

Neural mechanisms of proactive interference-resolution

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The ability to mitigate interference from information that was previously relevant, but is no longer relevant, is central to successful cognition. Several studies have implicated left ventrolateral prefrontal cortex (VLPFC) as a region tied to this ability, but it is unclear whether this result generalizes across different tasks. In addition, it has been suggested that left anterior prefrontal cortex (APFC) also plays a role in proactive interference-resolution although support for this claim has been limited. The present study used event-related functional magnetic resonance imaging (fMRI) to investigate the role of these regions in resolving proactive-interference across two different tasks performed on the same subjects. Results indicate that both left VLPFC and left APFC are involved in the resolution of proactive interference across tasks. However, different functional networks related to each region suggest dissociable roles for the two regions. Additionally, regions of the posterior cingulate gyrus demonstrated unique involvement in facilitation when short- and long-term memory converged. This pattern of results serves to further specify models of proactive interference-resolution.
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Introduction

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 Doshier, 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

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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.

Materials and methods

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 7 mm and another was removed due to a signal artifact. This resulted in 23 subjects for behavioral analyses and 21 for imaging analyses.

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.

Recent Probes task

As displayed in Fig. 1A, each trial began with a 1 s red fixation cue. Thereafter, subjects were presented with a display of 6 letters for 2 s (target set), followed by a 3 s retention interval. After the retention interval, a recognition probe was presented for 2 s. 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 4 s inter-trial interval (ITI) followed each probe (5 s 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). Twenty-five percent 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

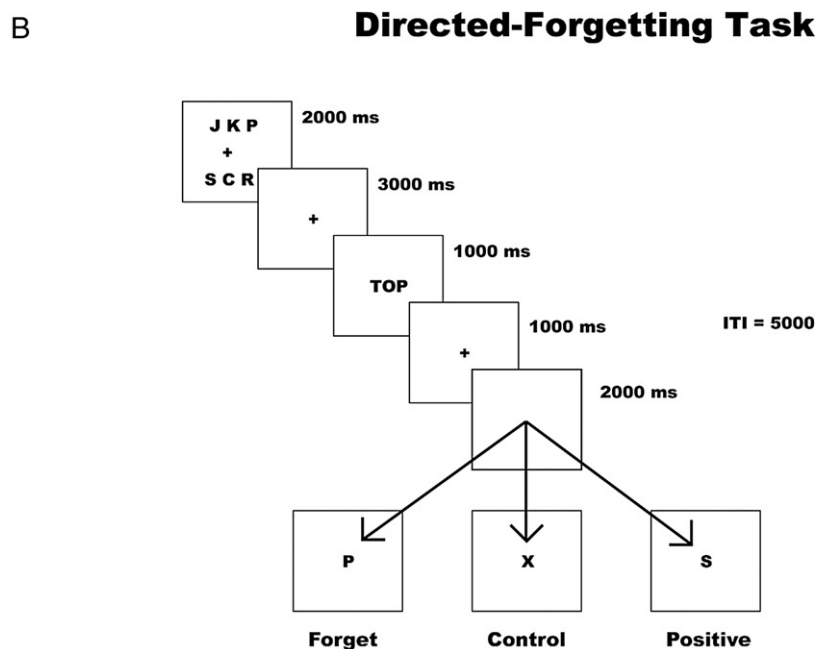
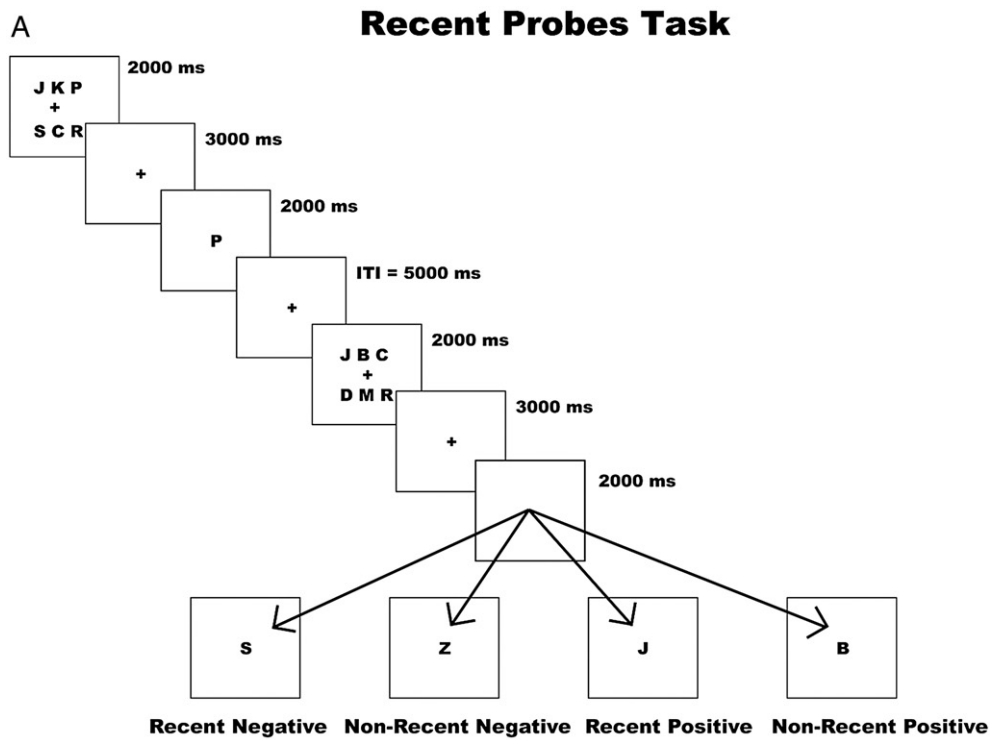


Fig. 1. Depiction of the Recent Probes and Directed-Forgetting tasks.

(Recent Negative probes), and 25% had not been presented in the previous 2 trials (Non-Recent Negative probes).

Directed-Forgetting task

As shown in Fig. 1B, each trial began with a 1 s red fixation cue. Thereafter, subjects were presented with a display of 6 letters for 2 s (initial set), followed by a 3 s retention interval. After the retention interval, a forget cue appeared for 1 s 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 1 s of fixation, followed by a recognition probe presented for 2 s. 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 4 s inter-trial interval (ITI) followed each probe (5 s 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. Fifty percent 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).

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 $3.44 \times 3.44 \times 3$ 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.stanford.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.

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 4th 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). 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 $p < 0.001$ 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 $p < 0.01$, once again producing a conjoint threshold of $p < 0.001$. 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 $p < 0.01$.

Results

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.

Self report

Fourteen 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).

Table 1
Neural activations

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 \cap 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 \cap Forget–Control \cap 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

Imaging results

Activation increases associated with proactive interference in the Recent Probes task were assessed by contrasting probe-related activity from Recent Negative probes vs. Non-Recent Negative probes (Table 1, Fig. 2A). This contrast yielded a large left lateral frontal cluster (MNI coordinate peak 4, -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 the 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 1, Fig. 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 1, Fig. 2C).

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 1, Fig. 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 the ventrolateral and dorsolateral prefrontal cortex (MNI coordinate center -46 24 20). In addition, significant clusters were found in the right dorsolateral prefrontal cortex, bilateral premotor cortex, left intraparietal sulcus, and left occipital cortex.

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

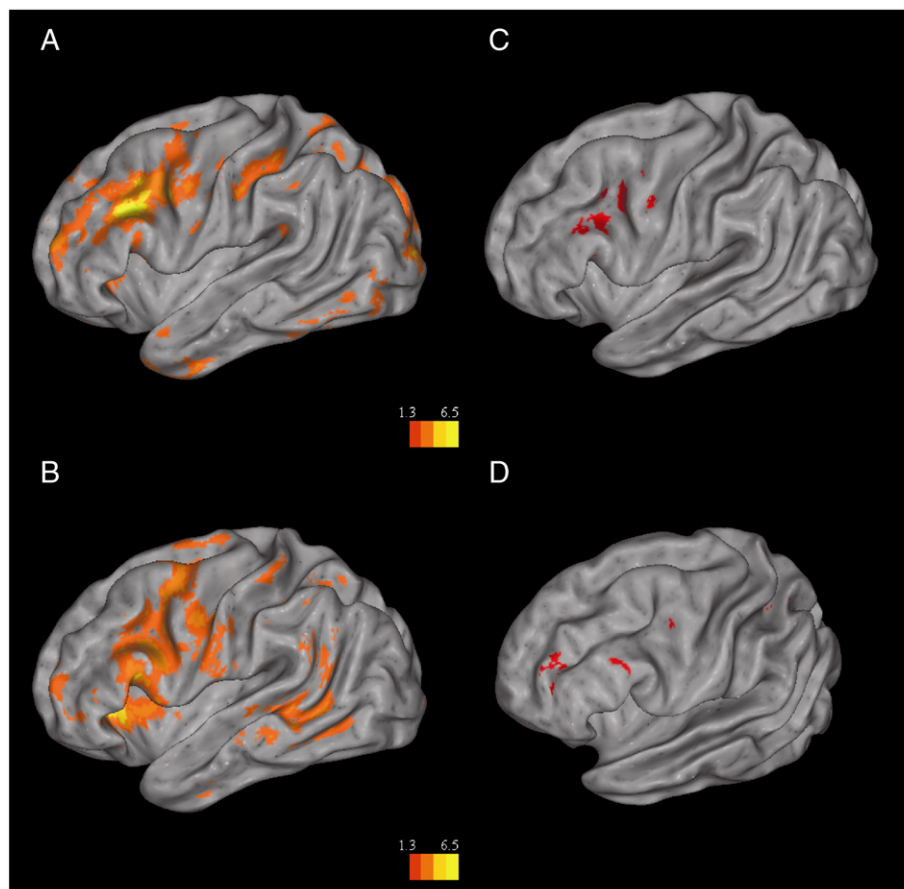


Fig. 2. Activation increases from the interference contrasts for the (A) Recent Probes (Recent Negative–Non-Recent Negative) and (B) Directed-Forgetting (Forget–Control) tasks. Colors represent t -values. (C) Regions showing activation increases for both interference contrasts (conjoint probability, $p < 0.001$). (D) Regions showing sensitivity to recency (Recent Negative–Non-Recent Negative, Recent Positive–Non-Recent Positive, Forget–Control) (conjoint probability, $p < 0.001$).

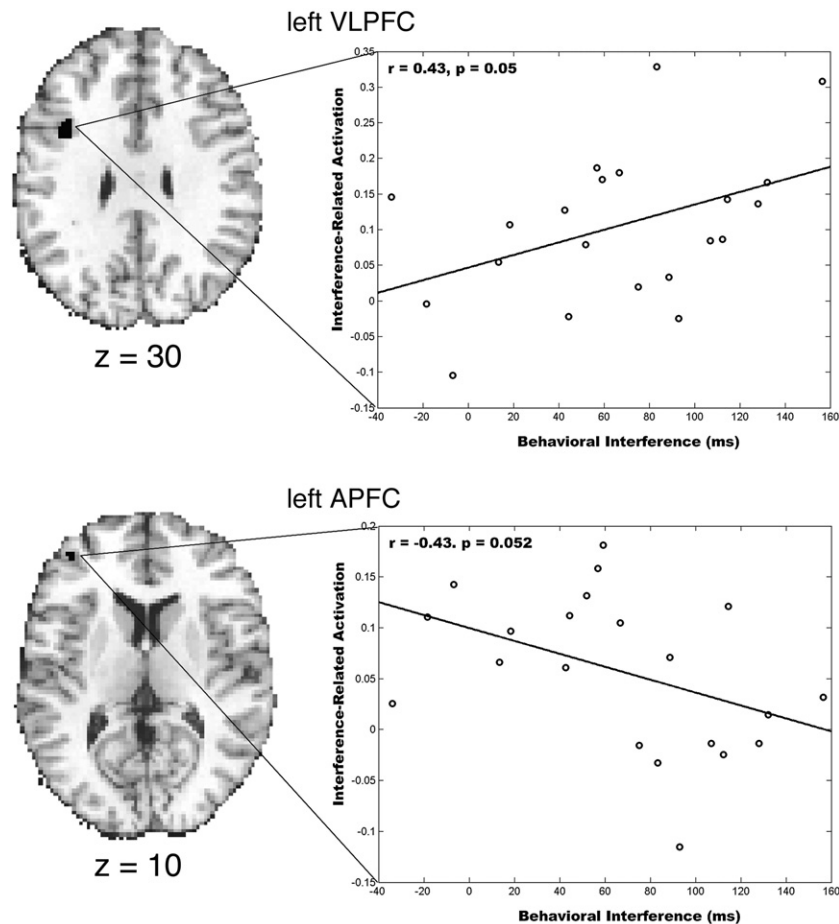


Fig. 3. Correlations between behavioral indices of proactive interference in reaction time and neural activation increases. Left VLPFC showed a positive correlation with interference, whereas left APFC showed a negative correlation.

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 (Fig. 3).

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).

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.¹ We then looked for regions showing increased connectivity to each seed region during interference trials (Recent Negative and Forget) vs. non-interference trials (Non-Recent Negative and Control) separately for each seed region. Contrasts were thresholded at $p<0.001$, with 5 contiguous voxels.

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,

¹ 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 \times 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.

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 \times 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 Fig. 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 \times 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 \times 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 \times 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 \times Probe interaction.

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 Materials and 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 Fig. 5).

Discussion

The present study sought to inform models of proactive interference by examining neural regions responsive to proactive

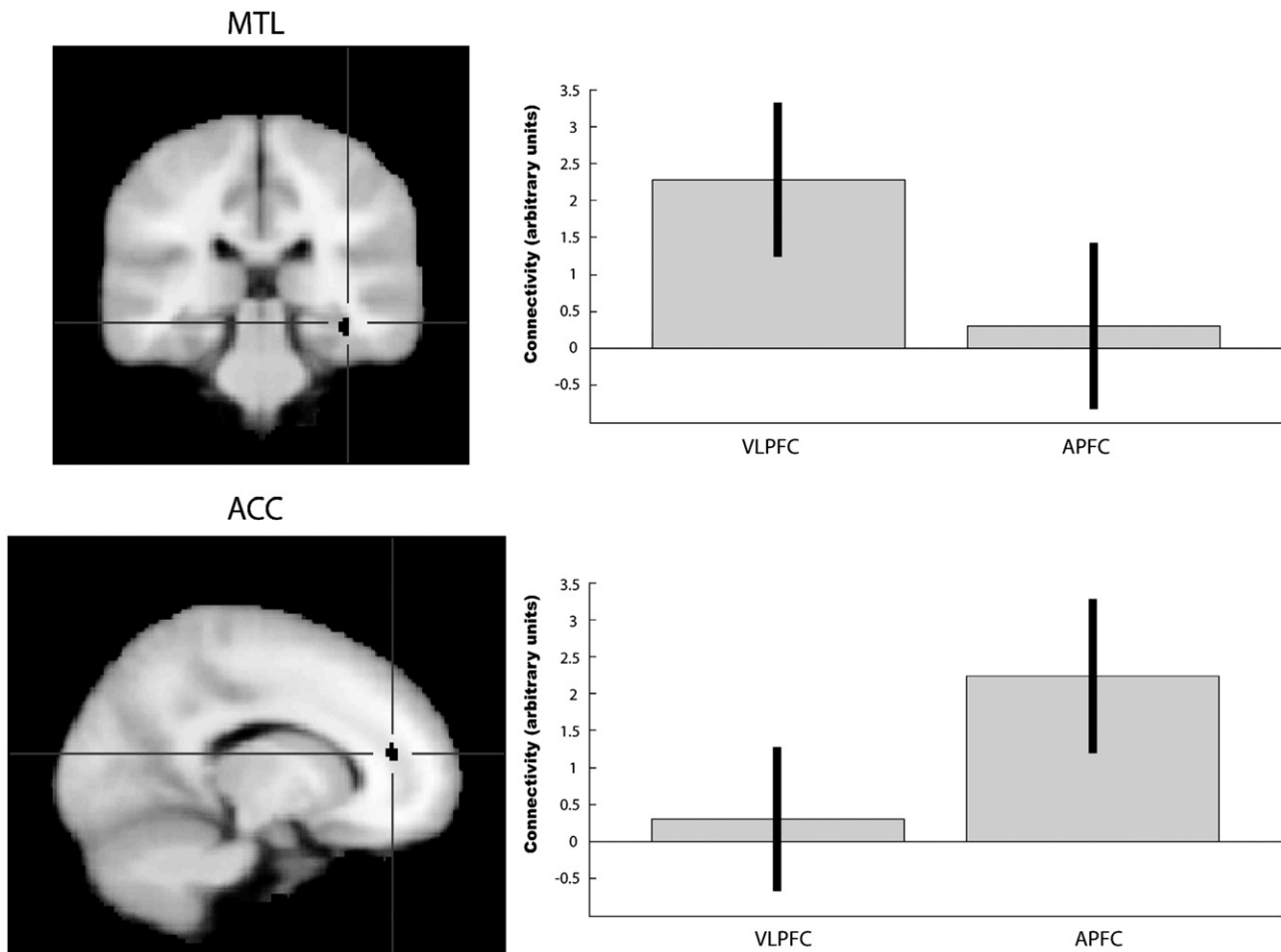


Fig. 4. The medial temporal lobe (MTL) showed stronger functional connectivity with VLPFC than APFC, whereas the anterior cingulate cortex (ACC) showed the opposite pattern.

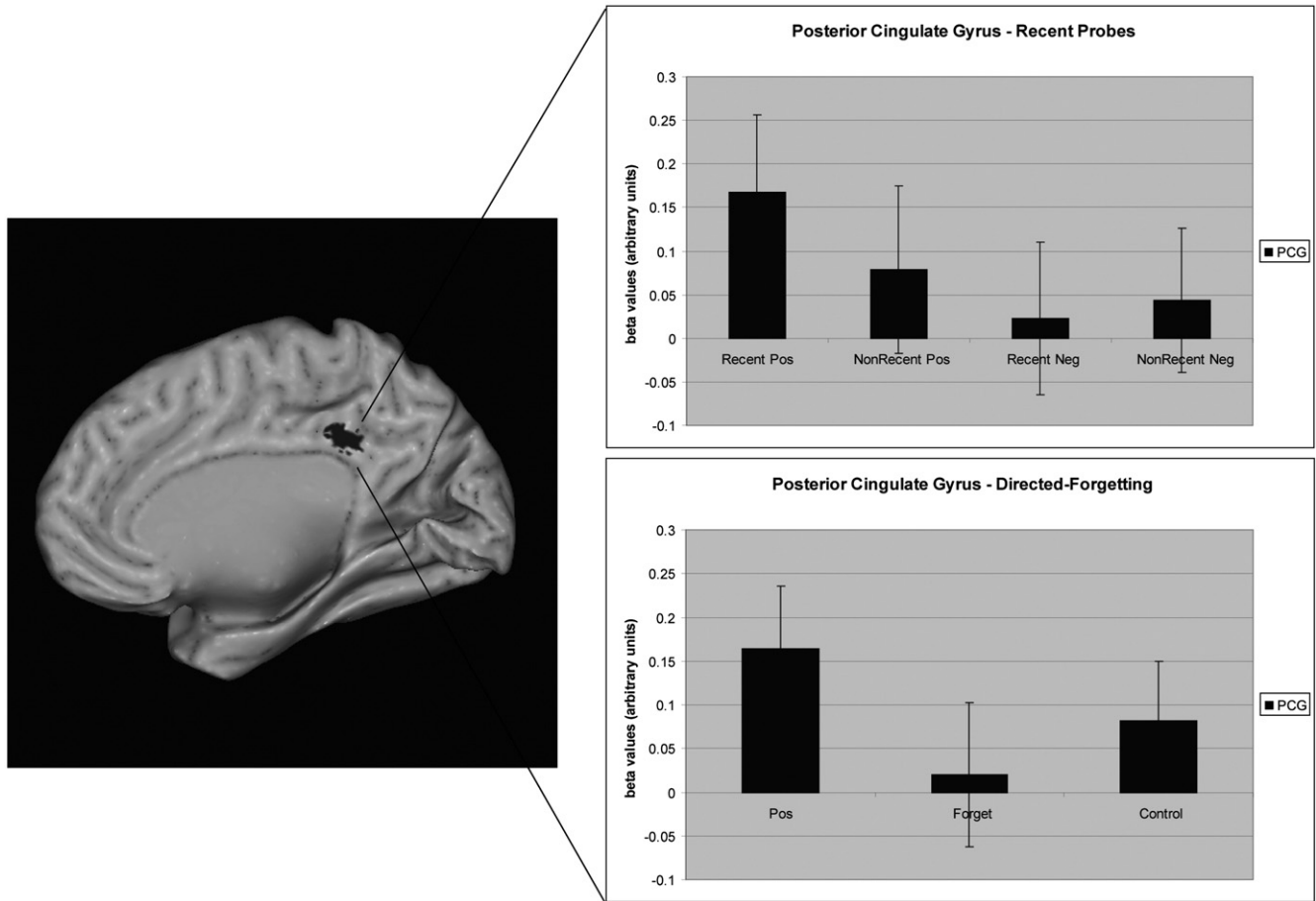


Fig. 5. Posterior cingulate region demonstrating increased activation for Recent Positive probes relative to Non-Recent Positive probes. Results shown at $p < 0.05$ uncorrected for display purposes.

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.

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., 2002; 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 the right medial temporal cortex may reflect the selection of episodic details, whereas the connectivity with the 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 is 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 \times 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).

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., 2002). 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.

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.

As a post hoc analysis to investigate this claim, 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.

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.

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 suggests 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.

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