

fMRI Evidence for an Organization of Prefrontal Cortex by Both Type of Process and Type of Information

Marcia K. Johnson, Carol L. Raye, Karen J. Mitchell, Erich J. Greene and Adam W. Anderson¹

Departments of Psychology and ¹Diagnostic Radiology, Yale University, New Haven, CT 06520-8205, USA

Neuroimaging evidence is conflicting regarding whether human prefrontal cortex (PFC) shows functional organization by type of processes engaged or type of information processed. Most studies use complex working or long-term memory tasks requiring multiple processes and the combinations of processes recruited for different materials may vary. Using functional magnetic resonance imaging (fMRI) and simple tasks suggested by a component process approach, we found activity in left PFC when participants thought about (refreshed) a just-seen item and in right PFC when participants noted whether an item had been presented previously. Furthermore, the distribution of activation in left or right PFC varied with type of information. Thus, at the component process level, PFC shows functional organization by both process and type of information.

Introduction

Working memory (WM) refers to the set of processes that allow one to sustain information and mentally manipulate it over intervals on the order of seconds. Long-term memory (LTM) refers to the set of processes that allow one to encode and remember information over intervals on the order of minutes, days, or years. There is considerable evidence that PFC is involved in both WM and LTM tasks; a major goal of current cognitive neuroimaging research is to characterize further the functional organization of PFC (D'Esposito *et al.*, 1998; Smith and Jonides, 1999; Cabeza and Nyberg, 2000; Wagner *et al.*, 2001).

Figure 1 depicts several logical possibilities for the functional organization of PFC. In model 1, distinct PFC regions are associated with different processes independent of the nature of the information the processes operate on. According to model 2, distinct PFC regions are associated with different types of information or representations engaged, independent of the process performed on those representations. In model 3, different PFC regions serve specific combinations of process and type of information. In model 4, PFC regions are not dedicated to, nor differentially recruited for, particular processes, nor for types of information, nor to unique combinations of process and information; rather, a PFC region's function changes flexibly depending on task demands and its transactions with other regions. Model 5 (not depicted) is a hybrid model in which characteristics of models 1–4 are exhibited throughout PFC (i.e. different regions of PFC correspond to different models).

As yet, there is no consensus on the functional organization of human PFC (Cabeza and Nyberg, 2000; Duncan and Owen, 2000; Goldman-Rakic, 2000; Miller, 2000; Fletcher and Henson, 2001). Although there is some evidence that PFC is organized with respect to processing distinctions such as maintenance (ventral PFC) versus manipulation (dorsal PFC) (D'Esposito *et al.*, 1998; Smith and Jonides, 1999; Haxby *et al.*, 2000), maintenance/retrieval (ventral) versus monitoring (middorsal) (Petrides, 2000), encoding (left PFC) versus retrieval (right PFC)

(Tulving *et al.*, 1994), or heuristic (right PFC) versus systematic (left or bilateral PFC) (Nolde *et al.*, 1998a), none of these distinctions fits the full range of available data (Cohen *et al.*, 1997; D'Esposito *et al.*, 1998; Nolde *et al.*, 1998a; Cabeza and Nyberg, 2000). Similarly, there is some evidence that PFC is organized with respect to distinctions between materials or information domains – verbal (left PFC) versus nonverbal (right PFC) (Smith and Jonides, 1997; Kelley *et al.*, 1998; Wagner *et al.*, 1998; Raye *et al.*, 2000) or spatial (dorsal) versus nonspatial (ventral) (Goldman-Rakic, 1987, 1995; Haxby *et al.*, 2000). However, again, there is contradictory evidence, including some findings suggesting that PFC may show little specificity (Nystrom *et al.*, 2000). Thus, PFC may be organized according to distinctions that do not fall neatly into the relatively global distinctions that predominantly have been used to frame this issue.

One reason for the lack of clarity about the functional organization of regions of PFC may be that the tasks typically used (e.g. the *n*-back task, reordering tasks, delayed item recognition tasks) are complex, involving multiple processes within and across phases of the task (perceiving information, recycling information, updating information, evaluating whether a test probe meets task criteria, etc.). In such tasks, especially as difficulty is increased, it is hard to say which processes are contributing the most to any particular brain activation pattern (Jha and McCarthy, 2000; Fletcher and Henson, 2001; Raye *et al.*, 2002). Furthermore, the more complex the task, the harder it is to assure that different materials are being subjected to the same cognitive operations. Hence, for many typical tasks, it is difficult to assess the degree to which PFC activity reflects the type of information operated upon rather than differences in the processing strategies that participants use for different materials.

We have used a component process approach to address the organization of PFC. The present studies investigated the brain areas involved in simple component cognitive operations as

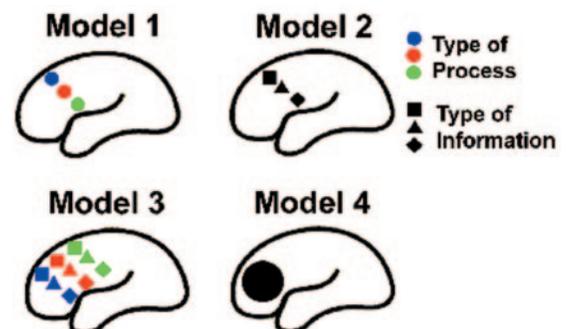


Figure 1. Four possible models of the functional organization of prefrontal cortex (see text).

characterized in the multiple entry modular memory model – MEM (Johnson, 1992). MEM assumes that memories are the byproduct of processing operations of two general types – perceptual (stimulus-driven) and reflective (internally generated). MEM proposes a mid-level cognitive description of component processes that are recruited in various combinations for various tasks (Johnson and Hirst, 1993). Reflective component processes include, for example, ‘refreshing’ (thinking of a just-activated representation), ‘rehearsing’ (recycling through one or more just-activated representations), ‘reactivating’ (relatively automatic activation of information that is no longer active), ‘retrieving’ (strategic activation of information that is no-longer active, e.g. through the self-presentation of cues), ‘noting’ (computing overlapping relations between items or between items and an agenda) and ‘shifting’ (changing focus, e.g. from one feature or element to another). Such reflective activities are the component processes that contribute to executive functions involved in WM, LTM and other higher-order cognitive functions (Johnson and Hirst, 1993; Johnson and Reeder, 1997), functions usually associated with prefrontal cortex (Stuss and Benson, 1986; Shallice, 1988).

The present studies investigated frontal brain regions involved in two reflective component processes: refreshing (experiment 1) and one type of noting – evaluating whether or not an item had been presented recently (experiment 2). We asked two basic questions: ‘do different regions of PFC subserve these two cognitive operations?’ and ‘does the region change with the kind of information a process operates upon?’ To answer the second question, three types of materials were included in experiment 1 (words, line drawings of common objects, abstract colored patterns) and two in experiment 2 (words, objects). Thus, together, these two experiments provide data for evaluating the potential models of PFC outlined in Figure 1.

Experiment 1

Event-related trials and instructions were similar for the three materials used (see top of Fig. 2). For word trials, participants were instructed to silently read individual words as each appeared on a screen. Some words were followed 550 ms later by a repetition of the word (‘repeat’), others were followed by a new word (‘read’) and others were followed by a dot (●) that

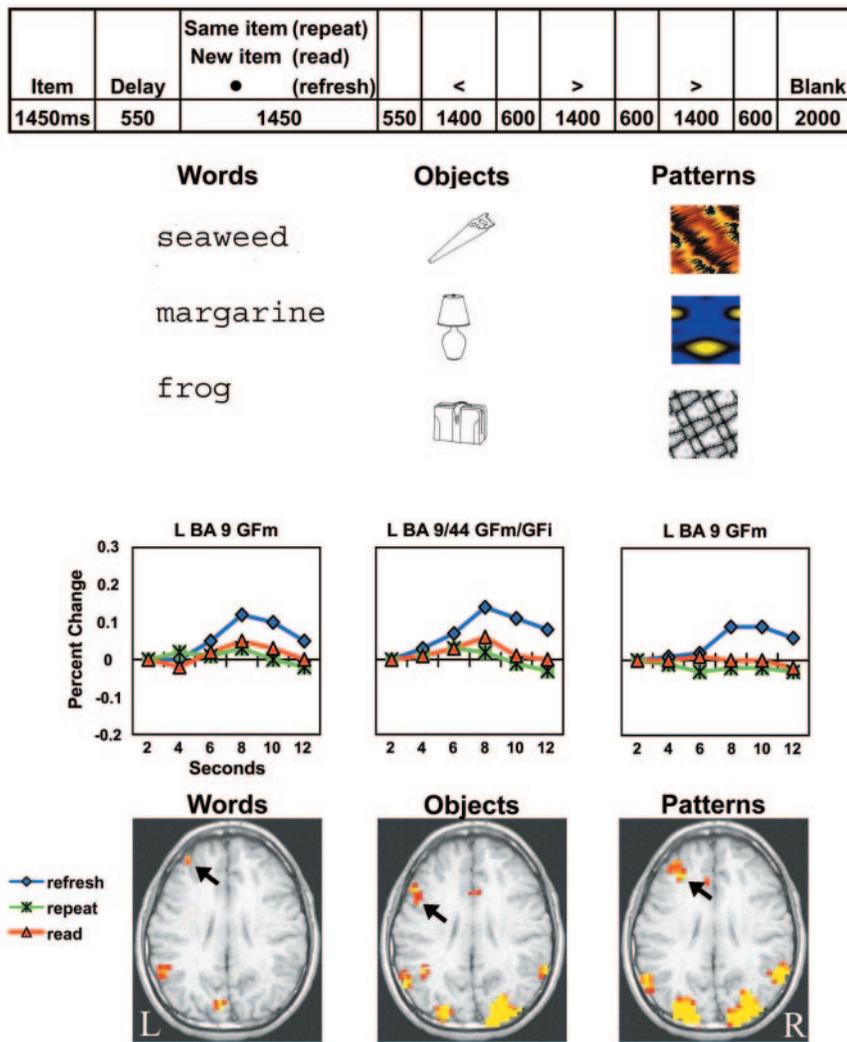


Figure 2. Frontal activations associated with refreshing. Axial slice $z = 28$. Trial event-sequence and timing for experiment 1 and example stimuli, together with left PFC regions of activation and their corresponding time-courses for three types of information: words, objects and patterns. Refresh regions shown were identified by the condition by time interaction. For the time-courses, the x-axis represents time within a trial (2, 4, 6, 8, 10, or 12 s, corresponding to volumes 1–6), the y-axis represents mean percentage change from time 1; blue diamonds, refresh; green asterisks, repeat; red triangles, read. The position of the peak reflects the lag in the hemodynamic response, typically 4–6 s.

signaled participants to think of ('refresh') the word that had just preceded the dot. Similarly, for the line drawings of objects and abstract pattern trials, participants were told to just look at each stimulus as it appeared on the screen: some items were followed by the same item ('repeat'), others by a new item (called 'read' for consistency, but, of course, participants simply looked at the objects and patterns on 'read' trials) and other items were followed by a dot that signaled participants to think of the object (pattern) that had preceded the dot (refresh). For each type of material, repeat, read and refresh trials were randomly intermixed. The interval between trials was filled with a task requiring participants to make left or right key presses in response to arrows. After scanning, participants received an old/new recognition test outside the scanner, in which previous repeat, read and refresh items (old items) were intermixed with new items, to assess LTM.

In a prior study (Raye *et al.*, 2002, experiment 1), using only words, we found greater activity in left dorsolateral PFC (BA 9) when participants refreshed a word they had just read compared to reading a word for the first time or reading the same word again. Two additional experiments – experiments 2 and 3 (Raye *et al.*, 2002) – ruled out alternative explanations that this left PFC activity was a result of task switching between trials or using a symbol to cue any thought. Thus, we expected again to find left dorsolateral PFC activated when verbal materials were the target of refreshing. Of interest in experiment 1 was whether refreshing pictorial materials (objects and patterns) activates an area of left PFC similar to that for refreshing words.

Materials and Methods

Participants

The Yale University School of Medicine Human Investigation Committee approved both experiments reported here. Participants in experiment 1 ($n = 14$, mean age 20.0 years, nine females) were healthy, right-handed young adult volunteers who gave written informed consent.

Procedure

During scanning, stimuli were projected onto a screen at the foot of the scanner, which participants viewed through a mirror mounted on the head coil. Word stimuli consisted of 80 common words of one to three syllables, such as 'knee', 'canoe' or 'professor'. Object stimuli consisted of 80 outline drawings of common objects, such as sandwich, pen or mushroom (Snodgrass and Vanderwart, 1980). The pattern stimuli were those used in previous work (Wagner *et al.*, 1998; Raye *et al.*, 2000); they were colored and abstract in appearance (see Fig. 2 for examples). The three types of materials were presented in separate runs, two for each material type. Order of material type was randomly assigned such that each material type appeared before any was repeated. Different orders were used across participants. In each run, three conditions (read, repeat and refresh, 10 trials of each) were pseudo-randomly intermixed. Across participants, for all material types each item occurred in each of the three conditions.

The structure and timing of individual trials within runs was the same for each type of material (see top of Fig. 2). Each trial was 12 s long. Participants were told that whenever they saw a word on the screen they should read it silently to themselves, when they saw an object or pattern they should just look at it and when they saw a black dot they should think back to the just-previous item. They were told that when they saw an arrow they should push the left button with the index finger of their right hand if the arrow pointed left and to push the right button with their middle finger if it pointed right. The arrows provided an 8 s intertrial-interval (ITI) task, common to all conditions, to allow the hemodynamic response associated with reading/looking or refreshing to return to baseline. We used this procedure rather than a 'rest' period in order to reduce variability among participants from uncontrolled mental activity (Raye *et al.*, 2002). It should be noted that the arrow task was not used as a baseline against which each experimental condition was contrasted,

but rather as a common activity across conditions to space out the trials. All statistical comparisons (described below) were between conditions (read, repeat, refresh).

About 7 min after exiting the scanner, participants were given a surprise old-new recognition test. The test was blocked by type of material. For each type of material, 45 old items from phase 1 (a random 15 each of refresh, repeat and read items) and 45 completely new items were intermixed in a pseudo-random order. Each item was presented via computer for 2 s with a 1 s interstimulus interval. The order in which the material types were tested was counterbalanced across participants. Participants responded by pressing one key to indicate 'old' and another to indicate 'new.'

Imaging Details

Both experiments reported here used a 1.5 T SIGNA scanner (GE Medical Systems) at the Yale University School of Medicine. T_1 -weighted anatomical images were acquired for each participant. Functional scans were acquired with a single-shot echo-planar gradient-echo pulse sequence ($T_R = 2000$ ms, $T_E = 35$ ms, flip angle = 65° , FOV 24). The 20 axial slices (resolution 3.75×3.75 mm in plane, 3.8 mm between planes) in each volume were aligned with the AC-PC line. In both experiments, each run began with 12 s of blank screen to allow tissue to reach steady-state magnetization and each run was followed by a 1 min rest interval. For each person, the number of volumes for each combination of condition and material type totaled 120 (experiment 1) and 144 (experiment 2).

Analyses of Behavioral Data

The LTM old/new recognition data obtained for each study are expressed as d' scores. For each study, planned pairwise comparisons among conditions (e.g. refresh versus read) were conducted for each type of material. Unless otherwise noted, $P < 0.05$. Because of a technical error in data collection, data from one participant's object trials were not included in the behavioral analyses and the participant was omitted from analyses of functional magnetic resonance imaging (fMRI) data comparing across materials or experiments.

fMRI Analyses

After reconstruction, time-series were shifted by sinc interpolation to correct for the slice acquisition times. Data were motion-corrected using a six-parameter automated algorithm – AIR (Woods *et al.*, 1992). A 12-parameter AIR algorithm was used to co-register participants' images to a common reference brain. For each experiment, data were mean-normalized across time and participants, and spatially smoothed (3-D, 8 mm FWHM Gaussian kernel).

The data were analyzed using NIS software (Laboratory for Clinical Cognitive Neuroscience, University of Pittsburgh and the Neuroscience of Cognitive Control Laboratory, Princeton University). In experiment 1, for each material type, we used an analysis of variance (ANOVA) with participant as a random factor and run (1–2), condition (read, repeat, refresh) and time within trial (volume 1–6) as fixed factors. Regions in the condition by time ($C \times T$) interaction were identified that had a minimum of six contiguous voxels, each significant at $P < 0.001$ (Forman *et al.*, 1995). These F -maps were transformed to Talairach space and areas of activation were localized using AFNI (Cox, 1996) and Talairach Daemon software (Lancaster *et al.*, 1997), as well as manually checked with atlases (Talairach and Tournoux, 1988; Mai *et al.*, 1997). In Figures 2 and 3, group activations are shown on a single reference brain. The coordinates reported (experiment 1, Table 1) represent local maxima in each $C \times T$ region of activation that also showed in subsequent analyses significantly ($P < 0.005$) greater percentage change (scans 4 and 5 relative to scan 1) in the refresh condition compared to the combined control conditions (read, repeat). We also conducted an overall ANOVA with the added factor of materials (words, objects, patterns) to examine potential condition by material interactions, followed by subsequent comparisons for each type of material of percentage change scores (scans 4 and 5 relative to scan 1) between refresh and read conditions.

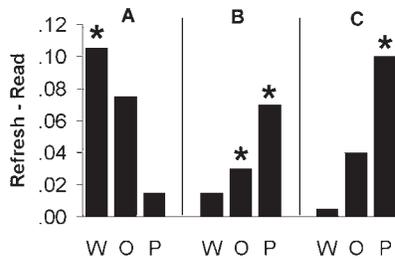


Figure 3. Areas of PFC showing a materials by condition interaction. The y-axis represents the difference between refresh and read in percentage change (times 4 and 5 relative to time 1); W, words; O, objects; P, patterns. (A) A region of left GfM, BA 9/8 ($x = -52, y = 12, z = 40$) showing refresh > read for words ($P < 0.10$), but not for objects or patterns ($P > 0.10$). (B) A region of left GFs/GfM, BA 10, 9 ($x = -18, y = 54, z = 20$) showing refresh > read for both objects ($P < 0.06$) and patterns ($P < 0.001$), but not for words ($P > 0.10$). (C) A region of right GFi, BA 47 ($x = 46, y = 20, z = -4$) showing refresh > read ($P < 0.07$) for patterns, but not for words or objects ($P > 0.10$).

Results and Discussion

Behavioral Results

The mean LTM recognition accuracy scores (d') showed the expected advantage (Johnson *et al.*, 2002) for items that had been refreshed: for words, refresh (1.78) > repeat (1.44) = read (1.41) and for objects, refresh (2.77) > repeat (2.49) = read (2.29). In contrast, for patterns, repeat (1.32) had a marginal ($P < 0.07$) advantage over read (1.02) and refresh (1.06) did not differ significantly from either read or repeat. We believe that the ordering of the conditions in LTM for patterns reflects the greater difficulty participants had in adequately refreshing, that is re-representing the visual patterns to themselves during encoding. Thus, a second thought is better than a second look for long-term recognition memory of words and objects (Johnson *et al.*, 2002), but not abstract patterns. [Note that a second thought might not be expected to be better than a second look for words and objects on an implicit memory test that draws on perceptual representations, for example item identification under degraded conditions, rather than explicit old/new recognition (Johnson *et al.*, 2002).]

fMRI Results

Figure 2 (left column; see also Table 1) shows that we replicated our previous findings (Raye *et al.*, 2002) – greater activity associated with refreshing a just-seen word in left dorsolateral prefrontal cortex, GfM, BA 9, extending into GFs (see footnote to Table 1 for a key to abbreviations). Figure 2 also shows that left PFC activity was associated with refreshing line drawings of objects and abstract patterns. Objects showed two areas of activation in left PFC: GfM/GFi, BA 9/44, 46 (Fig. 2 and Table 1) and GfM, BA 10 (Table 1). Patterns also showed two areas of left PFC activation, GfM extending into GFs, BA 9 (Fig. 2 and Table 1) and GfM, BA 46, 10 (Table 1). Table 1 shows representative coordinates for these frontal regions, as well as other regions that showed refresh-related activity (these other regions will be discussed in a subsequent paper).

An overall ANOVA with the added factor of materials produced three PFC regions showing refresh-related, materials by condition interactions ($P < 0.01$, six contiguous voxels). Planned subsequent comparisons of percentage change (times 4 and 5 relative to time 1) were conducted (see Fig. 3). An area of left PFC (GfM, BA 9/8) showed refresh > read for words ($P < 0.10$), but no significant difference between refresh and read for objects or textures ($P > 0.10$; see Fig. 3A); an area of left PFC

Table 1
Regions of activations for experiment 1 (separate analyses for each material)

| Material | Left/right | Region | BA | x | y | z | C × T F-value |
|----------|------------|-----------|----------|-----|-----|----|------------------|
| Words | L | GfM, GFs | 9, 10 | -34 | 46 | 28 | 3.87 |
| | L | Gsm, LPi | 40 | -54 | -42 | 42 | 4.50 |
| Objects | L | GfM/GFi | 9/44, 46 | -48 | 20 | 24 | 5.29 |
| | L | GfM | 10 | -38 | 48 | 7 | 4.55 |
| | L | GTm | 21 | -63 | -44 | 0 | 5.10 |
| | L | Gsm, LPi | 40 | -54 | -42 | 43 | 5.81 |
| | R | Gsm | 40 | 62 | -50 | 28 | 4.90 |
| | R | Caud, Put | | 14 | 10 | 9 | 3.96 |
| Patterns | M | PCC | 31 | -4 | -29 | 40 | 4.34 |
| | L | GfM, GFs | 9 | -29 | 32 | 32 | 4.18 |
| | L | GfM | 46, 10 | -38 | 46 | 16 | 5.00 |
| | L | Gsm, LPi | 40 | -55 | -42 | 44 | 8.19 |
| | R | Gsm, LPi | 40 | 54 | -40 | 41 | 5.92 |
| | L | GTm, GTs | 21, 22 | -56 | -47 | 9 | 4.17 |
| | L | Ins, Oper | | -39 | 10 | 1 | 5.63 |
| | L | GFi, GTs | 47, 22 | -47 | 15 | -4 | 5.38 |
| | M | ACC | 32 | -2 | 24 | 36 | 4.08 |

Abbreviations: BA, Brodmann area; ACC, anterior cingulate; Caud, caudate; GF, fusiform gyrus; GFi, inferior frontal gyrus; GfM, middle frontal gyrus; GFs, superior frontal gyrus; GH, parahippocampal gyrus; GOM, middle occipital gyrus; Gsm, supramarginal gyrus; GTi, inferior temporal gyrus; GTm, middle temporal gyrus; GTs, superior temporal gyrus; GTT, transverse temporal gyrus; Ins, insula; LPi, inferior parietal lobule; LPs, superior parietal lobule; Oper, operculum; PCC, posterior cingulate; PCu, precuneus; Put, putamen.

(GFs/GfM, BA 10, 9) showed refresh > read for both objects ($P < 0.06$) and patterns ($P < 0.001$), but not words ($P > 0.10$; see Fig. 3B); and an area of right PFC (GFi, BA 47) showed refresh > read for patterns ($P < 0.07$), but not for words ($P > 0.10$) or objects ($P > 0.10$; see Fig. 3C).

Taken together, the pattern of results indicates that refreshing words, objects and patterns were all associated with activation in left PFC and that there were differences in the distribution of activity across left PFC depending on the type of material being refreshed. In addition, when materials were directly compared, a region of right PFC was also identified with refresh > read for patterns, but no significant difference between refresh and read conditions for words or objects.

Experiment 2

Whereas experiment 1 investigated the neural correlates of refreshing just-seen information, experiment 2 investigated the neural correlates of noting whether or not information had been seen recently. Words and objects were again compared in experiment 2 to assess whether there was a difference in activation between materials with another process held constant. The trial structure and timing for experiment 2 are shown at the top of Figure 4. On each trial, an item was presented in black. It was followed after a short delay by another black item (a read trial) or by a red item that signaled the participant to note (silently) whether or not the item had been presented earlier (short-term old/new recognition). There were three types of red items on noting trials: an old item that was the same as the just-previous black item (immediate); an old item that was the same as a black item from two or three trials (i.e. up to 36 s) earlier (delay); or an item that had not previously been presented (new). Relative to read trials, these old/new recognition trials asked participants for an evaluation (noting whether the item was old or new). In this task, noting whether an item was old or new after minimal encoding and very short retention intervals presumably involved primarily evaluation of familiarity/novelty, or relative recency. Following this phase, participants received a

| | | | | | | | | | | |
|--------|-------|------------------|-----|------|-----|------|-----|------|-----|-------|
| | | New-item (read) | | | | | | | | |
| | | Old-item (immed) | | | | | | | | |
| | | Old-item (delay) | | | | | | | | |
| | | New-item (new) | | | | | | | | |
| Item | Delay | | < | > | > | | | | | Blank |
| 1450ms | 550 | 1450 | 550 | 1400 | 600 | 1400 | 600 | 1400 | 600 | 2000 |

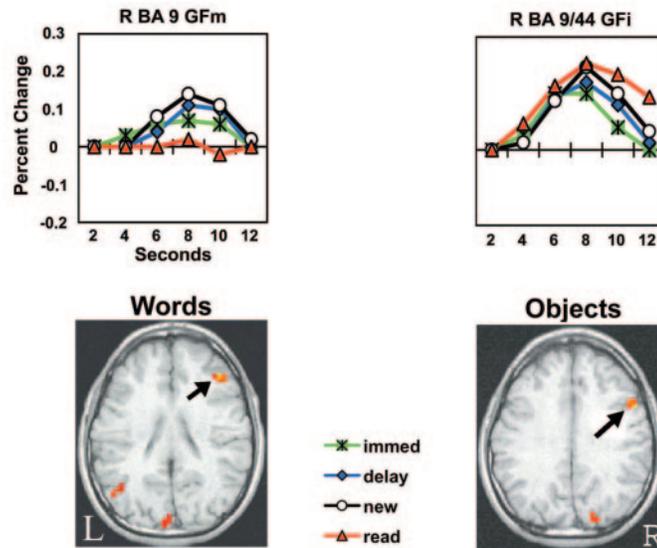


Figure 4. Frontal activations associated with noting old–new. Axial slice $z = 26$ (words) and $z = 32$ (objects). Trial event-sequence and timing for experiment 2, together with right PFC regions of activation and their corresponding time-courses for two types of information: words and objects. Regions associated with noting whether an item was old or new were identified by the condition by time interaction. For the time-courses, the x-axis represents time within a trial (2, 4, 6, 8, 10, or 12 s, corresponding to volumes 1–6), the y-axis represents mean percentage change from time 1; green asterisks, old (immediate); blue diamonds, old (delay); white circles, new; red triangles, read. The position of the peak reflects the lag in the hemodynamic response, typically 4–6 s.

LTM old/new recognition test, outside the scanner, in which phase 1 immediate, delay, new and read items (old) were intermixed with items that were entirely new.

Materials and Methods

Participants

Experiment 2 had 15 participants (mean age 20.9 years, 10 females).

Procedure

The trial timing was the same as in experiment 1. Words and objects were taken from the same pool as those used in experiment 1. Three runs using words (W) and three runs using objects (O) were ordered WOWOWO or OWOWOW. Each run included 32 trials, eight trials of each condition (read, immediate, delay and new), which were pseudo-randomly intermixed. Across participants, each item occurred in each of the four conditions for words and objects.

As in experiment 1, after ~7 min, participants were given a surprise old–new recognition test for the items outside of the scanner. The test was blocked by material type. For each material, 72 items from phase 1 (18 from each condition) and 72 new items were intermixed in a pseudo-random order. Each item was presented for 2 s with a 1 s interstimulus interval. Participants responded ‘old’ or ‘new’ by pressing corresponding keys. The order of material types was counterbalanced across participants.

The analyses of fMRI data followed the procedures described for experiment 1. For experiment 2, for each material type, participant was a random factor, and run (1–3), condition (immediate, delay, new, read) and time within trial (volume 1–6) were fixed factors. The coordinates reported (experiment 2, Table 2) represent local maxima in each $C \times T$ region of activation (a minimum of six contiguous voxels, $P < 0.001$) that also showed in subsequent analyses significantly different percentage change (mean times 4, 5 and 6 relative to time 1) in the note conditions (immediate, delay and new combined) compared to the read control

condition ($P < 0.01$). We also conducted an overall ANOVA including the additional factor of materials (words, objects) to compare type of material directly; it was followed by subsequent comparisons between conditions (as detailed below) of percentage change (mean times 4, 5 and 6 relative to time 1).

Behavioral data were analyzed as in experiment 1.

Results and Discussion

Behavioral Results

As in experiment 1, we looked at d' scores for the final, long-term old/new recognition test for each type of material separately (comparing phase-1 or encoding conditions – immediate, delay, new and read). For words, delay (1.54) > immediate (1.07) = new (1.00) \geq read (0.81; $P = 0.06$). For objects, delay (2.54) > immediate (1.99) > new (1.71) = read (1.78). In short, for both types of material, LTM benefited most from a delayed test. We suggest that the greater advantage of noting old/new in the delayed than immediate condition was because, in addition to the noting operation, the delay condition required reactivating a no-longer-active representation (Johnson, 1992; Johnson and Chalfonte, 1994), while the representation was still active at the time of noting in the immediate condition. This is consistent with other evidence that recalling information that is still active may have relatively little long-term benefit (Craig, 1970).

fMRI Results

In contrast to the left PFC activation found for refreshing, noting whether an item was old or new was associated with activation in right PFC (see Fig. 4): for words, GFm, BA 9 and for objects, BA 9, 44, on the border of the middle and inferior frontal gyri

Table 2

Regions of activation for experiment 2 (separate analyses for each material)

| Material | Left/right | Region | BA | x | y | z | C × T F-value |
|----------|----------------|-----------|--------|-----|-----|----|------------------|
| Words | R | GfM | 9 | 41 | 33 | 26 | 4.12 |
| | L | Gsm | 40 | -58 | -47 | 37 | 3.07 |
| | L* | LPI, GTT | 40, 41 | -51 | -28 | 21 | 3.25 |
| | L* | GTm, GTs | 39 | -49 | -63 | 22 | 3.77 |
| | R* | Ins, Oper | 13 | 42 | -7 | 16 | 3.22 |
| | L | GTs, GFi | 22, 47 | -52 | 14 | -3 | 4.45 |
| | R | GTs | 22 | 50 | 13 | -4 | 3.56 |
| | R | GH, GF | 19, 37 | 24 | -50 | -2 | 4.38 |
| | M | ACC | 32 | -2 | 26 | 33 | 3.93 |
| | R* | GfM, GFi | 9, 44 | 53 | 12 | 32 | 3.21 |
| Objects | L ^a | Gsm | 40 | -58 | -42 | 37 | 2.98 |
| | R* | LPs, PCu | 7, 19 | 29 | -67 | 40 | 3.22 |
| | R* | GTm | 37 | 41 | -65 | 10 | 3.72 |
| | L* | GTi, GOm | 19 | -48 | -68 | 0 | 5.12 |

Notes. See Table 1 for abbreviations. Noting old/new > read, except as noted with an asterisk, where read > noting old/new.

^a $P < 0.04$.

(see Table 2). From the timelines in Figure 4, it is also evident that the pattern of activity among conditions was different for words and objects. For words, activation was significantly greater in the three noting conditions compared to the read condition. In contrast, for objects, activation in the noting conditions was significantly less than in the read condition.

An overall ANOVA including materials as a factor produced two regions showing noting-related, materials by condition interactions ($P < 0.01$, six continuous voxels). The first was a right frontal region at the juncture of GfM, GFi and GPrC (BA 9), where subsequent comparisons of percentage change scores showed that for objects ($P < 0.02$), but not for words ($P > 0.10$), the activation for novel items (new, read) was greater than for old items (immediate, delayed) – see Figure 5A. The second was a left frontal region (GFi, BA 47/45/insula), where for words ($P < 0.04$), but not objects ($P > 0.10$), the activation for noting old/new (immediate, delay and new conditions) was greater than in the read condition (see Fig. 5B). This pattern suggests two conclusions. First, as suggested by the analyses conducted for each material separately (Fig. 4), novelty seems to have been a greater factor for objects than words. Secondly, although right PFC regions were associated with noting old/new for both words and objects (see Fig. 4 and Table 2), for words, a region of left PFC showed noting-related activity as well (Fig. 5B).

Comparison of Experiment 1 and Experiment 2 (Refreshing versus Noting)

In order to compare directly the refreshing process investigated in experiment 1 and the noting old/new (recognition) process investigated in experiment 2, we conducted an ANOVA including experiment as a factor [the means and variances of the blood oxygen level dependent (BOLD) signal for the two experiments did not differ significantly, $P_s > 0.50$]. The analysis included the read (control) and refresh (experimental) conditions for words and objects from experiment 1 and the read (control) and immediate noting (experimental) conditions for words and objects in experiment 2. This constituted a comparison, relative to their respective read controls, between refreshing an item or noting whether it was old or new after a comparable (550 ms) retention interval. This analysis identified a region of left PFC (GfM, BA 46) in which there was a condition by experiment interaction ($P < 0.01$, six contiguous voxels). Subsequent

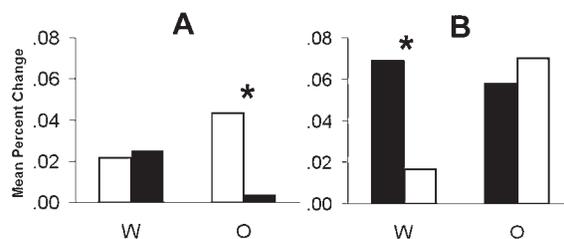


Figure 5. Areas of PFC showing a materials by condition interaction. (A) A region at the juncture of right GfM, GFi and GPrC, BA 9 ($x = 37, y = 9, z = 28$) in which, for objects only, the signal during processing of novel items [read, new (white)] was greater than during processing of old items [immediate, delay (black)] ($P < 0.025$). (B) A region of left GFi, BA 47/45/insula ($x = -32, y = 22, z = 2$) in which, for words only, the signal during noting old/new [immediate, delay, new (black)] was greater than in read (white) ($P < 0.04$). The y-axis represents the percentage signal change (times 4, 5, 6 relative to time 1) averaged across conditions as specified above. W, words; O, objects.

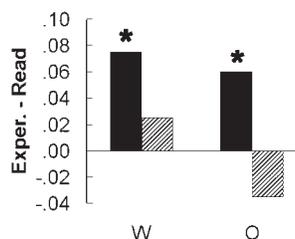


Figure 6. A region of left GfM, BA 46 ($x = -46, y = 30, z = 20$) showing a condition by experiment interaction ($P < 0.01$). In experiment 1 (refreshing, black bars), for both words ($P < 0.01$) and objects ($P < 0.07$), refresh > read. In experiment 2 (noting, hatched bars), differences between immediate and read were not significant for either words or objects. The y-axis represents the difference in percentage change signal between each experimental condition (refresh or immediate) and its own read control condition. W, words; O, objects.

comparisons were carried out to clarify this interaction. For both words ($P < 0.01$) and objects ($P < 0.07$), the percentage change (times 4 and 5 relative to time 1) in the refresh condition was greater than its corresponding read condition (see black bars in Fig. 6), but the immediate note condition was not significantly different from its corresponding read condition ($P > 0.10$; see hatched bars in Fig. 6). This pattern indicates that left PFC was more involved in refreshing an item than in noting whether an item was old or new. A noting-related area in the right PFC was not identified in this analysis that included materials as a factor. That is not surprising, however, given that the relation of noting to read conditions was in opposite directions in right PFC for words and objects (see Fig. 4) and thus would tend to cancel each other out.

General Discussion

Taken together, the results of these two experiments show that left PFC participates in refreshing verbal and pictorial information, including drawings of familiar objects and abstract patterns (Fig. 2) and right PFC participates in noting whether a word or object was recently presented (short-term old/new recognition; Fig. 4). For each type of process, the distribution of activity within these respective PFC areas depended on materials (arguing against model 1) and, for a given type of material, the regions most engaged depended on process (arguing against model 2). In short, at the mid-level characterization of component cognitive operations represented in MEM (Johnson and Hirst, 1993; Johnson and Reeder, 1997), PFC showed a different

distribution of activation depending on the specific combination of information and process (supporting model 3).

We should emphasize that functional specificity of PFC with respect to the self-initiated, reflective processes investigated here likely reflects differences in the characteristic distribution of participation of PFC regions, rather than distinct processing modules located in distinct regions of PFC (Haxby *et al.*, 2000). That left PFC is associated with refreshing and right PFC with noting does not imply that the opposite hemisphere is not engaged at all by a particular process or cannot be engaged when necessary (Banich, 1998). In fact, the present data show that the opposite hemisphere is sometimes recruited (more refresh-related activity in right PFC for patterns than for words or objects and more activity associated with noting old/new in left PFC for words than for objects). Nevertheless, across a number of conditions – in previously published work (Raye *et al.*, 2002), the present experiments and several unpublished studies – we have consistently observed left PFC activity when participants refresh a range of materials. Furthermore, our observation of right PFC activity associated with old/new recognition after short intervals for both words and objects is consistent with many prior observations of right PFC activity during longer-term old/new recognition (Tulving *et al.*, 1994; Nolde *et al.*, 1998a; Cabeza and Nyberg, 2000).

Our findings also suggest that, for a given process, different materials may result in a differential distribution of participation of areas within left and right PFC. This may reflect consistent differences between materials in distribution of neural activity that would show up across a variety of situations, perhaps reflecting different distributions within PFC of neurons tuned to different stimulus features (Goldman-Rakic, 1995). Alternatively, the particular pattern we observed may represent more temporary differences in distributions of activation ‘assigned’ to different types of materials within a given situation, perhaps reflecting flexible recruitment or tuning of the same neurons depending on task goals and context – model 4 (Miller, 2000). That is, activation in PFC may be segregated to some extent by materials and/or processes in temporary ways that facilitate ongoing cognition in particular contexts. Thus, model 4 may be correct in the abstract, but various versions of model 3 correct in practice (i.e. a context-dependent model 3). Additional studies will be needed to determine, for example, if the location of the significant region(s) of left PFC activation associated with refreshing a given type of material (or right PFC activation associated with old/new judgments for a particular type of material) depends on the entire task context (e.g. the particular types of other information being refreshed or recognized) or remains constant as the task context (e.g. the other types of items presented) is varied.

Our finding that refreshing was left lateralized and that noting was right lateralized, for both verbal and pictorial information, may appear at first to be inconsistent with prior findings showing that processing of verbal material is often left lateralized and processing of pictorial information is right lateralized (Kelley *et al.*, 1998; Wagner *et al.*, 1998; Raye *et al.*, 2000). However, studies that have compared materials have not necessarily separated perceptual from reflective processing and typically have had less overall control over the specific operations engaged than in the present studies. If considered separately, perceptual and reflective processes (Johnson, 1992; Johnson and Hirst, 1993) may show different lateralization patterns; furthermore, some perceptual and reflective component processes may show lateralization by materials and others may not. Another potentially important consideration is that laterality

differences are most consistently found when types of materials are directly contrasted (Wagner *et al.*, 1998; Raye *et al.*, 2000). As indicated by the present findings, although this approach identifies areas where activation differs by materials, it may underestimate commonalities across materials in general regions (e.g. hemispheres) participating in the processes that operate on them.

Both WM and LTM tasks are composed of various combinations of more specific component processes. For example, WM tasks, such as ordering information (e.g. alphabetizing) or the continuous *n*-back task, require participants to rehearse, compare items to each other, or compare each new item to another in the rehearsal set, then update the rehearsal set and continue rehearsing. We propose that selective refreshing is a primary component of functions such as updating (Raye *et al.*, 2002) and that the evaluation of each item with respect to the target set is a form of noting. Hence, many complex WM tasks may require repeated refreshing intermixed with repeated noting. Thus, component processes of refreshing and noting likely contribute to the left and right PFC activity often found in ordering and *n*-back tasks (Petrides *et al.*, 1993; Cohen *et al.*, 1997; Smith and Jonides, 1999).

Event-related designs in combination with simpler WM tasks such as delayed item recognition have allowed investigators to examine brain activity associated with different phases of a task–stimulus presentation, delay and test (Courtney *et al.*, 1998; Zarahn *et al.*, 1999). While it seems reasonable to assume that the processes recruited might differ in different task phases (e.g. refreshing during stimulus presentation, rehearsal during the delay and noting during the test), nevertheless, there should be different mixes of component processes during task phases, depending on the particulars of the task. For example, increasing the potential for intertrial interference may prompt additional encoding activities beyond refreshing (e.g. rehearsing), or additional delay activities beyond rehearsing (e.g. noting semantic or other relations), or test activities beyond noting (e.g. refreshing). That is, task phases do not constitute component cognitive processes but rather occasions for various component processes to be recruited.

With respect to LTM, the fact that left PFC was active when participants simply refreshed items suggests that some of the left PFC activity found in studies of episodic encoding (Tulving *et al.*, 1994; Cabeza and Nyberg, 2000) could reflect refreshing during more complex encoding operations. In effect, refreshing may extend the opportunity for more elaborate encoding to take place. The fact that right PFC was involved in noting whether items were old or new over the very short retention intervals used here (550 ms in the immediate condition and a maximum of 36 s in the delay condition) provides evidence that some of the right PFC activity commonly found in long-term episodic memory retrieval studies (Tulving *et al.*, 1994; Nolde *et al.*, 1998a; Cabeza and Nyberg, 2000; Lepage *et al.*, 2000) might not be specific to LTM, but may reflect more general component cognitive processes such as noting (Johnson, 1992; Duncan and Owen, 2000; Fletcher and Henson, 2001; Ranganath *et al.*, 2003). Thus, differential engagement of refreshing during encoding and noting during test phases of episodic memory tasks may help account for the hemispheric asymmetry often observed in neuroimaging studies of LTM (Tulving *et al.*, 1994).

As operationalized here, where the item to be refreshed occurred 550 ms before, refreshing could be thought of as either a minimal maintenance process or a minimal recall/revival process. Similarly, the type of noting investigated here, where participants evaluated/matched whether a probe was the same

as one that occurred only a few seconds before (some as recently as 550 ms), could be thought of as a minimal evaluation, monitoring, or old/new recognition process. Nevertheless, we would not want to suggest that we have identified the maintenance or the monitoring regions. Prior studies of WM show more ventrolateral regions associated with rehearsing (a form of maintenance) over longer delays than used here (Smith and Jonides, 1999; Chein and Fiez, 2001). Other studies of long-term episodic memory show that left, as well as right, PFC regions are recruited when monitoring requires more specific source (episodic) information than familiarity (Nolde *et al.*, 1998b; Ranganath *et al.*, 2000; Raye *et al.*, 2000). Taken together with the present results, such findings clearly indicate that terms such as maintenance and monitoring (or encoding and retrieval) are likely not the right level of analysis for identifying the functional organization of PFC.

Finally, reflective cognitive operations are presumably transactions between frontal areas and other brain regions (Goldman-Rakic, 1995; Johnson and Reeder, 1997; Buckner and Wheeler, 2001; Miller and Cohen, 2001). For example, we consistently find that left parietal cortex (and sometimes right as well) shows refresh-related activation (see Table 1). One possibility consistent with the present results is that left PFC and left, or left and right, parietal cortex are involved in a refresh circuit. Of course, areas other than PFC and parietal regions are likely to be involved in circuits underlying refreshing and noting (e.g. ACC, insula, inferior temporal, hippocampal gyrus; see Tables 1 and 2). Conversely, the PFC and other regions identified here may participate in other cognitive operations, depending on the specific combination of interacting regions. Additional work will be needed to specify more completely the circuits involved in various component cognitive operations and to investigate the extent to which those circuits generalize across contexts. Nevertheless, the present results demonstrate that, for simple tasks, PFC shows functional specificity in terms of combinations of processes and information. Such functional specificity may be obscured in more complex tasks in which multiple component processes are recruited.

Notes

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Address correspondence to Marcia K. Johnson, Department of Psychology, Yale University, Box 208205, New Haven, CT 06520-8205, USA. Email: marcia.johnson@yale.edu.

References

Banich MT (1998) The missing link: the role of interhemispheric interaction in attentional processing. *Brain Cogn* 36:128–157.

Buckner RL, Wheeler ME (2001) The cognitive neuroscience of remembering. *Nat Rev Neurosci* 2:624–634.

Cabeza R, Nyberg L (2000) Imaging cognition II: an empirical review of 275 PET and fMRI studies. *J Cogn Neurosci* 12:1–47.

Chein JM, Fiez JA (2001) Dissociation of verbal working memory system components using a delayed serial recall task. *Cereb Cortex* 11:1003–1014.

Cohen JD, Perlstein WM, Braver TS, Nystrom LE, Noll DC, Jonides J, Smith EE (1997) Temporal dynamics of brain activation during a working memory task. *Nature* 386:604–608.

Courtney M, Petit L, Maisog JM, Underleider LG, Haxby JV (1998) An area specialized for spatial working memory in human frontal cortex. *Science* 279:1347–1351.

Cox RW (1996) AFNI: software for analysis and visualization of functional magnetic resonance neuroimages. *Comput Biomed Res* 29:162–173.

Craik FIM (1970) The fate of primary memory items in free recall. *J Verb Learn Verb Behav* 9:143–148.

D'Esposito M, Aguirre GK, Zarahn E, Ballard D, Shin RK, Lease J (1998) Functional MRI studies of spatial and nonspatial working memory. *Brain Res Cogn Brain Res* 7:1–13.

Duncan J, Owen AM (2000) Common regions of the human frontal lobe recruited by diverse cognitive demands. *Trends Neurosci* 23:475–483.

Forman SD, Cohen JD, Fitzgerald M, Eddy WF, Mintun MA, Noll DC (1995) Improved assessment of significant activation in functional magnetic resonance imaging (fMRI): use of a cluster-size threshold. *Magn Reson Med* 33:636–647.

Fletcher PC, Henson RNA (2001) Frontal lobes and human memory: insights from functional neuroimaging. *Brain* 124:849–881.

Goldman-Rakic PS (1987) Circuitry of primate prefrontal cortex and regulation of behavior by representational memory. In: *Handbook of physiology*, vol. 5, section 1: the nervous system (Plum F, ed.), pp. 373–417. Bethesda, MD: American Physiological Society.

Goldman-Rakic PS (1995) Architecture of the prefrontal cortex and the central executive. *Ann NY Acad Sci* 769:71–83.

Goldman-Rakic PS (2000) Localization of function all over again. *Neuroimage* 11:451–457.

Haxby JV, Petit L, Ungerleider LG, Courtney, SM (2000) Distinguishing the functional roles of multiple regions in distributed neural systems for visual working memory. *Neuroimage* 11:145–156.

Jha AP, McCarthy G (2000) The influence of memory load upon delay-interval activity in a working-memory task: an event-related functional MRI study. *J Cogn Neurosci* 12(Suppl. 2):90–105.

Johnson MK (1992) MEM: mechanisms of recollection. *J Cogn Neurosci* 4:268–280.

Johnson MK, Chalfonte BL (1994) Binding complex memories: the role of reactivation and the hippocampus. In: *Memory systems 1994* (Schacter DL, Tulving E, eds), pp. 311–350. Cambridge, MA: MIT Press.

Johnson MK, Hirst W (1993) MEM: memory subsystems as processes. In: *Theories of memory* (Collins AF, Gathercole SE, Conway MA, Morris PE, eds), pp. 241–286. Hove: Erlbaum.

Johnson MK, Reeder JA (1997) Consciousness as meta-processing. In: *Scientific approaches to consciousness* (Cohen JD, Schooler JW, eds), pp. 261–293. Mahwah, NJ: Erlbaum.

Johnson MK, Reeder JA, Raye CL, Mitchell KJ (2002) Second thoughts versus second looks: an age-related deficit in reflectively refreshing just-active information. *Psychol Sci* 13:63–66.

Kelley WM, Miezin FM, McDermott KB, Buckner RL, Raichle ME, Cohen NJ, Ollinger JM, Akbudak E, Conturo TE, Snyder AZ, Petersen SE (1998) Hemispheric specialization in human dorsal frontal cortex and medial temporal lobe for verbal and nonverbal memory encoding. *Neuron* 20:927–936.

Lancaster JL, Summerlin JL, Rainey L, Freitas CS, Fox PT (1997) The Talairach Daemon, a database server for Talairach Atlas labels. *Neuroimage* 5:S633.

Lepage M, Ghaffar O, Nyberg L, Tulving E (2000) Prefrontal cortex and episodic memory retrieval mode. *Proc Natl Acad Sci USA* 97:506–511.

Mai JK, Assheuer J, Paxinos G (1997) *Atlas of the human brain*. San Diego, CA: Academic Press.

Miller EK (2000) The prefrontal cortex: no simple matter. *Neuroimage* 11:447–450.

Miller EK, Cohen JD (2001) An integrative theory of prefrontal cortex function. *Annu Rev Neurosci* 24:167–202.

Nolde SF, Johnson MK, Raye CL (1998a) The role of prefrontal cortex during tests of episodic memory. *Trends Cogn Sci* 2:399–406.

Nolde SF, Johnson, MK, D'Esposito M (1998b) Left prefrontal activation during episodic remembering: an event-related fMRI study. *Neuroreport* 9:3509–3514.

Nystrom LE, Braver TS, Sabb FW, Delgado MR, Noll DC, Cohen JD (2000) Working memory for letters, shapes, and locations: fMRI evidence against stimulus-based regional organization in human prefrontal cortex. *Neuroimage* 11:424–446.

Petrides M (2000) Frontal lobes and memory. In: *Handbook of neuropsychology*, 2nd edn (Boller F, Grafman J, eds), vol. 2, pp. 67–84. Amsterdam: Elsevier.

Petrides M, Alivisatos B, Meyer E, Evans AC (1993) Functional activation of the human frontal cortex during the performance of verbal working memory tasks. *Proc Natl Acad Sci USA* 90:878–882.

Ranganath C, Johnson MK, D'Esposito M (2000) Left anterior prefrontal

- activation increases with demands to recall specific perceptual information. *J Neurosci* 20:RC108.
- Ranganath C, Johnson MK, D'Esposito M (2003) Prefrontal activity associated with working memory and episodic long-term memory. *Neuropsychologia* 41:378-389.
- Raye CL, Johnson MK, Mitchell KJ, Nolde SF, D'Esposito M (2000) fMRI investigations of left and right PFC contributions to episodic remembering. *Psychobiology* 28:197-206.
- Raye CL, Johnson MK, Mitchell KJ, Reeder JR, Greene EJ (2002) Neuroimaging a single thought: dorsolateral PFC activity associated with refreshing just-activated information. *Neuroimage* 15:447-453.
- Shallice T (1988) *From neuropsychology to mental structure*. New York: Cambridge University Press.
- Smith EE, Jonides J (1997) Working memory: a view from neuroimaging. *Cogn Psychol* 33:5-42.
- Smith EE, Jonides J (1999) Storage and executive processes in the frontal lobes. *Science* 283:1657-1661.
- Snodgrass JG, Vanderwart M (1980) A standardized set of 260 pictures: norms for name agreement, image agreement, familiarity, and visual complexity. *J Exp Psychol Hum Learn Mem* 6:174-215.
- Stuss DT, Benson DF (1986) *The frontal lobes*. New York: Raven.
- Talairach J, Tournoux P (1988) *Co-planar stereotaxic atlas of the human brain. 3-Dimensional proportional system: an approach to cerebral imaging*. New York: Thieme.
- Tulving E, Kapur S, Craik FI, Moscovitch M, Houle S (1994) Hemispheric encoding/retrieval asymmetry in episodic memory: positron emission tomography findings. *Proc Natl Acad Sci USA* 91:2016-2020.
- Wagner AD, Poldrack RA, Eldridge LL, Desmond JE, Glover GH, Gabrieli JDE (1998) Material-specific lateralization of prefrontal activation during episodic encoding and retrieval. *Neuroreport* 9:3711-3717.
- Wagner AD, Maril A, Bjork RA, Schacter DL (2001) Prefrontal contributions to executive control: fMRI evidence for functional distinctions within lateral prefrontal cortex. *Neuroimage* 14:1337-1347.
- Woods RP, Cherry SR, Mazziotta JC (1992) Rapid automated algorithm for aligning and reslicing PET images. *J Comput Assist Tomogr* 16:620-633.
- Zarahn E, Aguirre GK, D'Esposito M (1999) Temporal isolation of the neural correlates of spatial mnemonic processing with fMRI. *Brain Res Cogn Brain Res* 7:255-268.