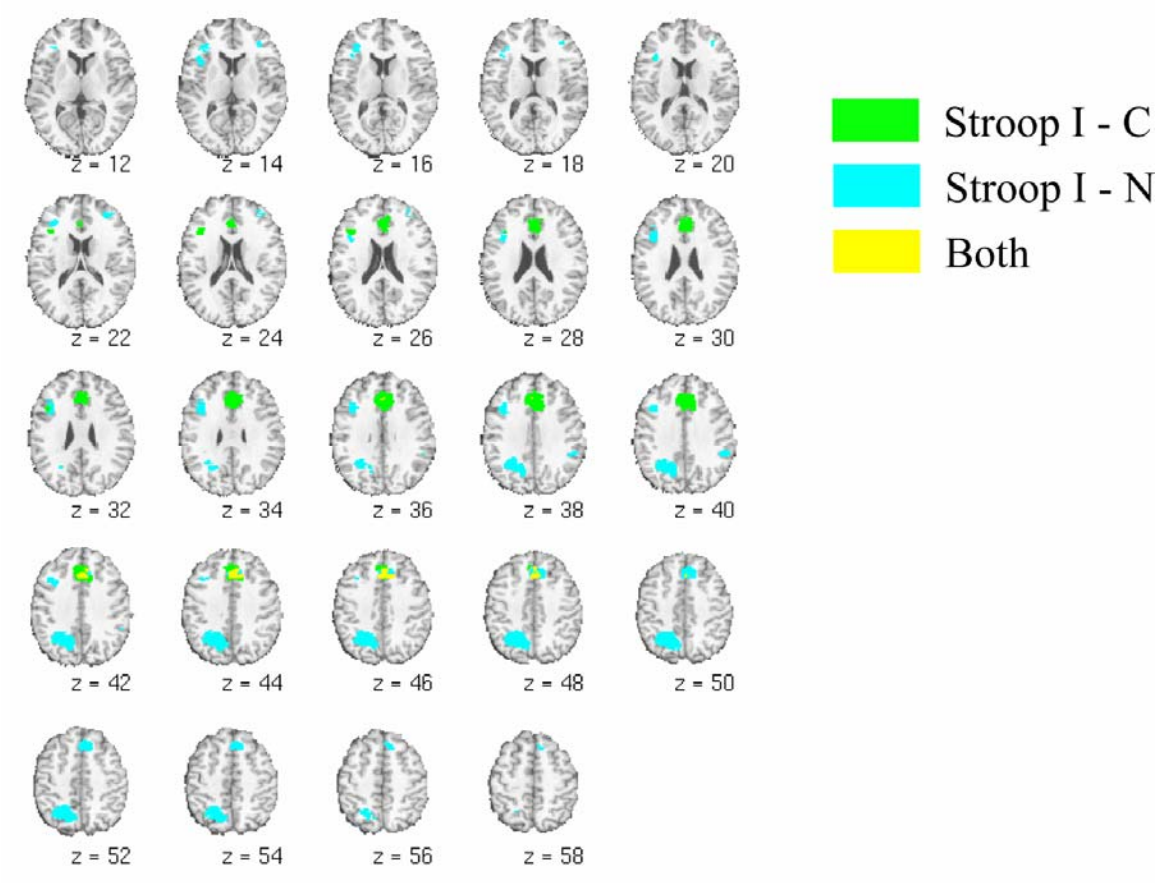

Figure 2.6. Stroop Slice Renderings. Slice renderings of the two different Stroop contrasts including their overlap.

Although we are uncertain what exactly to make of these differences, we can provide some speculation. Unlike neutral trials, congruent trials provide a competing response-eligible stimulus (Milham et al., 2002). If the strategy of the participant is to try hard to ignore the irrelevant word, the fact that the word is part of the color set may trigger mechanisms involved in selecting the correct stimulus dimension (color). By this account, we would expect increases in the left dorsolateral prefrontal cortex during congruent trials to filter out potentially distracting information. However, since the responses indicated by both the word

and color are the same, there is no conflict at the response-selection stage. Therefore, the reduction in actual response conflict may decrease demand on the anterior cingulate. These speculations are supported by a study that examined regions specifically recruited by conflict (incongruent > congruent and neutral trials) and those by competition (incongruent and congruent > neutral) (Milham & Banich, 2005). In this study, there was greater left dorsolateral prefrontal activity associated with competition (although still significant activation to a lesser extent in left dorsolateral prefrontal cortex for conflict), consonant with the idea that left dorsolateral prefrontal cortex is involved in both incongruent and congruent trials where there is a competing response-eligible word. By contrast, there was greater anterior cingulate activity associated with conflict (although a smaller, dissociable region of the anterior cingulate produced competition related activation). These results corroborate well with our finding of greater left dorsolateral prefrontal cortex activation for the incongruent minus neutral contrast, and greater anterior cingulate activation for the incongruent minus congruent contrast.

2.3.5 Putting It Together

We began by noting a network of regions involved in interference-resolution and then we interrogated the individual tasks to attempt to understand the functions that the individual pieces within this network are performing. What is revealed by piecing together the individual facts is a proposal of separate interference-resolution mechanisms acting upon different stages of processing. Specifically,

from the go/no-go and stop-signal data, it appears as though right inferior frontal regions are heavily involved in restraining an inappropriate response during response-execution. Commonalities in the go/no-go, flanker, SRC, and Stroop tasks implicate right dorsolateral prefrontal cortex and anterior cingulate cortex in interference-resolution during response-selection. For cases such as the Stroop and SRC tasks, the intraparietal sulcus and premotor cortex may also be involved during response-selection, perhaps as a means of switching from inappropriate to appropriate response sets or selecting among competing stimulus-response associations. Finally, the Stroop data point to left dorsolateral prefrontal cortex for resolution of stimulus conflict, perhaps via selective attention mechanisms, and left inferior frontal regions for resolution of verbal conflict. We are quick to note that these are merely hypotheses born out of the meta-analysis rather than conclusions. Each of these hypotheses needs further testing.

To bolster these hypotheses, we performed a logistic regression to investigate whether resolution of interference at different stages of processing predicted activation in a given region. We coded each study by whether the task included resolution during response-execution, response-selection, or stimulus encoding and examined whether these predictors explained activation in right inferior frontal gyrus, left inferior frontal gyrus, left dorsolateral prefrontal cortex, right dorsolateral prefrontal cortex, and the anterior cingulate. Additionally, since we hypothesized that resolution of verbal information may involve the left inferior frontal gyrus, we performed a separate logistic regression on left inferior frontal

gyrus using verbal conflict as a predictor (Jonides & Nee, 2006; Jonides et al., 1998; Leung et al., 2000; Nelson, Reuter-Lorenz, Sylvester, Jonides, & Smith, 2003). The results supported our hypotheses. Stimulus-conflict significantly predicted activation in left dorsolateral prefrontal cortex (Wald = 5.58, p = 0.018) and left inferior frontal gyrus (Wald = 6.9, p = 0.008). Verbal conflict also predicted left inferior frontal gyrus activation (Wald = 6.5, p = 0.01). Finally, conflict during response-execution marginally predicted activation in the right inferior frontal gyrus (Wald = 3.27, p = 0.07). We note that conflict during response-selection did not significantly predict activation in any region, but this is most likely due to the fact that all tasks other than the one stop-signal task included in our meta-analysis elicit conflict during response-selection, and therefore this predictor had insufficient variance to explain activation.

These results are consistent with the idea that different neural regions are responsible for the resolution of interference at different stages of processing. However, we recognize that there may be other ways to organize interference-resolution processes as well. Some authors have carefully distinguished several different forms of conflict, each of which may require its own dissociable resolution mechanisms (Kornblum, Hasbroucq, & Osman, 1990; Kornblum et al., 1999; Zhang et al., 1999). Unfortunately, most neuroimaging studies of interference-resolution confound several of these forms of conflict, thereby making it difficult to distinguish among them. Further investigation is needed to

determine whether interference-resolution mechanisms can be more finely dissociated than we suggest here.

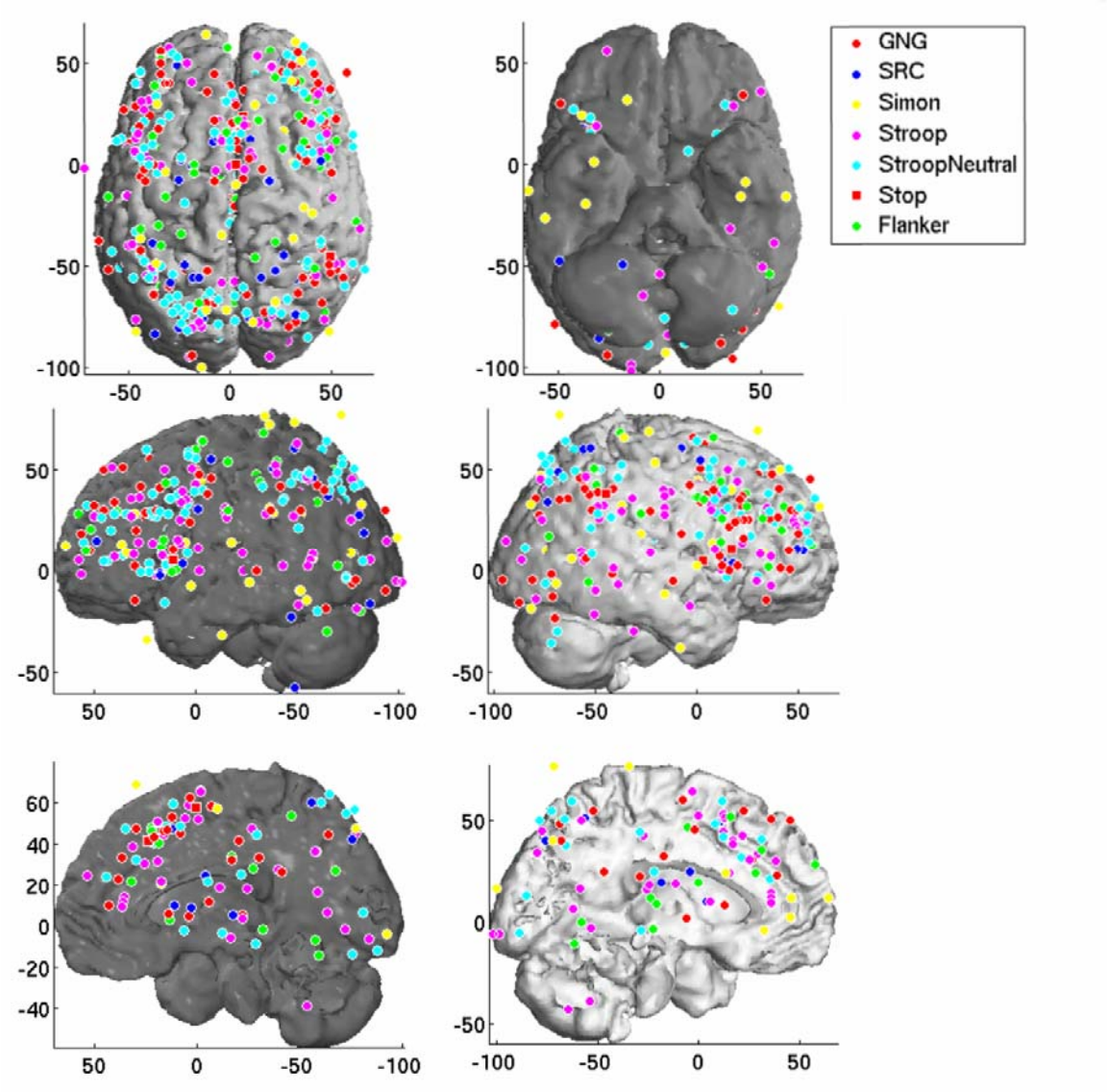

Figure 2.7. Peaks By Task. Peaks from all 47 studies plotted in a canonical brain, color coded by task.

2.3.6 Mechanisms of interference-resolution

We have implicated several regions as important in the resolution of interference, but we have not speculated how this conflict is resolved. Resolution may proceed via the facilitation of appropriate information, inhibition of inappropriate information, a combination of the two, or some other strategy such as switching response sets (Hasher, Zacks, & May, 1999; MacLeod, Dodd, Sheard, Wilson, & Bibi, 2003). We believe that the extant data cannot yet penetrate this question so we remain agnostic as to how interference is resolved.

2.3.7 Relation to Other Work

Several other meta-analyses have looked for consistencies among neuroimaging data (Cabeza & Nyberg, 2000; Duncan & Owen, 2000; Johnson et al., 2005; Wager et al., 2004; Wager & Smith, 2003). For example, Duncan and Owen (2000) demonstrated that regions of frontal cortex including the anterior cingulate and dorsolateral and ventrolateral prefrontal cortices were recruited by diverse cognitive demands not exclusive to conflict. Their analyses of 19 studies produced little if any discernible dissociation among the various tasks studied when all peaks were plotted on the same canonical brain. Similar to their analysis, combining all of our studies produced the same network of regions. However, when each task was interrogated individually, we found dissociations within this network. Why did we find dissociations when Duncan and Owen (2000) did not?

Figure 2.7 shows a plot of all of the peaks included in this study, color coded by the particular task contributing the peak. From this figure, it is difficult to discern dissociable patterns. Examining the data in this way demonstrates the clear need for clustering techniques. It is possible that with the inclusion of more studies and a clustering technique, dissociable patterns may emerge from the tasks studied by Duncan and Owen (2000).

Other meta-analyses looking at particular tasks have found regions overlapping with the regions we find here. As mentioned earlier, a meta-analysis of switching tasks produced clusters in parietal and premotor cortex similar to areas we found for the SRC and Stroop tasks, indicating that resolution for these tasks may have share a commonality with switching (Wager et al., 2004). Furthermore, a meta-analysis of working memory tasks implicated several frontal and parietal regions found here (Wager & Smith, 2003). This corroborates findings linking working memory with susceptibility to interference (de Fockert, Rees, Frith, & Lavie, 2001; Engle, Kane, & Tuholski, 1999; Hester, Murphy, & Garavan, 2004; Kane, Bleckley, Conway, & Engle, 2001; Kane & Engle, 2003; Kim, Kim, & Chun, 2005). Working memory tasks often require not only the active maintenance of information, but also the filtering out of distraction, and selecting among representations for both maintenance and response processes. Consonant with the idea that left dorsolateral prefrontal cortex is important for selective attention, increasing demand on left dorsolateral prefrontal cortex by imposing a working memory load increases interference from irrelevant perceptual material (de

Fockert et al., 2001). In addition, increasing demand on right dorsolateral prefrontal cortex by increasing working memory load decreases Go/No-Go performance, perhaps due to shared components of response-selection (Hester et al., 2004). These results suggest a close tie between working memory and interference-resolution.

Finally, “refreshing” or bringing to focus an item in mind recruits bilateral frontal, anterior cingulate, and posterior parietal cortex (Johnson et al., 2005). Refreshing verbal material preferentially activates left inferior frontal regions whereas no other refresh-related region demonstrates a verbal preference (Johnson et al., 2005). Left inferior frontal gyrus may be important in selecting the appropriate verbal material to refresh (Jonides & Nee, 2006; Thompson-Schill, D'Esposito, Aguirre, & Farah, 1997). This verbal selection role is consonant with our data demonstrating that left inferior frontal gyrus is needed for interference-resolution of verbal conflict. It is likely that other commonalities between regions found here and in refreshing also reflect selection of various sorts of representations. Further work is needed to examine the relation between interference-resolution and refreshing.

2.4 Conclusions

Examining the combination of many tasks that involve interference-resolution revealed that a network including bilateral dorsolateral prefrontal cortex, inferior frontal regions, posterior parietal cortex and the anterior cingulate that may

underlie the resolution of conflict. We hypothesize that separating functions by the stage of processing at which conflict is resolved may provide a useful framework for understanding interference-resolution. Although future research will be needed to test these hypotheses and further understand how each region performs interference-resolution, our data suggest that the right inferior frontal gyrus is important during response-execution, right dorsolateral prefrontal cortex and anterior cingulate during response-selection, and left dorsolateral prefrontal cortex during stimulus encoding. Additionally, switching-related regions in the intraparietal sulcus and premotor cortex may also contribute to some forms of interference-resolution.

Table 2.1

Study	Year	Flanker	GNG	SRC	Stroop	SS	Simon	Contrast	Peaks
Adleman	2002				X			I-N	3
Banich	2000				X			I-N	13
Banich	2001				X			I-N	9
Bench	1993				X			I-N	13
Bunge	2002	X						I-C	10
Carter	1995				X			I-C	9
					X			I-N	9
Casey	2002			X				I-Id	11
Dassonville	2001			X				I-C	14
Derbyshire	1998				X			I-C	2
Durston	2001		X					NoGo-Go	9
Durston	2002		X					NoGo-Go	7
Fan	2003	X						I-C	14
					X			I-C	14
							X	I-C	11
Garavan	1999		X					NoGo-Go	13
Garavan	2002		X					NoGo-Go	16
Hazeltine	2000	X						I-C	4
Iacoboni	1996			X				I-C	2
Iacoboni	1998			X				I-C	3
Kiehl	2000		X					NoGo-Go	8
Konishi	1998		X					NoGo-Go	10
Konishi	1999		X					NoGo-Go	2
Leung	2000				X			I-C	16
Liddle	2001		X					NoGo-Go	23
Liu	2004						X	I-C	34
Maclin	2001						X	I-C	5
Menon	2001		X					NoGo-Go	13
Milham	2001				X			I-N	7
Milham	2002				X			I-N	22
					X			I-C	7
Milham	2003				X			I-N	23
Milham	2005				X			I-N	37
					X			I-C	22
Pardo	1990				X			I-C	13
Paus	1993			X				I-C	10
Perlstein	2003		X					NoGo-Go	4
Peterson	1999				X			I-C	82
Peterson	2002				X			I-C	14
							X	I-C	14
Ravnkilde	2002				X			I-C	8
Rubia	2001		X					NoGo-Go	12
						X		Stop-Go	6
Ruff	2001				X			I-N	10
Schumacher	2002			X				I-C	2
Sylvester	2003			X				I-C	5
Tamm	2002		X					NoGo-Go	4

Taylor	1994			X			I-C	3
Taylor	1997				X		I-N	12
Ullsperger	2001	X					I-Id	34
van Veen	2001	X					I-C	8
Wager	2005	X					I-C	9
			X				NoGo-Go	13
				X			I-C	12
Watanabe	2002		X				NoGo-Go	5
Zysset	2001				X		I-N	9
					X		I-C	4

Table 2.1. Included Studies. Studies included in our meta-analysis catalogued by which tasks they included. Contrasts that were reported in the study are indicated in the table (I-C = incongruent – congruent or incompatible – compatible, I-N = incongruent – neutral, I-Id = incongruent – identical). There were a total of 6 flanker studies, contributing 79 peaks, 14 go/no-go studies, contributing 139 peaks, 9 SRC studies, contributing 62 peaks, 12 Stroop (I-N) studies, contributing 158 peaks, 11 Stroop (I-C) studies, contributing 190 peaks, 4 Simon studies, contributing 64 peaks, and 1 stop signal study contributing 6 peaks. GNG = go/no-go; SRC = stimulus-response compatibility; SS = stop signal

Table 2.2

Task	X	Y	Z	Voxels	BA	Region
All Tasks Combined	2	16	46	552	6/8/32	medial frontal/anterior cingulate
	42	24	28	115	9/8	right dorsolateral prefrontal cortex
	-40	4	38	76	6	left premotor cortex
	-36	16	4	48	13/45	left inferior frontal/insula
	-18	-72	42	43	7/19	left precuneus
	40	6	38	41	6/9	right dorsolateral prefrontal cortex
	44	14	8	21	44/13	right inferior frontal/insula
	40	-52	42	21	40/7	right inferior parietal lobule
	-36	-56	44	15	7/39/19	left inferior parietal lobule
	50	-44	32	9	40	right inferior parietal lobule
	-40	26	30	7	9	left dorsolateral prefrontal cortex
	34	18	4	5	13	right insula
Go/No-Go	42	22	24	1143	9/46/13/45	right dorsolateral prefrontal/inferior frontal
	-40	32	34	144	9/46	left dorsolateral prefrontal cortex
	42	-64	34	116	39/40	right angular gyrus
	0	8	54	106	6/32	anterior cingulate cortex
	-36	38	20	67	10	left middle frontal gyrus
	-2	26	42	20	32/8	left anterior cingulate cortex
	-44	10	38	12	9	left dorsolateral prefrontal cortex
	38	-84	-10	10	19/18	right inferior occipital gyrus
	32	-76	-10	5	18/19	right middle occipital gyrus
SRC	18	-62	48	216	7	right precuneus
	-8	8	52	31	6	left premotor/supplementary motor area
	0	4	36	10	24	anterior cingulate cortex
	-16	-62	48	9	7	left precuneus
	10	4	50	9	6	right premotor/supplementary motor area
	-22	4	52	8	6	left premotor cortex
	-6	4	40	6	24	left anterior cingulate cortex
	6	-68	48	5	7	right precuneus
Flanker	40	14	28	117	9	right dorsolateral prefrontal cortex
	36	16	20	15	13	right insula
Stroop	0	20	40	1426	6/32/8	medial frontal/anterior cingulate cortex
	-42	16	28	1385	9/6/46/8/13	left dorsolateral prefrontal

					cortex/inferior frontal
46	-48	38	301	40/39	right inferior parietal lobule
-22	-64	46	143	7	left precuneus
32	38	22	38	9/10	right dorsolateral prefrontal cortex
12	-78	10	26	17/18	right cuneate
46	16	30	11	9	right dorsolateral prefrontal cortex
0	-26	6	10		thalamus
-28	-66	34	7	19	left precuneus
44	20	22	5	46/9	right dorsolateral prefrontal cortex

Table 2.2. Cluster Peaks. Coordinates are reported in MNI space. Voxels is the area of the region in voxels. Only clusters of 5 voxels or more are reported. BA = Brodmann area.

Chapter 3

Neural Mechanisms of Proactive Interference-Resolution

Short-term memory plays an integral role in most forms of intelligent behavior. For example, differences in short-term memory capacity are related to differences in IQ, reasoning, reading comprehension, and problem-solving (Daneman and Carpenter, 1980; Carpenter et al., 1990; Daneman and Merikle, 1996; Just and Carpenter, 1999; Cowan et al., 2005). What determines how much information we can hold online at a given time? One powerful factor is the ability to mitigate proactive interference originating from previously relevant, but no longer relevant information (see, e.g., Keppel and Underwood, 1962; Jonides and Nee, 2006). Due to its central importance in understanding short-term memory, the neural mechanisms underlying proactive interference and its resolution have been a topic of intense interest (Jonides et al., 1998; D'Esposito et al., 1999; Jonides et al., 2000; Mecklinger et al., 2003; Nelson et al., 2003; Badre and Wagner, 2005; Jonides and Nee, 2006).

The lion's share of neural work on proactive interference has focused on variants of a single paradigm, which we shall refer to as the Recent Probes task (Monsell, 1978; Jonides and Nee, 2006). In the Recent Probes task, subjects are given a small set of items (the target set) to remember over a short retention-interval,

followed by a recognition probe (Sternberg, 1966). Recognition probes can either be members of the target set (positive probes) or not (negative probes). Additionally, probes can be members of the target set of the previous trial (recent probes) or not (non-recent probes). Crossing these 2 factors produces four types of probes: recent positive, non-recent positive, recent negative, and non-recent negative. What is of interest with this task is that subjects show slowed reaction times and increased error rates when rejecting recent negative probes compared to non-recent negative probes (Monsell, 1978; McElree and Dosher, 1989). This performance decrement is taken to be a marker of proactive interference. Subjects also tend to show faster reaction times and reduced error rates when responding to recent positive probes compared to non-recent positive probes although this facilitation effect is often far more subtle than the interference effect (Jonides and Nee, 2006).

There has been a burgeoning literature of neuroimaging studies examining the neural correlates of the resolution of proactive interference in the Recent Probes task (Jonides et al., 1998; D'Esposito et al.,1999; Jonides et al., 2000; Mecklinger et al., 2003; Nelson et al., 2003; Badre and Wagner, 2005; Jonides and Nee, 2006;). These studies have converged on left ventrolateral prefrontal cortex (VLPFC) as a region important in the resolution of proactive interference (see Jonides and Nee, 2006 for a review). Complementing these studies, neuropsychological work has demonstrated that damage to left VLPFC causes vastly increased proactive interference, while relatively sparing other aspects of

short-term memory performance (Thompson-Schill et al., 2002; Hamilton and Martin, 2005). Additionally, elderly subjects show reduced activation in this region relative to younger adults concomitant with an increase in susceptibility to proactive interference (Jonides et al., 2000; Thompson-Schill et al., 2002).

Although the role of left VLPFC in resolving proactive interference is well established in the Recent Probes task, there has been relatively little work testing the generality of this effect. Some efforts have demonstrated left VLPFC involvement in proactive interference-resolution in other tasks (Gray et al., 2003; Zhang et al., 2003; Derrfuss et al., 2004; Postle and Brush, 2004). However, when comparing across different groups of subjects and analysis methods, it is difficult to draw strong conclusions. Recognizing this shortcoming, several studies have examined interference-resolution using multiple paradigms in the same subjects (Peterson et al., 2002; Fan et al., 2003; Liu et al., 2004; Wager et al., 2005). However, all of these studies have focused upon interference caused by response conflict or perceptual distraction. By contrast, no study has examined proactive interference-resolution across multiple tasks. This is an important omission since there is evidence that the resolution of proactive interference may be uniquely distinct from other forms of interference-resolution (Friedman and Miyake, 2004). Therefore, to provide more generality to the claim that left VLPFC plays a critical role in proactive interference, it is important to demonstrate that it shows the same pattern of activity within the same set of subjects across different tasks.

Beyond this, the mechanisms by which left VLPFC participates in the resolution of proactive interference are unclear. Jonides and Nee (2006) reviewed several potential models of left VLPFC function in the service of proactive interference-resolution. These models postulate contrasting positions regarding whether left VLPFC is engaged in response selection, episodic retrieval, or biasing of internal representations. Each account relies on left VLPFC being a node in a functional network that overcomes proactive interference. However, each account varies in its prediction about the particular network involved. Therefore, whether left VLPFC is functionally correlated with response-related regions (e.g. the anterior cingulate, premotor cortex), memory related regions (e.g. medial temporal lobe), or both will inform models of proactive-interference resolution. To date, no study has examined the functional connectivity of left VLPFC in the face of proactive interference.

A recent study demonstrated that in the Recent Probes task, the left VLPFC not only showed enhanced activation to recent negative probes compared to non-recent negative probes, but also increased activation to recent positive probes compared to non-recent positive probes (Badre and Wagner, 2005). Behaviorally, whereas recent negative probes in this study led to interference relative to non-recent negative probes, recent positive probes demonstrated facilitation relative to non-recent positive probes. This paradoxical result is difficult to reconcile within current models of left VLPFC function that attempt to

lodge both interference and facilitation effects in this one region of cortex (Jonides and Nee, 2006). Therefore, it is of interest to explore regions related to the facilitation effect associated with recent positive probes.

In addition to left VLPFC, a recent study implicated left anterior prefrontal cortex (APFC) in the Recent Probes task (Badre and Wagner, 2005). The authors found that this region had a striking overlap with activations found in episodic recollection (Dobbins and Wagner, 2005). Also, this region was found to correlate negatively with susceptibility to proactive interference. This pattern of results led the authors to speculate that APFC plays a role in monitoring retrieved information in the service of arriving at a correct decision. Although one study examining the Recent Probes task also demonstrated sub-threshold activation in this region (Jonides et al., 1998), there is little other evidence that this region plays a role in proactive interference tasks. Furthermore, although Badre and Wagner (2005) speculated that APFC may interact with left VLPFC to enable proactive interference-resolution, this possibility has yet to be explored. Therefore, the role of left APFC in proactive interference-resolution is a topic needing additional research.

The present study sought to examine the neural regions involved in the resolution of proactive interference. Here, we scanned subjects using event-related functional magnetic resonance imaging (fMRI) while they performed two different proactive interference tasks: a Recent Probes task and a Directed-

Forgetting task. Our novel approach of examining the resolution of proactive interference across multiple tasks in the same subjects allows us to explore interference-related regions that are task-independent. Of particular interest are the behaviors of left VLPFC and left APFC across tasks, since these regions have been implicated during proactive interference-resolution in the Recent Probes task. A previous study examining directed-forgetting in short-term memory with fMRI implicated the left VLPFC for resolving interference from lure probes (Zhang et al., 2003). However, it was unclear that the activations overlapped with those found in the Recent Probes task and furthermore, the activation from Zhang et al. (2003) appeared to be somewhat weak, perhaps due to low power ($t(7) = 1.85$, $p = 0.05$, one-tailed). To address these concerns, we used a larger set of subjects to increase power and had subjects perform both tasks in alternating scans in order to determine whether there is common left VLPFC activation across tasks, as well as to further explore the role of left APFC in both tasks. In addition, we used functional connectivity analyses to examine whether left VLPFC and left APFC are functionally related in the face of interference and to explore other regions that show functional coupling to resolve proactive interference. This analysis allowed us to provide a critical test of models of proactive interference-resolution. Finally, we examined whether there are identifiably unique neural signatures of behavioral facilitation in the Recent Probes task, hence providing important data to round out models of proactive interference-resolution.

3.1 Materials and Methods

3.1.1 Participants

Twenty-five University of Michigan students (age range 18-24; mean age = 20.2; 11 male) participated in this study. All were right-handed and native English speakers with normal or corrected-to-normal vision. Subjects were health-screened and informed consent was obtained from all participants in accordance with the University of Michigan Institution Review Board. Participants received $40 in compensation for participation, as well as a bonus based on performance. Two subjects failed to maintain attentiveness throughout the study and were removed from analyses. One subject was removed from imaging analyses due to movement exceeding 7mm and another was removed due to a signal artifact. This resulted in twenty-three subjects for behavioral analyses and twenty-one for imaging analyses.

3.1.2 Behavioral Tasks

Stimuli were presented in black with a white background and were projected onto a screen at the head of the scanner. The screen was made visible to subjects via a pair of goggles with a mirror attached. Stimulus presentation was controlled using E-Prime experimental software (Psychology Software Tools, Inc.) and the IFIS 9.0 system with a 10-button response unit (MRI Devices Corp.). Subjects received 6 runs of each task, presented in ABAB order, counterbalanced across subjects. Each run consisted of 24 trials, for a total of 144 trials per task per subject.

3.1.2.1 Recent Probes Task

As displayed in Figure 3.1a, each trial began with a 1s red fixation cue. Thereafter, subjects were presented with a display of 6 letters for 2s (target set), followed by a 3s retention interval. After the retention interval, a recognition probe was presented for 2s. Subjects made a left index finger press if the probe matched the target set and a right index finger press if it did not. A 4s inter-trial interval (ITI) followed each probe (5s if the next trial fixation cue is included).

Each target set was composed of 3 letters from the previous target set, and 3 letters that had not been presented in the previous two trials. This allowed for half of the probes to match the target set of the previous trial (recent) and half to mismatch the previous target set (non-recent). 25% of the probes were members of the current target set, but not the last two target sets (Non-Recent Positive probes), 25% of the probes were members of the current target set and the last target set (Recent Positive probes), 25% were members of the previous target set but not the current target set (Recent Negative probes), and 25% had not been presented in the previous 2 trials (Non-Recent Negative probes).

3.1.2.2 Directed-Forgetting Task

As shown in Figure 3.1b, each trial began with a 1s red fixation cue. Thereafter, subjects were presented with a display of 6 letters for 2s (initial set), followed by a 3s retention interval. After the retention interval, a forget cue appeared for 1s

that instructed subjects to remove half of the letters from memory. The cue "TOP" instructed subjects to remove the 3 letters originally presented on the top-half of the screen and the cue "BOT" instructed subjects to remove the 3 letters originally presented on the bottom-half of the screen, leaving subjects with 3 letters in memory (target set). After the forget-cue, subjects were presented with 1s of fixation, followed by a recognition probe presented for 2s. Subjects made a left index-finger press if the probe matched the target set and a right index-finger press if it did not. A 4s inter-trial interval (ITI) followed each probe (5s if the next trial fixation cue is included).

Each initial set was chosen randomly from the set of all letters with the restriction that no letter had appeared in the previous two initial sets. 50% of the recognition probes were members of the target set (Positive probes), 25% were letters that subjects were instructed to forget (Forget probes), and 25% were letters that had not been presented on the previous 2 trials (Control probes).

3.1.3 Image acquisition and pre-processing

Images were acquired on a GE Signa 3T scanner equipped with a standard quadrature headcoil. Head movement was minimized using foam padding and a cloth restraint strapped across participants' foreheads. Experimental tasks were presented using E-Prime software (Psychology Software Tools, Inc.) and the IFIS 9.0 system with a 10-button response unit (MRI Devices Corp.).

Functional T2* weighted images were acquired using a spiral sequence with 40 contiguous slices with 3.44 x 3.44 x 3 mm voxels (repetition time (TR) = 2000 ms, echo time (TE) = 30, flip angle = 90, and field of view (FOV) = 22). A T1 weighted gradient echo (GRE) anatomical overlay was acquired using the same FOV and slices as the functional scans (TR = 250, TE = 5.7, and flip angle = 90). Additionally, a 106-slice high resolution T1 weighted anatomical image was collected using spoiled gradient-recalled acquisition in steady state (SPGR) imaging (TR = 10.5, TE = 3.4, flip angle = 25, FOV = 24, 1.5 mm slice thickness).

Each SPGR was corrected for signal inhomogeneity (G. Glover and K. Kristoff, http://www-psych.standford.edu/~kalina/SPM99/Tools/vol_homocor.html) and skull-stripped using FSL's Brain Extraction Tool (http://www.fmrib.ox.ac.uk/fsl). These images were then normalized to the MNI template (avg152t1.img) using SPM2 (Wellcome Department of Cognitive Neurology, London). Functional images were corrected for slice time differences using 4-point sinc interpolation (Oppenheim et al., 1999) and head movement, using MCFLIRT (Jenkinson et al., 2002). To reduce the impact of spike artifacts, functional images were winsorized on a voxel-by-voxel basis so that no voxel had a signal greater than 3.5 standard deviations from the mean of the run (Lazar et al., 2001). Spatial normalization transformations and 8 mm FWHM isotropic Gaussian smoothing were applied to all functional images prior to analysis using SPM2. All analyses included a temporal high-pass filter (128 s) and each image was scaled to have a global mean intensity of 100.

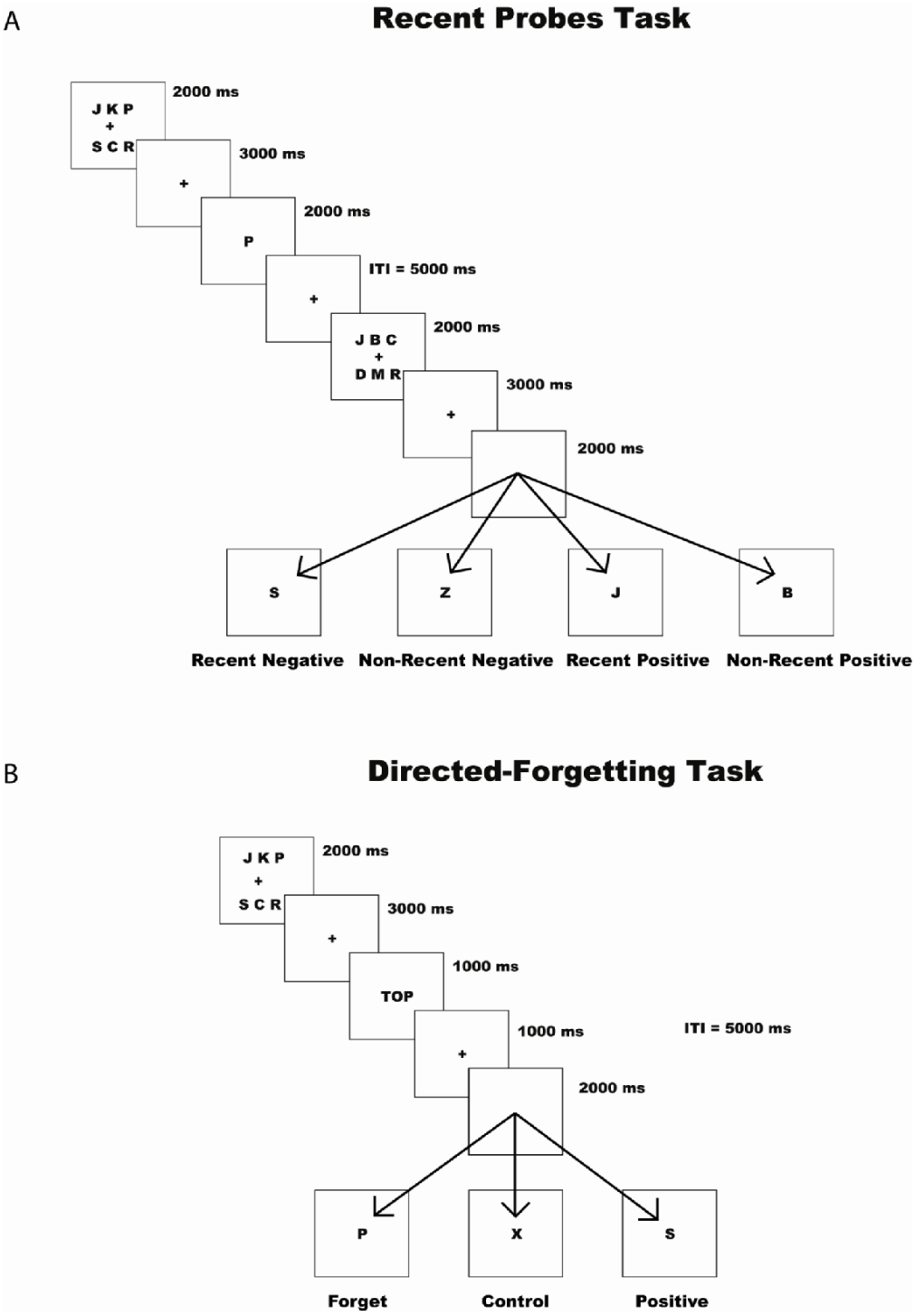

Figure 3.1. Depiction of the Recent Probes and Directed-Forgetting Tasks.

3.1.4 Image Analysis

Whole-brain analyses were conducted using the General Linear Model implemented in SPM2. Eight 2-s finite impulse response (FIR) regressors were included for all correct trials, onseting at probe presentation. To account for artifacts produced by head motion, linear, quadratic, differential, and quadratic differential motion regressors were calculated from the realignment parameters and included in the model (Lund et al., 2005). Contrast images for each participant were subjected to a random-effects group analysis. One sample t-tests were performed examining the 4^{th} 2-s time-bin after probe onset since it appeared that most voxels peaked at this time.

Interference contrasts for the Recent Probes task (Recent Negative probes – Non-Recent Negative probes) and the Directed-Forgetting task (Forget probes – Control probes) were thresholded at $p < 0.001$ uncorrected and restricted to regions demonstrating 5 contiguous supra-threshold voxels (Forman et al., 1995; Poline et al., 1997). These contrasts used probes that were matched in relevance and correct response, and avoided potential confounding effects of relevance and response hand when using Positive probes as matched controls for interference. To assess regions showing sensitivity to proactive interference, we performed a conjunction analysis on the interference contrasts of both tasks. The interference conjunction was thresholded at $p < 0.01$ for each task, producing a conjoint $p < 0.0001$ threshold and restricted to 5 contiguous voxels. We also assessed sensitivity to recency as the tripartite conjunction of Recent

Negative probes – Non-Recent Negative Probes, Recent Positive probes – Non-Recent Positive probes, and Forget probes – Control probes. The recency conjunction was thresholded at $p < 0.1$ for each task, once again producing a $p < 0.001$ conjoint threshold, restricted to 5 contiguous voxels.

Finally, we examined regions related to behavioral facilitation in the Recent Probes task. To do so, we first identified regions that showed stronger activation for positive probes relative to negative probes. This was done using a conjunction analysis searching for regions that showed positive probe > negative probe activation in both the Recent Probes task (i.e. (Recent Positive probes + Non-Recent Positive probes) > (Recent Negative probes + Non-Recent Negative probes) and the Directed-Forgetting task (i.e. (Positive probes > (Forget probes + Control probes)). Each individual analysis was thresholded at $p < 0.01$, producing a conjoint threshold of $p < 0.0001$. We used the resulting clusters as regions of interest (ROIs). Within these ROIs, we looked for voxels demonstrating greater activation for Recent Positive probes relative to Non-Recent Positive probes, thresholded at $p < 0.01$.

3.2 Results

3.2.1 Behavioral Results

Reaction times (RT) were calculated for correct trials only. One-way repeated measures ANOVAs were performed by trial-type separately on error rates (ER) and RT data for each task.

The effect of trial-type in the Recent Probes task was significant in ER ($F(1,20) = 12.059$, $p < 0.001$) and RT ($F(1,20) = 11.997$, $p < 0.001$). A planned t-test contrasting Recent Negative with Non-Recent Negative probes revealed a significant effect of interference in ER (7.6% vs. 2.6%, $t(22) = 4.711$, $p < 0.001$) and RT (844.31 ms vs. 747.13 ms, $t(22) = 5.241$, $p < 0.001$). Additionally, compared to Non-Recent Positive probes, Recent Positive probes demonstrated significant facilitation in ER (7.6% vs. 9.8%, $t(22) = 2.062$, $p = 0.05$). Facilitation in RT was in the same direction, but did not reach significance (724.15 ms vs. 733.46 ms, $t(22) = 0.922$, $p > 0.3$).

The effect of trial-type in the Directed-Forgetting task was significant in ER ($F(1,21) = 17.637$, $p < 0.001$) and RT ($F(1,21) = 27.016$, $p < 0.001$). A planned t-test comparing Forget and Control probes revealed a significant effect of interference in ER (8.0% vs. 3.3%, $t(22) = 4.794$, $p < 0.001$) and RT (704.69 ms vs. 644.89 ms, $t(22) = 4.46$, $p < 0.001$).

Finally, there was a modest correlation between interference in the Recent Probes and Directed-Forgetting tasks ($r = 0.39$, $p = 0.06$ ($p = 0.01$ after robust regression)). This correlation was in the same direction in ER, though it failed to reach significant ($r = 0.30$, $p > 0.15$). Although these correlations are not reliable at traditional thresholds, it must be noted that these are correlations among difference scores (an interference trial compared to its control), and correlations

between difference scores are, of course, less stable than correlations between raw scores. Thus, we take seriously the trends toward significance in these correlations.

3.2.2 Self Report

14 of the 21 subjects included in the imaging analyses reported that they did not notice the sequential ordering manipulation of the Recent Probes task. Those who did report noticing the ordering mentioned that they noted such contingencies only rarely. This is in line with previous reports that subjects are largely unaware of the conflict in the Recent Probes task (Bunge et al., 2001).

3.2.3 Imaging Results

Activation increases associated with proactive interference in the Recent-Probes task were assessed by contrasting probe-related activity from Recent Negative probes versus Non-Recent Negative probes (Table 3.1, Figure 3.2a). This contrast yielded a large left lateral frontal cluster (MNI coordinate peak 40, -16, 28) that spanned both dorsolateral and ventrolateral prefrontal cortex. To a lesser extent, there were similar activation increases in the right hemisphere. In addition, there were significant activation increases in bilateral anterior prefrontal cortex, right premotor cortex, left medial frontal cortex, left intraparietal sulcus, and bilateral occipital cortex.

Interference related activity in the Directed-Forgetting task as examined by contrasting Forget and Control probes, produced very similar frontal activation as in the Recent Probes task (Table 3.1, Figure 3.2b). As in the Recent-Probes task, the Directed-Forgetting task produced large clusters in left ventrolateral and dorsolateral prefrontal cortex. The ventrolateral activation increases were strongly bilateral. Additionally, there were increases in left premotor and left inferior temporal cortex.

The conjunction of these contrasts produced clusters in left dorsolateral prefrontal cortex, bilateral ventrolateral prefrontal cortex, medial prefrontal cortex, and the cerebellum (Table 3.1, Figure 3.2c). To ensure that these common results were not due to liberal thresholding, we also performed a more strict valid conjunction test, thresholding each contrast at $p < 0.001$ (Nichols et al., 2005). This test confirmed common activation in bilateral ventrolateral prefrontal cortex, stronger on the left, but not the other regions. Finally, we examined the averaged response for the interference contrast in both the Recent Probes and Directed-Forgetting tasks in the left ventrolateral prefrontal region found in our original conjunction analysis (i.e. region of interest analysis). Confirming that resolving proactive interference in both tasks involves left ventrolateral prefrontal cortex, there were highly significant interference-related activation differences in this region for both the Recent Probes ($t(20) = 3.83$, $p < 0.001$) and Directed-Forgetting ($t(20) = 4.23$, $p < 0.001$) tasks.

A previous study found that recency, as assessed by the conjunction of Recent Negative – Non-Recent Negative probes and Recent Positive – Non-Recent Positive probes, produced increased activation in left anterior prefrontal and bilateral ventrolateral frontal cortices (Badre and Wagner, 2005). To provide a stronger test that these regions are implicated in recency, we examined the conjunction of Recent Negative – Non-Recent Negative probes, Recent Positive – Non-Recent Positive probes, and Forget – Control probes (Table 3.1, Figure 3.2d). This conjunction produced significant clusters in several regions, most prominently in left anterior prefrontal cortex (MNI coordinate center -40, 48, 14) and left lateral prefrontal cortex spanning both ventrolateral and dorsolateral prefrontal cortex (MNI coordinate center -46, 24, 20). Follow up region of interest analyses confirmed that all contrasts demonstrated significant activation differences in left anterior prefrontal cortex (Recent Negative – Non-Recent Negative, $t(20) = 2.65$, $p < 0.01$; Forget – Control, $t(20) = 2.19$, $p < 0.05$; Recent Positive – Non-Recent Positive, $t(20) = 1.86$, $p < 0.05$). In left lateral prefrontal cortex a similar pattern emerged, but the Recent Positive – Non-Recent Positive contrast was only marginally significant (Recent Negative – Non-Recent Negative, $t(20) = 2.01$, $p < 0.05$; Forget – Control, $t(20) = 2.36$, $p < 0.05$; Recent Positive – Non-Recent Positive, $t(20) = 1.58$, $p < 0.07$). In addition, the conjunction analysis revealed significant clusters in right dorsolateral prefrontal cortex, bilateral premotor cortex, left intraparietal sulcus, and left occipital cortex.

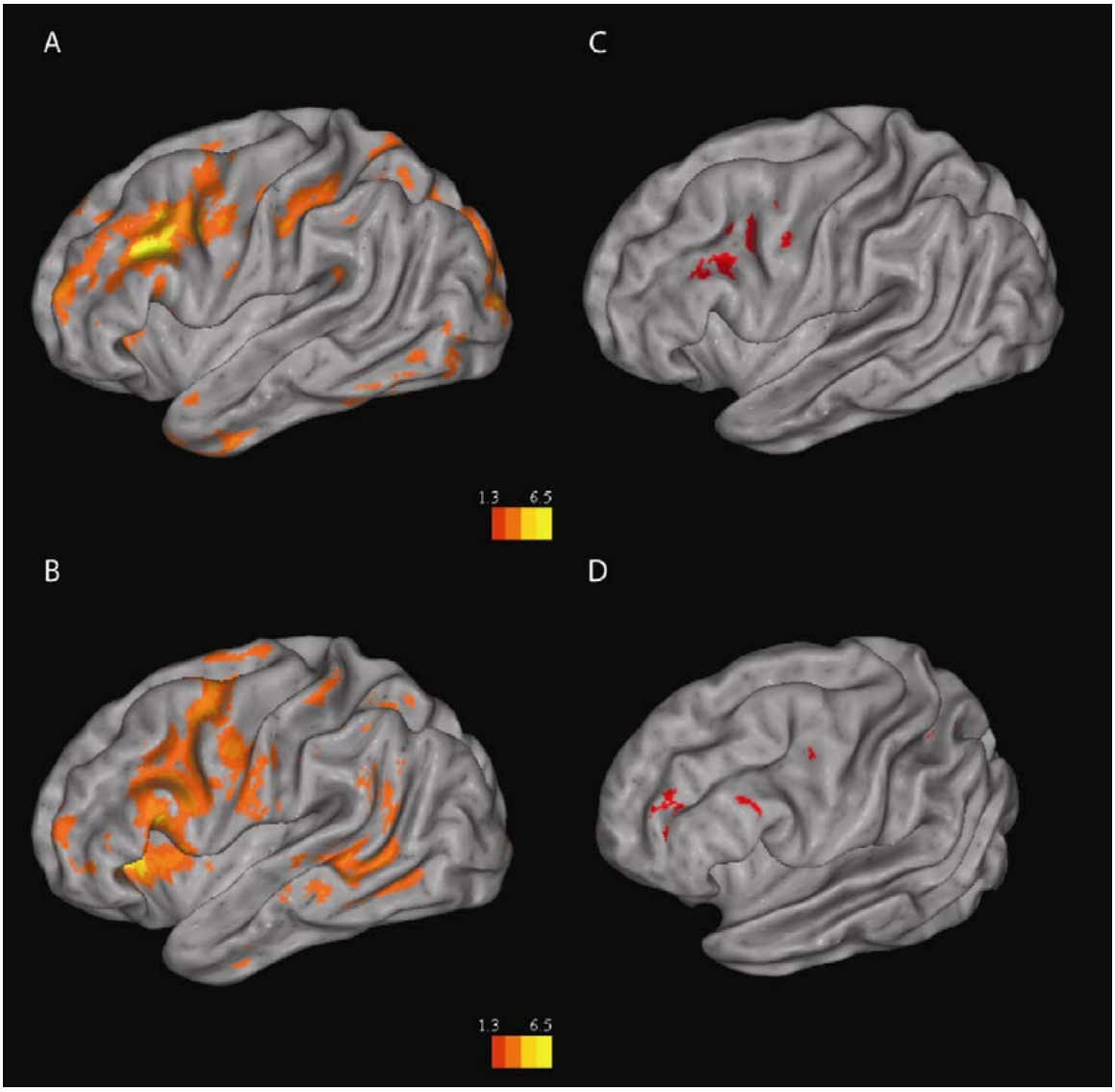

Figure 3.2. Neural Results. Activation increases from the interference contrasts for the (A) Recent Probes (Recent Negative – Non-Recent Negative) and (B) Directed-Forgetting (Forget – Control) tasks. Colors represent t-values. (C) Regions showing activation increases for both interference contrasts (conjoint probability, $p < 0.0001$). (D) Regions showing sensitivity to recency (Recent Negative – Non-Recent Negative, Recent Positive – Non-Recent Positive, Forget – Control) (conjoint probability, $p < 0.001$).

Previous work indicated that greater increases in activation in left VLPFC were associated with greater behavioral indices of proactive interference, whereas greater increases in activation in left APFC were associated with decreased behavioral indices of proactive interference (Badre and Wagner, 2005). To provide a stronger test of these claims, we calculated a behavioral index of proactive interference for each subject as the mean of the interference effects measured in both tasks in reaction time. We then created mean interference contrast images by averaging together the two interference contrasts. Finally, we looked for correlations between behavioral indices of proactive interference and neural indices of proactive interference, restricted to voxels found in our interference and recency conjunctions.

Two regions emerged from this analysis. A cluster in left posterior VLPFC (MNI center -40 10 30, BA 9/44, 29 voxels) correlated positively with proactive interference ($r = 0.43$, $p = 0.05$). Additionally, a cluster in left APFC (MNI center -40 48 12, BA 10, 17 voxels) correlated negatively with proactive interference ($r = -0.43$, $p = 0.052$). These results corroborate those found by Badre and Wagner (2005).

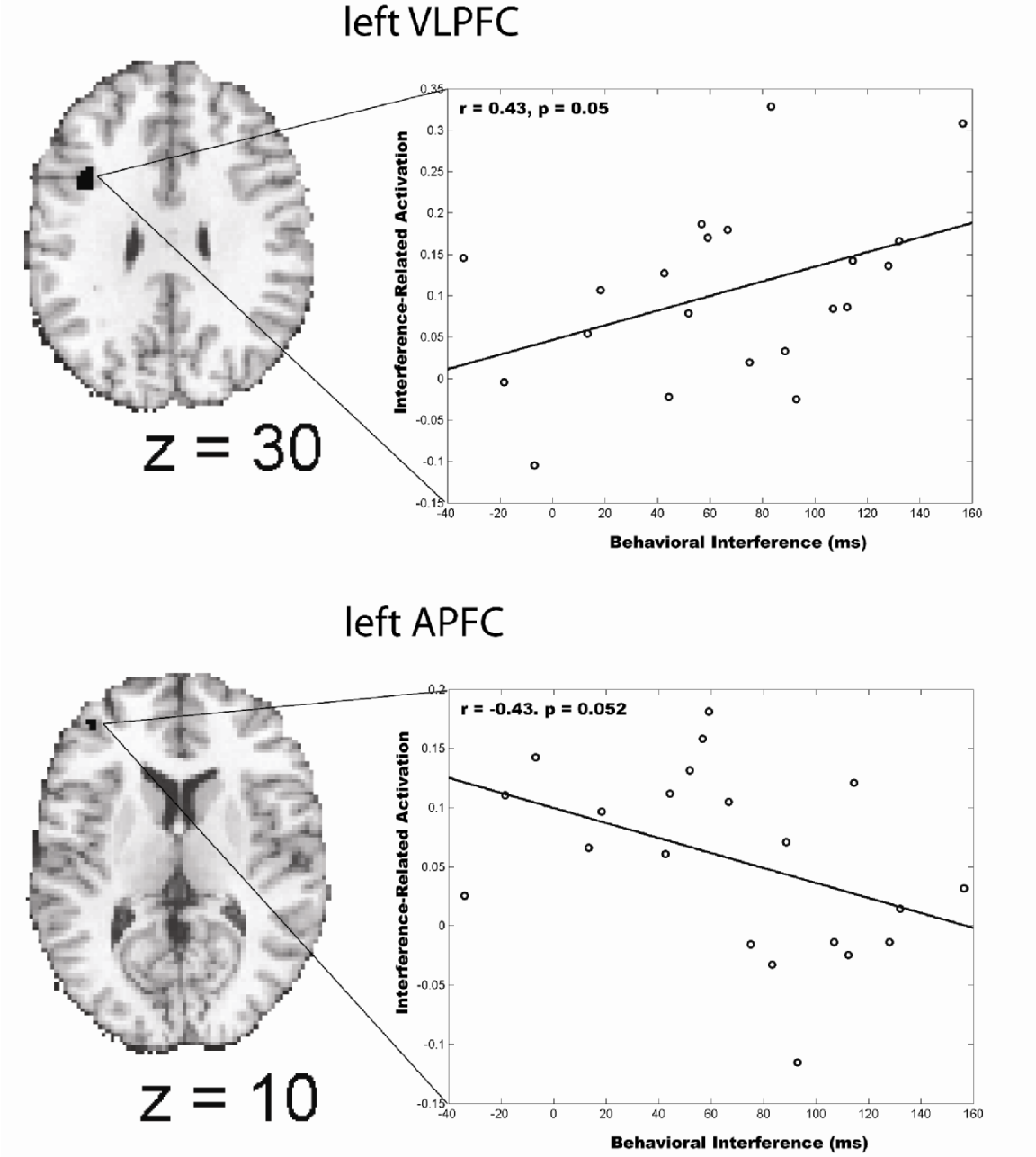

Figure 3.3. Brain-Behavior Correlations. Correlations between behavioral indices of proactive interference in reaction time and neural activation increases. Left VLPFC showed a positive correlation with interference, whereas left APFC showed a negative correlation.

Since the correlations with behavioral measures of proactive interference suggest a functional role for left VLPFC and left APFC in proactive interference and/or its resolution, we were interested in exploring whether these regions have a functional relationship. To do so, we used the left VLPFC and left APFC clusters found from the correlation analysis as seeds, and performed functional connectivity analysis. Details of the analysis method are described elsewhere (Rissman et al., 2004). Briefly, for each subject, separate beta values were estimated via SPM2's general linear model for the probe of each trial. For each subject, we then separately correlated beta values for Recent Negative probes, Non-Recent Negative probes, Forget probes, and Control probes, using the aforementioned seed clusters. The resulting r-maps were transformed into z-maps, and submitted to a repeated-measures ANOVA in SPM2 with separate predictors for each condition (i.e. Recent Negative, Non-Recent Negative, Forget, Control) crossed with region (i.e. left VLPFC, left APFC), producing a total of 8 predictors.[5] We then looked for regions showing increased connectivity to each seed region during interference trials (Recent Negative and Forget) versus non-interference trials (Non-Recent Negative and Control) separately for each seed region. Contrasts were thresholded at $p < 0.001$, with 5 contiguous voxels.

[5] This model pools error resulting from condition and region. We also tested a model that separately partitioned error from condition and region. To do so, we created pseudo-first level contrasts by using SPM2's ImCalc function to specify the contrasts of interest (i.e. Interference vs. Control separately for each seed region, as well as the condition x region interaction) before submitting the data to a second-level group model. These "contrasts" were then submitted to one-sample t-tests at the group level, one for each seed region. The resulting statistical maps did not differ appreciably from the pooled error model, so we discuss the pooled error results due to simplicity.

Left VLPFC and left APFC were not functionally related in the face of interference, even at a more liberal threshold ($p < 0.01$). Left VLPFC showed greater functional connectivity with left premotor cortex, right medial temporal cortex, right anterior cingulate cortex, left inferior temporal pole, right posterior cingulate cortex, and left caudate during interference trials. Left APFC, on the other hand, showed greater functional connectivity with left anterior cingulate cortex. To assess whether these patterns of activity were dissociable, we looked for voxels that showed significant connectivity with one region at $p < 0.001$, as well as significantly more connectivity with one region than the other at $p < 0.01$ (i.e. seed region x interference interaction). Left premotor cortex and right medial temporal cortex showed stronger connectivity with left VLPFC than left APFC in the face of interference. Left anterior cingulate showed the opposite pattern, displaying stronger connectivity with left APFC than left VLPFC (see Figure 3.4).

Badre and Wagner (2005) found that although contrasts of both Recent Negatives – Non-Recent Negatives and Recent Positives – Non-Recent Positives produced reliable activation in left APFC and VLPFC, there was a Recency x Probe interaction in left VLPFC, but not left APFC. This interaction was produced by greater activation in left VLPFC for the Recent Negatives – Non-Recent Negatives contrast. To investigate this claim, we assessed the same interaction in the left lateral and APFC clusters found in our recency conjunction. Contrary to Badre and Wagner (2005), we did not find a Recency x Probe interaction in left lateral prefrontal cortex ($F < 1$). Instead, there was a

significant main effect of Probe with negative probes producing greater activation in left lateral prefrontal cortex than positive probes ($F(1,17) = 7.648$, $p = 0.01$). Similarly, in left APFC, there was no Recency x Probe interaction ($F < 1$), but a marginally-significant main effect of Probe, once again with negative probes producing greater activation ($F(1,17) = 3.837$, $p = 0.06$). Right DLPFC and left premotor cortex also produced a similar main effect of Probe, but no region in our recency conjunction showed a Recency x Probe interaction.

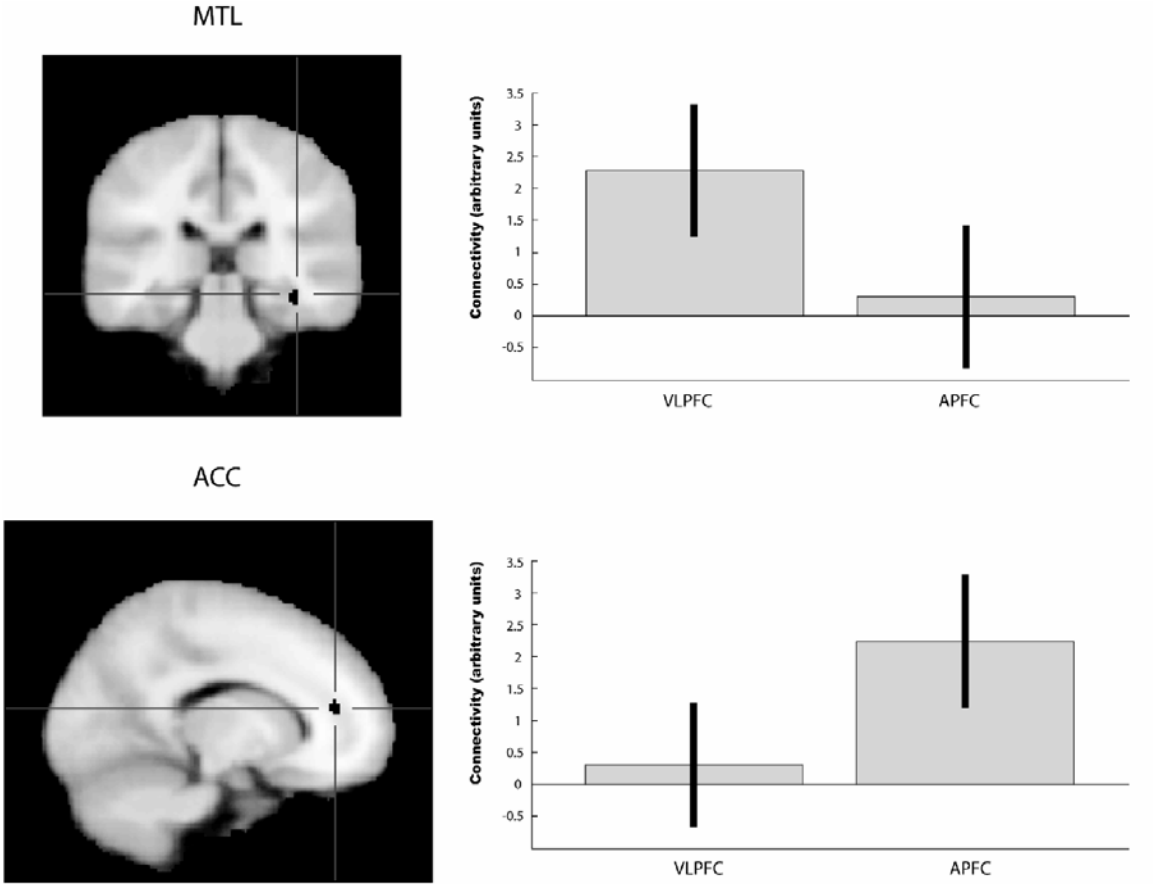

Figure 3.4. Functional Interactions. The medial temporal lobe (MTL) showed stronger functional connectivity with VLPFC than APFC, whereas the anterior cingulate cortex (ACC) showed the opposite pattern.

The sensitivity of left VLPFC to recency in general is difficult to reconcile with behavioral indications that Recent Negative probes produce interference relative to Non-Recent Negative probes whereas Recent Positive probes produce facilitation relative to Non-Recent Positive probes. To investigate whether there are distinct markers of facilitation, we looked for regions demonstrating increased activation for Recent Positive probes relative to Non-Recent Positive probes, restricted to voxels that showed increased activation to positive probes relative to negative probes (see Methods). This analysis produced a single significant cluster in the right posterior cingulate gyrus near retrosplenial cortex (MNI peak 4 -36 34, BA 23, 24 voxels). Reducing the threshold to $p < 0.05$ did not produce other significant clusters, but did increase the size of the posterior cingulate cluster to 106 voxels (see Figure 3.5).

3.3 Discussion

The present study sought to inform models of proactive interference by examining neural regions responsive to proactive interference across two separate tasks. First, we generalized the finding of interference-related activity in left VLPFC and left APFC across two different proactive interference tasks in the same subjects. Second, we replicated the finding that left VLPFC correlates positively with interference, whereas left APFC correlates negatively. Third, we demonstrated that although both of these regions are associated with proactive interference, their patterns of functional connectivity suggest separate roles for

each region. Fourth, we identified the posterior cingulate gyrus as a unique source of facilitation in the Recent Probes task.

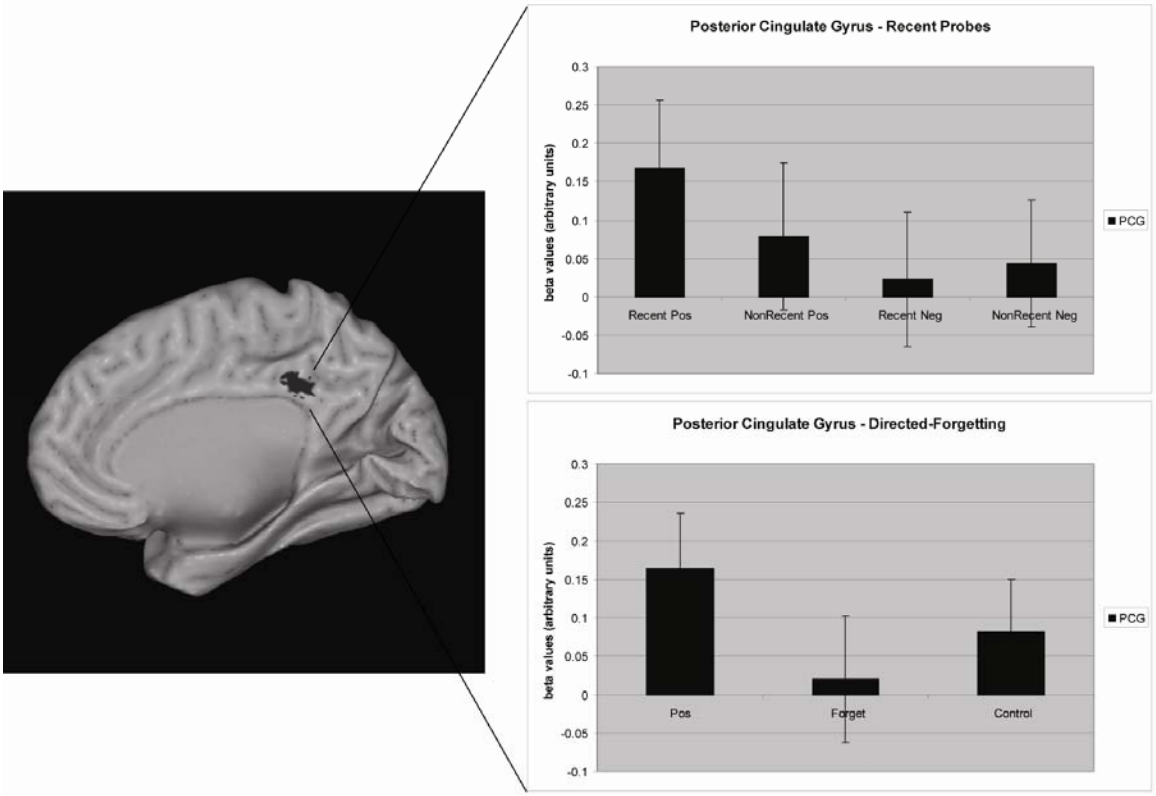

Figure 3.5. Posterior Cingulate. Posterior cingulate region demonstrating increased activation for Recent Positive probes relative to Non-Recent Positive probes. Results shown at $p < 0.05$ uncorrected for display purposes.

3.3.1 Left ventrolateral prefrontal cortex

Models of proactive interference-resolution differ regarding the role of left VLPFC (see Jonides and Nee, 2006 for a review). One possibility is that proactive interference causes conflict in selecting a response and that left VLPFC resolves this conflict. However, this idea cannot be reconciled with increased left VLPFC

activation to Recent Positive probes relative to Non-Recent Positive probes, where response conflict is absent. An alternative is that left VLPFC is recruited during retrieval, rather than response selection (Badre and Wagner, 2005). Models of this sort posit that left VLPFC may be important in selecting relevant contextual features in order to identify whether an item is a member of the target set or not (Badre and Wager, 2005; Jonides and Nee, 2006). For example, the familiarity of Recent Negative probes may elicit retrieval of the previous trial's context, which must be selected against to respond negatively. Likewise, Forget probes elicit a highly familiar, yet irrelevant context, as do Recent Positive probes. Consonant with the idea that left VLPFC is involved in context-selection, we found left VLPFC activation related to recency (Recent Negative > Non-Recent Negative, Recent Positive > Non-Recent Positive, Forget > Control). Additionally, we found that this activity correlated positively with behavioral indices of interference. This pattern suggests that increased conflict may call for increased selection demands.

Left VLPFC has also been correlated with increased selection demands in semantic retrieval (Thompson-Schill et al., 1997; Thompson-Schill et al., 1998; Persson et al., 2004; Nelson, 2005). A study examining this process and proactive interference-resolution in the same subjects found overlapping activations within left VLPFC, suggesting a similar mechanism mediating both processes (Nelson, 2005). These results suggest that left VLPFC may select among memorial representations more generally, be they episodic or semantic.

We also found that relative to non-interference probes, interference probes elicited stronger connectivity between left VLPFC and left premotor and right medial temporal cortex. Premotor cortex has often been implicated in selecting among competing responses (Iacoboni et al., 1998; Praamstra et al., 1999; Nee et al., 2007) and medial temporal cortex is well-known for its role in memory (Scoville and Milner, 1957). The connectivity with right medial temporal cortex may reflect the selection of episodic details, whereas the connectivity with left premotor cortex may reflect the use of those details to bias decision processes (Jonides and Nee, 2006). Interestingly, Ranganath et al., (2003) found a similar network of right posterior medial temporal cortex, left VLPFC, and left premotor cortex involved during encoding of items whose contexts were subsequently recollected. This may mean that the same network of regions that are used to establish item-context associations during encoding are elicited during retrieval when contextual information is needed to distinguish between relevant and irrelevant memories.

In addition to a main effect of Recency, Badre and Wagner (2005) reported a Recency x Probe interaction in left VLPFC, with disproportionately greater activation on Recent Negative trials than Recent Positive trials. These authors explained that although both Recent Positive and Recent Negative probes require increased selection demands relative to Non-Recent probes due to their relation to multiple contexts, selection demands may be eased for Recent

Positive probes since their context is more prepotent, producing the observed interaction. In contrast to Badre and Wagner (2005), we found a main effect of Probe in left VLPFC, with negative probes producing relatively greater activation than positive probes. This discrepancy may be due to differences in task details. Whereas Badre and Wagner (2005) used four words per trial, we used six letters per trial. Hence, our task differs in load and stimulus material. It is possible that selection demands increase as stimulus materials become less meaningful (i.e. letters are less meaningful than words). Additionally, increased memory load may also increase selection demands. Consistent with these ideas, a study that required subjects to maintain a variable number of letters in short-term memory demonstrated that left VLPFC showed a similar main effect of Probe, as well as sensitivity to load (Wolf et al., 2006). Increased selection demands may have a smaller impact on positive trials since the appropriate context is more prepotent, leading to disproportionate increases in left VLPFC activation on negative trials, producing the observed pattern of results (Badre and Wagner, 2005; Jonides and Nee, 2006).

In the Recent Probes task, subjects reported being largely unaware of manipulations of interference, suggesting that control operations of left VLPFC may operate without conscious awareness. This result is at odds of models of control that posit that one hallmark of control is conscious awareness (Shiffrin and Schneider, 1977) and suggests that frontal mechanisms need not operate with explicit awareness. Although we did not poll subjects regarding awareness

of conflict in the Directed-Forgetting task, it is likely that subjects are cognizant that forget probes queried information they were told to discard. Hence, a careful contrast of subjective awareness and control-related activation in the Recent Probes and Directed-Forgetting tasks may reveal critical networks needed for conscious control versus more automatic control.

Finally, proactive interference is generally thought of as a phenomenon that interferes with new learning. Here, we have examined its effects on rejecting information that should have been forgotten. Although the degree to which irrelevant information is forgotten clearly has a bearing on how much irrelevant information interferes with new learning, we did not explicitly tested this effect of proactive interference here. However, previous work has demonstrated that non-specific proactive interference that builds up over the course of an experiment, and presumably interferes with learning, is also associated with activation in left VLPFC (Postle and Brush, 2004). Hence, similar mechanisms are likely to underlie both phenemona.

3.3.2 Left anterior prefrontal cortex

It has been hypothesized that in the context of proactive interference-resolution, APFC functions to monitor retrieved information in the service of decision processes (Badre and Wagner, 2005; Jonides and Nee, 2006). Extending previous work, we found left APFC involvement in recency across both the Recent Probes and Directed-Forgetting tasks. Additionally, activation in this

region was associated with decreased interference, substantiating previous claims (Badre and Wagner, 2005).

In response to interference, we found increased connectivity between left APFC and the anterior cingulate. The anterior cingulate has also been postulated as a region that monitors for conflict, although more focused upon response conflict (Botvinick et al., 2001). Previous work has also shown that APFC and the anterior cingulate show correlated patterns of activity (Badre and Wagner, 2004). Therefore, APFC may work with the anterior cingulate to bias response processes.

Although it appears as though both left VLPFC and left APFC contribute to the resolution of proactive interference, we failed to find increased functional coupling between these regions during interference trials. This result suggests that these regions may make separable contributions to proactive interference-resolution. However, any conclusions drawn from a null result warrant caution. Further work will be needed to investigate the relatedness of these two regions in the service of resolving proactive interference.

3.3.3 Posterior cingulate gyrus

Models of left VLPFC function have difficulty reconciling that Recent Negative probes produce interference and Recent Positive probes produce facilitation, yet both probes produce increased left VLPFC activation relative to Non-Recent

probes (Jonides and Nee, 2006). Although both types of Recent probes may elicit selection of contextual details, it is difficult to conceive of how this selection produces both interference and facilitation. Therefore, there must be another region of cortex responsible for facilitation.

Our analyses suggest that the posterior cingulate gyrus is involved in the facilitation of Recent Positive probes relative to Non-Recent Positive probes. Previous work has demonstrated posterior cingulate gyrus involvement in episodic retrieval, showing increased activation for hits relative to misses, as well as increased activation when retrieving source details (see Wagner et al., 2005 for a review). The posterior cingulate region found here is adjacent to retrosplenial cortex and the two regions are strongly linked (Kobayashi and Amaral, 2003). Due to their strong connections with prefrontal and MTL regions, there has been speculation that the retrosplenial cortex and adjacent posterior cingulate may provide an interface between short- and long-term memory (Kobayashi and Amaral, 2003). Recent Positive probes contain both short-term information from the current trial, as well as longer-term information from the previous trial. Therefore, the short- and long-term memory interfacing functions of retrosplenial and posterior cingulate cortex are uniquely suited for Recent Positive probes. Hence, increased activation in this region may demonstrate a synchrony of short- and long-term memories that provide for quicker and easier responding. Alternatively, given the association of the posterior cingulate with recollective processes (Wagner et al., 2005), activation in this region associated

with Recent Positives may reflect additional recollective detail that recalled when a Recent Positive is presented, which again may facilitate responding.

As a post-hoc analysis to investigate these claims, we examined functional connectivity with the posterior cingulate, contrasting Recent Positive probes and Non-Recent Positive probes. Interestingly, the posterior cingulate demonstrated functional connectivity with right premotor cortex (MNI peak 56 4 12, 23 voxels at $p < 0.005$) and right motor cortex (MNI peak 44 -22 38, 68 voxels at $p < 0.005$) when subjects responded to Recent Positive probes compared to Non-Recent Positive probes. Since subjects made affirmative responses with their left hand, this pattern suggests a stronger motor biasing for Recent Positives, producing the observed behavioral facilitation effects. This result provides an interesting avenue for future research.

That both left VLPFC and the posterior cingulate demonstrate increased activation for Recent Positives may explain the fragility of the behavioral facilitation effect (Jonides and Nee, 2006). Whereas the selection processes of left VLPFC may slow processing, recollection processes of the posterior cingulate may speed processing. These processes may largely cancel each other out, producing smaller and less stable behavioral effects.

3.3.4 Relation to other work

Whether the results found here extend to other types of material (e.g. spatial or object stimuli) is unclear (see Jonides and Nee, 2006 for a review). There has been some evidence for left VLPFC involvement for non-verbal material in the Recent Probes task, but these results have generally been statistically weak (Postle et al., 2004; Badre and Wagner, 2005). Additionally, using a spatial analogue of the Directed-Forgetting task, Leung and Zhang (2004) failed to find significant increases in left VLPFC for Forget probes relative to Control probes, but there was a non-significant trend in left APFC. Instead, these authors found significant differences in the superior parietal lobule and precentral sulcus, suggesting that regions involved in resolving proactive interference may vary by type of material. Hence, it is possible that the results found here are specific to verbal material.

3.4 Conclusion

The work examined here provides important considerations for models of proactive interference-resolution. Left VLPFC and left APFC were involved in proactive interference across tasks providing robust evidence that these regions are central loci of proactive interference-resolution. The connectivity of left VLPFC with the MTL and premotor cortex suggest that this region is involved in selection of episodic details that bias responding. The connectivity of left APFC with the ACC, on the other hand, suggests a role of conflict monitoring. Finally, the posterior cingulate was the unique locus of the facilitation effect produced by contrasting Recent Positive probes and Non-Recent Positive probes. This region

may serve as an interface between short- and long-term memory recollection processes that facilitate responding when short- and long-term memories converge.

Table 3.1

	Recent Negative - Non-Recent Negative				
	Peak	Voxels	T-value	BA	Region
Frontal	-40 16 28	665	6.49	9/46/44	left dorsolateral/ventrolateral prefrontal cortex
	50 32 34	5	3.32	9	right dorsolateral prefrontal cortex
	36 28 4	10	3.31	47/45/13	right ventrolateral prefrontal cortex
	32 64 16	32	3.6	10	right anterior prefrontal cortex
	-42 54 14	26	3.53	10	left anterior prefrontal cortex
	-6 14 54	24	3.46	8/6	left medial frontal cortex
	-2 6 62	17	3.58	6	left medial frontal cortex
	50 2 34	32	3.62	9/6	right premotor cortex
Parietal	-26 -62 52	21	3.45	7	left intraparietal sulcus
	-26 -66 36	24	3.36	7/19	left occipito-parietal junction
Occipital	-30 -94 14	46	4.37	19	left occipital cortex
	-2 -86 16	282	4.11	18/17	left occipital cortex
	14 -78 16	77	3.93	18/31	right occipital cortex
	44 -78 -2	23	3.69	19	left occipital cortex

	Forget - Control				
	Peak	Voxels	T-value	BA	Region
Frontal	-50 10 22	187	4.04	44/9/45/46	left dorsolateral/ventrolateral prefrontal cortex
	-32 24 2	197	4.91	47/13/45	left ventrolateral prefrontal cortex
	38 30 2	261	4.2	47/13	right ventrolateral prefrontal cortex
	-38 0 48	62	3.63	6	left premotor cortex
Temporal	-62 -42 -6	5	3.22	21	left middle temporal gyrus

	Interference Conjunction (Recent Negative - Non-Recent Negative ∩ Forget - Control)			
	Center	Voxels	BA	Region
Frontal	38 28 2	162	47/13/45	right ventrolateral prefrontal cortex
	-32 24 8	39	13/45/47	left ventrolateral prefrontal cortex
	-44 8 32	504	9/6/46/44	left dorsolateral/premotor/ ventrolateral cortex
	0 20 50	22	8	medial frontal cortex
Other	50 -60 -34	5		Cerebellum

	Recency Conjunction (Recent Negative - Non-Recent Negative ∩ Forget - Control ∩ Recent Positive - Non-Recent Positive)			
	Center	Voxels	BA	Region
Frontal	-46 24 20	74	45/46	left ventrolateral/dorsolateral

				prefrontal cortex
	-40 48 14	90	10/46	left anterior prefrontal cortex
	40 14 32	7	9	right dorsolateral prefrontal cortex
	56 24 38	18	9	right dorsolateral prefrontal cortex
	-44 2 40	11	6	left premotor cortex
	36 2 42	15	6/9	right premotor cortex
Parietal	-32 -46 38	33	40/7	left intraparietal sulcus/superior parietal lobule
Occipital	-2 -78 6	51	17/23/18/30	left occipital cortex

Table 3.1. Neural Activations.

Chapter 4

Overcoming Interference in Memory and Responding

The concepts of inhibition and control over interference have been topics of intense interest (for reviews, see Dempster, 1995; MacLeod et al., 2003). This interest stems from the pervasive nature of processes that have inhibitory character throughout many cognitive activities. For example, changes in inhibitory functions have been used to explain cognitive development (Diamond & Gilbert, 1989; Ridderinkhof et al., 1997), as well as age-related cognitive decline (Hasher & Zacks, 1988; McDowd et al., 1995). Additionally, deficient inhibitory processes have been related to many disorders including attention-deficit/hyperactivity disorder (Barkley, 1997; Nigg, 2001), autism (Ciesielski & Harris, 1997), schizophrenia (Nestor & O'Donnell, 1998), and obsessive compulsive disorder (Enright & Beech, 1993). Although central to cognition, the concepts of inhibition and interference-control remain fuzzy and poorly understood.

Recently, there has been a movement to understand how different interference-resolution processes may interact. One hypothesis is that resolving all forms of interference depends on the single unitary process of inhibition (Hasher & Zacks, 1988; Hasher et al., 1999). For example, Hasher and colleagues (1999)

demonstrated similar age-related declines for perceptual selection, memory, and response production in the face of interference. These authors proposed that these declines may be explained by general inhibitory deficits. Other researchers have demonstrated that differences in working-memory capacity explain variations in several different interference tasks (Heitz and Engle, 2007; Kane et al., 2001; Kane and Engle, 2000; Rosen and Engle, 1998). Kane and colleagues (2001) suggested that such differences may reflect differences in controlled attention that serves to maintain relevant information amidst distraction. Neuroimaging studies examining multiple interference tasks have demonstrated similar frontal and parietal recruitment when subjects resolve different forms of interference (Fan et al., 2003; Nee et al, 2007; Wager et al., 2005). These studies converge on the idea that inhibition-related functions[6] may be of one sort, regardless of the form of interference.

By contrast, several recent theorists have proposed that inhibition-related functions form a family and cannot be distilled into a single unitary construct (Harnishfeger, 1995; Kramer et al., 1994; Nigg, 2000; Shilling et al., 2002). For example, behavioral correlations among interference tasks are generally low, often near zero (Fan et al., 2003; Kramer et al., 1994; Shilling et al., 2002; Wager et al., 2005). Moreover, despite common neural recruitment across different interference tasks, regions unique to different tasks are evident as well (Nee et

[6] We use the term "inhibition-related functions" recognizing that "inhibition" has historically linked to the processes of interest here. However, previous work has demonstrated that using the term "inhibition" can often be misleading and unnecessary (MacLeod et al., 2003). Therefore, rather than saying "inhibitory functions" we follow the precedent set by Friedman and Miyake (2004) and use the term "inhibition-related functions".

al., 2007; Wager et al., 2005). So, perhaps there *are* dissociable forms of inhibition-related functions. However, theories remain in conflict regarding the proper taxonomy of inhibition-related functions (Dempster and Corkill, 1999; Friedman and Miyake, 2004; Harnishfeger, 1995; Kornblum et al., 1990; Nigg, 2000).

Friedman and Miyake (2004) performed confirmatory factor analysis to examine the relationship among three putative inhibitory functions: prepotent response inhibition, resistance to distractor interference, and resistance to proactive interference (PI). These authors concluded that prepotent response inhibition and resistance to distractor interference formed a single construct (distractor-response inhibition), but that this construct was distinct from resistance to PI. Using a subset of the tasks studied by Friedman and Miyake (2004), Verbruggen and colleagues have examined the relationship between prepotent response inhibition and resistance to distractor interference by combining interference tasks (Verbruggen et al., 2004; 2005; 2006). These authors determined that prepotent response inhibition, as measured by the stop-signal paradigm (e.g. Logan and Cowan, 1984) interacted with several other interference tasks including the flanker, Simon, spatial Stroop, color-word Stroop, and global-local tasks (Verbruggen et al., 2004; 2005; 2006). These interactions remained even in the absence of response conflict (Verbruggen et al., 2004; 2006). This pattern of results confirms that prepotent response inhibition and resistance to distractor interference are closely related.

Although Friedman and Miyake (2004) suggested that distractor-response inhibition and resistance to PI are distinct, no study has examined this claim in more detail. Notably, the reliabilities of the measures of PI studied by Friedman and Miyake (2004) were very low (0.12 or lower) and substantially lower than the reliabilities of the other measures studied (0.59 to 0.87). Furthermore, due to their modeling of resistance to PI as residual variance not captured by pure recall, it is possible that much of their construct was due to measurement error, rather than actually reflecting the ability to resist PI. Therefore, the lack of relation between distractor-response inhibition and resistance to PI may be due to these substantial differences in measuring each function.

In this study, we examined the relationship between PI and prepotent response inhibition. In Experiment 1, we combined a directed-forgetting task that induces PI in working-memory, with a stop-signal task that requires prepotent response inhibition. We demonstrate that although both PI and prepotent response inhibition show robust behavioral signatures, these processes do not interact, suggesting that they are indeed separable inhibitory functions. In Experiment 2 we combined a variant of the go/no-go task (Rosvold et al., 1956) with the stop-signal task to examine whether different measures of prepotent response inhibition interact. In addition, we examined whether inhibition-related functions related to different stages of response production interact. We demonstrate a strong interaction between our prepotent response inhibition measures, verifying

that response inhibition is a robust construct. However, conflict during response selection did not interact with conflict during response execution. These results lead to a taxonomy of inhibition-related functions that distinguishes resistance to PI, prepotent response inhibition, and response selection.

4.1 Experiment 1

4.1.1 Methods

4.1.1.1 Participants

Twenty-nine participants (8 male, mean age 20) were recruited from the Ann Arbor area and were compensated $10/hour plus a performance bonus. All subjects were right-handed native English speakers who had not completed any similar experiments during the past two months. Eight subjects were eliminated for failure to follow instructions.

4.1.1.2 Design and Procedure

As shown in Figure 4.1, each trial began with 1s of fixation, followed by a memory set of 4 centrally displayed letters presented for 2s. After a 3s delay, 2 letters of the memory set were re-presented. Subjects were instructed to remove these letters from their memory and to retain the 2 letters that had not been re-presented. After a 1s delay, subjects responded to a probe letter affirmatively (by pressing 1 on a standard keyboard) if the probe letter was one of the to-be-remembered letters or negatively (by pressing 0) if it was not.

Each memory set was chosen randomly from the set of consonants excluding 'W' with the restriction that no letter had appeared in the previous two trials. 50% of the probes were members of the target set (Positive probes), 25% were letters that subjects were instructed to forget and hence had to reject (Forget probes), and 25% were letters that had not been presented on the previous 2 trials (Control probes). PI was measured by differences between Forget probes and Control probes. Before the experiment, subjects were given written and oral instructions, and were administered 16 practice trials under experimenter supervision. The experiment consisted of 4 runs of 60 trials each.

On 20% of all trials, an auditory stop-signal (a ring that was presented for 1 second or until a response, whichever occurred first) was presented shortly after the probe. If a stop-signal was presented, the subject was instructed to refrain from responding. Subjects were also instructed not to adopt the strategy of simply waiting for stop-signals before deciding whether to respond because this would decrease their monetary bonus. Stop-signals were equally distributed among all types of probes.

The delay between presentation of the probe and the stop-signal (the stop-signal delay) varied in a staircase fashion with the first stop-signal set at 350 ms after probe onset (Logan, Cowan, Davis, 1984). The stop-signal delay was increased by 50ms following a correct stop and decreased by 50ms following a failure to

withhold a response. Separate staircase functions were used for each type of probe. We measured stop-signal reaction time (SSRT) by subtracting the final stop-signal delay value of a particular type of probe (e.g., Control probes) from the mean RT on that same type of trial. SSRT provides a presumed latency to stop.

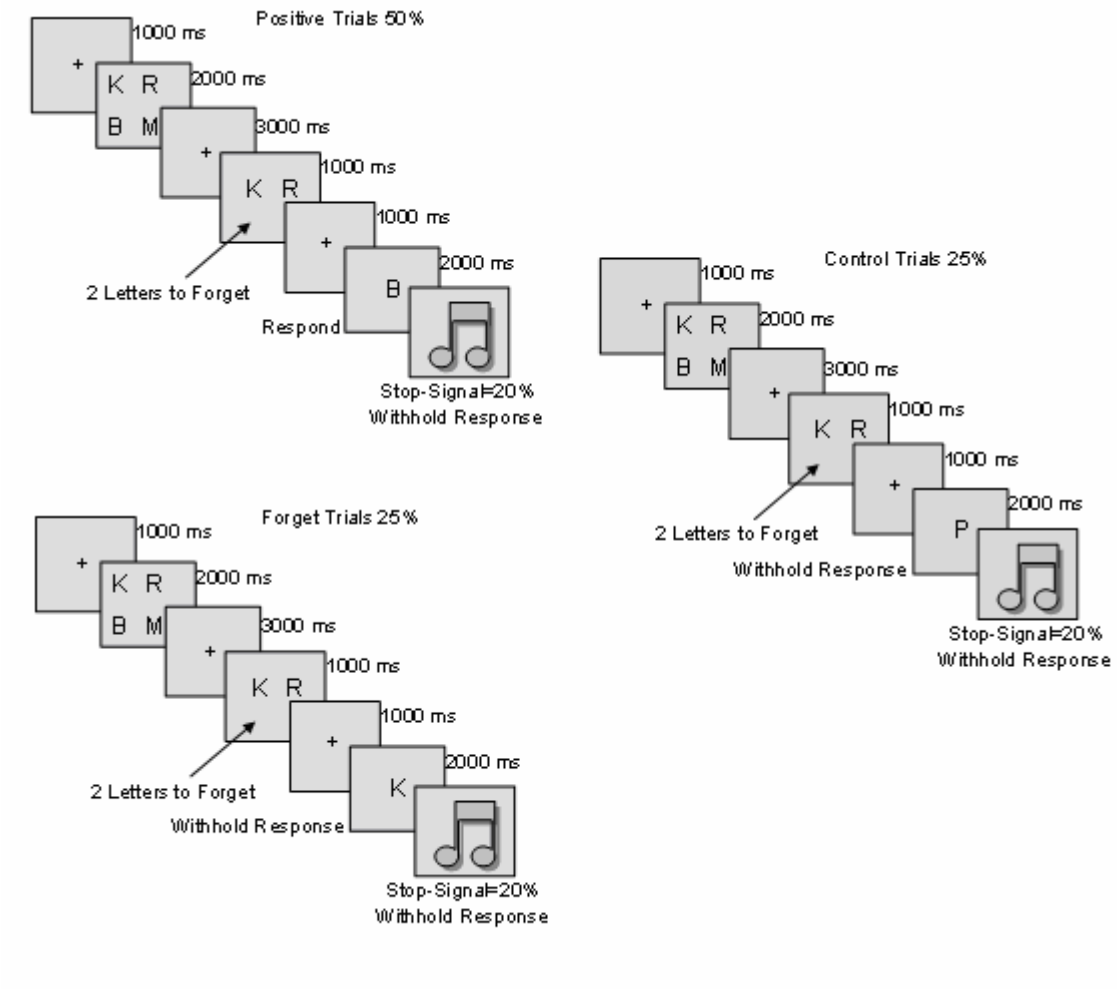

Figure 4.1. Experiment 1 Task Schematic. Schematic of the 3 trial types within experiment 1. Presentation duration is in the upper-right corner of each slide in milliseconds.

A horse-race model has been proposed to explain stop-signal results (Logan & Cowan, 1984). It is assumed that there are two processes whose finishing times are independent: a “Go” process and a “Stop” process. If the Go process finishes first, the subject will respond, and if the Stop process finishes first, a response will be successfully inhibited. The staircase procedure for varying stop-signal presentation yields an SSRT value which is the amount of time necessary after the stop-signal delay for the Stop process to finish at the same time as the Go process. That is, this is the duration necessary for the subject’s go response and stop response to finish at the same time (Logan & Cowan, 1984). This calculation is necessary as there is no overt response recorded during a successful stop-signal trial.

Of interest is whether SSRT varied as a function of probe type (Control, Forget, or Positive probe). If prepotent response inhibition and resistance to PI rely on the same processes, we would expect an interaction such that SSRT for Forget probes that require proactive interference-resolution to be greater than SSRT for Control probes that do not require proactive interference-resolution. This pattern follows the logic of additive factors that posits that two variables that act upon the same process will yield over-additive contributions (Sternberg, 1969).

4.1.2 Results

Reaction times (RT) were computed only on correct trials where no stop-signal was present (signal-absent). Results are summarized in Table 4.1. The results demonstrate significant effects of PI in RT and error rates (ER), but no interaction between resolving PI and prepotent response inhibition. Separate one-way ANOVAs were computed for RT, SSRT, ER for signal-absent trials, and ER for signal-present trials, using probe type as a factor. These tests revealed a significant effect of probe type in RT [$F(2,20)=47.14$, $MS_e=1000.83$, $p<.001$] and ER on signal-absent trials [$F(2,20)=13.13$, $MS_e=.001$, $p<.001$]. Planned t-tests revealed that these differences were due to worse performance on Forget probes compared to Control probes (Table 4.1, $t(20)=6.257$ for RT, $t(20)=4.54$ for ER). These results establish robust effects of PI.

Table 4.1 Experiment 1 - Directed-Forgetting Task

Measure	Control Mean	Forget Mean	Positive Mean	Forget vs. Control t-statistic	Forget vs. Control p-value
RT	570.77	624.96	530.51	6.257	$p < 0.001$
ER	2.8%	6.9%	7.7%	4.54	$p < 0.001$
SSRT	249.34	251.15	256.7	0.08607	$p > 0.9$

Table 4.1. Experiment 1 Behavioral Results. Mean reaction time, error rate, and stop-signal reaction time for 3 conditions and planned t-test results for forget vs. control trials.

SSRT (see Figure 4.2) did not vary as a function of probe type [$F(2,20)=.065$, $MS_e=4744.92$, $p>.9$]. A planned t-test comparing SSRT to Forget probes and SSRT to Control probes revealed no difference ($t(20)=0.086$, $p>0.9$). However, there was a significant effect of probe type on ER on signal-present trials [$F(2,20)=3.526$, $MS_e=.003$, $p<.039$], and this was driven by a slightly higher accuracy on Forget probes. Presumably, this was because the initial stop-signal delay was equal across all trials (350 ms), and subjects generally responded more slowly to forget probes, giving them more time to refrain from responding at the beginning of the experiment.

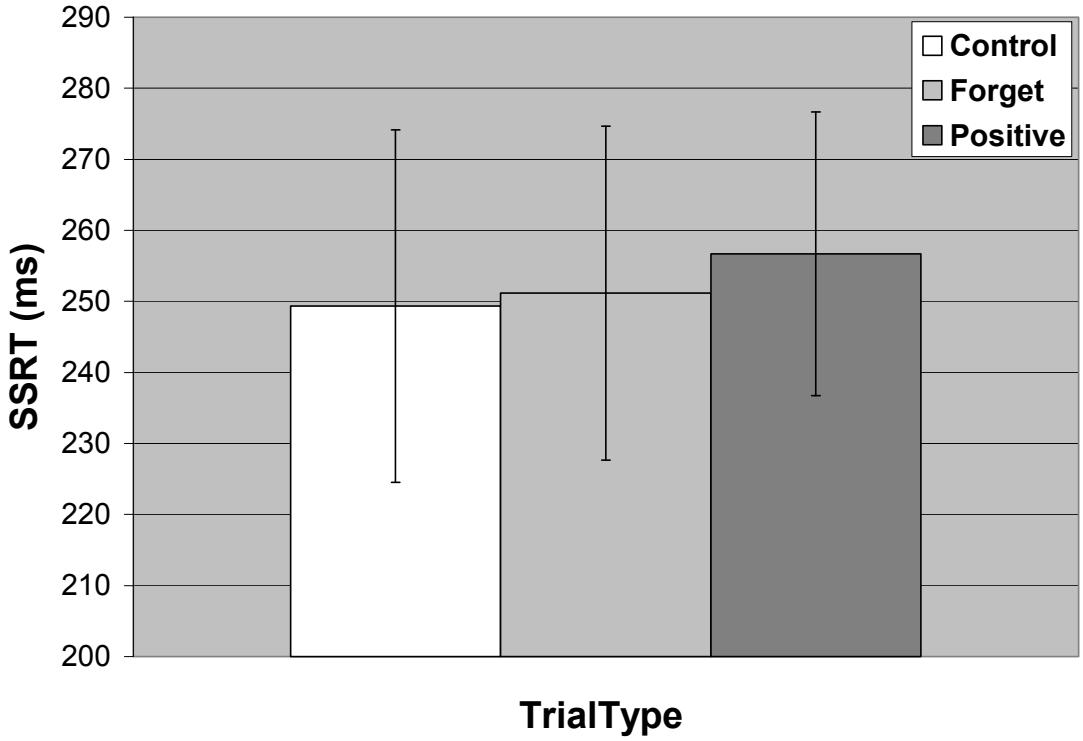

Figure 4.2. Experiment 1 SSRTs. Experiment 1 stop-signal reaction time for 3 trial types. Error bars denote one standard error of the mean.

4.1.3 Discussion

Experiment 1 examined the relationship between resistance to PI and prepotent response inhibition by combining a directed-forgetting task with the stop-signal task. Despite a robust effect of PI, we were unable to find an interaction between resistance to PI and prepotent response inhibition. This result supports the idea that resistance to PI and prepotent response inhibition are separable inhibition-related functions (Friedman and Miyake, 2004).

Previous studies that have combined the stop-signal task with a variety of interference paradigms have demonstrated interactions with SSRT despite smaller interference effects (as small as 13ms) (Kramer et al., 1994; Verbruggen et al., 2004; 2005; 2006). Therefore, it is unlikely that our lack of an interaction is due to insufficient effect size. Even so, we wanted to demonstrate that a significant interaction in SSRT would be present if two tasks that tap the same inhibition-related function were combined. Hence, we examined prepotent response inhibition in Experiment 2 by combining the stop-signal task with a variant of the go/no-go task.

4.2 Experiment 2

In addition to the stop-signal task, prepotent response inhibition is often measured using the go/no-go task that requires subjects to respond to a stream of stimuli but withhold a response to a particular target stimulus (Rosvold et al., 1956). In the variant used here, we examined prepotent response inhibition, as well as conflict during response selection. Combining this task with the stop-signal task affords us the ability to 1) affirm that different measures of prepotent response inhibition interact and 2) determine whether interference effects at different stages of response production interact. There is a good deal of controversy on this latter issue. Logan and Irwin (2000) demonstrated that prepotent response inhibition interacted with response conflict in a stimulus-response compatibility (SRC) task, but only for eye movements, not manual responses. Kramer et al., (1994) and Ridderinkhof et al., (1999) demonstrated interactions between prepotent response inhibition and conflict in the flanker task. However, Verbruggen and colleagues have argued that this may be due to stimulus and not response conflict (Verbruggen et al., 2004; 2006). In the present experiment, we included no stimulus conflict, allowing for a unique assessment of response conflict. Our design thus gives us the ability to separably examine conflict during response selection and during response execution.

4.2.1 Methods

4.2.1.1 Participants

Twenty-one participants (9 male, mean age 22) were recruited from the Ann Arbor area and compensated $10/hour plus a performance bonus. All subjects were right-handed native English speakers who had not completed any similar experiments during the past two months.

4.2.1.2 Design and Procedure

As displayed in Figure 4.3, on each trial, subjects saw a prime letter for 0.5s, followed by a delay that varied between 0.5s and 1.5s (equally distributed among discrete values of .5s, 1s, and 1.5s). Thereafter, subjects were presented with a target letter for 1s. Subjects were instructed to respond via keypress to the second letter unless the second letter was an X preceded by an A (AX trials). The letters were pseudo-randomized such that 40% of trials were AX trials, 20% were A followed by any non-X (AY trials), 20% were non-A followed by X (BX trials), and 20% were non-A followed by non-X (BY trials). Non-A and Non-X letters were randomly chosen from all consonants except for X and W. This version of the AX-CPT paradigm (Barch et al., 1997; Cohen et al., 1996) uses RT as the main dependent measure, allowing us to embed stop-signals on critical trials of interest. Similar to Experiment 1, an auditory stop-signal was presented on 20% of all trials, equally distributed among all trial-types, indicating that a response should be withheld, regardless of prior instructions. The staircase procedure for varying stop-signal delay and the calculation of SSRTs proceeded in the same manner as Experiment 1, except that the stop-signal delay was initialized to 250ms recognizing that the average responses were faster for this

task. Subjects performed 20 runs of 25 trials each. Before the experiment, subjects were given written and verbal instructions, and had 20 practice trials under experimenter supervision.

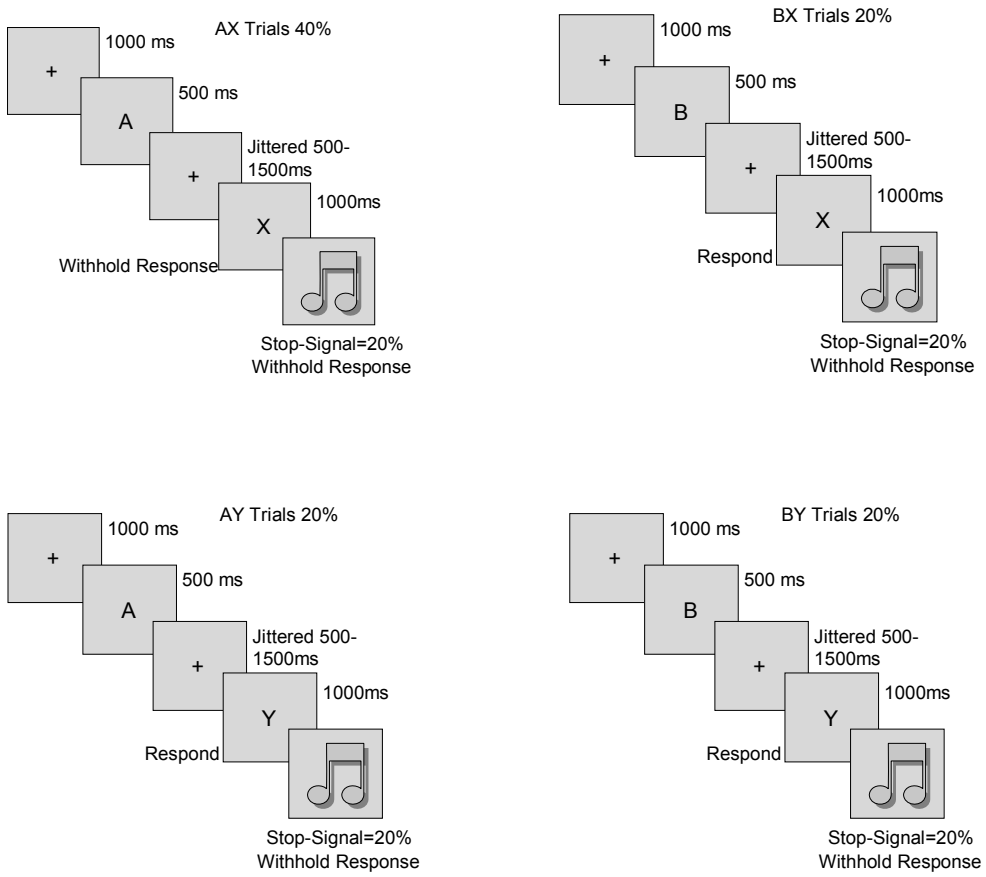

Figure 4.3. Experiment 2 Task Schematic. Schematic of the 4 trial types within Experiment 2. B denotes non-A first letter, and Y denotes non-X second letter. Presentation duration is in the upper-right corner of each slide in milliseconds.

We posited that when an "A" was presented as a prime letter, subjects would establish a prepotency to withhold a response. On AY trials, this prepotency would have to be overcome in order to respond correctly. Hence, responses to

AY trials examine the ability to overcome prepotent response inhibition. Of particular interest is SSRT on AY trials, since stop-signal trials require subjects to first overcome their initial prepotent response inhibition (i.e. respond to the 'Y'), and then re-establish inhibition of a prepotent response (i.e. withhold a response to the stop-signal). In addition, on BX trials, subjects must respond, despite the fact that an "X" often indicates a non-response cue. Hence, BX trials induce conflict while subjects select a response (response selection). Therefore, it is also of interest to examine whether this form of response selection conflict interacts with the prepotent response inhibition due to the stop-signal. Presumably, response inhibition necessitated by the stop-signal occurs after a response has been selected. This allows us to assess whether conflict during response selection interacts with inhibiting response execution.

4.2.2 Results

RT's were computed only on correct trials without stop-signals. Results are summarized in Table 4.2. Separate one-way ANOVAs were computed for RT, SSRT, ER on signal-absent trials, and ER on signal-present trials, with trial-type as a factor. The results demonstrated significant effects of prepotent response inhibition and response selection conflict in the AX-CPT task. However, only prepotent response inhibition interacted with SSRT (see Figure 4.4).

There was a signficant effect of trial-type on RT [$F(2,20)=25.43$, $MS_e=1193.39$, $p<.001$] and ER on signal-absent trials [$F(3,20)=4.591$, $MS_e=.002$, $p<.01$]. Planned t-tests demonstrated that subjects were significantly slower on AY trials

compared to BY trials (t(20)=7.015, p<0.001) although these trials did not differ in ER (t(20)=0.3668, p>0.7). Additionally, subjects were significantly slower and more error prone on BX trials compared to BY trials (t(20)=6.378, p<0.001 for RT, t(20)=3.569, p<0.01 for ER). These results demonstrate the expected interference effects in the AX-CPT task.

Table 4.2 Experiment 2 - AX-CPT Task

Measure	AX	AY	BX	BY	AY vs BY		BX vs BY	
	Mean	Mean	Mean	Mean	t-statistic	p-value	t-statistic	p-value
RT	N/A	514.97	487.38	439.82	7.015	p < 0.001	6.378	p < 0.001
ER	4.9%	3.0%	6.8%	2.8%	0.3668	p > 0.7	3.569	p < 0.005
SSRT	N/A	274.5	199.28	197	3.49	p < 0.005	0.0996	p > 0.9

Table 4.2. Experiment 2 Behavioral Results. Mean reaction time, error rate, and stop-signal reaction time for 4 conditions and planned t-test results for conditions AY vs BY and BX vs BY.

There was a significant effect of trial-type on SSRT [$F(2,20)=6.718$, $MS_e=6081.575$, p<.01]. A planned t-test revealed that SSRT on AY trials was greater than SSRT on BY trials (t(20)=3.49, p<0.01). However, SSRT on BX trials did not differ from SSRT on BY trials (t(20)=0.0996, p>0.9). There was a significant effect of ER on stop-signal trials [$F(3,20)=250.71$, $MS_e=.004$, p>.001], but this was largely due to subjects rarely failing to withhold a response on AX trials, which already called for a non-response. A separate one-way ANOVA on

AY, BY, and BX trials did not demonstrate a significant difference on ER on signal-present trials [$F(2,20)=1.658$, $MS_e=.003$, $p>.2$].

4.2.3 Discussion

Experiment 2 demonstrated a strong interaction between two independent measures of prepotent response inhibition. This result validates that the null finding of Experiment 1 was not due to SSRT having insufficient sensitivity to yield an interaction. Moreover, the interaction that we found in Experiment 2 demonstrates that prepotent response inhibition is a consistent measure across different paradigms. By contrast, compared to BY trials, BX trials demonstrated a robust interference effect in RT, but there was no comparable difference in SSRT. It is most likely that the interference effect in RT is due to interference during response selection is caused by the relationship between the letter "X" and a non-response. However, overcoming conflict due to response selection did not affect SSRT. This result suggests that the response inhibition necessitated by the stop-signal occurs after a response is selected, and that response selection and inhibition of response execution do not interact. Therefore, control mechanisms of response selection and response execution appear to be dissociable.

4.3 General Discussion

Two experiments investigated whether inhibitory processes of PI, prepotent response inhibition, and response selection are dissociable. Whereas different

measures of prepotent response inhibition interacted, prepotent response inhibition did not interact with PI or response selection conflict. These results suggest a taxonomy that distinguishes these three control processes.

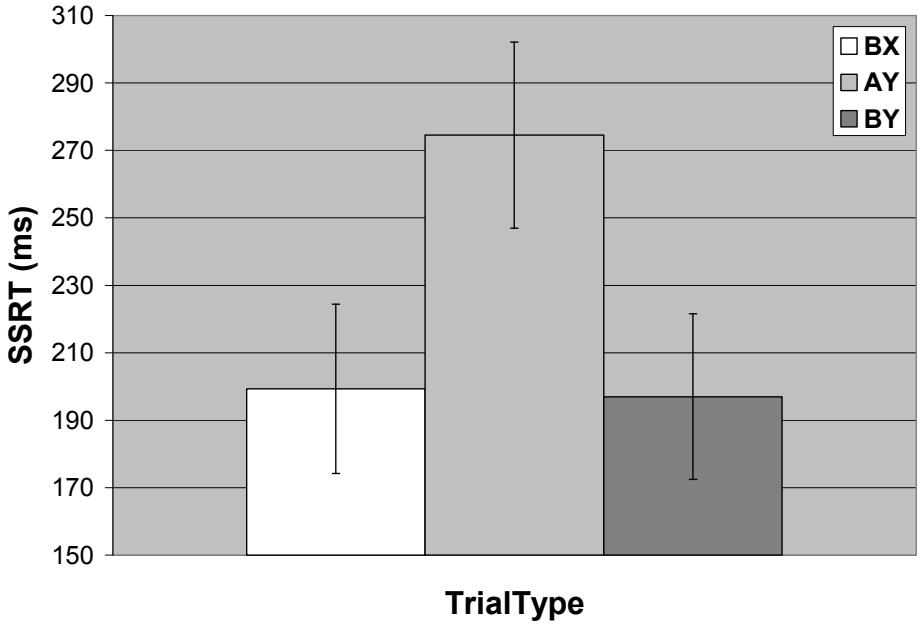

Figure 4.4. Experiment 2 SSRTs. Experiment 2 stop-signal reaction time for 3 overt response conditions. Error bars denote one standard error of the mean.

Previous work had suggested dissociable roles of prepotent response inhibition and resistance to PI. Using confirmatory factor analysis, Friedman and Miyake (2004) demonstrated that prepotent response inhibition and resistance to PI are distinct inhibitory functions. Using event-related fMRI, Nelson and colleagues (2003) examined the neural correlates of PI and response conflict. These authors discovered that whereas the left inferior frontal gyrus was involved in the resolution of PI, the anterior cingulate was uniquely involved in response conflict.

Hence, using very different methodologies, these studies converge on the idea that resistance to PI is distinct from inhibitory processes operating on responses.

Prior studies investigating the relationship of conflict during response selection and prepotent response inhibition provided mixed evidence regarding their separability. Using a flanker task, Kramer and colleagues (1994) found that SSRTs were slowed in the presence of response competition. Ridderinkhof and colleagues (1999) replicated this result using a different flanker. However, the flanker task combines two forms of conflict: stimulus conflict when the flanker stimuli do not match the target stimulus in form, and response conflict when the flanker stimuli are associated with a competing response. Verbruggen and colleagues (2004; 2006) separably examined whether stimulus conflict, response conflict, or both interacted with SSRT. In two flanker tasks, these authors found that stimulus, but not response, conflict interacted with prepotent response inhibition. Therefore, prepotent response inhibition and resolving distracting stimulus conflict may rely on the same inhibition-related functions (Friedman and Miyake, 2004; Verbruggen et al., 2004; 2005; 2006). However, distractor-response inhibition appears to be distinct from response selection conflict.

Neural work has suggested that prepotent response inhibition and response selection conflict may have distinct neural loci. Rubia and colleagues (2001) examined the neural correlates of the go/no-go and stop-signal tasks. These authors found common activation for both tasks in the right inferior frontal gyrus,

suggesting that this region may be involved in prepotent response inhibition (see Aron et al., 2004 for the relationship between prepotent response inhibition and the right inferior frontal gyrus). However, the go/no-go task showed unique recruitment of more dorsal regions of frontal cortex, as well as parietal cortex. These authors reasoned that these regions may be involved in response selection, a function absent in the stop-signal task. A meta-analysis of inhibition-related tasks produced similar results (Nee et al., 2007). Therefore, the neural work provides converging evidence that there are dissociable inhibition-related functions of response selection and execution.

The results of the current study have implications that extend beyond cognitive psychology. Specifically, depression and anxiety disorders have been linked to an inability to suppress unwanted thoughts (Muris et al., 1996; Wegner & Zanakos, 1994), and successful suppression of intrusive, unwanted thoughts requires resistance to PI. In addition, children with ADHD, but not anxious children, show impaired response inhibition (Oosterlaan et al., 1998). Therefore, the separability shown in this study can help to orient future research in these important fields.

Chapter 5

Dissociable Interference-Control Processes in Perception and Memory

Successful cognition depends upon performing goal-directed actions in the face of interference. Most tasks require selective attention to some inputs and filtering out of others, and most activities require holding certain relevant thoughts in mind while shielding these from potential intrusion by irrelevant thoughts. Goal-directed actions therefore require the selection of information and/or the de-selection of irrelevant information. Understanding how we are able to perform such selection is central to understanding cognition.

For over a century, inhibition has been a popular account of how we are able to filter out intrusive information (see Smith, 1992, and MacLeod, Dodd, Sheard, Wilson, & Bibi, 2003, for reviews). The idea is that inhibition can attenuate the representation of distracting information so that it poses a reduced threat to ongoing cognition. Failures of inhibition have been associated with various disorders including schizophrenia (MacQueen, Galway, Goldberg, & Tipper, 2003), attention-deficit/hyperactivity disorder (Nigg, 2001), depression (Joorman, 2005), and obsessive compulsive disorder (Enright & Beech, 1993). Moreover, improved inhibition has been used to explain cognitive advances during

development (Diamond & Gilbert, 1989), and declining inhibition has been linked to cognitive deficits associated with aging (Hasher & Zacks, 1988). These examples demonstrate the central importance of the concept of inhibition in accounts of cognitive functioning.

Although central to many cognitive models, inhibition remains a phenomenon that is poorly understood. There is contention regarding whether processes that down-regulate distracting information are uniform in character (Hasher and Zacks, 1988; Kane, Bleckley, Conway, & Engle, 2001) or whether there is a family of such functions (Harnishfeger, 1995). Theories that posit multiple inhibition-related functions remain conflicted regarding the appropriate taxonomy of these functions (Dempster, 1995; Friedman & Miyake, 2004; Harnishfeger, 1995; Kornblum, Hasbroucq, & Osman, 1990). Importantly, some theorists doubt whether inhibition exists at all and instead posit that performance costs thought to be related to inhibition are actually products of conflict-resolution resulting from memory retrieval (MacLeod, et al., 2003).

Negative priming (NP) has long been taken as a hallmark of inhibitory function (see Fox, 1995; May, Kane, and Hasher, 1995; Tipper, 2001 for reviews). In a typical version of a NP task, subjects are required to attend to a target while ignoring an irrelevant distractor. When the target of the current trial was a distractor on a previous trial, subjects generally demonstrate slowed and less accurate responding. Initial accounts posited that distracting items are inhibited

in order to shield processing from interference (Tipper, 2001). Then, when an inhibited item later becomes a target, additional processes have to be recruited to overcome the inhibition, and this leads to slowed and more errorful performance.

A contrasting position is that inhibition need not be invoked to explain these findings (MacLeod et al., 2003). Instead, the costs associated with NP are claimed to be a result of episodic retrieval processes. By this position, presentation of an item automatically retrieves prior episodes associated with that item. These episodes include attributes such as identity information, location, the status of the item (e.g. relevant or irrelevant), as well as responses to the item (e.g. "respond" or "do not respond"). Hence, when a previous distractor becomes a target, current goals will clash with some retrieved details (e.g. relevance, response). It is the resolution of this episodic retrieval-related conflict that causes the observed reduction in performance by this account.

MacLeod and colleagues (2003) supposed that conflict in episodic retrieval underlies performance costs involved not only in NP, but also in Stroop, task-switching, and directed-forgetting situations. This model is parsimonious in explaining a variety of data, providing a single account for many interference effects previously associated with inhibition. The impact of this model on theories of cognitive control, development, aging, and various disorders has generated a great deal of debate (see Gorfein & MacLeod, 2007, for a summary

of conference proceedings on this matter). However, there is now accruing evidence that response-related processes do, in fact, enlist an inhibitory process (see Aron, 2007 for a review). Moreover, there is some evidence that functions that inhibit responses are dissociable from functions that resolve interference in memory (Friedman & Miyake, 2004; Bissett, Nee, & Jonides, submitted). Therefore, although some reputed interference effects may be due to problems in episodic retrieval, those that act upon responses may be inhibitory in character. Is it possible that other interference effects are also due to inhibitory mechanisms that are distinguishable from episodic retrieval?

The present study inquires further about the control of interference to see whether it is due to a single process or to multiple processes. In a single experimental paradigm, we combined NP and a directed-forgetting procedure that induces proactive interference (PI) in order to examine whether dissociable patterns emerge. The claim has been made that these two interference effects may be due to conflict during episodic retrieval (MacLeod et al., 2003; Jonides & Nee, 2006; Nee, Jonides, & Berman, in press). Using event-related functional magnetic resonance imaging (fMRI), we looked for common and dissociable neural patterns that underlie NP and the resolution of PI. Interrogation of these patterns allowed us to determine whether 1) interference-control processes related to distracting information and intruding memories are common or dissociable and 2) whether NP is a phenomenon related to inhibition, episodic retrieval, or both.

5.1 Methods

5.1.1 Participants

Sixteen right-handed adults (12 female, ages 19-26) participated in this study. One subject was removed from imaging analyses due to motion artifacts, leaving sixteen subjects for behavioral analyses, and fifteen subjects for imaging analyses.

5.1.2 Materials and Procedure

Subjects performed two tasks, presented in Figure 5.1. Both tasks were randomly intermixed.

In the "Ignore" task, each trial began with a 1s red fixation cue. A 1s Ignore cue followed, instructing subjects to ignore words of a particular color (either "Ignore Teal" or "Ignore Blue"). After 1.5s of fixation, 6 words were presented for 3s, 3 in blue and 3 in teal. Displays were arranged such that words of the same color appeared either in a "V" or upside-down "V" shape. Subjects were required to commit the 3 words they were *not* told to ignore to memory, and ignore the other 3 words. After a 3s retention interval, subjects received a probe for 1.5s. Fifty percent of the probes were members of the target set (Positive-I probes), 25% were words subjects were told to ignore (Ignore probes), and 25% were words that had not appeared in the last 2 trials (Control-I probes). Subjects were told to respond affirmatively with a left index press to Positive-I probes, and respond

negatively with a right index press to all other probes. Trials were separated by a 4s interval. NP was measured by contrasting Ignore probes with Control-I probes.

In the "Forget" task, each trial began with a 1s red fixation cue. After 2.5s of fixation, 6 words were presented for 3s, 3 in blue and 3 in teal. Subjects were required to commit all 6 words to memory. Displays were arranged such that words of the same color appeared in a "V" or upside-down "V" shape. After a 1s retention interval, a forget cue was presented for 1s, instructing subjects to remove words of a particular color from memory (e.g. Forget Teal). After another 1s retention interval, subjects received a probe for 1.5s. Fifty percent of the probes were members of the target set (Positive-F probes), 25% were words subjects were told to forget (Forget probes), and 25% were words that had not appeared in the last 2 trials (Control-F probes). Subjects were told to respond affirmatively with a left-index press to Positive-F probes, and respond negatively with a right index press to all other probes. Trials were separated by a 4s interval. PI was measured by contrasting Forget probes with Control-F probes.

Subjects performed 8 runs of 24 trials each, for a total of 96 trials of each task. All words were drawn randomly from a list of eighty 4-letter nouns with the restriction that no word had appeared in the previous two trials.

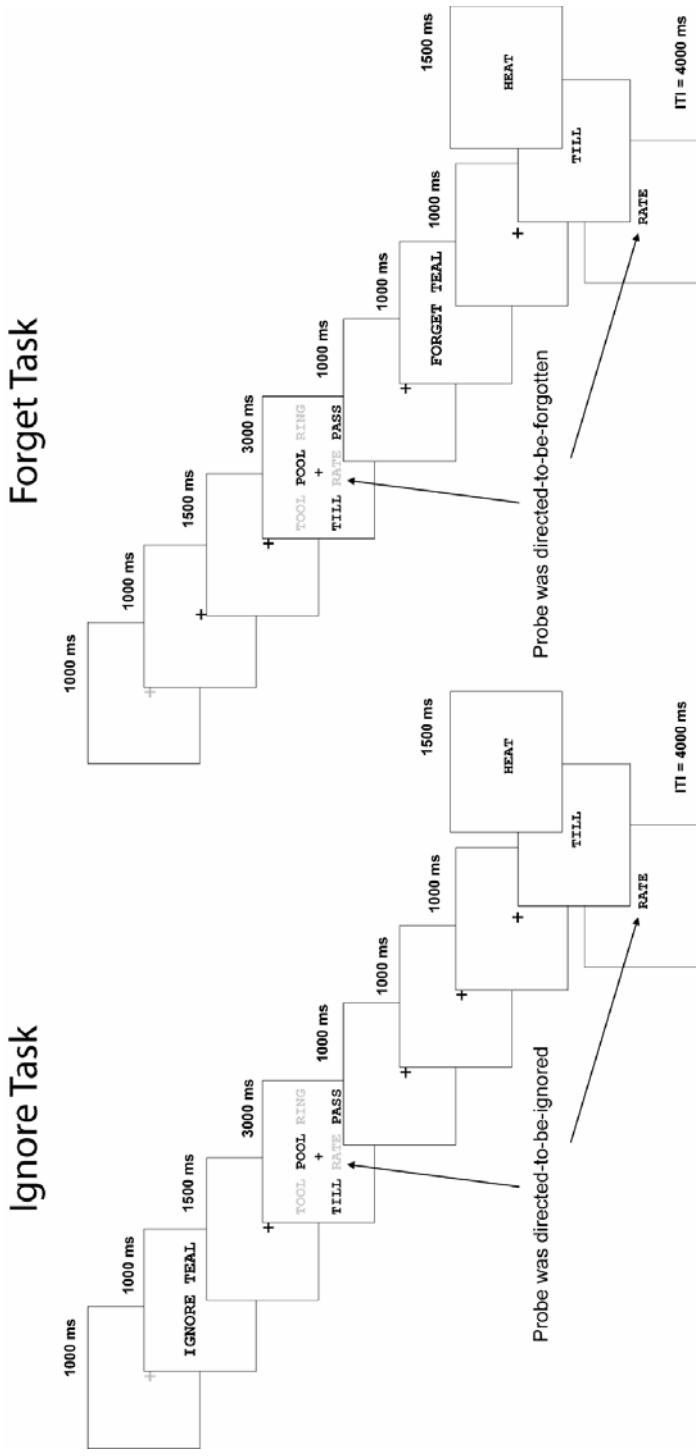

Figure 5.1. Task Schematics. On each trial, half of the words were presented in teal (gray in the figure) and half in blue (black in the figure). Both tasks were

randomly intermixed. Hemodynamic effects were assessed at the probe of each task.

5.1.3 Image acquisition and pre-processing

Images were acquired on a GE Signa 3T scanner equipped with a standard quadrature headcoil. Head movement was minimized using foam padding and a cloth restraint strapped across participants' foreheads. Experimental tasks were presented using E-Prime software (Psychology Software Tools, Inc.) and the IFIS 9.0 system with a 10-button response unit (MRI Devices Corp.).

Functional T2* weighted images were acquired using a spiral sequence with 40 contiguous slices with 3.44 x 3.44 x 3 mm voxels (repetition time (TR) = 2000 ms, echo time (TE) = 30, flip angle = 90, and field of view (FOV) = 22). A T1 weighted gradient echo (GRE) anatomical overlay was acquired using the same FOV and slices as the functional scans (TR = 250, TE = 5.7, and flip angle = 90). Additionally, a 106-slice high resolution T1 weighted anatomical image was collected using spoiled gradient-recalled acquisition in steady state (SPGR) imaging (TR = 10.5, TE = 3.4, flip angle = 25, FOV = 24, 1.5 mm slice thickness).

Each SPGR was corrected for signal inhomogeneity (G. Glover and K. Kristoff, http://www-psych.standford.edu/~kalina/SPM99/Tools/vol_homocor.html) and skull-stripped using FSL's Brain Extraction Tool (http://www.fmrib.ox.ac.uk/fsl). These images were then normalized to the MNI template (avg152t1.img) using

SPM2 (Wellcome Department of Cognitive Neurology, London). Functional images were corrected for slice time differences using 4-point sinc interpolation (Oppenheim, Schafer, & Buck, 1999) and head movement, using MCFLIRT (Jenkinson, Bannister, Brady, & Smith, 2002). To reduce the impact of spike artifacts, functional images were winsorized on a voxel-by-voxel basis so that no voxel had a signal greater than 3.5 standard deviations from the mean of the run (Lazar, Eddy, Genovese, & Welling, 2001). Spatial normalization transformations and 8 mm FWHM isotropic Gaussian smoothing were applied to all functional images prior to analysis using SPM2. All analyses included a temporal high-pass filter (128 s) and each image was scaled to have a global mean intensity of 100.

5.1.4 Image Analysis

Whole-brain analyses were conducted using the General Linear Model implemented in SPM2. Probe-locked predictors were convolved with a canonical hemodynamic response function, including time and dispersion derivatives. To account for artifacts produced by head motion, linear, quadratic, differential, and quadratic differential motion regressors were calculated from the realignment parameters and included in the model (Lund, Norgaard, Rostrup, Rowe, & Paulson, 2005). Contrast images for each participant were subjected to a random-effects group analysis. Trials with incorrect responses were excluded from analysis.

To examine neural correlates of NP, we contrasted Ignore probes with Control-I probes. To examine neural correlates of PI-resolution, we contrasted Forget probes with Control-F probes. Both of these contrasts were thresholded at $p < 0.001$ uncorrected and restricted to regions demonstrating 5 contiguous supra-threshold voxels (Forman et al., 1995; Poline, Worsley, Evans, & Friston, 1997).

To assess regions showing dissociable responses to NP versus PI, we examined regions showing task (Ignore vs. Forget) x probe (Interference vs. Control) interactions. Interactions were assessed using a separate whole-brain random-effects analysis. Interaction regions were defined as regions showing both significant interference-related activation increases in one task at $p < 0.001$ and greater interference-related activation increases for one task than the other at $p < 0.01$, both restricted to 5 contiguous voxels.

To assess regions showing common responses to NP and PI, we performed a conjunction analysis on the contrasts of both tasks. The conjunction was thresholded at $p < 0.01$ for each task, producing a conjoint $p < 0.001$ threshold that was restricted to 5 contiguous voxels.

5.2 Results

5.2.1 Behavioral Results

Reaction times (RT) were calculated for correct trials only. Two 2 x 3 repeated-measures ANOVAs were performed separately on error rates (ER) and RT using

task and probe as factors. We found significant effects of NP and PI in RT. Results are summarized in Table 5.1.

Table 5.1 – Behavioral Data

	Ignore Task			Forget Task		
Probe	Ignore	Control-I	Pos-I	Forget	Control-F	Pos-F
RT	642.89 (31.14)	619.82 (23.65)	619.88 (25.50)	698.89 (32.59)	619.43 (29.87)	614.18 (33.29)
ER	1.8 (2.5)	3.3 (5.3)	3.5 (3.4)	9.8 (7.0)	5.2 (6.5)	14.8 (10.9)

Table 5.1. Behavioral Data. Standard deviations are given in parentheses. RT = reaction time, ER = error rate.

There was a main effect of task in ER ($F(1,15) = 28.442$, $p < 0.001$) and marginally in RT ($F(1,15) = 4.19$, $p < 0.06$). Inspection of the data revealed that this was due to worse performance on the Forget task. There was also a main effect of probe in ER ($F(2,14) = 5.651$, $p < 0.05$) and RT ($F(2,14) = 15.467$, $p < 0.001$). There was a significant task x probe interaction in ER ($F(2,14) = 7.823$, $p < 0.01$) and RT ($F(2,14) = 5.48$, $p < 0.05$).

Planned contrasts revealed a significant effect of NP in RT, with slower responses to Ignore probes compared to Control-I probes (23.1ms, $t(15) = 2.392$, $p < 0.05$). There was no comparable effect in ER ($t(15) = -1.112$, $p > 0.25$). There was also a significant effect of PI in RT, with slower responses to Forget probes compared to Control-F probes (79.5ms, $t(15) = 4.545$, $p < 0.001$). The effect in ER was in the same direction, but did not reach significance (4.6%, $t(15) = 1.808$, $p < 0.1$).

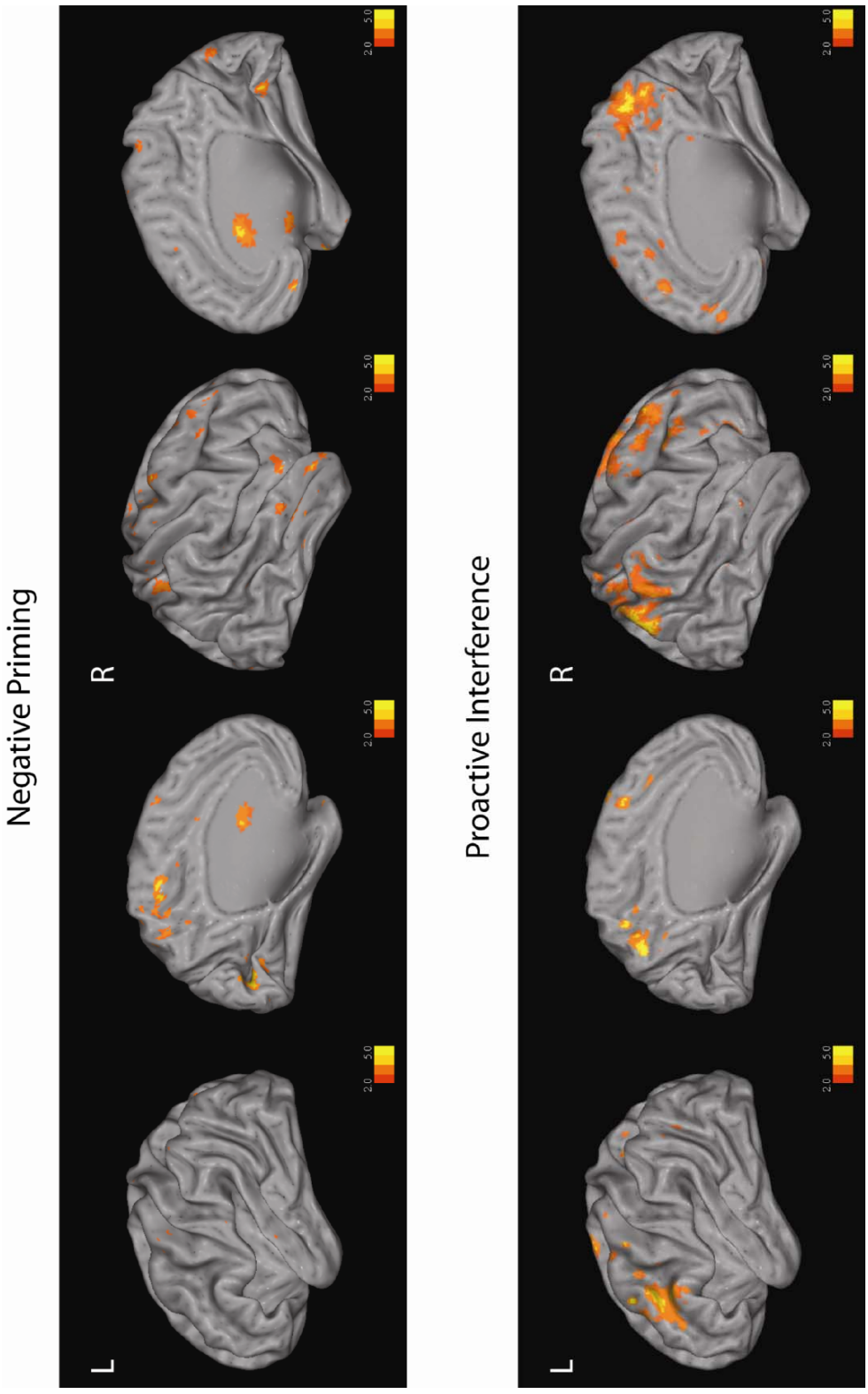

Figure 5.2. Whole-brain results. Activation increases related to negative priming (Ignore – Control-I) and proactive interference (Forget – Control-F).

5.2.2 Imaging Results

Activation increases associated with NP were most notable in occipital cortex, in the left calcarine sulcus and right lingual gyrus. There were also significant activation increases in right inferior temporal gyrus, right premotor cortex, left paracentral gyrus, and the right intraparietal sulcus (Table 5.2, Figure 5.2).

Table 5.2 - Neural correlates of negative priming and proactive interference

Peak	Voxels	T-value	BA	Region
Ignore > Control-I				
38 18 -32	7	4.83	38	right inferior temporal gyrus
2 -64 0	14	4.79	18	right lingual gyrus
-10 -84 6	42	4.54	17	left calcarine sulcus
36 -4 60	13	4.38	6	right premotor cortex
-8 -34 54	15	4.29	5	left paracentral gyrus
36 -46 56	8	4.2	7/40	right intraparietal sulcus
Forget > Control-F				
-38 22 40	133	6.16	9/8	left dorsolateral prefrontal cortex
-48 18 30		4.05	44/9/46	left inferior/middle frontal gyrus
0 -66 42	45	5.01	7	precuneus
14 -54 54	59	4.89	7	right precuneus
-6 -52 48	21	4.41	7	left precuneus
42 -68 50	38	4.4	7	right intraparietal sulcus
44 -74 38		4.33	19/39	
48 -68 42		4.31	7	
8 -68 -46	6	4.36		right cerebellum
30 12 54	26	4.36	6/8	right premotor
32 34 46	7	4.16	9/8	right dorsolateral prefrontal cortex

Table 5.2. Neural correlates of negative priming and proactive interference. Whole-brain results reported at $p < 0.001$, 5 contiguous voxels. Peaks are reported in MNI space. BA = Brodmann's area

PI-related activation was most prominent in left lateral prefrontal cortex, largely in dorsolateral prefrontal cortex, but also reaching ventrolateral prefrontal cortex. Additionally, activation increases were found in bilateral precuneus, right

intraparietal sulcus, right premotor cortex, right dorsolateral prefrontal cortex, and right cerebellum (Table 5.2, Figure 5.2).

To examine whether any regions demonstrated unique interference-specific activation, we looked for regions demonstrating a task x probe interaction. Whereas left occipital cortex demonstrated unique NP-related activation, left dorsolateral prefrontal cortex demonstrated unique PI-related activation (Table 5.3, Figure 5.3). Follow up analyses that averaged responses in these regions confirmed greater NP-related than PI-related activation in left occipital cortex ($t(14) = 2.88$, $p < 0.01$) and greater PI-related than NP-related activation in left dorsolateral prefrontal cortex ($t(14) = 3.33$, $p < 0.01$). Moreover, at a stricter whole-brain threshold of $p < 0.001$, there similar interactions in left occipital cortex and left dorsolateral prefrontal cortex, albeit reduced in extent. To assess whether these dissociable regions were related to performance, we looked for brain-behavior correlations in left occipital and left dorsolateral prefrontal cortex (Figure 5.4). A region in left occipital cortex (MNI center -14 -88 10, BA 17, 17 voxels) correlated with NP ($r = 0.6031$, $p < 0.05$), but not PI ($r = -0.0657$, $p > 0.8$). By contrast, a region in left dorsolateral prefrontal cortex (MNI center -42 20 34, BA 9/44, 33 voxels) correlated with PI ($r = -0.6439$, $p < 0.01$), but not NP ($r = -0.1925$, $p > 0.4$).

Finally, we assessed whether NP and PI produced any common neural correlates using a conjunction analysis. Three regions emerged from this

analysis: right dorsolateral prefrontal cortex, right intraparietal sulcus, and left precuneus (Table 5.3, Figure 5.5). However, none of these regions remained using a stricter valid conjunction analysis thresholded at $p < 0.001$ for each contrast (Nichols et al., 2005).

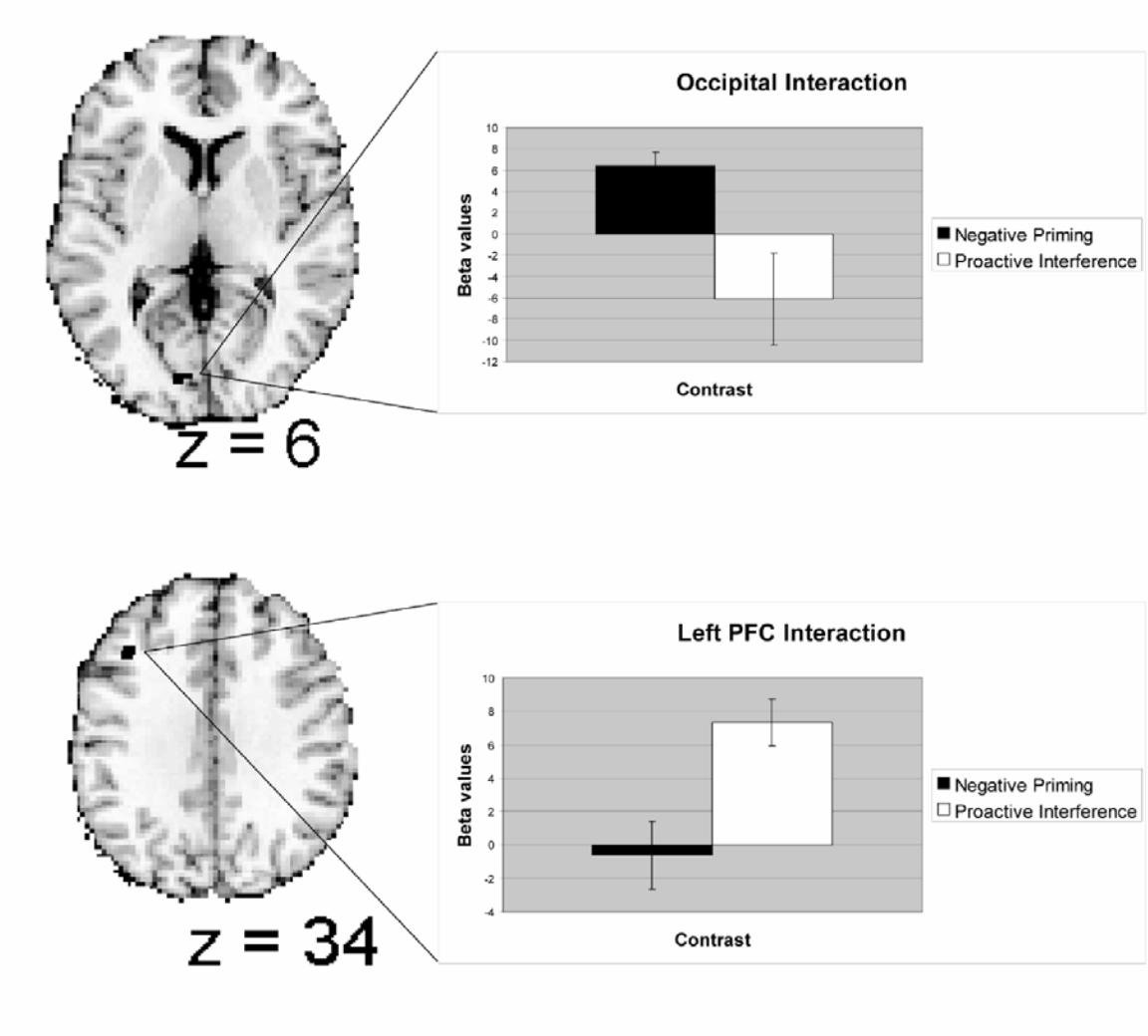

Figure 5.3. Occipital and PFC Interactions. Occipital cortex demonstrated unique negative priming-related activation whereas left dorsolateral prefrontal cortex demonstrated unique proactive interference-related activation.

Table 5.3 - Common and distinct regions of interference-control

Center	Voxels	BA	Region
Ignore – Control-I > Forget – Control-F			
-10 -86 6	16	17	left calcarine sulcus
Forget – Control-F > Ignore – Control-I			
-40 26 38	40	9	left dorsolateral prefrontal cortex
46 -70 40	26	39	right intraparietal sulcus
2 -64 44	9	7	right precuneus
14 -54 52	36		
32 36 44	6	9/8	right dorsolateral prefrontal cortex
30 10 54	17	6/8	right premotor
4 -66 -48	6		right cerebellum
Ignore – Control-I ∩ Forget – Control-F			
32 32 42	9	9/8	right dorsolateral prefrontal cortex
38 -50 50	26	40	right intraparietal sulcus
-8 -54 50	7	7	left precuneus

Table 5.3. Common and distinct regions of interference-control.

5.3 Discussion

Theories of interference-control disagree about whether NP and PI involve a single process acting during episodic retrieval (MacLeod et al., 2003) or distinct forms of control (e.g. Friedman & Miyake, 2004). We found dissociable neural recruitment for the two effects, with occipital cortex demonstrating unique involvement in NP and left lateral prefrontal cortex demonstrating unique activation related to PI. These results support the notion that NP and PI involve at least partially distinct control mechanisms. Using confirmatory factor analysis in a correlational study, Friedman & Miyake (2004) proposed that resistance to distractor interference and resistance to PI were distinguishable factors. However, ours is the first study that combined both forms of interference-control

into a single experimental paradigm. Our results, together with those of Friedman & Miyake (2004), provide strong support for the position that interference-control processes for filtering perceptual material versus memories are distinct.

5.3.1 Accounting for Negative Priming

Our results showed activation increases in primary visual cortex that were unique to NP. Moreover, this occipital region demonstrated a strong correlation with behavioral indices of NP. Why would primary visual cortex be associated with NP? Of course, one possibility is that the NP trials (Ignore probes) yield longer response times and hence more time-on-task. However, if this portion of cortex were simply responding to time on task, it also should yield greater activation on the PI trials (Forget probes). Yet this region demonstrated *decreases* in the face of PI. So, time-on-task is not the mediating factor.

A second possibility is that the occipital activation increases somehow represent difficulty in episodic retrieval. This seems implausible in that activation of primary visual cortex should precede any memory-related processes. Furthermore, any episodic conflict should be present for both the NP conflict and the PI conflict. Yet, the occipital activation is present only for NP. An alternative is that NP and PI elicit the retrieval of different episodic details. For example, subjects may retrieve visual details to respond to Ignore probes and phonological details (e.g. placement in rehearsal loop) to respond to Forget probes, causing the observed

occipital/left frontal dissociation. However, both Ignore and Forget items are distinguishable from relevant material by *both* color *and* phonology. Hence, this account would likely predict a more quantitative distinction between Ignore and Forget probes, whereas the observed data indicate a qualitative distinction.

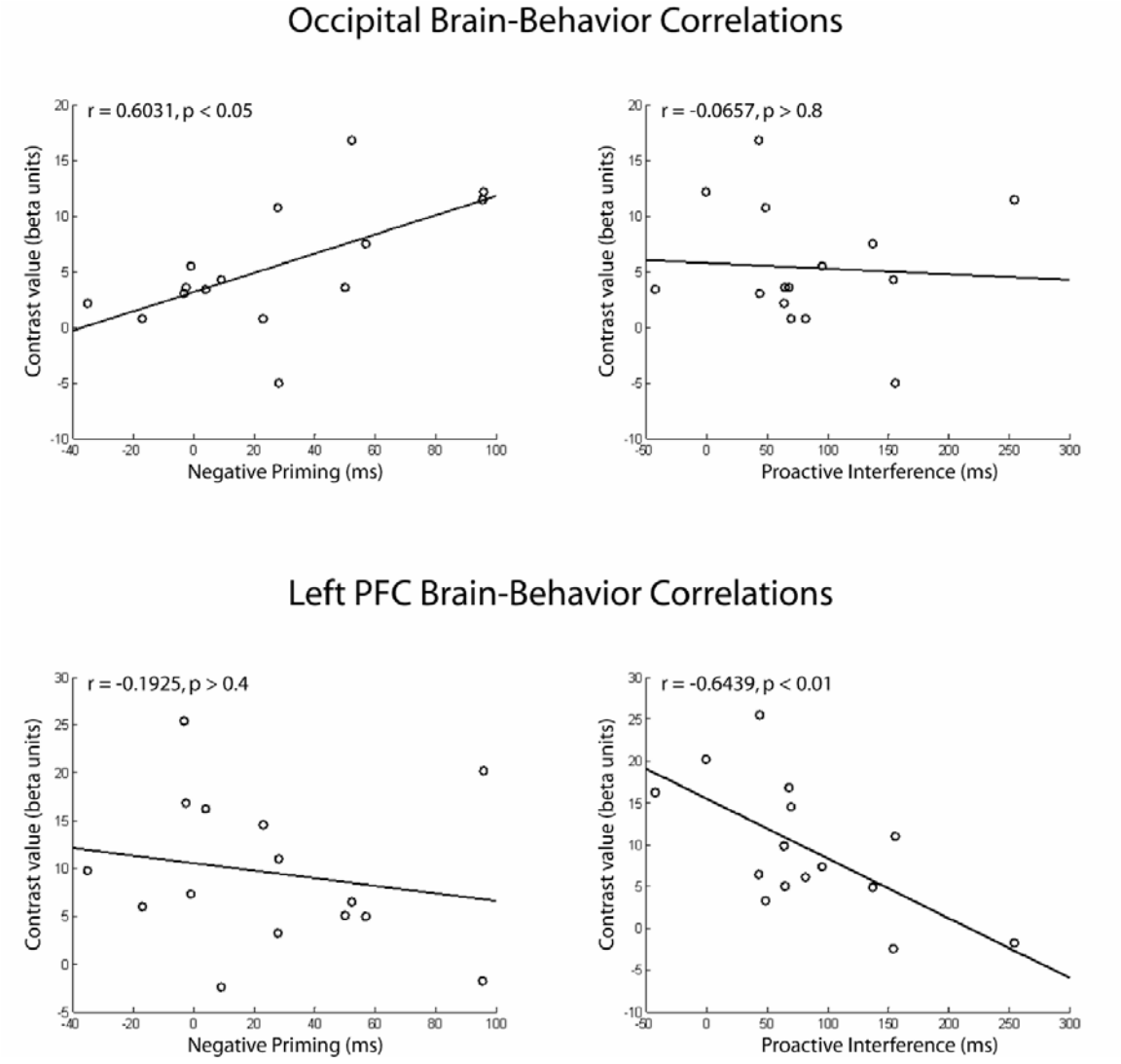

Figure 5.4. Brain-Behaviora Correlations. Correlations between behavioral indices of interference-control and neural activity. PFC = prefrontal cortex.

We believe that the pattern of activations we found for NP is best accounted for by an inhibitory mechanism. Some models of NP have lodged the effect of inhibition at the level of semantic representations (e.g. Tipper, 2001). Our task, however, seems better suited to an account where the inhibitory processes occur earlier in the processing stream, with the visual representations themselves. The task we used requires subjects to filter out 3 distractors, while making saccades to encode the 3 relevant items. The likelihood of encoding the wrong item in this situation may therefore recruit early selection processes. Consequently, the actual *perceptual* representation of the ignored items may be inhibited. If so, then when an ignored item is presented as a probe, visual processes must overcome this inhibition in order to encode the item. Hence, the primary visual activation increases seen here may be related to overcoming perceptual inhibition.

Notably, research has suggested that whether negative priming involves inhibition or episodic retrieval varies as a function of task parameters (Kane et al., 1997). For example, Kane and colleagues (1997) argued that when encoding a target is made more difficult via stimulus degradation or brief presentations, there is a greater reliance of retrieval processes to aid encoding, thereby shifting negative priming from inhibition to episodic retrieval. Our long presentation duration of recognition probes and lack of degradation may therefore have favored inhibitory rather than retrieval processes. Hence, an interesting follow-up would be to examine neural correlates of negative priming when recognition

probes are more difficult to encode versus when they are easier to encode to see if difficult encoding recruits stronger left lateral PFC activation.

5.3.2 Accounting for Proactive Interference

A growing body of literature has implicated left lateral prefrontal cortex in the resolution of PI (see Jonides & Nee, 2006 for a review). Consistent with this, we found unique PI-related activation in lateral prefrontal cortex that correlated with performance. These activation increases were somewhat more dorsal than in previous reports (e.g. Nee et al., in press) which may be due to increased selection difficulty in the task studied here. There is evidence that more dorsal regions of frontal cortex are recruited as processing demands increase (e.g. Postle, Berger, & D'Esposito, 1999). Previous studies of directed forgetting in short-term memory have used item- or location-based forget cues (Nee et al., in press; Zhang, Leung, & Johnson, 2003; Zhang, Feng, Fox, Gao, & Tan, 2004). These cues have had obvious mappings to the items to be maintained and discarded, making it relatively easy to distinguish relevant and irrelevant items in short-term memory. However, the color-cue we used here does not have an obvious mapping to the items to be maintained and forgotten, thereby making selection potentially more difficult.

Is the left lateral frontal area somehow involved in inhibitory processing? Although early accounts claimed this (Jonides, Smith, Marshuetz, & Koeppe, 1998), more recent models have gravitated toward the notion that this region is

involved in selection of contextual details during episodic retrieval (Badre & Wagner, 2005; Jonides & Nee, 2006; Nee et al., in press). Nee and colleagues (in press) have demonstrated that this region shows increased functional connectivity with the medial temporal lobe and premotor cortex in the face of PI, suggesting that left lateral prefrontal cortex selects episodic details in order to bias decision processes. Our data suggest that these processes are distinct from those related to NP.

5.3.3 Common Activations

We also found common recruitment of right dorsolateral prefrontal cortex, right intraparietal sulcus, and left precuneus for both NP and PI. A previous study examining NP in a Stroop task also found activation increases in right dorsolateral prefrontal cortex (Egner & Hirsch, 2005). Since this region has been associated with episodic retrieval, these authors took this as evidence supporting the episodic retrieval account of NP. Moreover, the common parietal regions that we found activated have also been implicated in the retrieval of specific episodic details (see Wagner, Shannon, Kahn, & Buckner, 2005 for a review). These results suggest that there are common episodic components to both NP and PI. These components may reflect contrasting episodic details when an item is a probe ("respond to me") versus when it is ignored or removed from memory ("do not respond to me"). However, none of these regions demonstrated a significant correlation with behavior ($p > 0.05$) and none of these regions survived a stricter

valid conjunction analysis (Nichols et al., 2005), so accepting these regions as reflecting common episodic components must be taken with caution.

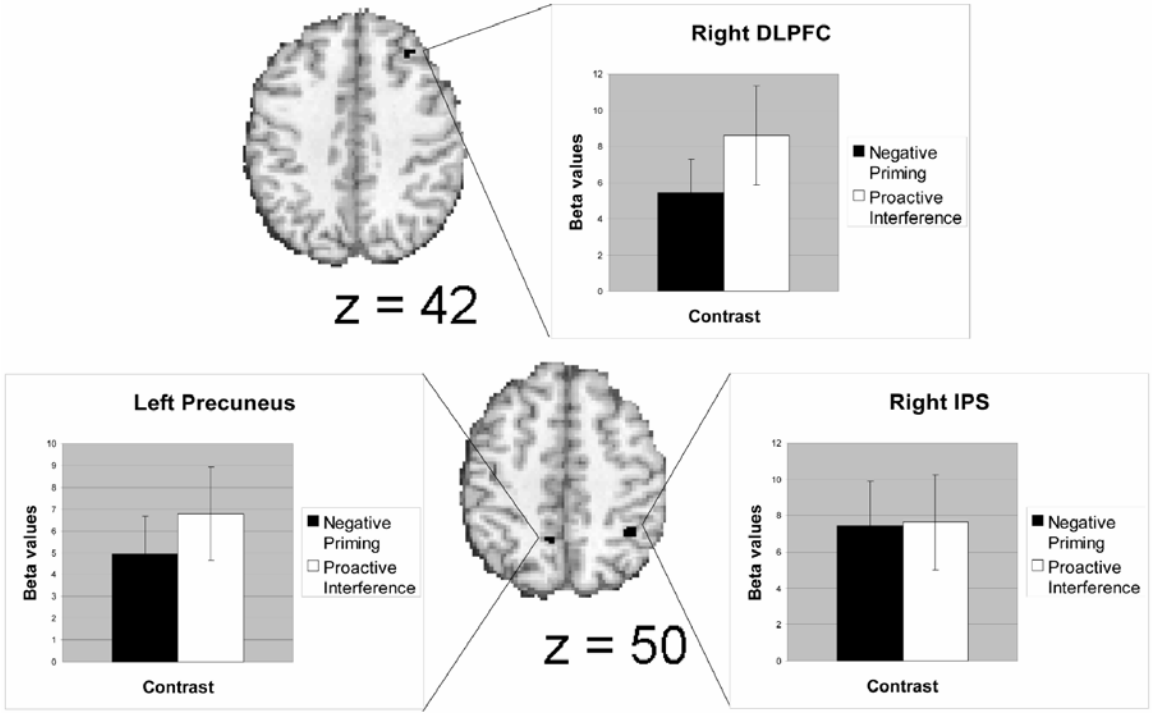

Figure 5.5. Common Regions. Regions demonstrating common interference-related activity for negative priming and proactive interference. DLPFC = dorsolateral prefrontal cortex; IPS = intraparietal sulcus.

Egner & Hirsch (2005) also reported NP-related activation in the medial dorsal thalamus (MNI peak 10 -20 14, 30 voxels). Moreover, these authors reported that activation in this region correlated negatively with behavioral indices of NP. In a post-hoc analysis, we interrogated the medial dorsal thalamus for comparable activity. At a more liberal threshold ($p < 0.01$), we found a similar region for our NP contrast (MNI peak -10 -18 16, 10 voxels) that also demonstrated a marginally significant correlation with behavioral indices of NP (r

= -0.4831, p = 0.07). However, this region did not show comparable activation related to PI (p > 0.9). Egner & Hirsch (2005) noted the relation of this region to schizophrenia. Schizophrenics demonstrate reduced NP (MacQueen et al., 2003) with a concomitant decrease in medial dorsal thalamus volumes (e.g. Kemether et al., 2003). Schizophrenics also show decreased metabolic activity in the medial dorsal thalamus (Buchsbaum et al., 1996). Egner & Hirsch (2005) interpreted NP-related activity in the medial dorsal thalamus to indicate that episodic retrieval and not inhibition is deficient in schizophrenia. However, our results speak to the contrary in that activation increases in this region were uniquely associated with NP, not PI. Rather, this evidence is more consistent with models of schizophrenia that posit deficient inhibition (MacQueen et al., 2003).

In summary, the data here suggest some dissociable interference-control processes related to NP and PI. This indicates that beyond responding, not all interference costs can be cast as problems in episodic retrieval. Rather, resisting perceptual interference and resolving PI appear to be dissociable functions. Moreover, our data suggest that there are inhibitory components to NP, acting as early as primary visual cortex, and perhaps involving the medial dorsal thalamus as well. However, NP may have some components related to conflict during episodic retrieval, as retrieval-related regions are recruited for both NP and PI.

Understanding how control is achieved over perceptual and memorial representations is central to understanding cognition. Our data highlight the importance of distinguishing different forms of interference-control that are overcome by different mechanisms. Beyond this, our data also highlight the value of neuroimaging as a way to parse different psychological mechanisms that are critical to cognitive processing, something that can be applied to studying deficits in cognitive processing as well (e.g. Jonides and Nee, 2005).

Chapter 6

The Spotlight Casts a Shadow: Attentionally-Mediated Visual Suppression Produces Object-Specific Inhibition

Searching through a cluttered environment requires an interplay between visual and attentional systems. Many traditional accounts rely on the metaphor of attention as a spotlight that highlights certain aspects of the visual scene allowing for closer inspection of specific details (Posner and Petersen, 1990). However, recent data suggest that attention does more than simply enhance relevant visual information; attentional processes also appear to suppress competing distracting information (Muller and Ebeling, 2008; Muller and Kleinschmidt, 2004; Nee and Jonides, in press; Tootell et al., 1998). Research has demonstrated that when humans focus attention on a location, neural activation corresponding to ignored locations is reduced (Muller and Ebeling, 2008; Muller and Kleinschmidt, 2004; Tootell et al., 1998), and response time to information at suppressed locations is impaired (Muller and Ebeling, 2008). Although it has been assumed that visual suppression is a function of top-down modulation of visual cortex, as yet there has been no demonstration of an interplay between frontal/parietal attentional regions and visual suppression. Additionally, it is unclear whether the observed suppression effects function only to aid encoding, or whether they may underlie a longer lasting phenomenon that safeguards the cognitive system from recurrent

distraction. That is, can these suppressive influences on the visual system provide a means to inhibit unwanted, intrusive information?

A rich behavioral tradition has demonstrated that when distracting visual information is filtered out, subjects show slowed response latencies when they must revisit the previously ignored information (Fox, 1995; May et al., 1995; Tipper, 2001). This effect, commonly referred to as negative priming, has been taken as a measure of the cognitive system's ability to inhibit distracting information that may otherwise be deleterious to performance. Evidence of the importance of this ability comes from demonstrations that reduced negative priming accompanies clinical disorders such as schizophrenia (MacQueen et al., 2003), attention-deficit hyperactivity disorder (Nigg, 2001) and depression (Joorman, 2005). It is thought that cognitive impairments related to these disorders may involve the impairment of the ability to inhibit unwanted perceptual distraction (Joorman, 2005; MacQueen et al., 2003; Nigg, 2001). However, alternative accounts that do not rely on inhibition have been proposed, and these accounts provide parsimonious explanations of many of the cognitive phenomena in question (MacLeod et al., 2003). Moreover, precise neural and psychological accounts of inhibition are lacking and do not specify the mechanism by which inhibition might be achieved.

Recently, we demonstrated that when subjects encoded a previously ignored word, activation in early visual cortex was increased relative to when subjects

encoded a word that had not been recently presented (Nee and Jonides, in press). Moreover, occipital activation was related to behavioral manifestations of negative priming. We speculated that the visual representations of the ignored words were inhibited. Then, when the previously ignored words had to be encoded once again, this inhibition had to be overcome, resulting in a need for increased visual encoding processes and a commensurate slowing of reaction time. However, our experiment neither demonstrated inhibition nor provided a rationale for how inhibition might have occurred. Here, we demonstrate that visual suppression may produce the lasting inhibition that mediates negative priming.

Based on previous data, we predicted that if inhibition is at work, then it may be observable as a neural suppression of occipital regions involved in representing distracting information. Such visual suppressive effects should be caused by top-down influences by frontal and/or parietal regions involved in attentional control. Moreover, if suppression of early visual cortex underlies negative priming, then reductions in visual cortical responsiveness should predict the magnitude of behavioral costs incurred when revisiting ignored information. Here, we examine these predictions. First, we document regions of attentional control. Next, we look for visual regions that may underlie negative priming. Finally, we examine the relationship between attentional control regions and their presumed targets in visual cortex.

To examine attentional-modulation as subjects filtered out distraction, we used a modified item-recognition task similar to our previous design (Nee and Jonides, in press) while examining neural activation using event-related functional magnetic resonance imaging. On each trial, subjects received a display and had to commit 3 target words to memory (Figure 6.1). On half of the trials, target words were accompanied by distracting words that were presented in a different color. On a quarter of the trials, a string of 4 pound-signs appeared in place of distracting words, and on the other quarter of the trials, no distractors were presented. All trial types were randomly intermixed. Before each display was presented, subjects were alerted to the color of the target words so that attentional processes could select relevant words among potential distractors. To provide a behavioral assay of attentional control, we instructed subjects to make a keypress after they had encoded the target words. We reasoned that longer keypress latencies denoted larger demands on attentional control. To ensure that subjects faithfully encoded targets and ignored distractors, subjects responded to recognition probes following a variable delay. These recognition probes queried target words (requiring a positive response), words that had not appeared (requiring a negative response), and words that were to-be-ignored (also requiring a negative response). Accuracy to these recognition decisions was over 95%, confirming that subjects performed the task appropriately.

6.1 Methods

6.1.1 Participants

Eighteen right-handed adults (8 female; ages 19-25) participated in this study. All subjects had normal or corrected to normal vision and had no reported illnesses. Subjects were compensated $20/hr plus a bonus for fast and accurate performance. One run from one subject was excluded from analysis due to her difficulty with task instructions.

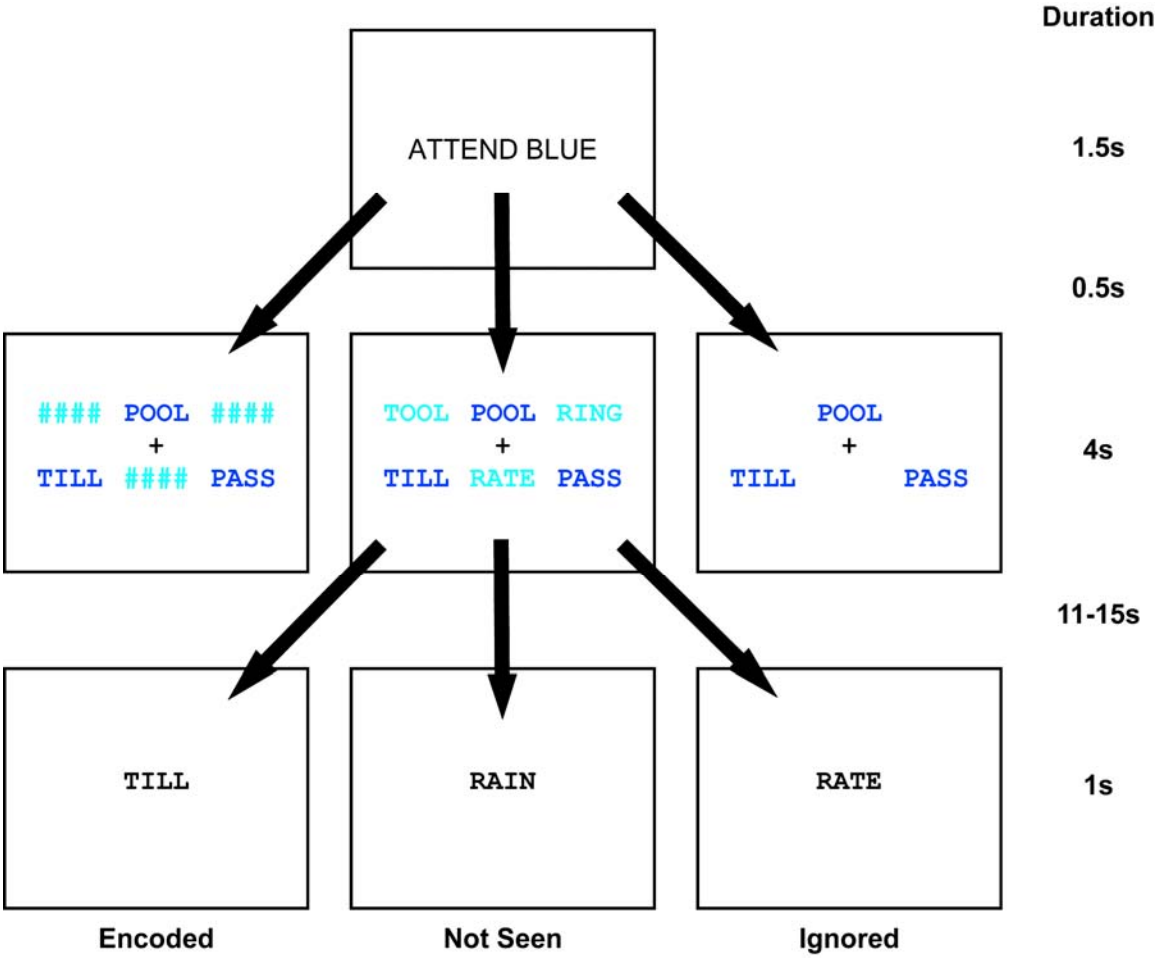

Figure 6.1. Task Schematic. A depiction of the task with the duration each event described on the right. The attentional cue denoted the color of the target words. Subjects encoded target words while either filtering out distracting pound signs (pound-distraction), words (word-distraction), or with no distraction present (no-distraction). After a varied retention interval, subjects responded to recognition

probes that were encoded, not seen, or ignored. Ignored probes only followed the word-distraction condition, since words were not ignored in other conditions.

6.1.2 Materials and Procedure

Words were drawn from a list of 100 four-letter nouns. Words were drawn randomly for each trial with the exception that words could not have been presented in the previous 2 trials in order to control for potential effects of proactive interference. All responses were recorded on a 10-button response unit that accompanied the IFIS 9.0 system (MRI Devices Corp., Latham, NY) with one button for each finger. Stimuli were presented via a projector at the back of the scanner, reflected off a mirror placed above the head of the subject. Experimental tasks were presented using E-Prime software (Psychology Software Tools, Inc., Pittsburgh, PA).

Each trial began with a red fixation cross presented for 1 second to alert the subject that the trial was beginning. Thereafter, an attention cue ("ATTEND BLUE", "ATTEND TEAL", "IGNORE BLUE", or "IGNORE TEAL") was presented for 1.5 seconds that informed the subject of the color of the relevant stimuli. On half of the trials the words printed in blue were made relevant and on the other half the words printed in teal were made relevant. Three-fourths of the cues involved "attend" instructions, with the other one-fourth involving "ignore" instructions. We collapsed across different cue instructions and "ignore"

instructions were used only to parallel another experiment not reported here. “Attend” and “ignore” instructions did not produce appreciably different results.

The attention cue was followed by 0.5 seconds of fixation, followed by the target display. The target display consisted of three words presented in the relevant color in a “V” or upside-down “V” shape. On one-half of the trials, three distractor words (word-distraction) were presented in the alternate color (blue if the relevant words were teal, teal if the relevant words were blue). On one-fourth of the trials, a string of four pound signs was used in place of distracting words (pound-distraction) and on the other one-fourth of the trials, no distracting information appeared (no-distraction). All of the stimuli considered together subtended approximately 9.7 degrees of visual angle horizontally, and approximately 3.5 degrees vertically. Each word or string of pound signs subtended approximately 2.6 degrees of visual angle horizontally, and 0.88 degrees vertically. Stimuli were separated by 0.88 degrees horizontally, and 1.76 degrees vertically.

Subjects were instructed to read the three relevant words subvocally once and make a left thumb press after doing so. Subjects were told to maintain the relevant words in memory. The target display was presented for 4 seconds, and subjects were instructed to stare at the fixation cross and continue to attend to relevant words and ignore irrelevant information when they had completed encoding the relevant words.

A fixation interval of 4 to 6 seconds followed the target display, varied in equal steps of 1 second. Thereafter, a cue (rehearsal cue) appeared instructing subjects to rehearse the relevant words once and make a left thumb press after doing so. The cue stated “REMEM BLUE” or “REMEM TEAL” (always the relevant color), and was included to parallel another experiment not described here. This cue was followed by a 6 to 8-second fixation interval, varied in equal steps of 1 second. Finally, a recognition probe was presented for 1 second, followed by an inter-trial interval of 3 to 5 seconds, varied in equal steps of 1 second. Subjects responded with a right index press if the probe matched one of the three words held in memory (positive probe), and made a left index press otherwise (negative probe). One-half of the probes were positive probes and one-half were negative probes. Three-quarters of the negative probes were words that had not appeared for the last 2 trials (control probes) and one-quarter were probes that matched a word that had appeared as a distractor on the target display (ignore probes). The asymmetry of the number of ignore probes is due to the fact that ignore probes could only follow the word-distraction condition. Within the word-distraction condition, control and ignore probes were equally distributed. All combinations of cue and probe were randomly intermixed.

Subjects performed four runs of 18 trials each, for a total of 72 trials. Runs were interleaved with another task not describe here and the order of runs was counterbalanced between subjects. The day prior to scanning, subjects performed two runs of the task with accuracy and latency feedback. On the day

of scanning, subjects performed an additional run of practice also with feedback. Feedback was not given during scanning, but average accuracy and reaction times were presented during rest breaks between scans so that subjects could monitor their performance.

6.1.3 Image Acquisition and Preprocessing

Images were acquired on a GE Signa 3-T scanner equipped with a standard quadrature head coil. Head movement was minimized using foam padding and a cloth restraint strapped across participants' foreheads.

Functional T2*-weighted images were acquired using a spiral sequence with 40 contiguous slices with 3.44 × 3.44 × 3 mm voxels (repetition time, or TR = 2,000 ms; echo time, or TE = 30 ms; flip angle = 90°; field of view, or FOV = 22 mm^2). A T1-weighted gradient-echo anatomical overlay was acquired using the same FOV and slices (TR = 250 ms, TE = 5.7 ms, flip angle = 90°). Additionally, a 124-slice high-resolution T1-weighted anatomical image was collected using spoiled-gradient-recalled acquisition (SPGR) in steady-state imaging (TR = 9 ms, TE = 1.8 ms, flip angle = 15°, FOV = 25-26 mm^2, slice thickness = 1.2 mm).

Each SPGR anatomical image was corrected for signal inhomogeneity and skull-stripped using FSL's Brain Extraction Tool (Smith et al., 2004). These images were then normalized to the Montreal Neurological Institute (MNI) template using SPM2 (Wellcome Department of Cognitive Neurology, London). Functional

images were corrected for differences in slice timing using 4-point sinc interpolation (Oppenheim et al., 1999) and were corrected for head movement using MCFLIRT (Jenkinson et al., 2002). To reduce the impact of spike artifacts, we winsorized functional images on a voxel-by-voxel basis so that no voxel had a signal greater than 3.5 standard deviations from the mean of the run (Lazar et al., 2001). Spatial normalization transformations and 8-mm full-width/half-maximum isotropic Gaussian smoothing were applied to all functional images prior to analysis using SPM2. All analyses included a temporal high-pass filter (128 s), and each image was scaled to have a global mean intensity of 100.

6.1.4 Image Analysis

Analyses were conducted using the General Linear Model implemented in SPM2. Predictors of interest were locked to the onset of the target display and convolved with a canonical hemodynamic response function provided by SPM2. Additional predictors were used to model the rehearsal cue and the probe, which were not involved in the present analyses. To account for artifacts produced by head motion, we calculated linear, quadratic, differential, and quadratic differential motion regressors from the realignment parameters and included these regressors in the model (Lund et al., 2005). Trials in which subjects failed to make a keypress to the target set or rehearsal cue and/or trials in which subjects responded incorrectly to the recognition probe were excluded (less than 7% of the trials).

Separate regressors were calculated for word-distraction, pound-distraction, and no-distraction. Attentional control was assessed by comparing estimated responses to word-distraction versus pound-distraction and no-distraction. This analysis was conducted over the entire collected volume and was thresholded at $p < 0.001$ with a cluster extent of at least 20 suprathreshold voxels (Forman et al., 1995; Poline et al., 1997). Visual suppression was assessed by comparing estimated responses when distraction was present (word-distraction and pound-distraction) compared to no-distraction. The contrast was informed by demonstrations that visual suppression occurs in the presence of distracting information, but not at empty ignored locations (Muller and Ebeling, 2008). This analysis was restricted to occipital cortex as a region of interest and thresholded at $p < 0.01$ with a cluster extent of at least 20 suprathreshold voxels. Occipital cortex was identified by anatomical inspection and early visual regions of interest in V1 and V2 were verified using a probabilistic atlas (Amunts et al., 2000).

Notably, we did not use separate regressors to model different probe events in order to investigate probe-related changes in neural activation. Of interest would be the neural differences in activation between ignore probes and control probes to examine neural correlates of negative priming. However, only 9 ignore probes were included per subject and our prior work with a similar paradigm suggested that this analysis would have insufficient power to detect the anticipated difference (Nee and Jonides, in press). Hence, considerations of probe-related effects rely on our previously published report.

Correlations between behavioral effects and neural activation were restricted to regions demonstrating significant neural activation in the analysis of interest as per the criteria above. Correlations were computed on a voxel-by-voxel basis and contiguous voxels demonstrating correlations significant at $p < 0.05$ were pooled together for subsequent analysis. Only regions demonstrating a cluster extent of 20 or more voxels were examined. All correlations were confirmed using robust regression, a method less sensitive to outliers than ordinary least squares approaches.

To examine interactions between visual suppression and attentional control, we first extracted the contrast estimates for visual suppression in left early visual cortex, restricted to regions demonstrating a significant difference for distraction versus no-distraction at $p < 0.005$. The resultant region was 40 voxels in size. For each subject, we averaged the contrast estimates within the left occipital region and used the subject-by-subject variation of this estimate as a predictor. Within regions that demonstrated significant activation increases to attentional control (as per the criteria above), we looked for regions that correlated inversely with visual suppression on a voxel-by-voxel basis. Regions composed of 20 or more contiguous voxels that correlated negatively with visual suppression at $p < 0.05$ were pooled for further examination.

6.2 Results

6.2.1 Behavioral Results

Trials in which subjects failed to make a keypress to the target display or rehearsal cue were excluded from behavioral analysis (less than 2% of the trials). First, we assessed accuracy to recognition probes. Accuracy was high overall (> 95%) and did not differ by probe type (positive, control, ignore; $F(2,34) < 1$), nor did accuracy differ as a function of the type of distraction present (word-distraction, pound-distraction, no-distraction; $F(2,34) < 1$). For all latency data, we excluded trials in which subjects responded incorrectly to the recognition probe.

To explore behavioral effects of attentional control, we examined the latency with which subjects made a keypress after encoding the target set as a function of the type of distraction present. There was a significant effect of type of distraction ($F(2,34) = 24.17$, $p < 0.001$). Planned t-tests demonstrated that word-distraction produced slower latencies to respond than pound-distraction (1430ms vs. 1176ms, $t(17) = 6.6$, $p < 0.001$) and no-distraction (1430ms vs. 1183ms, $t(17) = 4.68$, $p < 0.001$). Pound-distraction and no-distraction did not differ ($t(17) = 0.22$, $p > 0.8$). These results confirmed that word-distraction called for increased attentional control compared to pound-distraction and no-distraction.

Next, we examined reaction times to recognition probes. Recognition probes demonstrated a significant effect of probe type ($F(2,34) = 10.59$, $p < 0.001$). This was largely driven by faster responses to positive probes (651ms) compared to

control probes (704ms) and ignore probes (736ms). There was no effect of type of distraction on reaction time for recognition probes ($F(2,34) = 1.91$, $p > 0.15$). To assess negative priming, we contrasted reaction times to ignore probes with control probes. This test revealed a significant effect of negative priming ($t(17) = 1.76$, $p < 0.05$, one-tailed, 32ms). That we did not see a more robust effect is likely due to the small number of ignore probes (9 per subject).

6.2.2 Neural Results

6.2.2.1 Attentional Control

Previous work has suggested that a network of frontal and parietal regions underlies attentional control (Corbetta and Shulman, 2002; Desimone and Duncan, 1995; Kastner and Ungerleider, 2000; Posner and Peterson, 1990, Yantis and Serences, 2003). We reasoned that attentional control would be strongest when subjects filtered out distracting words, and weaker when subjects filtered out pound signs or were presented with no distracting information. To identify regions of attentional control, we therefore contrasted neural responses when subjects ignored distracting words versus distracting pound signs or no distraction. As predicted, this contrast produced robust activation differences in several frontal and parietal regions (see Table 6.1 for complete results). To provide stronger evidence that these regions were involved in attentional control, we examined whether activation in these regions was predicted by behavioral measures of attentional control. For each subject, we calculated an index of attentional control from his/her encoding keypress latencies. We contrasted the

latency to encode target words among distracting words versus the latency to encode target words among distracting pound signs or no distraction. This behavioral measure of attentional control predicted activation in bilateral SPL, left inferior parietal lobule, and bilateral precuneus (all $r > 0.55$, $p < 0.05$; Figure 6.2; Table 6.2). All of these correlations remained significant after robust regression, demonstrating that the correlations were not a result of high-leverage outliers. Hence, attentional control processes, as measured by neural activation and its relation to behavior, appear to be subserved by posterior parietal cortex.

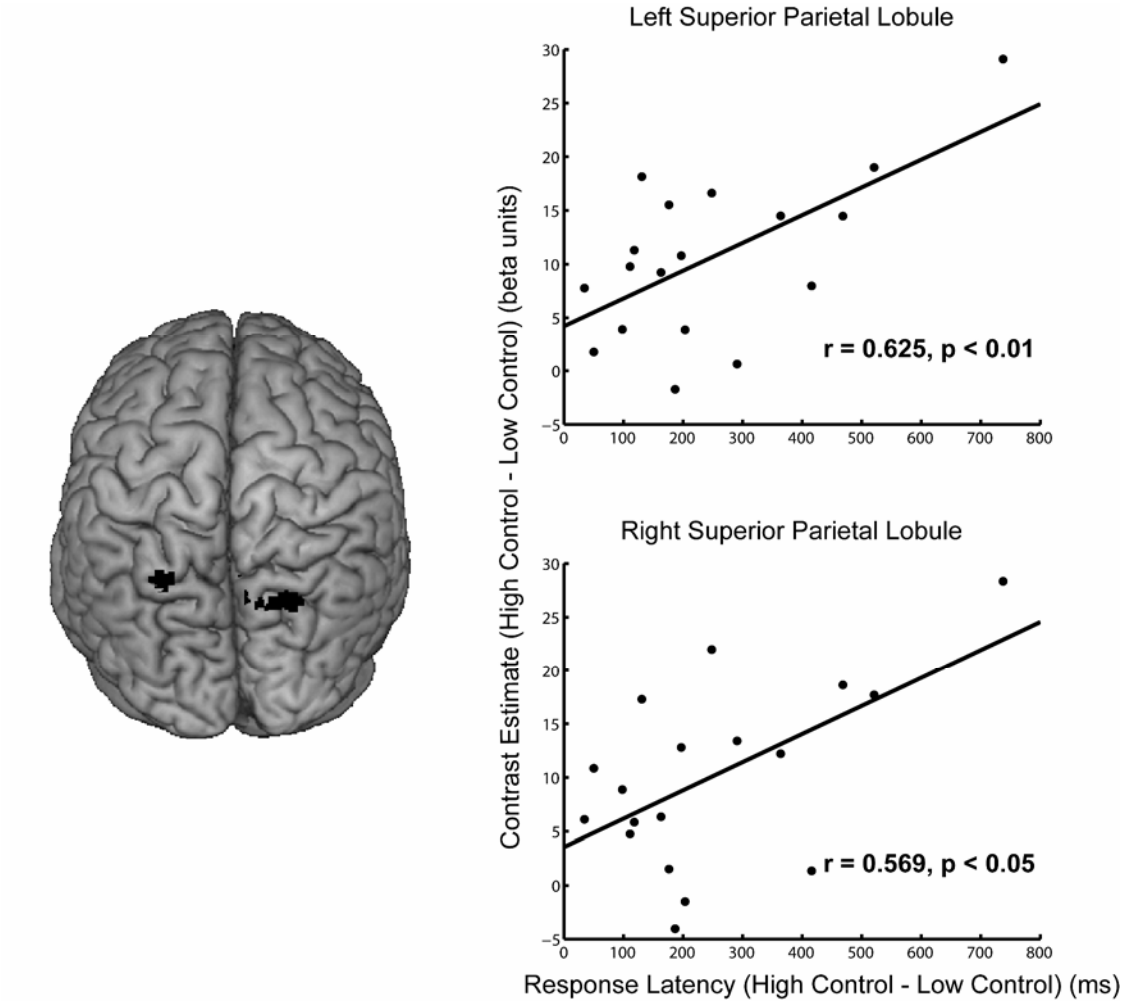

Figure 6.2. Parietal Control Regions. Parietal regions demonstrating significant activation increases to heightened demands on attentional control and significant correlations with behavior measures of attentional control. High-control corresponds to the word-distraction condition, and low-control is a composite of the pound-distraction and no-distraction conditions.

6.2.2.2 Visual Suppression

Previous research has demonstrated that when attention is drawn to target information, activation related to nearby distractors is reduced relative to passive viewing (Muller and Ebeling, 2008; Muller and Kleinschmidt, 2004; Nee and Jonides, in press; Tootell et al., 1998). This attentionally-driven reduction appears to depend upon the presence of distracting information, since reductions are not seen in nearby locations that are empty (Muller and Ebeling, 2008). We hypothesized that suppression of distractors may mediate negative priming. To test this proposal, we looked for regions in occipital cortex that showed reduced responsiveness when distractors (words or pound signs) were present versus when no distraction was present. This analysis revealed bilateral reductions in occipital cortex, in and inferior to the calcarine sulcus (Figure 6.3a; Table 6.3) when distractors were present versus absent. Comparisons with a probabilistic atlas (Amunts et al., 2000) revealed that the peaks of these regions were likely to be in V1 (see supporting online material), and that they extended inferiorly into at least V2. The left peak was in the vicinity of the region that we previously documented as correlating with negative priming (Nee and Jonides, in press).

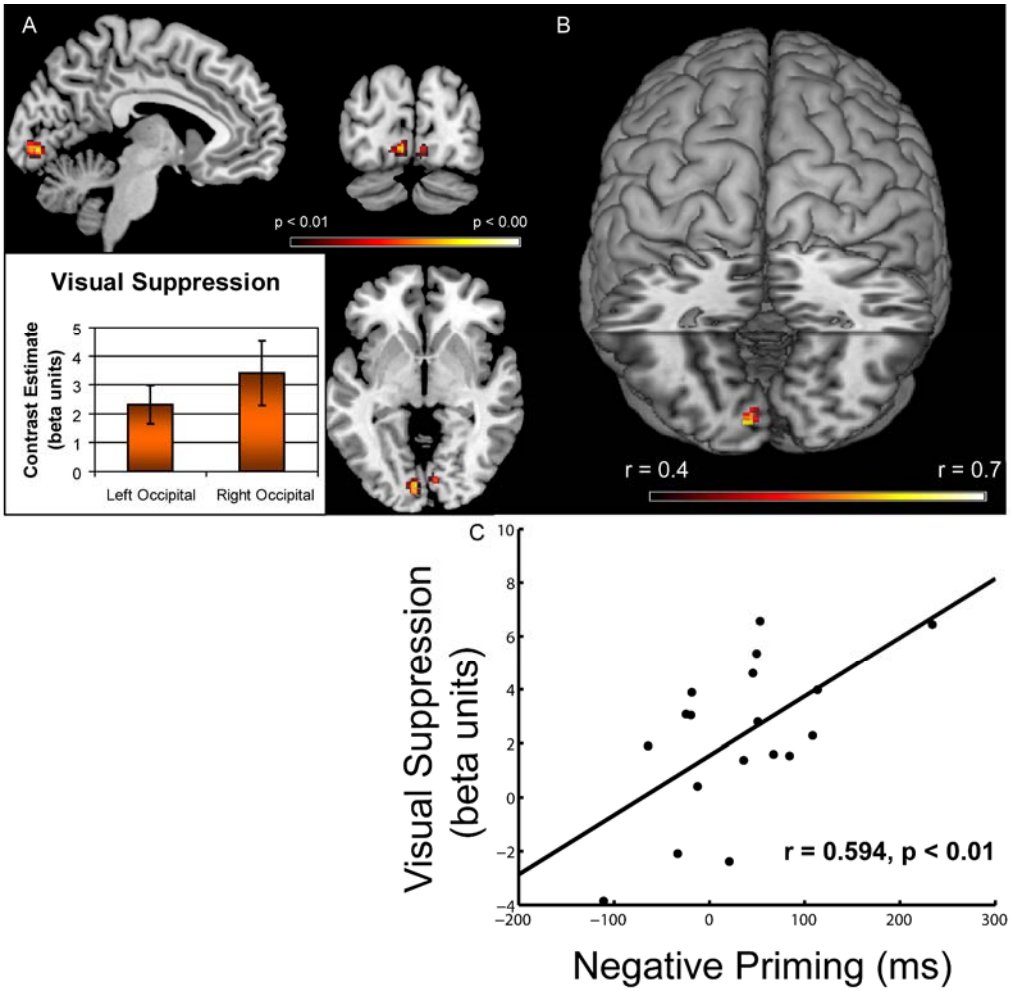

Figure 6.3. Occipital Visual Suppression and Inhibition. Occipital regions demonstrating visual suppression effects. A) Reductions in bilateral occipital cortex when no distractors were present compared to when distractors were present. B) Renderings of voxels demonstrating correlations between visual suppression and negative priming. C) Scatterplot of the correlation between left occipital cortex and negative priming, pooled across the 29 most significant voxels.

This result suggests that distractor-related reductions in early visual cortex are related to slowed responding when a distractor has to be encoded once again. To test this claim, we examined whether subjects who showed greater distractor-related reductions in visual cortex demonstrated heightened negative priming (i.e. more inhibition). Left occipital cortex reflected this prediction; behavioral indices of negative priming showed a significant correlation with activation reductions in left occipital cortex (averaged over the 29 most significant voxels: $r = 0.59$, $p < 0.01$; Figure 6.3b,c). This correlation remained significant after robust regression; it was not due to outliers. Hence, visual suppression predicted the amount of negative priming produced 11-15 seconds later. The combination of this result with our previous work strongly suggests that visual representations of individual distracting words are inhibited, and the amount of inhibition predicts later slowing when these words need to be re-encoded.

6.2.2.3 Parietal-Occipital Interactions

Research on attentional-modulation of early visual cortex has for the most part focused on activations in visual cortex itself. Although it is assumed that variations in visual cortex are a product of top-down attentional signals in frontal/parietal regions, little work has demonstrated explicit correlations between top-down signals and their occipital influences. To explore this matter, we examined whether the amount of visual suppression observed in occipital cortex could be linked to parietal regions that correlated with attentional control. To this end, we looked for parietal regions that showed an inverse relationship with

visual suppression in the occipital region described above. That is, greater attentional control should be related to greater visual suppression. This relationship was found in the left SPL ($r = -0.54$, $p < 0.05$; Figure 6.4). Subjects who showed greater activation in the left SPL when distraction was present showed greater suppression in left occipital cortex. Although the correlational data do not permit causal conclusions, the idea that the SPL provides a top-down attentional signal to visual regions is consistent with previous proposals (Corbetta and Shulman, 2002; Desimone and Duncan, 1995; Kastner and Ungerleider, 2000; Posner and Peterson, 1990, Yantis and Serences, 2003).

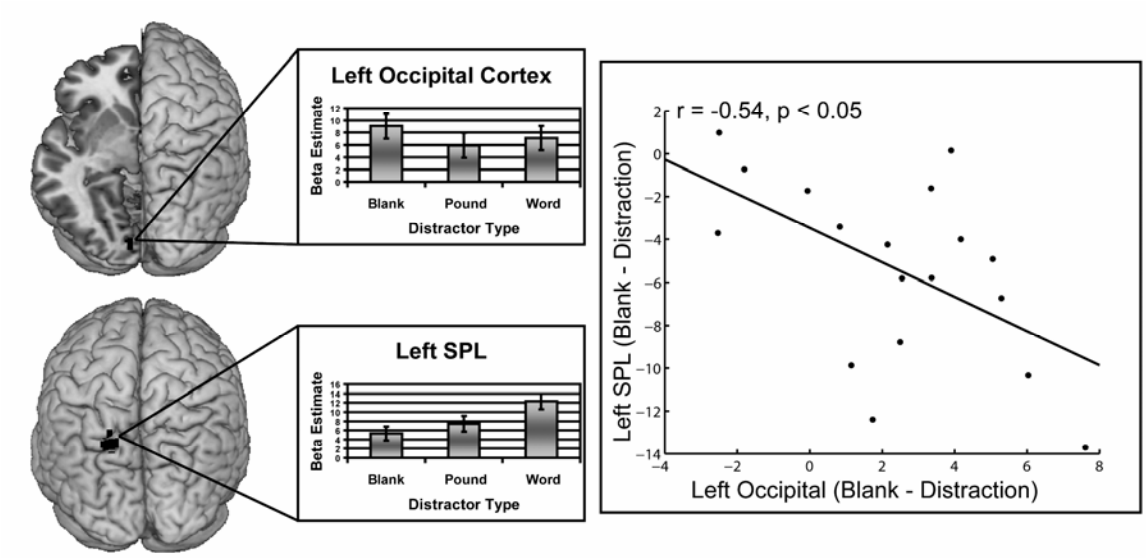

Figure 6.4. Parietal-Occipital Interactions. Shaded portions denote cortical regions showing visual suppression (top left) and attentional control (bottom left). The scatterplot (right) demonstrates that left occipital cortex and left superior parietal lobule show an inverse relationship; greater control is associated with greater visual suppression. SPL = superior parietal lobule.

6.3 Discussion

Our results suggest that top-down influences from posterior parietal cortex can cause visual suppression of distractors. Visual suppression appears to produce an inhibitory effect on specific object representations (individual words), making it difficult to revisit ignored information. Negative priming was assessed after a retention interval of 11-15 seconds, indicating that inhibitory influences on visual representations can persist for several seconds. Such persistent inhibition is beneficial because it reduces the impact of recurrent perceptual distraction. Deficiencies in this ability may lead to cognitive declines such as those observed in clinical populations (Joorman, 2005; MacQueen et al., 2003; Nigg, 2001) and the elderly (Hasher et al., 1999).

Interestingly, we observed attentional-modulation in early visual cortex, which according to a probabilistic atlas (Amunts et al., 2000), likely corresponded to V1. Although initial studies of primates (Moran and Desimone, 1985) and humans (Kastner et al., 1999) failed to find modulations of V1, there have been other demonstrations that V1 can be modulated in both primates (McAdams and Reid, 2005; Motter, 1993; Roelfsema et al., 1998) and humans (Martinez et al., 1999; Muller and Ebeling, 2008; Muller and Kleinschmidt, 2004; Tootell et al., 1998), and attentional-modulation can even occur in earlier visual structures such as the lateral geniculate nucleus (O'Connor et al., 2002). V1 modulations are presumed to reflect a feedback influence from top-down regions that exert control sometime after initial input, rather than an attentional modulation at the time of initial input

(Martinez et al., 1999; Pessoa et al., 2003; but see Kelly et al., 2008 for presumably earlier modulation). Our results suggest that posterior parietal cortex may be the source of this feedback signal. Although the pathway by which posterior parietal cortex could exert an influence on V1 is unclear, recent reviews suggest that the pathway may involve the superior colliculus and/or the pulvinar nucleus of the thalamus (Kastner et al., 2004; Moore, 2006). Our imaging methods were too coarse to map these regions, but closer examination of these regions would be an interesting avenue for future research.

When visual suppression has been demonstrated, it has been accompanied by enhancements in portions of visual cortex where attention is drawn (Muller and Ebeling, 2008; Muller and Kleinschmidt, 2004; Tootell et al., 1998). For instance, Muller and Ebeling (2008) demonstrated that in contrast to visual suppression seen in ignored peripheral locations, attention produced enhancements in the occipital pole which presumably reflected foveal target processing. Similar to these results, we saw enhancements at occipital polar locations which demonstrated patterns opposite to those seen in locations corresponding to the periphery (Figure 6.5). Hence, these results suggest that in the face of distraction, attention is enhanced at relevant locations (here, the fovea) and dampened at irrelevant locations (here, the periphery). Although we did not perform precise retinotopic mapping, the occipital locations we see here correspond well with previously published reports (Muller and Ebeling, 2008; Muller and Kleinschmidt, 2004; Tootell et al., 1998).

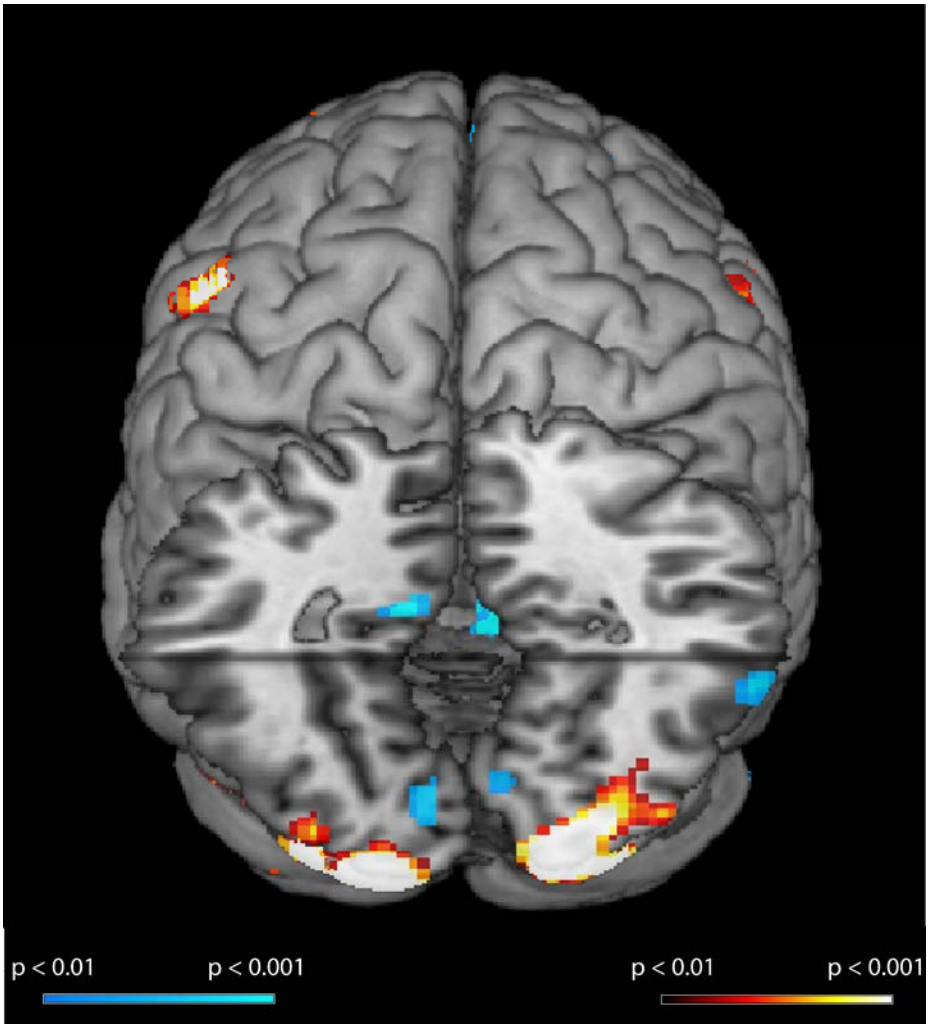

Figure 6.5. Enhancement and Suppression. Regions showing attentional enhancement (distraction > no-distraction; hot colors) and suppression (no-distraction > distraction; cool colors). Enhancement effects are seen at polar regions of occipital cortex that likely correspond to the fovea, whereas suppression effects are seen in more anterior portions that likely correspond to the periphery.

There has been an increasing interest in frontal influences on selective attention with the idea that frontal regions may also be a source of top-down control for

visual regions (Egner and Hirsch, 2005; Gazzaley et al., 2007). Recent work has suggested that dorsolateral prefrontal cortex (DLPFC) may influence extra-striate regions to enhance relevant inputs and/or filter out irrelevant inputs (Desimone and Duncan, 1995; Egner and Hirsch, 2005; Gazzaley et al., 2007; Kastner and Ungerleider, 2000). Although we did find bilateral recruitment of DLPFC with increased attention demands, these regions did not correlate with our behavioral assays of attentional control, and these regions were small in extent compared to the observed posterior parietal and FEF regions. It may be that modulations of extra-striate cortex may depend upon frontal interactions, whereas modulations of striate cortex and earlier stages of visual processing may depend more critically upon posterior parietal regions. This speculation would be testable by comparisons of frontal and parietal regions and their presumed modulatory targets.

6.4 Conclusion

We have provided evidence that distracting information can be suppressed in early visual cortex, and that this suppression can have a lasting inhibitory effect on specific object representations. Early visual suppression appears to be modulated by attentional processes lodged in posterior parietal cortex. Our results suggest that attention is not merely a spotlight that enhances relevant information, but that this spotlight also casts a shadow to filter out distracting information. This shadow creates an inhibitory effect on specific representations that may protect the cognitive system from distraction.

Table 6.1 - Neural Correlates of Attentional Control

Region	X	Y	Z	Voxels	T-value	BA
Frontal						
left frontal eye fields	-28	4	56	684	8.08	6
left premotor cortex	-42	-4	44		6.65	6
left premotor cortex	-48	0	56		5.52	6
left dorsolateral prefrontal cortex	-46	30	30	60	5.62	9/46
right frontal eye fields	14	0	68	843	5.28	6
right premotor cortex	48	4	38		5.2	6/9
right frontal eye fields	24	-2	52		5.19	6
anterior cingulate cortex/medial prefrontal cortex	4	20	44	213	5.16	32/8
right dorsolateral prefrontal cortex	42	46	26	33	3.96	10
right dorsolateral prefrontal cortex	34	46	24		3.87	10
Parietal						
right inferior parietal lobule	52	-48	26	147	9.08	40
right temporo-parietal junction	58	-48	8		3.81	40/22
left superior parietal lobule	-26	-66	56	1085	6.87	7
left superior parietal lobule	-14	-66	54		6.4	7
left posterior intraparietal sulcus	-32	-84	26		5.58	7/19
right superior parietal lobule	22	-66	58	955	4.65	7
right intraparietal sulcus	34	-52	46		4.6	7/40
right superior parietal lobule	26	-60	54		4.21	7
Temporal						
right middle temporal gyrus	50	-34	2	85	4.15	22/21
right middle temporal gyrus	56	-44	2		3.12	22/21
left middle temporal gyrus	-52	-36	0	35	4.82	22
left superior temporal gyrus	-60	-52	4	31	4.19	21/22
Occipital						
right occipital pole	20	-100	-8	72	5.02	17/18
right occipital pole	28	-98	-14		3.89	18
left occipital pole	-16	-102	-6	96	4.88	17/18
left occipital pole	-20	-96	-12		4.11	18
Other						
right thalamus	6	-8	0	57	4.04	

right cerebellum	18	-82	-30	43	4.84
right cerebellum	26	-74	-32		3.71
putamen	20	-14	-14	56	4.42
putamen	18	-2	16		4.19

Table 6.1. Neural Correlates of Attentional Control. Regions demonstrating increased activation for word-distraction versus pound-distraction and no-distraction conditions. Results were thresholded $p < 0.001$ with 20 or more contiguous voxels. Coordinates are reported in Montreal Neurological Institute (MNI) space. BA = Brodmann Area.

Table 6.2 - Neural and Behavioral Correlates of Attentional Control

Region	X	Y	Z	Voxels	r	p
left superior parietal lobule	-28	-66	60	25	0.625	< 0.01
left inferior parietal lobule	34	-50	48	26	0.64	< 0.01
right superior parietal lobule	20	-72	52	73	0.569	< 0.05
right precuneus	8	-64	52	30	0.635	< 0.01

Table 6.2. Neural and Behavioral Correlates of Attentional Control. Regions demonstrating significant activation increases to attentional control (word-distraction > pound-distraction and no-distraction, $p < 0.001$) and significant correlations with behavioral indices measuring attentional control ($p < 0.05$). Coordinates are reported in Montreal Neurological Institute (MNI) space.

Table 6.3 - Neural Correlates of Visual Suppression

Region	X	Y	Z	Voxels	T-value	BA
right calcarine sulcus/ lingual gyrus	-4	-92	0	94	3.36	17/18
right lingual gyrus	8	-82	-4	43	3.06	18
right cuneus	20	-90	24	39	3.66	18/19
left middle occipital gyrus	-30	-82	2	28	2.63	18/19
right lingual gyrus	22	-72	-6	23	3.15	18/19

Table 6.3. Neural Correlates of Visual Suppression. Regions demonstrating significant visual suppression to distractors (no-distraction > distraction). Results are thresholded at $p < 0.01$ with 20 or more contiguous voxels. Coordinates are reported in Montreal Neurological Institute (MNI) space. BA = Brodmann Area.

Chapter 7

Common and Distinct Neural Correlates of Perceptual and Memorial Selection

In order to function efficiently, the cognitive system must choose to represent information that is relevant to current goals. When salient distracting information is present, control processes are elicited to select relevant information and/or de-select irrelevant information. Models of cognitive control posit that regions of prefrontal cortex (PFC) and posterior parietal cortex (PPC) play a critical role in selecting among competing representations (Deco and Rolls, 2005; Desimone and Duncan, 1995; Gazzaley and D'Esposito, 2007; Kastner and Ungerleider, 2000; Miller and Cohen, 2001). Fronto-parietal regions are thought to provide top-down signals that bias the cognitive system to represent only relevant information. Under this framework, fronto-parietal regions are presumed to operate upon several levels of representation including percepts, memories, and responses.

In particular, several proposals suggest that processes of selective attention and working memory are closely linked (Awh and Jonides, 2001; Deco and Rolls, 2005; Desimone and Duncan, 1995; Kastner and Ungerleider, 2000; Lavie, 2005;

Miller and Cohen, 2001; Gazzeley and D'Esposito, 2007). That is, the same prefrontal and parietal regions involved in maintaining an outward focus on relevant stimuli may also be recruited to maintain an inward focus on relevant thoughts. These ideas are bolstered by demonstrations that maintaining information in working memory causes decrements in the ability to filter out distracting perceptual information (de Fockert et al., 2001; Lavie, 2005; Lavie et al., 2004), consistent with the idea that working memory and selective attention draw upon the same resources. Furthering the notion that selective attention and working memory are interrelated, subjects who have relatively large working memory spans tend to perform better on selective attention tasks than subjects with relatively low spans (Engle et al., 1999; Kane et al., 2001). Research with nonhuman primates has shown that both selective attention and working memory produce similar modulations of inferior temporal regions thought to maintain object representations (Chelazzi et al., 1993; 1998). These modulations are presumed to originate from frontal and parietal regions (Fuster et al., 1985). Finally, lesions of the PFC cause high distractability, impairing both attention (Heilman and Valenstein, 1972; Damasio et al., 1980) and working memory (Mishkin, 1957; D'Esposito and Postle, 1999); similarly, lesions of parietal cortex cause attentional deficits in processing of external stimuli and internal memories (Bisiach and Luzzati, 1978; Bisiach et al., 1979).

Drawing upon hypothesized commonalities, several studies have explored overlapping neural correlates of attention and memory within the same subjects

(Corbetta et al., 2002; Labar et al., 1999; Mayer et al., 2007; Nobre et al., 2004; Pollmann and von Cramon, 2000). These studies have all documented overlapping activations for attention and working memory in the frontal eye fields (FEF), premotor cortex, and PPC most often in the intraparietal sulcus (IPS) and superior parietal lobule (SPL). The large amount of overlap suggests that the same processes that support attention to the outside world also direct attention internally to memorial representations (Lepsien and Nobre, 2006; Nobre et al., 2004). Notably absent from these studies, however, are overlapping activations in more anterior regions of PFC (anterior lateral PFC) presumed to be involved in cognitive control, such as dorsolateral prefrontal cortex (DLPFC) in Brodmann Areas (BA) 9 and 46, and ventrolateral prefrontal cortex (VLPFC) in BA 44 and 45 (Smith and Jonides, 1999). In several of these studies, regions in anterior lateral PFC were involved in memory, but not attention (Labar et al., 1999; Pollmann and von Cramon, 2000; Nobre et al., 2004; Mayer et al., 2007).

One reason for this dissociation may have to do with demands elicited by the attention tasks. In the aforementioned studies, the tasks used to examine attention investigated processes involved in either maintaining attention on a particular location or searching for a target in a visual array. Such tasks place a relatively low demand on selective attention processes that filter out visual distraction. By contrast, selective attention tasks that require the filtering of distraction are known to robustly recruit regions of anterior lateral PFC (Nee et al., 2007b). A similar filtering function has been proposed to protect working

memory representations, especially when demands on control are increased (Smith and Jonides, 1999; D'Esposito and Postle, 1999; Jonides et al., 2005; Ranganath et al., 2006). Therefore, there may be similar anterior lateral PFC recruitment when selection processes need to maintain relevant information in the face of irrelevant distracting information.

Despite hypothesized similarities, we are unaware of any study that has directly compared processes of selective attention and working memory in the same subjects. Direct comparisons are critical for understanding the extent to which selective attention and working memory are truly similar functions. For instance, although it is well-established that there is activation in PFC for both selective attention and working memory tasks, it is less well-established that the same subregions of the PFC are responsible for the two processes. Investigating this matter can provide critical data for understanding the functions of different regions of PFC. Similarly, research into PPC has suggested differentiable roles for subregions of the PPC in attention (Corbetta and Shulman, 2002; Yantis and Serences, 2003) and memory (Wagner et al., 2005), and understanding which of these subregions contribute commonly or uniquely to attention and memory would further our understanding of computations in the PPC.

In addition to investigating neural overlap, it is also critical to relate neural data to behavioral measures in order to directly demonstrate relationships between brain and behavior. That is, even if a region appears to be involved in both selective

attention and working memory, that region may play a very different role in each (Rowe et al., 2005). Relating brain data to behavioral data may uncover these relationships and further our understanding of the neural regions subserving selective attention and working memory.

Here, we compared selection processes operating upon percepts and memories. To do so, we adapted an item-recognition paradigm that forced subjects either to filter out irrelevant perceptual information or to expel irrelevant memorial information from working memory. Perceptual and memorial selection were assessed in the same subjects to allow for careful comparisons between these processes. If top-down processes of selection are common between perceptual and memorial selection, we would expect to see similar recruitment of frontal and parietal control regions. However, if distinct selection functions operate in perception and memory, we should see regions that are engaged by one form of selection but not the other. For all analyses, we examined the relation between neural activation and behavioral assays of selection in order to provide strong evidence that neural regions were closely related to behavioral phenomena of interest.

Subjects alternated between runs of the perceptual selection task and memorial selection task (Figure 7.1; also see Nee and Jonides, submitted, for another description of the perceptual selection task). In both tasks, subjects committed a set of words (target set) to memory and responded to recognition probes that

queried the target set several seconds later. In the perceptual selection task, subjects encoded three relevant words from a visual display while filtering out three distracting words (word-distraction), three distracting strings of pound signs (pound-distraction), or no distraction (no-distraction). Relevant words were printed in one color (blue or teal), with irrelevant words printed in an alternate color (blue if the relevant words were teal; teal if the relevant words were blue). A cue on each trial alerted subjects which words they would have to encode. Subjects were instructed to read the three relevant words subvocally and make a keypress after doing so, providing a behavioral measure of the duration and difficulty of perceptual selection processes.

In the memorial selection task, subjects saw the same three types of displays, except that subjects were instructed to encode and remember all printed words. Hence, subjects encoded either six or three words. Several seconds after encoding, subjects received a cue that told them to update memory if they had encoded six words (update) or subvocally rehearse if they had encoded three words (rehearse). Update cues informed subjects to retain three words in memory and discard the other three words from memory. Update cues were phrased in a manner that instructed subjects either to remember words of a given color (e.g. “REMEM TEAL”, remember cue) or to forget words of a given color (e.g. “FORGET BLUE”, forget cue). Both remember and forget cues left subjects with three words in memory and were functionally equivalent. On update trials, subjects were instructed to update memory and then subvocally rehearse the

three relevant words once and make a keypress after doing so. On rehearse trials, subjects were instructed to rehearse the three words in memory once and make a keypress after doing so. Contrasting keypress latencies following update and rehearse trials provided a behavioral measure of memorial selection.

Successful selection was examined behaviorally by responses to recognition probes (Nee and Jonides, in press). Recognition probes queried relevant words (positive probes), words that had not appeared and therefore required a negative response (control probes), or words that had been ignored (ignore probes) or discarded from memory (forget probes). Both ignore and forget probes demanded a negative response. Hence, comparing responses to ignore and forget probes with responses to control probes provides a measure of successful selection. In previous reports, forget probes have induced slowed and less accurate responses compared to control probes, presumably due to effects of proactive interference (Zhang et al., 2003; Jonides and Nee, 2006; Nee and Jonides, in press). Increased effects of proactive interference are likely to be related to poorer memorial selection. Examinations of ignore probes have been explored elsewhere (Nee and Jonides, in press; Nee and Jonides, submitted), and will not be further examined here.

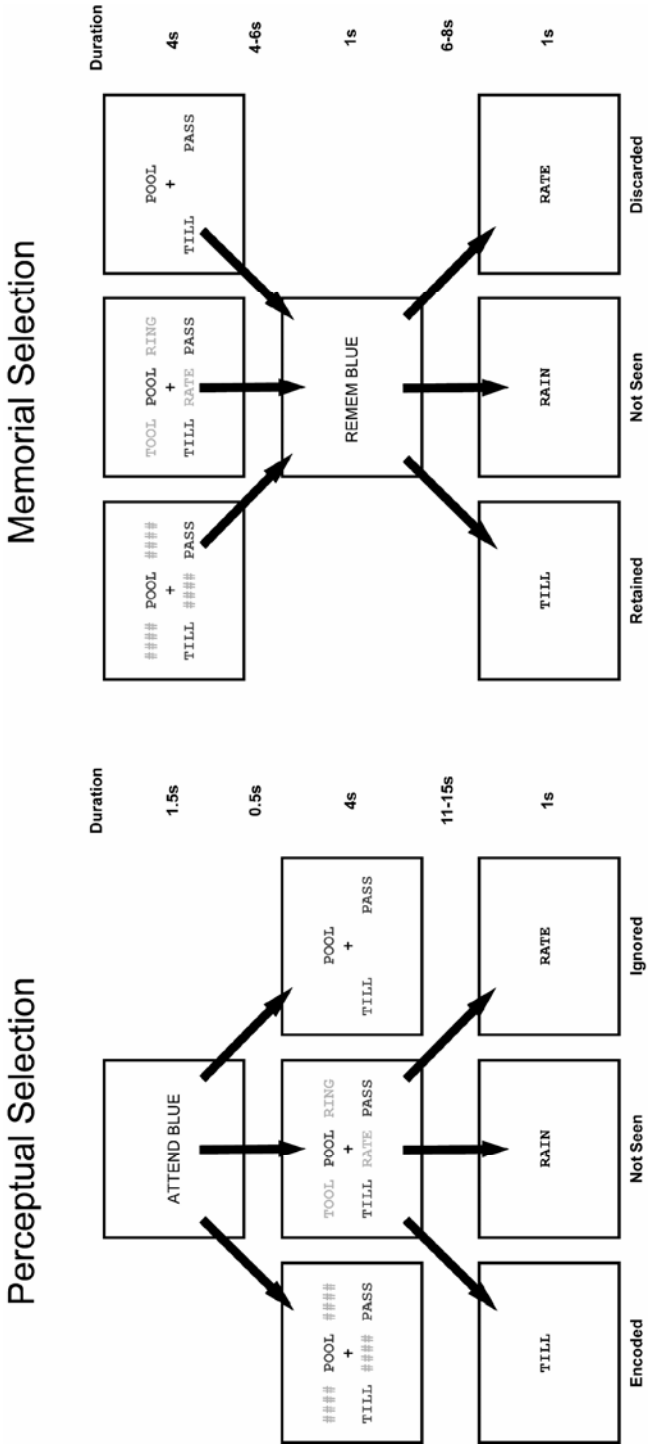

Figure 7.1. Experimental protocol. In the perceptual selection task (left), subjects committed a set of three target words to memory while filtering out distracting words (word-distraction), pound signs (pound-distraction), or with no

distraction present (no-distraction). In the memorial selection task (right), subjects committed all available words to memory and were later told to either update memory to reduce their memory load to three (update), or rehearse the three words already in memory (rehearse). At the end of each trial, subjects were probed to verify that selection was done appropriately. Neural activation of interest was locked to the onset of the target display for the perceptual selection task, and to the onset of the memory cue in the memorial selection task. Words printed in light gray appeared in teal, and words printed in dark gray appeared in blue. All other characters were presented in black.

7.1 Methods

7.1.1 Participants

Eighteen right-handed adults (8 female; ages 19-25) participated in this study. All subjects had normal or corrected-to-normal vision and had no reported illnesses. Subjects were compensated $20/hr plus a bonus for fast and accurate performance. Two runs from one subject were excluded from analysis due to her difficulty with task instructions, and one run was excluded from another subject due to problems with the visual setup.

7.1.2 Materials and Procedure

Description of materials and the perceptual selection task are provided elsewhere (Nee and Jonides, submitted). Words were drawn from a list of 100 four-letter nouns. Words were drawn randomly for each trial with the exception

that words could not have been presented in the previous 2 trials in order to control for potential effects of proactive interference. All responses were recorded on a 10-button response unit that accompanied the IFIS 9.0 system (MRI Devices Corp., Latham, NY) with one button for each finger. Stimuli were presented via a projector at the back of the scanner, reflected off a mirror placed above the head of the subject. Experimental tasks were presented using E-Prime software (Psychology Software Tools, Inc., Pittsburgh, PA).

During the perceptual selection task each trial began with a red fixation cross presented for 1 second to alert the subject that the trial was beginning. Thereafter, an attention cue ("ATTEND BLUE", "ATTEND TEAL", "IGNORE BLUE", or "IGNORE TEAL") was presented for 1.5 seconds that informed the subject of the color of the relevant stimuli. On half of the trials the words printed in blue were made relevant and on the other half the words printed in teal were made relevant. Three-fourths of the cues involved "attend" instructions, with the other one-fourth involving "ignore" instructions. We collapsed across different cue instructions and "ignore" instructions were used only to parallel the memorial selection task. "Attend" and "ignore" instructions did not produce appreciably different results.

The attention cue was followed by 0.5 seconds of fixation, followed by the target display. The target display consisted of three words presented in the relevant color in a "V" or upside-down "V" shape. On one-half of the trials, three distractor

words (word-distraction) were presented in the alternate color (blue if the relevant words were teal, teal if the relevant words were blue). On one-fourth of the trials, a string of four pound signs was used in place of distracting words (pound-distraction) and on the other one-fourth of the trials, no distracting information appeared (no-distraction). All of the stimuli considered together subtended approximately 9.7 degrees of visual angle horizontally, and approximately 3.5 degrees vertically. Each word or string of pound signs subtended approximately 2.6 degrees of visual angle horizontally, and 0.88 degrees vertically. Stimuli were separated by 0.88 degrees horizontally, and 1.76 degrees vertically.

Subjects were instructed to read the three relevant words subvocally once and make a left thumb press after doing so. Subjects were told to maintain the relevant words in memory. The target display was presented for 4 seconds, and subjects were instructed to stare at the fixation cross and to continue to attend to relevant words and ignore irrelevant information when they had completed encoding the relevant words.

A fixation interval of 4 to 6 seconds followed the target display, varied in equal steps of 1 second. Thereafter, a cue (memory cue) appeared instructing subjects to rehearse the relevant words once and make a left thumb press after doing so. The cue stated “REMEM BLUE” or “REMEM TEAL” (always the relevant color), or “REMEM ALL” and paralleled the memorial selection task. All memory cues in the perceptual selection task were functionally equivalent in that they all required

a simple rehearsal of the three words in memory. The cue was followed by a 6 to 8-second fixation interval, varied in equal steps of 1 second. Finally, a recognition probe was presented for 1 second, followed by an inter-trial interval of 3 to 5 seconds, varied in equal steps of 1 second. Subjects responded with a right index press if the probe matched one of the three words held in memory (positive probe), and they made a left index press otherwise (negative probe). One-half of the probes were positive probes and one-half were negative probes. Three-quarters of the negative probes were words that had not appeared for the last 2 trials (control probes) and one-quarter were probes that matched a word that had appeared as a distractor on the target display (ignore probes). The asymmetry of the number of ignore probes is due to the fact that ignore probes could only follow the word-distraction condition. Within the word-distraction condition, control and ignore probes were equally distributed. All combinations of cue and probe were randomly intermixed.

The memorial selection task was nearly identical to the perceptual selection task and we describe only the differences here. In the memorial selection task, the attention cue stated either “ATTEND BLUE”, “ATTEND TEAL”, or “ATTEND ALL”. Following “ATTEND BLUE” and “ATTEND TEAL” instructions, three words were presented in the relevant color, and the three other positions were either unfilled or filled with strings of pound signs so that no competing word stimuli were present (initial memory load three). Following “ATTEND ALL” instructions, six words were presented, three printed in blue and three printed in teal, and

subjects were instructed to encode and remember all six words (initial memory load six). After encoding relevant words, subjects made a left thumb press, as in the perceptual selection task.

In the memorial selection task, memory cues told subjects to either remember words of a relevant color (e.g. “REMEM BLUE”; remember cue) or forget words of an irrelevant color (e.g. “FORGET TEAL”; forget cue). The classification of cue depended upon the information held in memory. Rehearse cues followed initial memory loads of three and always instructed subjects to remember words of the relevant color. Subjects were instructed to rehearse the three words in memory once and make a left thumb press after doing so. Update cues followed initial memory loads of six and instructed subjects to select the three relevant words from their memory set, rehearse those three words, and make a left thumb press after doing so. Hence, the critical difference between rehearse and update cues was the need to perform memorial selection to the latter. Half of the update cues instructed subjects to remember words of the relevant color, and the other half instructed subjects to forget words of the irrelevant color. Both cues were functionally equivalent in that they left subjects with the three relevant words in memory. However, we hypothesized that forget cues placed a greater demand on memorial selection processes due to the stimulus-memory incompatibility inherent in these cues. In other words, forget cues lead subjects to the irrelevant information, much as stimulus-response incompatible stimuli lead subjects to an inappropriate response. Just as stimulus-response incompatibilities place larger

demands on response-selection processes (Fitts and Seeger, 1953), we hypothesized that stimulus-memory incompatibilities would place greater demands on memorial selection processes.

Subjects alternated between runs of the perceptual selection task and memorial selection task, with order counterbalanced between subjects. For each task, subjects performed four runs of 18 trials each, for a total of 72 trials. The day prior to scanning, subjects performed two runs of each task with accuracy and latency feedback. On the day of scanning, subjects performed an additional run of practice for each task also with feedback. Feedback was not given during scanning, but average accuracy and reaction times were presented during rest breaks between scans so that subjects could monitor their performance.

7.1.3 Image Acquisition and Preprocessing

Images were acquired on a GE Signa 3-T scanner equipped with a standard quadrature head coil. Head movement was minimized using foam padding and a cloth restraint strapped across participants' foreheads.

Functional T2*-weighted images were acquired using a spiral sequence with 40 contiguous slices with 3.44 × 3.44 × 3 mm voxels (repetition time, or TR = 2,000 ms; echo time, or TE = 30 ms; flip angle = 90°; field of view, or FOV = 22 mm^2). A T1-weighted gradient-echo anatomical overlay was acquired using the same FOV and slices (TR = 250 ms, TE = 5.7 ms, flip angle = 90°). Additionally, a 124-

slice high-resolution T1-weighted anatomical image was collected using spoiled-gradient-recalled acquisition (SPGR) in steady-state imaging (TR = 9 ms, TE = 1.8 ms, flip angle = 15°, FOV = 25-26 mm^2, slice thickness = 1.2 mm).

Each SPGR anatomical image was corrected for signal inhomogeneity and skull-stripped using FSL's Brain Extraction Tool (Smith et al., 2004). These images were then normalized to the Montreal Neurological Institute (MNI) template using SPM2 (Wellcome Department of Cognitive Neurology, London). Functional images were corrected for differences in slice timing using 4-point sinc interpolation (Oppenheim et al., 1999) and were corrected for head movement using MCFLIRT (Jenkinson et al., 2002). To reduce the impact of spike artifacts, we winsorized functional images on a voxel-by-voxel basis so that no voxel had a signal greater than 3.5 standard deviations from the mean of the run (Lazar et al., 2001). Spatial normalization transformations and 8-mm full-width/half-maximum isotropic Gaussian smoothing were applied to all functional images prior to analysis using SPM2. All analyses included a temporal high-pass filter (128 s), and each image was scaled to have a global mean intensity of 100.

7.1.4 Image Analysis

Analyses were conducted using the General Linear Model implemented in SPM2. Predictors of interest were locked to the onsets of the target display and memory cue and were convolved with a canonical hemodynamic response function provided by SPM2. Additional predictors were used to model the probe, which

were not involved in the present analyses. To account for artifacts produced by head motion, we calculated linear, quadratic, differential, and quadratic differential motion regressors from the realignment parameters and included these regressors in the model (Lund et al., 2005). Trials in which subjects failed to make a keypress to the target set or rehearsal cue and/or trials in which subjects responded incorrectly to the recognition probe were excluded (less than 9% of the trials).

For perceptual selection, separate regressors were calculated for word-distraction, pound-distraction, and no-distraction. Selection-related activation for word-distraction was considered high selection, and pound-distraction and no-distraction were collapsed into low selection. For memorial selection, separate regressors were calculated for update cues (high selection) and rehearse cues (low selection). Update cues were also divided into remember cues and forget cues for follow-up analyses.

For both perceptual and memorial selection, whole-brain analyses contrasted high and low selection and were thresholded at $p < 0.001$ with a cluster extent of at least 20 suprathreshold voxels (Forman et al., 1995; Poline et al., 1997). This threshold required a minimum t-statistic of 3.65, which was similar to the minimum t-statistic required by a multiple comparisons corrected threshold for the perceptual selection contrast (false discovery rate (FDR) minimum t-statistic of 3.87 for $p < 0.05$), and more conservative than the same threshold for the

memorial selection contrast (FDR minimum t-statistic of 2.97 for $p < 0.05$). We used an uncorrected threshold to hold the minimum t-statistic constant between contrasts.

For the conjunction analysis, perceptual and memorial selection contrasts were thresholded at $p < 0.01$, producing a conjoint threshold of $p < 0.0001$. Once again, we used a minimum cluster extent of 20 voxels.

We identified unique regions by a three-part criterion: 1) Significant activation for one contrast at $p < 0.001$; 2) Significantly more activation for one contrast than the other at $p < 0.01$; 3) No significant activation in the other contrast at $p < 0.01$. Once again, we used a minimum cluster extent of 20 voxels.

The examination of forget versus remember cues was restricted to regions significant in the memorial selection contrast at $p < 0.01$. Within these regions, we looked for voxels significantly more active for forget cues versus remember cues at $p < 0.05$, with a minimum cluster extent of 20 voxels. The reduced threshold was used due to the reduction in power of considering only half of the memorial selection trials.

Correlations between neural activation and behavior were restricted to voxels significant by the criterion above for each contrast of interest. Correlations are

reported only if they were significant at $p < 0.05$, and only if they were significant after robust regression to reduce the impact of outliers.

7.2 Results

7.2.1 Behavioral Results

7.2.1.1 Accuracy Data

We used a modified item-recognition task (Figure 7.1) to examine processes of perceptual and memorial selection. All trials in which subjects failed to make a keypress after encoding or after updating memory were excluded from behavioral analysis (less than 3% of the trials).

First, we assessed accuracy to recognition probes. Accuracy was high overall (> 94%), and significantly higher on the perceptual selection task (96.0%) than the memorial selection task (92.3%, $t(17) = 2.8$, $p < 0.05$). The high accuracies demonstrate that subjects performed the tasks appropriately. Follow up tests considered each task separately. In the memorial selection task, accuracy differed significantly by probe type (positive, control, forget; ($F(2,34) = 6.3$, $p < 0.01$). This was driven largely by reduced accuracy to forget probes (83.3%), which was significantly lower than accuracy to control probes (94.7%, $t(17) = 2.4$, $p < 0.05$) and positive probes (94.5%, $t(17) = 2.9$, $p < 0.05$). This is to be expected due to the high degree of proactive interference associated with forget probes (Jonides and Nee, 2006). There was also a significant effect of initial

memory load with higher accuracy to low initial load (96.7%) than high initial load (88%, $t(17) = 3.6$, $p < 0.01$). Although memory load was equivalent by the time subjects made recognition decisions (i.e., a load of three words), these load effects on accuracy may reflect differences during retention before the memory update, or difficulties with memory updating. No factors had an effect on accuracy in the perceptual selection task as previously reported (Nee and Jonides, submitted). For all subsequent analyses with latency data, trials in which subjects made an incorrect response to the recognition probe were excluded (< 6% of the trials).

7.2.1.2 Behavioral Measures of Memorial and Perceptual Selection

After encoding the target set (perceptual selection) or after updating and/or rehearsing the contents of working memory (memorial selection), subjects made a keypress to denote that selection processes were complete. These keypress data were entered into a 2-way ANOVA, with factors of selection demands (high or low) and selection type (perceptual or memorial) as factors. There were significant main effects of selection demands ($F(1,17) = 59.25$, $p < 0.001$) and selection type ($F(1,17) = 7.19$, $p < 0.05$). However, there was no interaction between selection demands and type ($F(1,17) < 1$). These results indicated that high selection demands led to slower keypress latencies than low selection demands, and that subjects took longer to perform perceptual selection than memorial selection. The lack of interaction between selection demands and type

suggests that selection demands were equivalently increased for high versus low selection in both perceptual and memorial selection tasks.

Follow up analyses examined keypress latencies for memorial selection alone. A planned t-test demonstrated that keypress latencies following update instructions were significantly longer than keypress latencies following rehearsal instructions (1211 ms vs. 919 ms, mean difference = 292 ms, $t(17) = 5.24$, $p < 0.001$). This difference provides an assay of the time it takes to perform the memory update function. Next, we examined whether updates following forget cues were significantly different from updates following remember cues. We predicted that forget cues would require increased memorial selection demands because forget cues lead the subject toward the irrelevant information, whereas remember cues lead the subject toward the relevant information. As such, forget cues have a stimulus-memory incompatibility that may mimic stimulus-response incompatibility effects (Fitts and Seeger, 1953). In line with this prediction, keypress latencies following forget cues were slowed relative to remember cues (mean difference = 51 ms, $t(17) = 1.81$, $p < 0.05$, one-tailed). These results suggest that memorial selection demands were enhanced for forget cues relative to remember cues. Behavioral results for perceptual selection are reported elsewhere (Nee and Jonides, submitted). Those data indicated that word-distraction led to slower keypress latencies than pound-distraction and no-distraction, but that pound-distraction and no-distraction did not differ.

7.2.1.3 Recognition Probe Data

Next, we examined reaction times to recognition probes. Reaction times were slower during the memorial selection task (723 ms) compared to the perceptual selection task (680 ms, $t(17) = 5.4$, $p < 0.001$). Follow up tests considered each task separately. In the memorial selection task, there was a significant effect of probe type on recognition latency ($F(2,34) = 41.3$, $p < 0.001$). This was largely driven by increased reaction times to forget probes (852 ms) compared to control probes (700 ms, $t(17) = 5.9$, $p < 0.001$) and positive probes (661 ms, $t(17) = 7.9$, $p < 0.001$). Once again, these differences are to be expected due to the high degree of proactive interference associated with forget probes (Jonides and Nee, 2006). There was also a significant effect of initial memory load with slower responses following initially high loads (752 ms) than low loads (669 ms, $t(17) = 6.8$, $p < 0.001$). Once again, although load was equivalent across all conditions by the time subjects made recognition decisions, increased latencies for initially high memory loads may reflect difficulties encountered during earlier processing. Latency data to recognition probes in the ignore task are reported elsewhere (Nee and Jonides, submitted) and demonstrated slowed latencies to ignore probes compared to control probes.

7.2.1.4 Behavioral Summary

To summarize, we found anticipated behavioral effects of selection demands during perceptual and memorial selection. Moreover, selection effects were carried out to subsequent memory probes, giving an assay of the success (or

lack thereof) of selection. High interference to forget probes demonstrated a large degree of proactive interference that carried over to recognition decisions, suggesting that memory updating processes failed to completely discard irrelevant memorial information (Nee and Jonides, 2006; Nee and Jonides, in press).

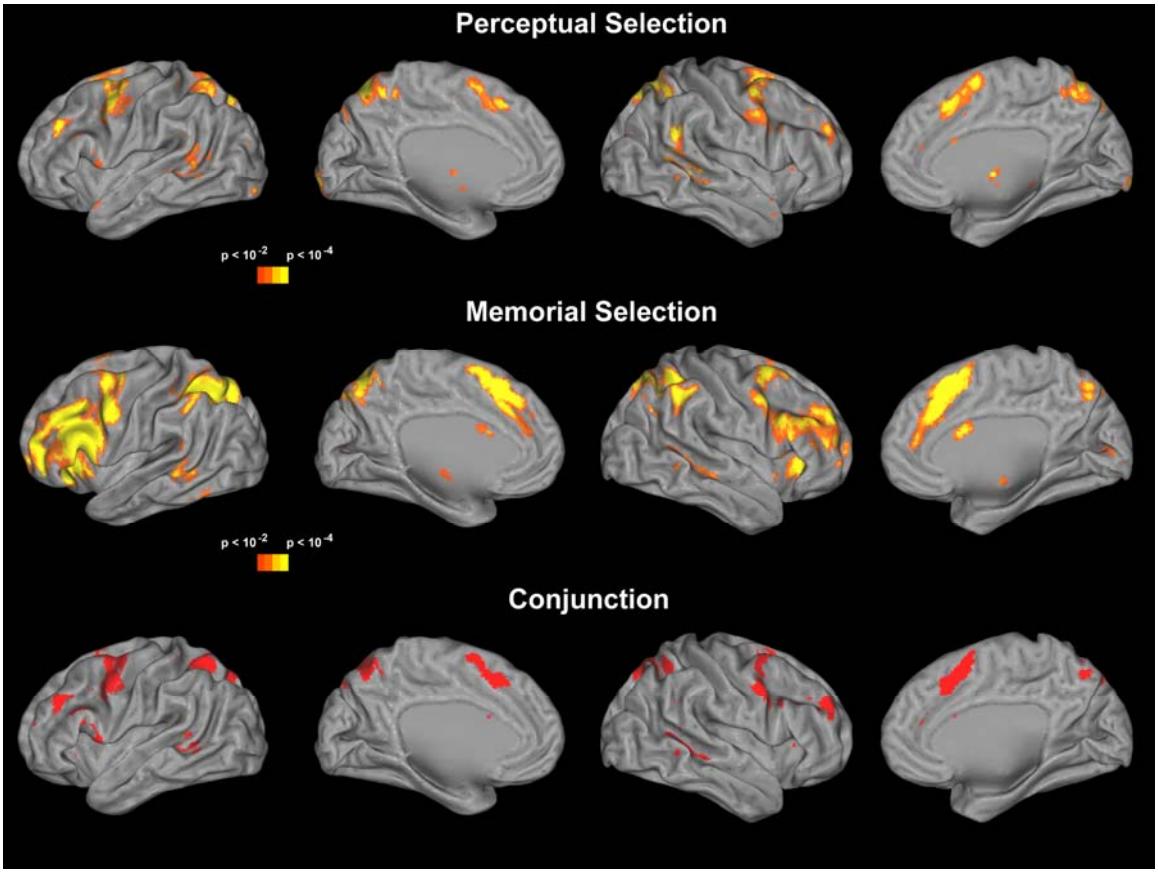

Figure 7.2. Whole-Brain Neural Results. Regions active for high versus low selection in the perceptual selection task (top), memory selection task (middle), and the conjunction of both tasks (bottom).

7.2.2 Neural Results

7.2.2.1 Perceptual Selection

Regions involved in perceptual selection have been reported previously (Nee and Jonides, submitted). Activation increases corresponding to increased demands on perceptual selection recruited several frontal regions including bilateral FEF, premotor cortex, DLPFC, and the anterior cingulate and surrounding medial prefrontal cortex (Figure 7.2). Hence, not only were posterior regions of PFC, such as the FEF and premotor cortex, involved in perceptual selection, but also more anterior regions in left (BA 9/46) and right DLPFC (BA 10). In addition, activation increases to selective attention demands were found in PPC, mostly in bilateral SPL, but also including some portions of the IPS, right inferior parietal lobule, and right temporo-parietal junction.

7.2.2.2 Memorial Selection

Regions involved in memorial selection largely included regions involved in perceptual selection, but with notable additions in bilateral IPS and VLPFC (Table 7.1; Figure 7.2). VLPFC activation was particularly pronounced in the left hemisphere, including all of pars triangularis (BA 45), as well as portions of more posterior left inferior frontal gyrus (pars opercularis, BA 44), and more anterior in pars orbitalis (BA 47). There was also extensive recruitment of anterior portions of the left middle frontal gyrus in BA 10.

7.2.2.3 Conjunction

Confirming the hypothesis that perceptual and memorial selection are similar processes, a conjunction analysis produced largely overlapping activations in frontal and parietal regions (Figure 7.2; Table 7.2). Frontal overlap was most prominent in posterior regions of PFC including bilateral FEF, premotor cortex, and the anterior cingulate and surrounding medial prefrontal cortex. However, in contrast to previous reports (Labar et al., 1999; Mayer et al., 2007; Nobre et al., 2004; Pollmann and von Cramon, 2000;), both perceptual and memorial selection recruited more anterior regions of PFC in DLPFC. All of these regions remained using a stricter valid conjunction analysis with each contrast thresholded at $p < 0.001$ (Nichols et al., 2005), confirming that commonalities were not the result of a liberal threshold. That regions of DLPFC were common to both perceptual and memorial selection is consistent with the idea that similar PFC top-down control is exerted across both domains (Deco and Rolls, 2005; Desimone and Duncan, 1995; Gazzaley and D'Esposito, 2007; Kastner and Ungerleider, 2000; Miller and Cohen, 2001).

Interestingly, parietal overlap was almost exclusively restricted to the SPL, sparing most portions of the IPS. This result is in stark contrast with previous reports that attention and memory produce common activations in the IPS (Labar et al., 1999; Mayer et al., 2007; Nobre et al., 2004; Pollmann and von Cramon, 2000). It is unlikely that the lack of common IPS activation is due to lack of power

since over 8000 common voxels were uncovered in our conjunction analysis. We return to the lack of IPS involvement in the discussion.

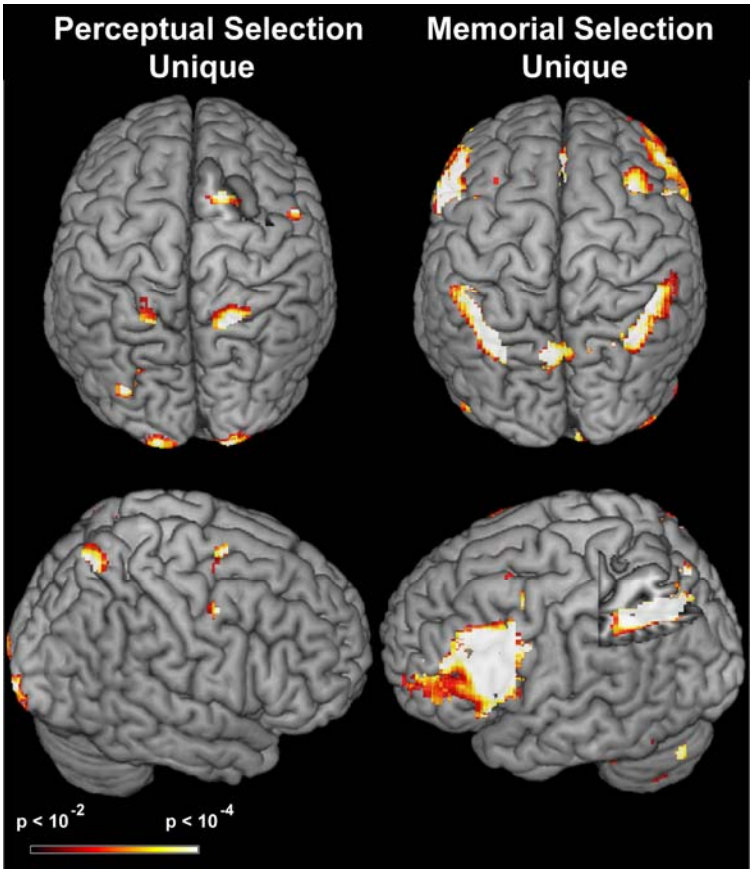

Figure 7.3. Selection-specific results. Regions unique to perceptual selection are depicted on the left, and regions unique to memorial selection are depicted on the right.

7.2.2.4 Unique Perceptual Selection Regions

Although there was clearly a good deal of overlap between perceptual and memorial selection, we were interested in whether any regions were uniquely recruited for perceptual selection. To examine this, we searched for regions that demonstrated significant activation for perceptual selection, significantly more

activation for perceptual selection than memorial selection, and no significant activation for memorial selection (see Image Analysis 7.1.4).

Fronto-parietal regions unique to perceptual selection were found most prominently in bilateral SPL, and right FEF (Figure 7.3; Table 7.4). These regions were adjacent to regions found in the conjunction analysis and suggest that the SPL and FEF, although common to both perceptual and memorial selection, may be more strongly related to perceptual selection. Regions unique to perceptual selection were also found in the right temporo-parietal junction, which has been linked to functions of attentional orienting (Corbetta et al., 2002; Corbetta and Shulman, 2002). The bilateral SPL and right temporo-parietal junction remained unique to perceptual selection using a stricter interaction threshold of $p < 0.001$, although the FEF did not survive this criterion. However, a region of interest analysis averaged over the FEF region found with the more liberal threshold demonstrated significantly greater perceptual selection related activation than memorial selection related activation ($t(17) = 4.84$, $p < 0.001$).

7.2.2.5 Unique Memorial Selection Regions

We also assessed regions unique to memorial selection by searching for regions that demonstrated significant activation for memorial selection, significantly more activation for memorial selection than perceptual selection, and no significant activation for perceptual selection.

Fronto-parietal regions unique to memorial selection included large portions of bilateral VLPFC, most prominently on the left (Figure 7.3; Table 7.4). In the left hemisphere, unique activation due to memorial selection was largely localized to pars triangularis of the left inferior frontal gyrus (BA 45), but also included posterior (BA 44) and anterior (BA 47) portions of the inferior frontal gyrus, and spread further anterior into BA 10. Activation increases also stretched dorsally into the inferior frontal sulcus and inferior portions of the middle frontal gyrus (BA 9/46). A similar, but less pronounced pattern was observed in the right hemisphere, including BA 45 and 13 ventrally, 9/46 dorsally, and BA 10 in the anterior portions of the middle frontal gyrus. Regions of the medial prefrontal cortex including the anterior cingulate also showed a preferential pattern for memorial selection.

The horizontal portion of bilateral IPS was also uniquely involved in memorial selection. These activations spread inferiorly to the most dorsal aspects of the inferior parietal lobule. This result is surprising given that the IPS has been found to be a region common to both attention and memory in previous reports (Labar et al., 1999; Mayer et al., 2007; Nobre et al., 2004; Pollmann and von Cramon, 2000). Additionally, unique activation due to memorial selection was observed in the medial portions of parietal cortex in the precunues. All frontal and parietal memorial selection unique regions but the precuneus remained at a stricter interaction threshold of $p < 0.001$.

7.2.2.6 Memorial Selection Specificity

Our memorial selection contrasts have thus far assessed memory updating processes that reduce a memory load of six down to three, compared to simple rehearsal of three items. Whereas we are primarily interested in the processes that select memorial information, our results may potentially be contaminated by differences in load before the memory cue. To address this concern, we compared selection-related activation to forget cues contrasted with remember cues. In both cases, subjects began with a memory load of six and used selection processes to reduce the load down to three. However, our behavioral data suggest that selection is more difficult to forget cues. Just as stimulus-response incompatibility calls for increased processes of response selection (Fitts and Seeger, 1953), forget cues may elicit stimulus-memory incompatibilities that call for increased memorial selection. Therefore, we hypothesized that contrasting forget and remember cues would more clearly isolate memorial selection processes.

To investigate memorial selection processes with more specificity, we therefore looked for regions that showed increased activation to forget cues compared to remember cues, restricted to regions that were reliable in our original memorial selection contrast. This analysis produced a very similar network of regions including bilateral VLPFC, DLPFC, medial PFC including the anterior cingulate, FEF, premotor cortex, and bilateral IPS and SPL. Hence, our memorial selection

results are unlikely to be due to memory load, and seem to instead reflect memorial selection processes.

To bolster this claim, we looked for regions that correlated with behavioral selection latency differences between forget and remember cues, restricting ourselves to the regions found active above. Confirming their role in memorial selection, left lateral PFC (MNI center -46 20 26; BA 46/9/45; 166 voxels; $r = 0.52$, $p < 0.05$), left IPS (MNI center -34 -64 52; BA 7/40; 164 voxels; $r = 0.63$, $p < 0.01$), and left medial PFC (MNI center -2 30 46; BA 8; 139 voxels; $r = 0.64$, $r < 0.01$) all demonstrated a correlation between neural activation and behavioral performance (Figure 7.4). Not only did these regions show greater activation for forget cues compared to remember cues, all of these regions also demonstrated significantly more activation for remember cues than rehearse cues (all $t(17) > 4$, $p < 0.001$). Hence, these regions varied parametrically with memorial selection demands, rather than being unique to forget cues.

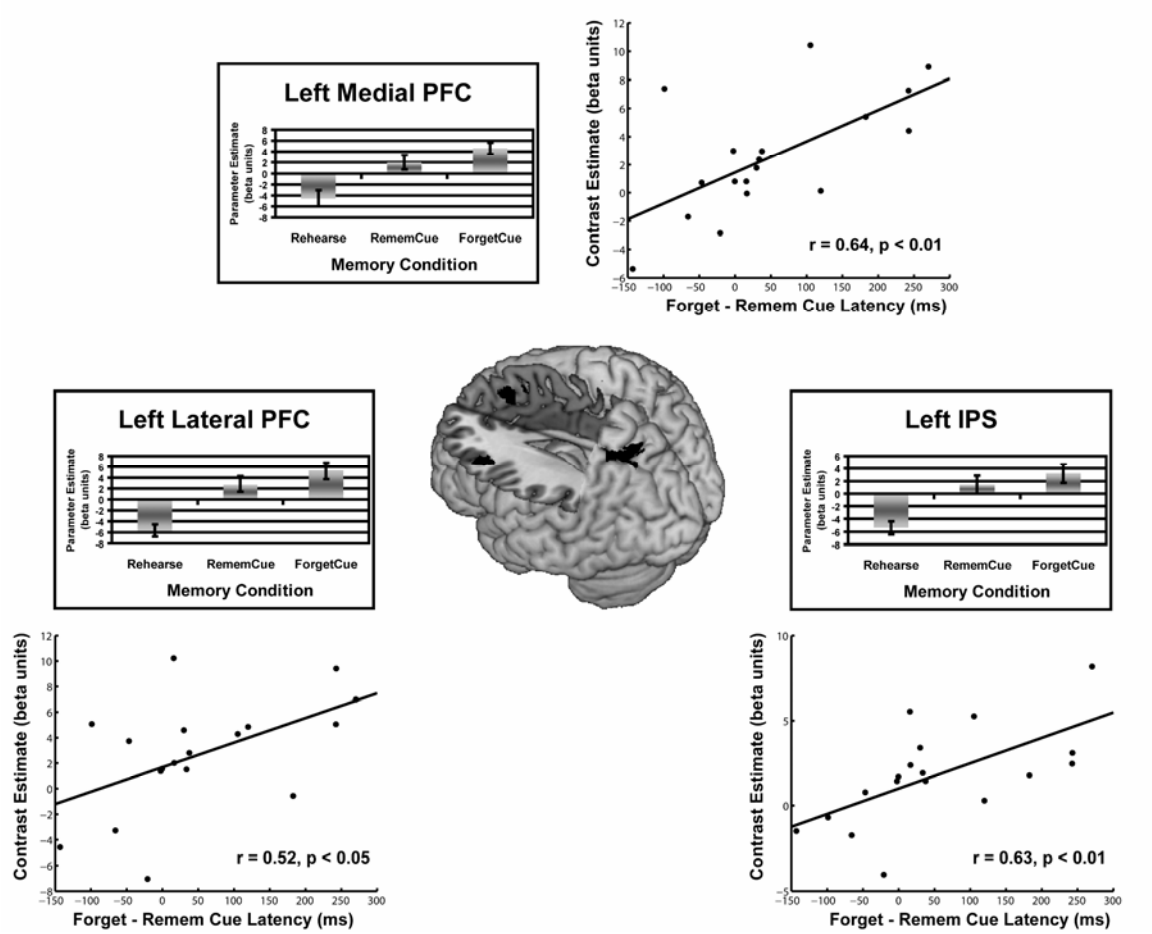

Figure 7.4. Memorial Selection-Specific Brain-Behavior Correlations. Regions that were involved in memorial selection, more strongly activated for forget cues compared to remember cues, and that correlated with behavioral measures of selection latency. PFC = prefrontal cortex; IPS = intraparietal sulcus.

7.2.2.7 Left Ventrolateral Prefrontal Cortex and Proactive Interference

Left VLPFC, particularly in BA 45, has been shown to have a strong engagement in the resolution of proactive interference (Badre and Wagner, 2005; D'Esposito et al., 1999; Jonides and Nee, 2006; Jonides et al., 1998; Nee and Jonides, in press; Nee et al., 2007a; Nelson et al., 2003; Thompson-Schill et al., 2002;

Zhang et al., 2003). Such demonstrations have generally relied on item-recognition tasks that probe highly familiar but irrelevant information. Recent hypotheses have theorized that left VLPFC may be involved in selecting among memorial representations, placing items into appropriate contexts in order to guide recognition performance (Badre and Wagner, 2005; Jonides and Nee, 2006; Nee et al., 2007a). Braver and colleagues (2007) have suggested that these selection operations need not be restricted to recognition decisions, but rather, subjects may act in a proactive manner to reduce proactive interference by performing appropriate selection during delay intervals before a recognition probe. In our task, subjects are required to perform such a selection in that the update cue forces subjects to discard irrelevant information and rehearse relevant information. Therefore, left VLPFC activation during memorial selection may protect the cognitive system from later proactive interference. This would suggest that greater selection-related activation during memorial selection may lead to reduced proactive interference during probe decisions.

An alternative possibility is that both memory updating and resolving probe-related proactive interference are the same function, and the degree to which subjects have difficulty with one, they are likely to have difficulty with the other. That is, in both instances subjects are selecting among memorial representations, and difficulty in selection during memory updates should predict difficulty in selection when probed with a highly familiar irrelevant item. We have shown that left VLPFC activation increases during memorial selection correlate

positively with behavioral measures of memorial selection, suggesting that greater difficulty with selection is associated with greater left VLPFC activation. If left VLPFC reflects general memorial selection demands, we would expect that greater selection-related activation may also predict higher proactive interference during probe decisions.

To test these alternative predictions, we examined whether activation in left VLPFC predicted the amount of proactive interference subjects experienced during recognition decisions. Proactive interference was indexed as the reaction time difference between decisions to forget probes compared to control probes, consistent with previous reports (Jonides and Nee, 2006; Nee and Jonides, in press; Zhang et al., 2003). We looked in left VLPFC regions that showed significant activation increases to memorial selection demands and examined whether any of these regions were correlated with behavioral measures of proactive interference at the time of the probe.

Activation during memorial selection in left VLPFC correlated strongly with subsequent proactive interference (MNI center -52 22 18, BA 45, 178 voxels, $r = 0.71$, $p < 0.001$; Figure 7.5). The correlation was positive indicating that subjects who demonstrated increased activation during memorial selection also experienced greater proactive interference to later probes. Hence, this region was correlated with increased behavioral measures of memorial selection demands during selection, as well as increased behavioral measures of proactive

interference several seconds after selection. The combination of these results suggests that memory updating and resolving proactive interference recruit common mechanisms of memorial selection, and that subjects that show difficulty in one process also show difficulty in the other.

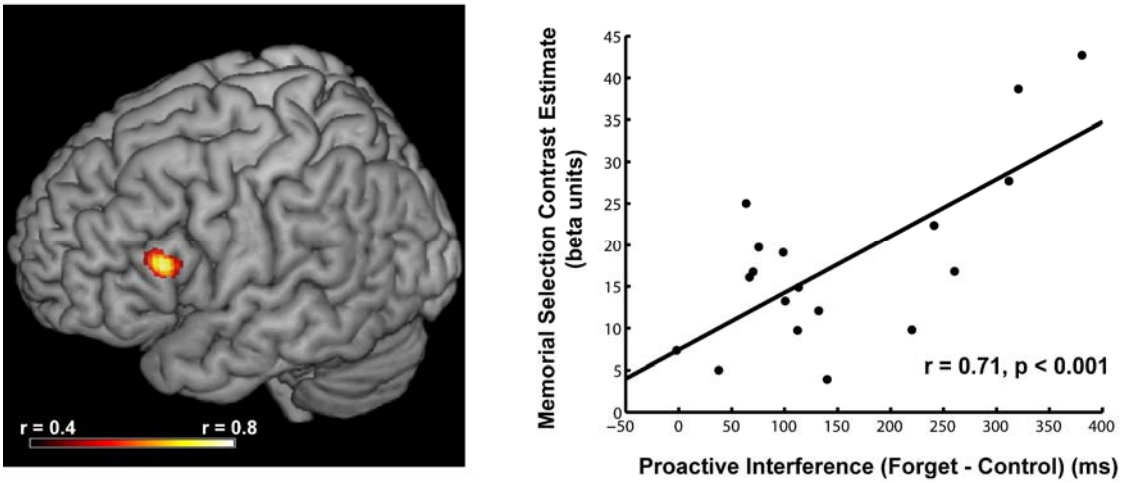

Figure 7.5. Left VLPFC and Proactive Interference. Memorial selection-related activation in left ventrolateral prefrontal cortex predicted the amount of proactive interference experienced to forget probes compared to control probes. Voxel-wise correlations between activation and behavior are rendered on the left. Correlations pooled over all significant voxels are plotted on the right.

7.2.2.8 Common Neural and Behavioral Interactions

We were interested in whether neural activation in any of the common regions uncovered by our conjunction analysis could reveal a demonstrable relation to behavior. To explore this issue, we looked for regions where neural indices of selection demands correlated with behavioral indices of selection demands for

both perceptual and memorial selection. We restricted this search to voxels that were significant in our conjunction analysis.

In left premotor cortex, lateral and inferior to the FEF (MNI center -54 6 42, BA 6/8, 17 voxels; Figure 7.6a), activation increases related to increased selection demands were positively correlated with behavioral measures of both memorial selection ($r = 0.51$, $p < 0.05$) and perceptual selection ($r = 0.54$, $p < 0.05$). It is unlikely that this region reflected a response to the keypress since selection-related keypresses were all made with the left thumb. However, responses to recognition probes were all made with the right hand. Recognition probes appeared several seconds after perceptual and memorial selection occurred. Hence, it is possible that commonalities in this region may reflect preparation for upcoming recognition decisions. Such preparation may involve the biasing of relevant stimulus-response associations under high demand, to prevent potential interference from irrelevant stimulus-response associations.

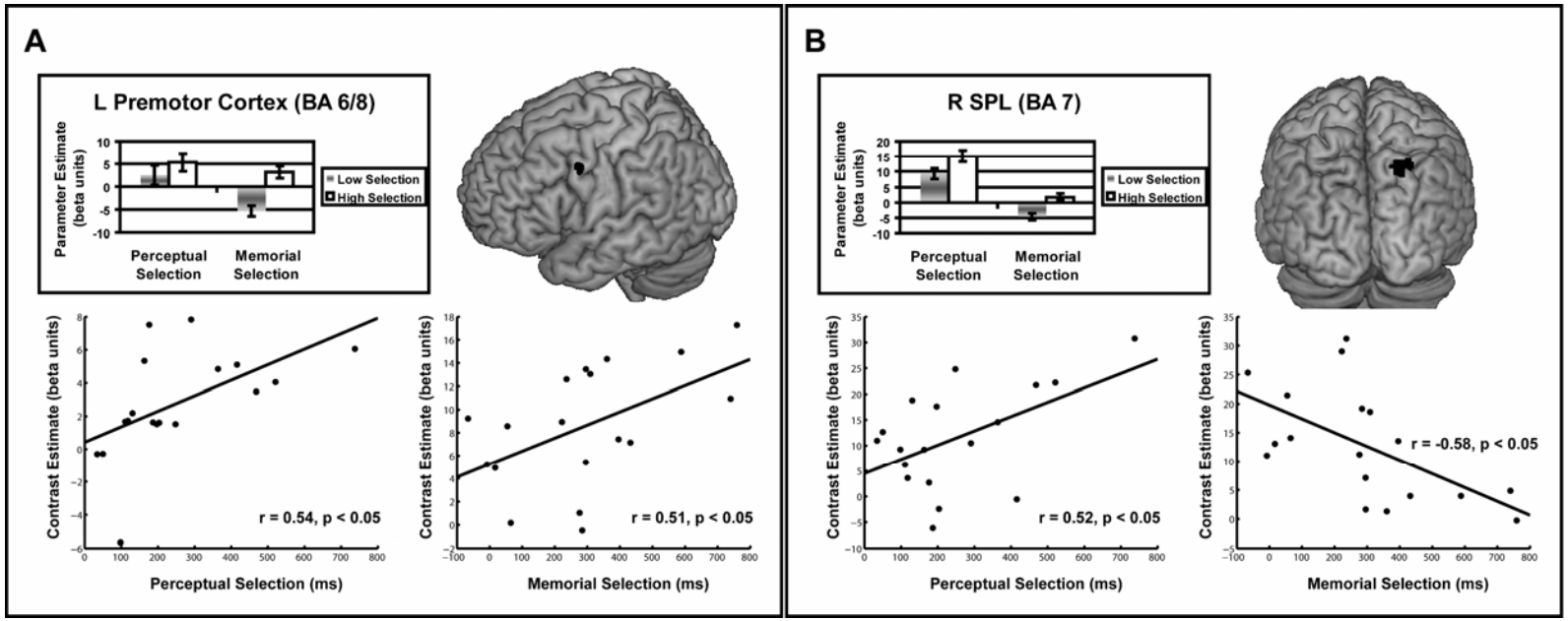
A
L Premotor Cortex (BA 6/8)
Parameter Estimate (beta units)
Low Selection
High Selection
Perceptual Selection
Memorial Selection
Contrast Estimate (beta units)
r = 0.54, p < 0.05
Perceptual Selection (ms)
r = 0.51, p < 0.05
Memorial Selection (ms)
B
R SPL (BA 7)
Parameter Estimate (beta units)
Low Selection
High Selection
Perceptual Selection
Memorial Selection
Contrast Estimate (beta units)
r = 0.52, p < 0.05
Perceptual Selection (ms)
r = -0.58, p < 0.05
Memorial Selection (ms)

Figure 7.6. Common Brain-Behavior Correlations. Regions significant in the conjunction analysis that correlated with behavioral measures of selection difficulty for both perceptual and memorial selection. Selection-related activation in the left premotor cortex (A) correlated positively with behavioral measures of both perceptual and memorial selection. Selection-related activation in the right superior parietal lobule (B) correlated positively with behavioral measures of perceptual selection, but negatively with behavioral measures of memorial selection. SPL = superior parietal lobule.

7.2.2.9 Individual Differences in Common Control

A region in the right SPL also demonstrated brain-behavior correlations for both kinds of selection (MNI center 24 -72 56, BA 7, 74 voxels; Figure 7.6b). Interestingly, correlations in this region were in opposite directions for perceptual and memorial selection. Whereas selection-related activation increases were positively correlated with behavioral measures of perceptual selection ($r = 0.52$, $p < 0.05$), the opposite held true for memorial selection ($r = -0.58$, $p < 0.05$). That is, greater activation increases in this region were related to reduced behavioral differences between high and low selection for the memorial selection task. By contrast, activation increases in this region during perceptual selection scaled with behavioral selection effects for the perceptual selection task.

As depicted in Figure 7.6b, the right SPL region was much more engaged during the perceptual selection task than the memorial selection task ($t(17) = 7.5$, $p < 0.001$), suggesting a strong attentional role for this region. Moreover, our

previous analysis identified other portions of the SPL to be unique to perceptual selection, suggesting that the SPL in general may be more strongly related to selective attention than working memory. Therefore, one way to interpret this result is that subjects vary in the degree to which they recruit perceptual selection resources to perform memorial selection. Some subjects show strong commonalities, using attention-related SPL resources to perform memorial selection. As the correlation in Figure 7.6b indicates, such recruitment may be beneficial in that these subjects demonstrated reduced behavioral differences between high and low memorial selections. Other subjects, by contrast, may show greater distinctions between perceptual and memorial selection. Such subjects would likely show greater use of regions unique for memorial selection, such as left VLPFC, when performing memorial selection.

To examine this proposal, we performed a median split on the data, dividing subjects into 2 groups: a high SPL group that showed greater activation increases in the right SPL for memorial selection, and a low SPL group that showed lower activation increases in the right SPL for memorial selection. Next, we re-ran whole-brain contrasts for memorial selection for each group separately. The results are depicted in Figure 7.7. Not surprisingly, the high SPL group demonstrated stronger activation increases in the right SPL. This group also showed greater selection-related increases in the bilateral FEF and right premotor cortex. These frontal regions overlapped with our conjunction analysis and were close to regions that were unique to perceptual selection. Hence,

memorial selection in these subjects appeared very similar to perceptual selection. By contrast, the low SPL group did not show significant activation increases in the right SPL, or FEF. Instead, this group showed much greater memorial selection-related activation increases in the left VLPFC, a region that we demonstrated to be unique to memorial selection. Finally, the groups demonstrated significant differences in behavioral measures of memorial selection with the high SPL group showing reduced differences between high and low selection compared to the low SPL group ($t(16) = 2.5$, $p < 0.05$).

This pattern of results suggests that subjects vary a great deal in the degree to which they recruit common neural resources of perceptual and memorial selection. Using common neural resources for perceptual and memorial selection was associated with better performance (i.e. reduced increases in latency for high selection demands), suggesting that it is beneficial to use selective attention resources to aid memorial selection.

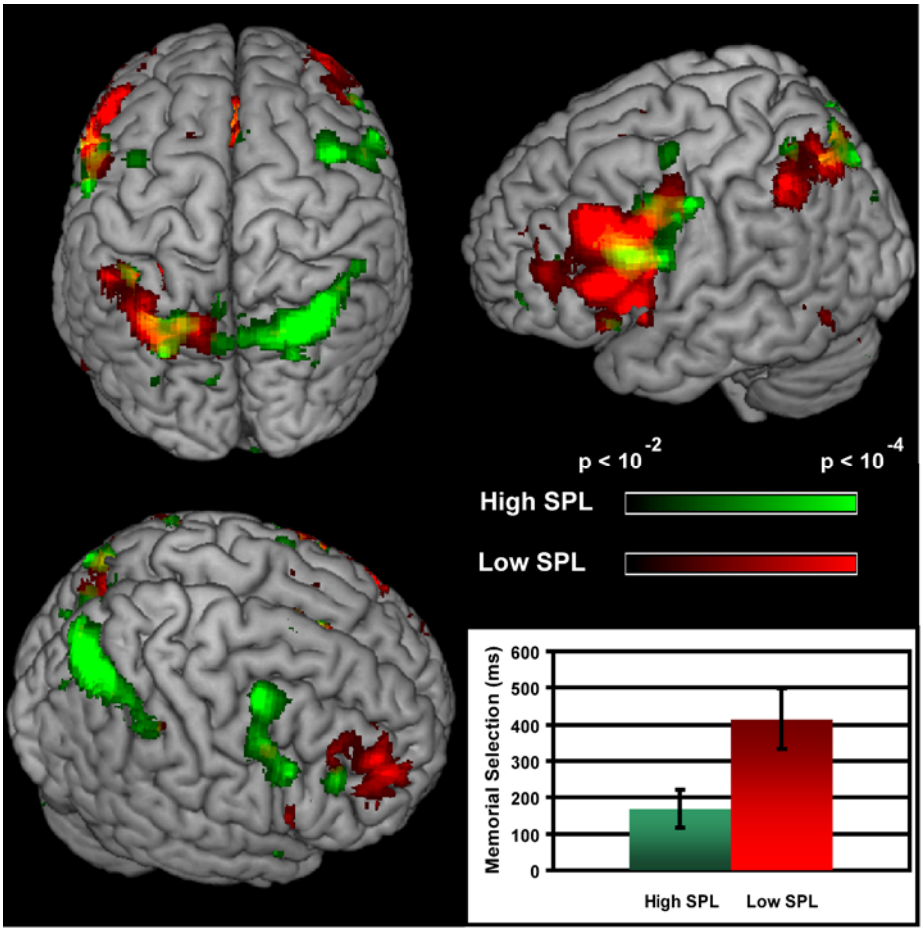

Figure 7.7. Individual Differences in Memorial Selection. Differences in memorial selection as a function of right superior parietal lobule recruitment. Subjects that showed large activation increases in the right superior parietal lobule (SPL) for memorial selection (high SPL; green) demonstrated enhanced activation in perceptual selection-related regions. Subjects that showed smaller activation increases in the right SPL (low SPL; red) demonstrated more robust activation in left ventrolateral prefrontal cortex, which was unique to memorial selection. Behavioral results indicated less selection difficulty for high SPL subjects compared to low SPL subjects.

7.3 Discussion

We examined the common and unique neural components of selecting among competing percepts and memories. Consistent with models that posit that similar selection processes operate on all varieties of information, we found a broad network of overlapping activation between perceptual and memorial selection. Selection of both sorts was associated with activation increases in bilateral FEF, premotor cortex, DLPFC, medial PFC, anterior cingulate cortex, and the SPL. However, our results suggest that regions of the FEF and SPL are more strongly associated with perceptual selection, while memorial selection was uniquely associated with VLPFC, particularly on the left, and bilateral IPS. Moreover, left VLPFC activation correlated with behavioral measures of memorial selection demands, and activation in this region also predicted behavioral measures of proactive interference that appeared several seconds later. Finally, there was a considerable amount of individual variability in the degree to which subjects recruited the same neural resources for perceptual and memorial selection, and those subjects that more closely recruited overlapping resources demonstrated better performance.

Common Dorsolateral Prefrontal Recruitment

In contrast to previous reports (Labar et al., 1999; Mayer et al., 2007; Nobre et al., 2004; Pollmann and von Cramon, 2000), we found common selection-related activation increases in bilateral DLPFC. Models of selection posit that this region may store goal or template information used to guide selection in more posterior

regions of cortex (Desimone and Duncan, 1995; Kastner and Ungerleider, 2000; Miller and Cohen, 2001). Goal or template information is especially important when selection cannot proceed in a purely bottom-up fashion. When competing distractors are present, information about current goals must be able to bias competition so that only goal-relevant information is processed. Consistent with these ideas, in both selective attention (Nee et al., 2007b) and working memory (D'Esposito and Postle, 1999; Jonides et al., 2005; Smith and Jonides, 1999; Wager et al., 2003), the DLPFC appears to be especially important when selection demands are increased by the presence of distracting information. In previous reports that have compared attention and memory, competition from distracting information has been minimized (Labar et al., 1999; Mayer et al., 2007; Nobre et al., 2004; Pollmann and von Cramon, 2000), which may account for previous failures to find common DLPFC recruitment across attention and memory. Here, we were careful to highlight selection processes of both attention and memory, rather than examining processes that simply maintain attention or hold information online. Hence, our results suggest that the DLPFC is critically involved in both attention and memory when selection processes must resolve competition from salient distraction.

7.3.1 Common Attentional Circuit

As in previous reports (Labar et al., 1999; Mayer et al., 2007; Nobre et al., 2004; Pollmann and von Cramon, 2000), we found common involvement of the FEF, premotor cortex, and SPL across both perceptual and memorial selection. These

regions have been robustly associated with attention (Corbetta et al., 2002; Kastner et al., 1999; Kastner and Ungerleider, 2000) and spatial working memory (Awh and Jonides, 2001; Awh et al., 1999; Awh et al., 2006). Awh and colleagues have suggested that in spatial working memory, this network acts as a focus of attention that cycles through spatial locations held in mind. In other words, spatial working memory is akin to cycled deployments of covert attention, explaining the great deal of overlap between attention and spatial working memory. However, our results demonstrate that this network need not be restricted to spatial information in that we assessed working memory for verbal material. That this network is also engaged in selecting among verbal representations suggests that attentional processes need not be spatial in manner, but can highlight information that lacks a visuo-spatial component.

Another possibility is that during memorial selection, subjects created a visuo-spatial representation of the information held in working memory, and used attentional processes to select among this information. For example, subjects may have imagined the original display and used attention to select among items in this visuo-spatial representation. An alternative account is that subjects stored the verbal information in an articulatory loop (Baddeley, 2003), which has a natural dimension of time (i.e. position within the rehearsal loop). Using such a representation, subjects may have translated the update cues to positional cues that targeted different serial positions within rehearsal. In any case, it is clear that attentional selection can be deployed to select among memorial representations.

Common recruitment of left premotor cortex closely tracked behavioral measures of both perceptual and memorial selection. Since responses to selection demands were made with the left hand, it is unlikely that these results reflect response processes. However, responses to recognition probes performed several seconds later were made with the right hand. Therefore, activation in this region may have reflected the biasing of stimulus-response pathways to guard against interference in preparation for future response production. Alternatively, this region may also have been involved in the deployment of attention. Although the human FEF is most often localized to the junction of the superior frontal sulcus and precentral sulcus, there are demonstrations of oculomotor-associated cortex more lateral and inferior near the premotor region we found here (Lobel et al., 2001). Hence, this region may also be associated with attentional biasing to resolve competition.

7.3.2 Left Ventolateral Prefrontal Cortex and Memorial Selection

Our results indicated that left VLPFC was unique to memorial selection and that activation in this region was closely tied to behavioral manifestations of selection difficulty and proactive interference. Lesions in this region, particularly in BA 45, cause selective deficits in the ability to resolve proactive interference (Hamilton and Martin, 2005; Thompson-Schill et al., 2002), but spare other forms of working memory performance. Based on these results, some authors have hypothesized that this region is involved in selecting among contextual information in order to

appropriately categorize the source of highly familiar information (Badre and Wagner, 2005; Jonides and Nee, 2006; Nee et al., 2007a). This region is also involved in selecting among competing semantic representations (Badre and Wagner, 2007; Thompson-Schill et al., 1997; Nelson, 2005) and hence, this region may serve a general memorial selection function (Zhang et al., 2004). Our results are consistent with these ideas in that activation in this region was associated with memorial selection difficulty, and activation also predicted future difficulty in how well subjects resolved proactive interference.

Braver and colleagues (2007) have suggested that selection processes of left VLPFC may be engaged in a proactive manner in order to mitigate future effects of proactive interference. Engagement of this region during updating had the potential to investigate whether greater use of selection processes of left VLPFC during updating would lead to reduced proactive interference at the time of the probe. We did not find this pattern. Instead, difficulty during memory updating was associated with difficulty during recognition decisions, suggesting that the same process was elicited in both scenarios. However, our results do not preclude other potential proactive strategies such as increased selection during the retention interval after updating and before the recognition probe. Although our design did not permit a separate assessment of delay period activation, an interesting future pursuit would be to examine the interplay between cue-related, delay-related, and probe-related activation in left VLPFC to investigate potential processes of proactive and reactive control.

Preferential involvement of left VLPFC in memorial selection may also have been due to the verbal nature of memorial selection. Although perceptual selection was also performed on verbal materials, such selection was done in a visuo-spatial manner that may have attenuated verbal aspects of processing. However, previous studies contrasting attention and working memory using objects that are difficult to name (Mayer et al., 2007), as well as spatial locations (Nobre et al., 2004) also found greater memory-related activation in left VLPFC compared to attention. Left VLPFC involvement in the resolution of proactive interference has also been found for non-verbal material (Postle et al., 2004; Jonides and Nee, 2006), although these effects have not always been found (Badre and Wagner, 2005; Leung and Zhang, 2004). Hence, although we cannot rule out a verbal involvement for left VLPFC, it remains possible that this region responds generally to memorial selection.

7.3.3 Control Operations of the Intraparietal Sulcus

Previous comparisons of attention and memory have demonstrated largely overlapping activation in the IPS (Labar et al., 1999; Mayer et al., 2007; Nobre et al., 2004; Pollmann and von Cramon, 2000). Our results demonstrated very little overlap in this region, with the IPS being almost exclusively associated with memorial selection. One difference between our attention task and others is that for all of our conditions, attention shifting was closely matched, whereas in other studies, contrasts of interest included processes involved in shifting attention.

The IPS is known to be involved in attentional shifts (Wager et al., 2004) and the lack of involvement during perceptual selection here may be because our contrasts subtracted out this process. By contrast, there may have been shifting operations during memorial selection as subjects shifted from maintenance operations to updating, or shifting their attention among different information in memory.

Alternative accounts suggest that rather than being associated with shifting, the IPS is involved in maintaining attention on target information (Serences et al., 2004; Yantis and Serences, 2003). Tonic activation in the IPS is associated with maintaining attention both to perceptual (Serences et al., 2004) and memorial information (Todd and Marois, 2004; 2005; Vogel and Machizawa, 2004; Vogel et al., 2005; Xu and Chun, 2006). Once again, our perceptual selection contrast may have subtracted this process out, but alterations in maintenance operations likely occurred for memory updating operations. During memory updates, maintenance is interrupted and attention is shifted and maintained on updated information. Hence, the reason that we found IPS involvement in memory, but not attention may be due to the particular contrasts performed here. It is clear from other work that the IPS is involved in both attention and memory (Labar et al., 1999; Mayer et al., 2007; Nobre et al., 2004; Pollmann and von Cramon, 2000), and our design may simply not have afforded detecting these commonalities.

7.3.4 Individual Variations in Common Control

Our analyses suggested that regions of the FEF, premotor cortex, and SPL may have been preferentially engaged in perceptual selection, and that subjects varied in the degree to which they used these same networks for memorial selection. Such variation may be accounted for by differences in representational strategy. As alluded to above, subjects may have differed in the degree to which they relied on visuo-spatial or timing strategies in working memory. Memorial representations that highlighted visuo-spatial or timing aspects of the information in working memory may have been more amenable to perceptual selection types of processes. Subjects who recruited more perceptual selection regions of the SPL and FEF for memorial selection also demonstrated less difficulty for high memorial selection demands, compared to subjects who relied more on left VLPFC. These results suggest that perceptual selection strategies may be beneficial to memory performance. An interesting avenue for future research would be to examine whether explicitly giving subjects such perceptual selection strategies for memorial selection can improve performance.

Notably, in our tasks, perceptual and memorial selection were performed independently. Previous studies that have examined selective attention and memory in dual task situations have found that these processes interfere with one another when performed concurrently (de Fockert et al., 2001; Lavie, 2005; Lavie et al., 2004). This research may predict that those subjects who demonstrated *less* sharing of perceptual and memorial selection may actually

demonstrate *better* performance under dual task situations, since those subjects can draw from separate neural resources to perform each function. This is another interesting avenue for future investigation.

7.4 Conclusion

Top-down control allows the cognitive system to represent only information that is relevant to current goals. We have demonstrated that similar forms of top-down control underlie selecting among competing percepts and memories. These processes may be subserved by interactions between goal and template information held in the DLPFC that biases the deployment of FEF and SPL attentional processes in the face of competing distraction. When selecting among competing memories, regions of the left VLPFC are additionally recruited. Although not all control processes are shared, there appear to be benefits to a cognitive economy of re-using the same processes for perceptual and memorial selection, at least when both selections can be performed independently.

Table 7.1 - Memorial Selection

Region	X	Y	Z	Voxels	T-value	BA
Frontal						
left inferior frontal gyrus (pars triangularis)	-52	20	28	5247	9.27	45/9
left inferior frontal gyrus (pars opercularis)	-54	14	22		8.8	44/45
left middle frontal gyrus	-48	26	34		8.06	9/46/10
left precentral sulcus	-56	10	38		7.25	6/9
left precentral gyrus	-50	-4	39		7.21	6
left supplemental motor area	-2	18	50	1719	9.45	6/32
right anterior cingulate cortex	6	28	32		6.56	32/8
left supplemental motor area	6	8	68		3.87	6
right precentral sulcus	50	8	40	1390	6.61	6/9
right frontal eye field	36	4	56		6.47	6/8
right middle frontal gyrus	50	36	30		5.66	9/46
right anterior middle frontal gyrus	40	46	28		4.99	10
right inferior frontal gyrus	60	14	32		4.66	44/9
right insula	34	26	2	406	5.98	13
right insula/inferior frontal gyrus	48	14	-4		4.63	13/47
right inferior frontal gyrus	46	28	2		4.18	45
left superior frontal sulcus	-30	8	60	53	4.45	6
left superior frontal sulcus	-28	8	66			
Parietal						
left intraparietal sulcus	-24	-66	42	4502	9.48	7/40
left intraparietal sulcus	-34	-66	50		8.73	7/40
left anterior intraparietal sulcus	-36	-50	42		8.34	7/40
right intraparietal sulcus	34	-60	42		7.76	
right intraparietal sulcus	32	-62	34		7.34	
right anterior intraparietal sulcus	36	-44	44		6.81	
Temporal						
left middle temporal gyrus	-52	-46	4	71	4.63	22/21
left middle temporal gyrus	-60	-38	0		3.87	22/21
right middle temporal gyrus	48	-42	2	55	4.54	22/21
	52	-34	2		4.01	22/21
Other						
right cerebellum	16	-76	-34	135	5.39	
left global pallidus/putamen	-16	-2	4	34	5.27	

left cerebellum	-40	-70	-36	220	5.26
corpus callosum	4	12	20	39	4.63
right cerebellum/vermis					4.5
left cerebellum/vermis	-6	-84	-26	38	4.45

Table 7.1. Memorial Selection. Whole-brain results for the memorial selection contrast (high selection – low selection). All regions are significant at a threshold of $p < 0.001$, with 20 or more contiguous voxels. Peak coordinates are listed in Montreal Neurological Institute (MNI) space. BA = Brodmann Area

Table 7.2 - Common Regions for Perceptual and Memorial Selection

Region	X	Y	Z	Voxels	BA
Frontal					
left frontal eye fields/premotor cortex	-25	5	52	2577	6/8
left middle frontal gyrus	-44	32	30		9/46
left precentral sulcus/middle frontal gyrus	-48	0	48		6/9
right anterior cingulate/medial prefrontal cortex	2	18	44		32/8
right supplemental motor area	2	6	60		6
right frontal eye fields/precentral sulcus	44	6	44	1023	6/9
right anterior middle frontal gyrus	38	44	26	286	10/9/46
left inferior frontal gyrus (pars opercularis)/superior temporal gyrus	-56	14	2	180	44/47/22
left inferior frontal gyrus (pars opercularis	-36	28	-4	63	47
left insula/left inferior frontal gyrus (pars triangularis)	-38	22	16	51	13/46/45
right inferior frontal gyrus	36	28	-8	27	47
right anterior cingulate cortex	14	30	20	24	32
Parietal					
left precuneus/superior parietal lobule	-6	-64	52	2761	7
left superior parietal lobule/anterior intraparietal sulcus	-22	-66	52		7/40
right superior parietal lobule	24	-66	52		7
left inferior parietal lobule	-50	-38	42		40
Temporal					
right suprerior temporal sulcus	52	-40	4	274	22/21
left middle temporal gyrus/superior temporal sulcus	-54	-46	2	207	22/21
right superior temporal gyrus	52	14	-4	26	22/38
left superior temporal pole	-56	16	-14	22	38
Other					
right cerebellum	28	-76	-32	307	
right putamen	20	2	12	84	
right thalamus	8	-6	2	35	
left caudate/putamen	-14	0	14	34	

left cerebellum	-34	-60	-32	24
left thalamus	-8	-12	0	22
left putamen/caudate	-18	6	8	21

Table 7.2. Common Regions for Perceptual and Memorial Selection. Results from a conjunction analysis comparing for both perceptual and memorial selection. All regions were significant for perceptual and memorial selection contrasts (high selection – low selection) at $p < 0.01$ (conjoint $p < 0.0001$) with at least 20 contiguous voxels. Coordinates are reported in MNI space and reflect center of mass. BA = Brodmann Area.

Table 7.3 - Selection Unique Regions

Perceptual Selection Unique

Region	X	Y	Z	Voxels	BA
Frontal					
right superior frontal gyrus/frontal eye fields	16	-2	64	187	6
right premotor/precentral gyrus	50	-6	54	34	6
Parietal					
right superior parietal lobule	18	-60	64	179	7
left superior parietal lobule	-22	-58	66	121	7
right temporo-parietal junction	54	-44	22	72	40/13
left precuneus	-10	-50	54	52	7
Occipital					
left occipital pole	-20	-98	-10	480	18/17
right occipital pole	22	-98	-8	228	18/17
left lateral occipital cortex	-32	-84	22	56	19
Other					
Putamen	-22	6	0	66	
Brainstem	-6	-34	-46	31	

Memory Selection Unique

Region	X	Y	Z	Voxels	BA
Frontal					
left lateral prefrontal cortex	-48	26	12	3445	9/46/10/ 47/45/44
right lateral prefrontal cortex	46	38	18	1212	46/10/45/ 9
left medial prefrontal cortex/anterior cingulate	-2	28	42	1200	8/32/9/6
right superior frontal gyrus	38	12	56	180	6/8
right ventrolateral prefrontal cortex	34	30	0	149	47
right anterior cingulate cortex/medial prefrontal cortex	10	42	16	62	32/10/9
Parietal					
left intraparietal sulcus	-38	-56	44	1383	40/7
right intraparietal sulcus	44	-52	44	1165	40/7
precuneus	0	-74	46	233	7
Other					
left cerebellum	-42	-68	-38	204	

right cerebellum	58	-64	-38	24
right cerebellum	46	-58	-38	46
right cerebellum	4	-88	-34	98
right cerebellum	46	-82	-30	71
midbrain/pontine tegmentum	6	-30	-22	29
corpus callosum	2	8	20	39

Table 7.3. Selection Unique Regions. Regions unique to perceptual and memorial selection. Unique regions were significantly active for one task (high selection – low selection), significantly more active for one task than another task (task x selection interaction), and not significantly active for the other task (high selection – low selection). Coordinates are reported in MNI space and reflect center of mass. BA = Brodmann Area.

Table 7.4 - Forget versus Remember Cues

Region	X	Y	Z	Voxels	T-value	BA
Frontal						
left precentral sulcus	58	6	36	1624	5.81	6
left posterior middle frontal gyrus	-50	12	50		5.08	8/6
left inferior frontal gyrus (pars triangularis)	-36	28	26		4.81	45
left middle frontal gyrus	-44	22	36		4.18	9
left medial frontal gyrus	-8	26	52	744	5.2	6/8
left superior frontal gyrus/frontal eye fields	-16	6	70		3.59	6
left supplemental motor area	-8	14	66		3.44	6
left medial frontal gyrus	-4	40	36		3.12	9
left medial frontal gyrus/anterior cingulate cortex	-8	42	28		3.06	9/32
right inferior frontal gyrus	50	26	26	457	3.41	45
right posterior middle frontal gyrus	46	10	48		3.29	8/6
right inferior frontal sulcus	50	16	32		2.96	9/46
right middle frontal gyrus	52	16	42		2.59	9
right anterior middle frontal gyrus	30	56	2	104	2.49	10
right anterior superior frontal gyrus	28	60	10		2.37	10
right supplemental motor area	10	10	68	42	3.1	6
right insula	32	34	-4	42	2.42	13
left inferior frontal gyrus (pars triangularis)	50	38	8	30	2.48	45
right anterior cingulate cortex	12	16	36	24	2.08	32
Parietal						
left inferior parietal lobule	-46	-58	56	550	4.38	40
left inferior parietal lobule/intraparietal sulcus	-42	-66	50		3.79	7/40
left superior parietal lobule	-22	-72	50		3.3	7
left inferior parietal lobule	-50	-48	52		3.05	40
left intraparietal sulcus	-36	-52	54		2.1	7/40
right superior parietal lobule/intraparietal sulcus	28	-64	58	158	2.44	7/40

right intraparietal sulcus	36	-66	54		2.35	7/40
right inferior parietal lobule	44	-60	52		2.11	40
right inferior parietal lobule	54	-36	42	49	2.36	40
left intraparietal sulcus	-24	-60	49	28	2.44	7/40

Table 7.4. Forget versus Remember Cues. Regions significantly more active for memory updates to forget cues versus remember cues ($p < 0.05$), restricted to regions active for the memorial selection contrast (high selection – low selection) at $p < 0.01$. Only regions of 20 or more contiguous voxels are reported. Peaks are reported in MNI space. BA = Brodmann Area.

Chapter 8
Conclusion

Across six studies, we examined the psychological and neural processes underlying interference control. Through the combination of meta-analytic techniques, cognitive psychology, and brain imaging, we uncovered common and unique components to interference control. Some of the patterns of dissociation that we have observed have suggested that interference control may be parceled by the stage of processing at which control operates. I consider each stage in turn.

8.1.1 Interference Control Over Percepts – Selective Attention

Consistent with previous reports, we found that selective attention was related to activation in the FEF, premotor cortex, PPC, and DLPFC (Desimone and Duncan, 1995; Kastner and Ungerleider, 2000; Kastner et al., 1999). We found anterior portions of right DLPFC involved both when subjects filtered out distracting information (Chapter 7) and when subjects had to revisit ignored information (Chapter 5). In both cases, these activations overlapped with similar control-related activation acting upon memories. In Chapter 7, we also found comparable common DLPFC activation for perceptual and memorial selection in

the left hemisphere, about 1 cm posterior the right-sided activations. We suggested that common DLPFC recruitment across memory and perception may reflect a similar reliance on goal information to bias processing in the face of interference (Miller and Cohen, 2001). Although we did not directly assess neural activation to response conflict, our meta-analysis suggested that similar DLPFC regions were recruited across an assortment of response conflict tasks (Chapter 2). Consistent with this idea, Rowe and colleagues (2005) demonstrated common activation in the DLPFC when subjects selected amongst colors (perceptual selection) and responses (response selection). Interestingly, in addition to common activation across both forms of selection, the DLPFC produced different patterns of connectivity when subjects selected among color or response information. The DLPFC showed stronger connectivity with extra-striate cortex during color selection and stronger connectivity with premotor cortex during response selection, suggesting that the DLPFC provided a top-down signal for regions critical for representation in each task. Hence, the DLPFC may act as a common source of control, storing goal information that provides a modulatory signal that can act upon multiple representational cortices. Such representational cortices can correspond to percepts (visual cortex), responses (motor cortex), or memories (temporal cortex).

DLPFC influence on posterior regions of cortex may act through intermediaries such as the PPC (Chafee and Goldman-Rakic, 2000). In Chapter 6, we demonstrated a close association between the SPL and visual suppression in

early visual cortex, suggesting that the SPL exerted attentional control that filtered out distracting inputs. The SPL, in turn, may have received goal or template information from the DLPFC that prescribed what sorts of information to filter out. A future study examining functional connectivity between the DLPFC and SPL may find such an interaction. An alternative account is that the SPL may receive signals from the FEF regarding where to direct attention (Yantis and Serences, 2003). These interactions may also be modulated by goal information arising from the DLPFC. Consistent with this idea, Sakai and colleagues (2002) demonstrated that sustained activation in the DLPFC predicted stronger correlations between the FEF and PPC that in turn led to more accurate performance during spatial working memory, suggesting interactions between goal-information held in DLPFC and spatial working memory subserved by the FEF and PPC. Since spatial working memory and selective attention are closely intertwined (Awh and Jonides, 2001), there is reason to believe that similar interactions subserve selective attention.

Our direct comparison of selection functions acting upon perception and memory (Chapter 7) suggested that very few regions were unique to perceptual selection. Regions that were uniquely elicited by perceptual selection demands were very close to regions that overlapped with memorial selection, suggesting that variations were quantitative rather than qualitative. Behavioral work by Friedman and Miyake (2004) suggests that selective attention also has close ties to response control. Hence, selective attention may be a common component to

several forms of control. These results give neural support to the controlled attention account of interference control (Kane et al., 2001). That is, control of various forms is the act of attending to relevant representations. Such attentional processes can be brought to bear not only on perception, but also memories and responses. Our results in Chapter 7 suggest that some subjects favor more diverse strategies for different forms of selection, but subjects that more strongly recruited common control for perception and memory demonstrated better performance. Subjects that recruit common control processes may correspond to high span subjects studied by Engle and colleagues, who are hypothesized to have better controlled attention than low span subjects (Engle et al., 1999; Kane et al., 2001). Using diverse strategies to perform multiple kinds of control may actually be a compensatory mechanism to overcome difficulties with controlled attention. Hence, an interesting avenue for future research would be to compare high and low spans and the degree to which they recruit common control resources.

In contrast to hypotheses of MacLeod and colleagues (2003), we demonstrated that selective attention processes can be associated with an inhibitory mechanism (Chapters 5 and 6). In our studies, negative priming was associated with the down-regulation of early visual cortex during selective attention, and the up-regulation of that same cortex to overcome inhibition during re-encoding. However, it is unclear whether inhibition generalizes to other levels of processing. Negative priming can act at levels later than visual processing, such

as in semantic memory (Fox, 1995; May et al., 1995; Tipper, 2001). It remains possible that inhibition does not act at these later levels. Investigations into whether inhibition also exists in later stages of processing may proceed by the careful identification of relevant representational cortex and the assessment of neural down- and up-regulation during selection and re-encoding, respectively.

In summary, selective attention appears to be common to several forms of control, and may act to resolve competition from distracting percepts, memories, and responses. When selecting among percepts, control may proceed with the activation of goal information subserved by the DLPFC providing a modulatory influence on the FEF and PPC. The PPC may, in turn, select among competing inputs, selectively enhancing relevant inputs and de-selecting irrelevant inputs. De-selection appears to produce a lasting inhibitory influence that underlies visual negative priming.

8.1.2 Interference Control Over Memories – Memorial Selection

In addition to regions involved in selective attention, we demonstrated that left lateral PFC, particularly in the VLPFC, shares close ties to memorial selection (Chapters 3, 5, and 7). Left VLPFC responded to memorial selection demands across different tasks, and across different time points of selection, acting during both memory updating and retrieval. Moreover, other work has demonstrated that left VLPFC responds to demands in both short- and long-term memory (Braver et al., 2001; Cabeza et al., 2002; Ranganath et al., 2003; Nee and

Jonides, submitted), as well as demands on selection within semantic memory (Thompson-Schill et al., 1997; 2002). Hence, left VLPFC plays a broad role in memorial selection.

Recently, Badre and Wagner (2007) have hypothesized different functions for different regions of left VLPFC. In particular, they claim that anterior and inferior regions of left VLPFC (pars orbitalis, BA 47) may be involved in episodic retrieval, whereas more dorsal and posterior regions (pars triangularis, BA 45) may act more generally to resolve post-retrieval competition. Much of our work has focused upon BA 45 and has demonstrated that activation in this region correlates with interference, consistent with the claims of Badre and Wagner (2007). Moreover, this region was also responsive to the difference between forget and remember cues in Chapter 7, a putatively specific contrast of memorial selection demands. We hypothesized that forget cues had a stimulus-memory incompatibility that lured subjects to the inappropriate information. Resolving this conflict required additional activation in BA 45. Although we have not explicitly discussed BA 47, activation during memorial selection (high selection versus low selection contrast) did include BA 47. Interestingly, activation in BA 47 to memorial selection (high selection – low selection) also correlated with behavioral measures of selection demands (MNI center -52 22 2; BA 47, 153 voxels, $r = 0.66$, $p < 0.01$). High selection conditions may have placed a more general demand on retrieval operations (in addition to selection operations), producing the observed result. However, this region was not found

to differentiate forget and remember cues, suggesting that it did not respond to memory conflict. The combination of these results suggest that this task may hold some promise for dissociating mechanisms of episodic retrieval and general interference resolution.

We demonstrated that during high conflict situations, the left VLPFC demonstrates greater functional connectivity with the medial temporal lobe (Chapter 3). This result has been replicated with a different paradigm that manipulated demands on left VLPFC through trace strength, rather than interference (Nee and Jonides, submitted). Hence, in situations of high demand, the left VLPFC may work with the medial temporal lobe to perform memorial selection. This network of activation may draw parallels to the selective attention network. We hypothesized that selective attention proceeds via a network of goal-related information in DLPFC exerting an influence on attentional regions of the FEF and SPL which, in turn, influence visual cortex. In a similar way, left VLPFC may receive goal information from the DLPFC and work with the medial temporal lobe to select among memories in regions of storage such as inferior temporal cortex. An interesting avenue for future research would be to examine whether the common recruitment of DLPFC that we observed across perceptual and memorial selection begins different network cascades during different forms of selection (FEF to SPL to visual cortex for perception, left VLPFC to medial temporal lobe to inferior temporal lobe for memory). A richer data set coupled with structural equation modeling may provide answers to these questions.

Some of our findings provided somewhat mixed evidence for DLPFC involvement in memorial selection. We found robust DLPFC activation for memorial selection in Chapter 7, weaker, but still reliable DLPFC activation for resolving proactive interference in Chapter 5, but no common DLPFC recruitment for resolving proactive interference in Chapter 3. What might account for these variations? One possibility is that reliance on the DLPFC may vary as a function of selection demands. In Chapters 5 and 7, we used color cues to elicit memory updating, whereas in Chapter 3 we used a spatial cue. The phonological rehearsal loop, due to its reliance on timing, has a natural spatio-temporal characteristic. Therefore, spatial cues may map somewhat naturally to the phonological rehearsal loop, providing a means to perform selection. By contrast, color cues do not have such a natural mapping, and may therefore rely heavily on biasing by goal information stored in the DLPFC. A comparison of different selection cues may provide a means of testing this claim.

In Chapter 3 and elsewhere (Jonides and Nee, 2006) we have presented a view of left VLPFC function that does not involve inhibition. However, in Chapters 5 and 6, we posited that inhibitory processes underlied the ability to filter out irrelevant perceptual material. Hence, it is possible that some of our dissociations between memorial and perceptual selection may hinge on the fact that we have examined different processes (inhibition and recollection) across different representational domains (perception and memory). A putative

inhibitory complement to our memorial selection task may be the think/no-think paradigm of Anderson and colleagues (Anderson et al., 2001; 2004). Interestingly, activation during the no-think (memory inhibition) phase of this task relative to the think (recall) phase recruits a similar network of frontal and parietal regions that we found for memorial selection, most notably in the left lateral PFC (Anderson et al., 2004). Furthermore, lateral PFC activation is related to better memorial inhibition, as well as decreased hippocampal activation when subjects attempt to keep inappropriate memories from entering their minds. By contrast, we have demonstrated increased correlations between lateral PFC and the medial temporal lobe with increased retrieval demands (Chapter 3 and Nee and Jonides, submitted). These results suggest that the same neural regions are recruited for both inhibitory and non-inhibitory settings, but that the use of inhibition or the lack thereof alters the patterns of connectivity. Lateral PFC may co-activate with the medial temporal lobe during recollection, but suppress the medial temporal lobe when memories need to be kept from entering mind.

8.1.3 Interference Control Over Responses – Response Selection and Response Inhibition

Both the behavioral study described in Chapter 4 and the meta-analysis in Chapter 2 suggested that response control may be subdivided into response selection and response inhibition. Response selection reflects control while a response is being chosen, and response inhibition reflects control that ceases the execution of an already selected response. The meta-analysis suggested

that more dorsal aspects of the frontal lobe (DLPFC) may load heavily on response selection whereas more ventral aspects (right VLPFC) may be more heavily involved in response inhibition. Our behavioral data suggested that performing two concurrent forms of response inhibition at once was deleterious to performance, whereas performing response selection and response inhibition at the same time caused no behavioral decrement.

As we suggested earlier, the DLPFC may play a common role across perceptual, memorial, and response selection as a region that holds goal information to bias processing. In the meta-analysis, we found a significant cluster in left DLPFC when combining all of our conflict tasks together (MNI center -40 26 30) that was quite close to the common left DLPFC region found comparing perceptual and memorial selection in Chapter 7 (MNI center -44 32 30). However, several tasks included in the meta-analysis also required selective attention (e.g. Stroop and Flanker tasks), so the closeness of these clusters may be due to common perceptual selection demands. Mitigating this possibility, the go/no-go task, which had no selective attention component, also produced a significant left DLPFC cluster in the same vicinity (MNI center -40 32 34). Therefore, common DLPFC recruitment may underlie all forms of selection demands.

Response inhibition has been most closely associated with the right VLPFC, as assessed by tasks such as the stop signal task (Aron, 2007; Aron et al., 2003; 2004). Interestingly, this region also demonstrates robust activation increases

when subjects need to reorient their attention to imperative stimuli at unexpected locations (Corbetta et al, 2002; Shulman et al., 2007). The efficacy of appropriately withholding a response to a stop signal depends on the degree to which the system can orient to the stop signal and use it to guide performance. Moreover, the ability to reorient attention depends critically upon the ability to disengage attention from an inappropriate location. Thus, there may be common processes underlying response inhibition and attention reorienting, either at inhibiting inappropriate information (responses or locations), or reorienting to appropriate information (stop signals or unexpected targets).

What might distinguish response selection and response inhibition at a neural level? One distinction is that response selection can generally be prepared for in that responses are selected on the basis of current goals. By contrast, in tasks that involve response inhibition such as the stop signal task, one does not know in advance that a stop signal will occur on a given trial, giving less room for preparation. Hence, goal information (represented by the DLPFC), may be inherent in response selection tasks, but not response inhibition tasks. As a result, response inhibition tasks may be more bottom-up in nature, by letting a salient external stimulus quickly produce a non-response. By contrast, response selection tasks may be more top-down in nature, using goal information to prescribe the appropriate response to select. If response inhibition is truly bottom-up, a candidate region involved may be the right temporo-parietal junction (TPJ). The right TPJ is known to remain deactivated until a salient target

appears, at which point it activates (Shulman et al., 2007). This activation may feed-forward to the right VLPFC, which then inhibits an inappropriate response. As far as I know, this network has not been explored. By contrast, top-down processing for response selection may proceed via DLPFC to premotor connections as described earlier (Rowe et al., 2005). Premotor cortex would then, in turn, feed to motor cortex to perform the appropriate response.

The meta-analysis suggested that the anterior cingulate is a region robustly associated with response control. Much debate has centered around whether this region responds to conflict (Botvinick et al., 2002), errors (Gehring et al., 1993), or error-likelihood (Brown and Braver, 2005). Regardless of what the anterior cingulate responds to, one pattern that appears to emerge is that activation in the anterior cingulate modulates future behavior (Kerns et al., 2004; Brown and Braver, 2005). For example, Kerns and colleagues (2004) demonstrated that greater anterior cingulate activation produced greater DLPFC activation on the subsequent trial, which was in turn associated with reduced conflict. Hence, the anterior cingulate may enhance goal information stored in the DLPFC, which bolsters goal-relevant biasing.

8.1.3 The Unity and Diversity of Interference Control

Our extant data point to some poignant commonalities, as well as clear differences between multiple forms of interference control. For perceptual, memorial, and response selection, I have hypothesized that the DLPFC provides

a common goal representation that biases processing in more posterior networks. For each form of selection, the biased network differs. Visual perceptual selection may rely most strongly on the FEF and SPL to select within visual cortex. Memorial selection may proceed from left VLPFC to the medial temporal lobe to select within temporal cortex. Response selection may proceed from premotor cortex to select within motor cortex. In all cases a common DLPFC signal may give rise to posterior modulation, but in all cases, a different posterior network is involved. Response inhibition may be a uniquely bottom-up system that dissociates from these other varieties of control.

The hypothesis of common and dissociable recruitment may explain the checkered landscape of interference control. Whereas correlations among different forms of control have been extremely low (Kramer et al., 1994; Shilling et al., 2002), variables such as working memory capacity have explained variance across multiple control tasks (Engle et al., 1999; Kane et al., 2001). Common variances may be due to common recruitment of the DLPFC, whereas differences may be due to tasks that differentially load on different components of more posterior networks. These results highlight the value and need for neuroimaging. Behavioral studies provide correlations, interactions, and their absence to posit commonalities and differences. However, many such behavioral measures tap only one level of the cognitive system, whereas all cognitive tasks require a complex interplay of multiple levels of processing. It is difficult to measure each individual level of processing with data such as reaction

times, but neuroimaging provides a way to picture several component processes at once, simultaneously unveiling commonalities and distinctions. Hence, although neuroimaging studies are costly compared to behavioral research, the gains that can be obtained by the richness of brain data may far exceed these costs.

8.1.4 Open Questions and Areas for Future Work

Although we have learned a great deal about processes of interference control, several open questions remain. First, we have demonstrated that inhibition underlies some interference control processes acting during perception (Chapter 5 and 6), and others have provided similar demonstrations on output systems (Aron, 2007). However, it is unclear whether inhibition also acts in-between input and output. That is, does inhibition also act upon memories and stimulus-response associations? We have yet to find evidence for or against this proposition and answering this question would provide important data for models of interference control.

Second, I have hypothesized various different networks involved in interference control of each sort. Strong tests of this hypothesis will require large data sets suitable for computing cross-correlations among brain regions of interest across different conditions. These data sets will have to be large enough at the individual subject level to allow for accurate assessment of dynamic neural networks for each form of selection. Although we have done some functional

connectivity analyses with the extant data, the number of data points that contribute to each correlation of interest is relatively small and sensitive to outliers. Hence, accurate assessments of connectivity patterns may require much larger data sets collected over several sessions. I argue that the collection of these data sets is critical to understand how the brain performs interference control.

Our work has only briefly touched upon individual differences in interference control. I have suggested that measures such as working memory span may provide interesting individual difference data that would explain some of the variations that we have observed. Moreover, our work has carefully identified different component processes of interference control that can be applied to the study of patient populations (Jonides and Nee, 2005). Our work suggests that deficits across multiple forms of interference control in patients may reflect deficient DLPFC processing, whereas deficits unique to an individual form of interference control (e.g. memorial selection), may arise via deficient processing in other nodes of our interference control networks (e.g. left VLPFC). Precise identification of the processing pathways that are insulted can prescribe appropriate forms of treatment, and may provide a more careful means of interrogating deficits than gross neuropsychological tests.

Finally, our work may inform programs targeted at training cognitive functions. Our results suggest that the broadest impact on interference control may be

achieved by strengthening the processing of the DLPFC. Such training may take the form of requiring subjects to maintain goal information in mind while juggling multiple tasks or filtering out various forms of distraction. Hence, multi-task situations may be the best exercise to influence the various forms of interference control.

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