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NeuroImage

NeuroImage 20 (2003) 1531–1539

www.elsevier.com/locate/ynimg

Frontal activations associated with accessing and evaluating information in working memory: an fMRI study

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Received 21 February 2003; revised 24 July 2003; accepted 24 July 2003

Abstract

To investigate the involvement of frontal cortex in accessing and evaluating information in working memory, we used a variant of a Sternberg paradigm and compared brain activations between positive and negative responses (known to differentially tax access/evaluation processes). Participants remembered two trigrams in each trial and were then cued to discard one of them and maintain the other one as the target set. After a delay, a probe letter was presented and participants made decisions about whether or not it was in the target set. Several frontal areas—anterior cingulate (BA32), middle frontal gyrus (bilateral BA9, right BA10, and right BA46), and left inferior frontal gyrus (BA44/45)—showed increased activity when participants made correct negative responses relative to when they made correct positive responses. No areas activated significantly more for the positive responses than for the negative responses. It is suggested that the multiple frontal areas involved in the test phase of this task may reflect several component processes that underlie more general frontal functions.

Introduction

The Sternberg (1966) task has been one of the most influential working memory (WM) paradigms in memory research. In a typical Sternberg task, participants are asked to hold in mind a set of items (usually letters) over a brief delay and then to make a speeded decision about a test item (i.e., the probe). They indicate their decision by making either a positive (i.e., "yes") response if the probe matches one of the memory set items or a negative response (i.e., "no") if it does not. There are two central findings from studies using this task. First, the time for participants to respond to the probe increases as a linear function of the number of items in the memory set regardless of response type. Second, negative responses are significantly slower than positive ones regardless of set size (Sternberg, 1966).

Recent neuroimaging studies have capitalized on the first finding to study the neural basis of the maintenance function of working memory. Inspired by neurophysiological research revealing delay activity in frontal regions of the nonhuman primate brain (e.g., Fuster and Alexander, 1971; Funahashi et al., 1989; Goldman-Rakic, 1987), human brain imaging studies focused on identifying maintenance-related frontal areas by varying the number of memory set items ("load," e.g., Jha and McCarthy, 2000; Rypma et al., 1999; Rypma and D'Esposito, 1999; Druzgal and D'Esposito, 2001; Leung et al., 2002). The extent to which prefrontal cortex (PFC) is sensitive to load as measured by imaging techniques in humans, however, is still a controversial topic. For example, some studies with fMRI either failed to find a load effect in PFC or attributed it to the encoding or to the early delay period rather than to an extended maintenance interval (Rypma and D'Esposito, 1999; Postle et al., 1999; Jha and McCarthy, 2000). However, other recent fMRI studies with working memory tasks for letters and spatial locations, some using delays as long as 18 s, did find delay period activity in PFC that was greater for more compared to fewer items (Rypma, et al., 2002; Leung et al., 2002).

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doi:10.1016/j.neuroimage.2003.07.016

Most relevant to the present purpose, no attempt has been made in the neuroimaging literature to take advantage of the finding that negative responses are slower than positive responses, which may provide a robust behavioral basis for investigating the neural mechanisms of working memory. Because the positive trials (where a positive response to a target is accurate) and the negative trials (where a negative response to a distractor item is accurate) at a given set size in the Sternberg task are indistinguishable to the participants until after the probe is presented, the behavioral differences between the two types of trial arise solely from the test stage. In this stage, information encoded and maintained earlier in a trial is accessed and evaluated against the probe to make a decision.

"Access" is a generic way of referring to processes by which memorial information is contacted or revived and "evaluation" is a generic way of referring to processes by which information is utilized for immediate purposes. For example, access is neutral with respect to whether these processes involve relatively automatic refreshing or reactivation, or more strategic retrieval (e.g., Johnson, 1992; Johnson and Hirst, 1993), and evaluation is neutral with respect to whether judgments are relatively automatic (e.g., based on familiarity or recency) or more controlled (e.g., involving conscious recollection of or deliberation about specific features). Access and evaluation may not be strictly sequential but rather can be temporally intermixed. Regardless, access and evaluation presumably involve processes in addition to those motor planning and execution processes underlying the participants' overt responses.

Such access and evaluation processes, like maintenance processes, are important functions of working memory. In this fMRI study, we compared the brain activation when participants made correct positive responses with that when they made correct negative responses to investigate the neural activity associated with accessing and evaluating information in working memory.

Our task was a variant of the standard Sternberg paradigm in which we asked participants to select a subset of items held in working memory before the test probe appeared (Zhang and Johnson, 2001). In the current study, this working memory selection task (WMST) allows us to investigate an fMRI finding reported by D'Esposito et al. (1999), which was a follow-up of a PET study by Jonides et al. (1998). Jonides et al. (1998) asked their participants to remember four letters (the target set) in each trial and then tested them with a single probe letter for recognition. In "Recent negative" trials, the probe was not in the present target set but had been in the target set of the two immediately previous trials; in "Non-recent negative" trials, it was in neither current nor the previous two trials. Participants were considerably slower in the "Recent negative" trials than in the "Non-recent negative" trials. Jonides et al. (1998) suggested that in the "Recent negative" trials, participants had a prepotent tendency to make a positive response, which Jonides et al. (1998) hypothesized had to be inhibited before correctly making a negative response. Their PET analysis localized left inferior frontal gyrus, BA45, which they interpreted as the neural correlate of this inhibition process. D'Esposito et al. (1999) replicated this finding with fMRI. In addition, with an event-related design, they were able to show that this greater activation for "Recent negative" than "Non-recent negative" trials in area BA45 originated from the response phase, and not from the encoding or maintenance phase of the task. This finding reported by Jonides et al. (1999) and D'Esposito et al. (1999) is quite robust and has been further replicated by Postle et al. (2001) and Jonides et al. (2000).

In the current study, in addition to comparing correct positive and negative responses, we included a manipulation similar to the distinction between "Recent-negative" and "Non-recent negative" trials. This allows us to see if we can replicate the Jonides et al. (1998) and D'Esposito et al., (1999) results under a new task situation that should involve a similar interference resolution process and, if yes, to further examine the role of area BA45 in evaluating positive and negative responses.

The basic structure of the WMST (Zhang and Johnson, 2001) is shown in Fig. 1. In each trial, participants first saw a study display with a row of six letters and were told to remember all of them. Following a short blank delay, a second cue display re-presented either the left or the right three letters in the center of the screen. Participants were asked to discard these three letters from the initial set of six and remember only the remaining three as the memory set. After another blank interval, the test display came up with a single probe letter at the center. Participants had to make a speeded "yes/no" judgment indicating whether or not the probe was in the memory set.

For example, as shown in Fig. 1, participants saw "W S B K D T" in the study display and "K D T" in the cue display. They should ignore "K D T" and remember only "W S B" for their response. As in the standard Sternberg task, there were positive trials where the probe, such as an "s" (shown in Fig. 1), was in the memory set and negative trials (called "Low-familiar negative" trials here) where the probe, such as an "m," was not in the memory set.

We also included another type of negative trial (called "High-familiar negative" trials), where the probe (e.g., "d"), although not in the memory set, was drawn from the discarded set of "K D T." We assume that the prepotent tendency to respond "yes" in the "Recent negative" trials in the Jonides et al. (1998) and other follow-up studies was because the probe letter in these trials, compared to the probe in the "Non-recent negative" trials, was familiar due to its recent appearance in the two immediately previous trials. In the current task, probes in the High-familiar negative trials were made familiar, relative to those in the Low-familiar negative trials, by re-presenting them in the cue display. Therefore, our High-familiar negative trials are similar to the "Recent negative" trials in the Jonides et al.

(1998) and related studies and our Low-familiar negative trials are similar to their "Non-recent negative" trials.

Methods

Participants

Eight Yale University undergraduate students (mean age = 21 years; 5 male) participated in this study. All were right-handed and native English speakers. None of them reported any medical, neurological, or psychiatric illness or taking any type of prescription medication. All had normal or corrected-to-normal vision and were naïve as to the purpose of the study. Informed consent was obtained from all participants in accordance with a protocol approved by the Human Investigations Committee of the Yale University Medical School.

Procedure

All visual stimuli were in black with a white background, backprojected onto a screen positioned at the front of the magnet bore opening. The screen was made visible to the participants through a mirror mounted above their eyes on a head coil. Stimulus presentation was controlled using the VisionShell software (Micro M.L., Quebec, Canada; http://www.mlink.net/~ml/index.html) on a Mac G3 computer.

As shown in Fig. 1, each trial started with the presentation of a warning screen for 1000 ms. The study display was then shown for 2000 ms followed by a blank interval of 3000 ms. The cue display was presented for 1000 ms followed by another delay of 2000 ms. The probe was shown for 1000 ms and then removed for another 1000 ms before the 13-s rest period started. A central fixation cross was presented during the rest period. The total length of each single trial was 24 s.

Participants were told to remember the initial letter set in the study display until the cue came up. They were then to ignore the cue letters and hold only the other three letters as the memory set. Upon seeing the probe, they were to respond "yes" if the probe was in the memory set or "no" if it was not. Both response speed and accuracy were emphasized. They responded by pressing one of two buttons with the index and the middle finger of their right hand. The mapping between "yes/no" responses and the two fingers was counterbalanced across participants. During the rest period, participants were told to simply look at the fixation cross and wait for the next trial.

For each trial, seven letters were randomly drawn without replacement from a pool of 21 consonants. The first six were used in the study display. For the Low-familiar negative trials, the seventh letter was used as the probe. For the positive trials, the probe was randomly drawn from the three letters in the memory set. For the High-familiar negative trials, it was drawn from the three letters in the cue display. It was equally likely that either the left or the right three letters in the study display was re-presented in the cue display.

The rectangle and the fixation subtended to the participants 10.0° × 6.3° and 0.5° × 0.5° in visual angle, with their centers aligned with the screen center. The six letters in the study display were symmetrically positioned relative to the screen center along the horizontal meridian. The center-to-center distance between every two neighboring letters was 1.2°. The cue display was constructed by centrally presenting either the left or the right three letters in the study display. All letters except the probe letter were upper case in bold Helvetica font of size 48, extending a visual angle of 1.2° × 1.2°. The probe letter was of the same font and size but in lower case.

All participants completed 8 runs of 12 trials each inside the scanner. In each run, there were 6 positive trials, 3 Low-familiar negative trials, and 3 High-familiar negative trials, randomly intermixed. They were also given a practice block outside the scanner to familiarize them with the task. The practice block had the same trial structure as the testing blocks except for a shortened intertrial rest period of 4.5 s.

Image acquisition

Imaging was conducted on a 1.5-T Signa (GE Medical Systems, Milwaukee, WI) scanner at the Yale Magnetic Resonance Imaging Research Center using the standard quadrature head coil and a T2*-sensitive gradient-recalled single-shot echo-planar pulse sequence. The head coil was used with foam pillows and a band across the participant's forehead to comfortably restrict head motion.

Sagittal localizers were first obtained to prescribe axial-oblique structural images parallel to the anterior-posterior commissural (AC-PC) line. Depending on the head size and shape of each individual participant, either 38 or 40 structural images were taken to cover the whole brain.

The 20 functional images (TR = 2000 ms, TE = 35 ms, flip angle = 65 degrees) were aligned with a subset of the structural images so that the sixth image numbered from the inferior to the superior was on the AC-PC line. The acquisition matrix was 64 × 64 and the field of view (FOV) was 24 cm. In-plane voxel resolution was 3.75 × 3.75 mm and slice thickness was 3.8 mm with no skip. Image acquisition started eight scans (16 s) after the start of each run for the magnet to get stabilized. TR was 2 s and there were 12 scans in each trial. The scanning was synchronized with the stimulus presentation so that the fifth scan in each trial started with the onset of the test probe display.

Image analysis

Imaging data analysis was performed with a statistical package called fMRI (Skudlarski; http://mri.med.yale.edu/individual/pawel/fMRIpackage.html). First, the SPM99 mo-

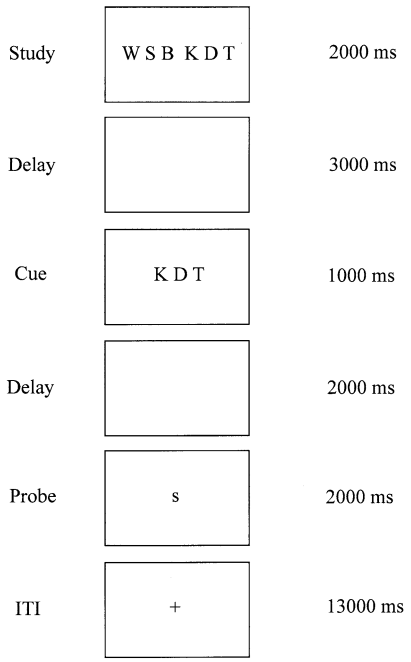

Fig. 1. A schematic view of the sequence of events in a single trial. Participants first remembered the two trigrams in the study display and then focused on the one that was different from the trigram in the cue display and maintained it as the target set. In this particular display, they should focus on "W S B" after they had seen the cue display. When they saw the probe item, they indicated whether the probe matched one of the three target letters. Each trial had a fixed length of 24 s with a 13-s intertrial interval (ITI). The fifth scan (TR = 2 s) in each trial was synchronized with the presentation of the probe. The probe was shown for 1000 ms and then replaced with a blank screen for another 1000 ms. Stimuli are not drawn to scale.

tion correction algorithm (Friston et al., 1995) was used to realign all functional images for each participant. Images from incorrect trials or from trials with excessive motion were excluded from further analysis. A total of 3.9% trials were discarded across all participants. The functional images were also manually shifted in-plane relative to the structural images to correct for motion between the structural scan and the first functional scan. They were then spatially smoothed with a Gaussian filter (FWHM 7.5 mm).

Our design was an event-related design with the two types of trial, the positive and the negative trials, randomly mixed within each block. BOLD signals corresponding to each trial type were obtained by selective averaging (see Buckner et al., 1998). Specifically, two images (3D volumes) were constructed for each subject, one for the positive trials and one for the negative trials.[1] The image for the positive trials was a voxel-by-voxel average of images at all time points (corrected in time with the hemodynamic response delay) in all positive trials across the whole scanning session (8 runs). The negative image was constructed similarly with images from negative trials.

The averaged images were then normalized in reference to the standard Talairach atlas (Talairach and Tournoux, 1988) using eight anatomical landmarks (AC, PC, the superior, inferior, anterior, posterior, left, and right edge on the cortical surface). The resulting eight pairs of standardized images, one pair for each subject, was put in a paired test yielding a t statistic for each voxel. The t value indicates the statistical significance for the difference in activation in that voxel between the two trial types. The t maps thus generated were thresholded to generate the ROAs (regions of activation). The analysis was a random-effect analysis with $df = 7$ ($N = 8$). A pixel-wise intensity threshold ($P < 0.01$) and a spatial extent threshold (cluster size greater than 6 voxels) were combined to set the corrected false positive rate at $P < 0.0025$ (Forman, et al., 1995; Poline et al., 1997). Time series for each ROA were obtained by averaging the fMRI signal at each time point from all voxels within that ROA.

Results

Behavioral data

The mean RTs and error rates for the three types of trial are shown in Table 1. Only correct trials were included in the analysis. Based on RTs, 2.6% of the correct responses were identified as outliers and omitted from the analysis with a procedure from Van Selst and Jolicoeur (1994). A one-way analysis of variance (ANOVA) of the RTs showed a significant main effect of response type [$F(2,14) = 33.39$, $P < 0.0001$]. Subsequent contrasts indicate that the negative trials were slower than the positive trials [904 vs. 749 ms, $t(7) = 42.37$, $P < 0.0001$], and the High-familiar negative trials were slower than the Low-familiar negative trials [972 vs. 836 ms, $t(7) = 24.41$, $P < 0.0002$]. In the analysis of errors, there was no difference between negative and positive trials or between the two types of negative trials ($F < 1$).

Imaging data

As shown in Fig. 2, all areas that showed significantly greater activation for the negative trials than for the positive

Table 1
RTs and error rates for the three types of response ($n = 8$)[a]

Response type	Positive	Low-familiar negative	High-familiar negative
RT (ms)	749 (42)	836 (48)	972 (63)
Error rate (%)	3.0 (1.7)	2.5 (1.1)	5.1 (3.0)

[a] Standard errors shown in parentheses.

[1] No direct comparison on time-averaged image data was made between the two types of negative response as such comparison has low statistical power compared to the comparison between positive and negative responses (the number of trials for the High-familiar negative and for the Low-familiar negative responses was only half of that for the positive responses).

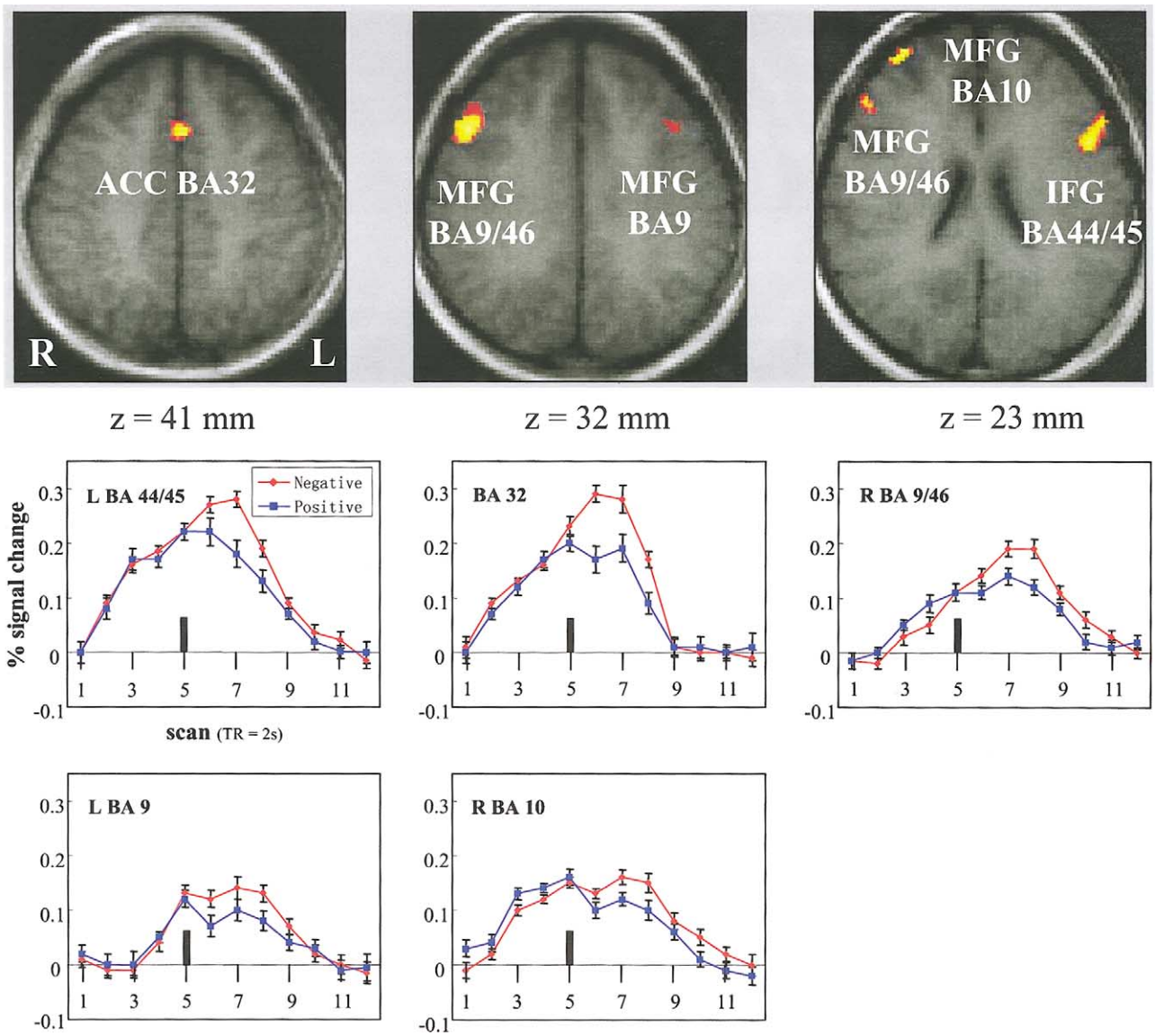

Fig. 2. Activation maps showing regions more active in the negative (pooled across the two types of negative trial) than in the positive trials ($P < 0.01$, minimal 6 contiguous voxels) superimposed on the averaged anatomical brain across all participants. Following radiological convention, the left side of each image is the right hemisphere of the brain and the right side the left hemisphere.

Fig. 3. Time series for the activated areas shown in Fig. 2. The *x*-axis shows the scan number (12 scans for each single trial, TR = 2 s) and the *y*-axis shows the percent fMRI signal change. The red line (diamonds) is for negative responses and the blue (squares) for positive responses. The black bar on the *x*-axis shows when the probe item was presented within a trial. Error bars show standard errors.

trials were in the frontal cortex. They are cingulate, BA32 (0, 17, 41); bilateral dorsal lateral prefrontal cortex, BA9 (−38, 18, 32; 45, 18, 32); right BA10 (33, 49, 23); right BA46 (47, 27, 23), and left inferior frontal gyrus, BA44/45 (−46, 14, 23). The coordinates are for the peak voxel in Talairach space. Across the whole brain, no area showed significantly more activation in the positive trials than in the negative trials.

The time series of the fMRI signal for each ROA, separated for the positive and negative responses, are shown in Fig. 3. Right BA9 and BA46 were pooled in the same graph given their spatial proximity. The bar at scan 5 indicates the onset of the test probe within a trial. In all the ROAs, the signal was greater for the negative trials than for the positive trials, reflecting the outcome of the *t* test. More critically, the time series data show that, considering the temporal delay of the fMRI signal, the differences between the two types of response started to emerge following the onset of the test probe. The greater activity in these prefrontal regions in the negative trials relative to the positive trials is the result of processing differences between the two types of condition during the test stage.

Finally, to compare our results with the D'Esposito et al. (1999) study, we examined the difference in time series between the High-familiar negative and the Low-familiar negative responses for the ROA at BA44/45 (see Fig. 4).

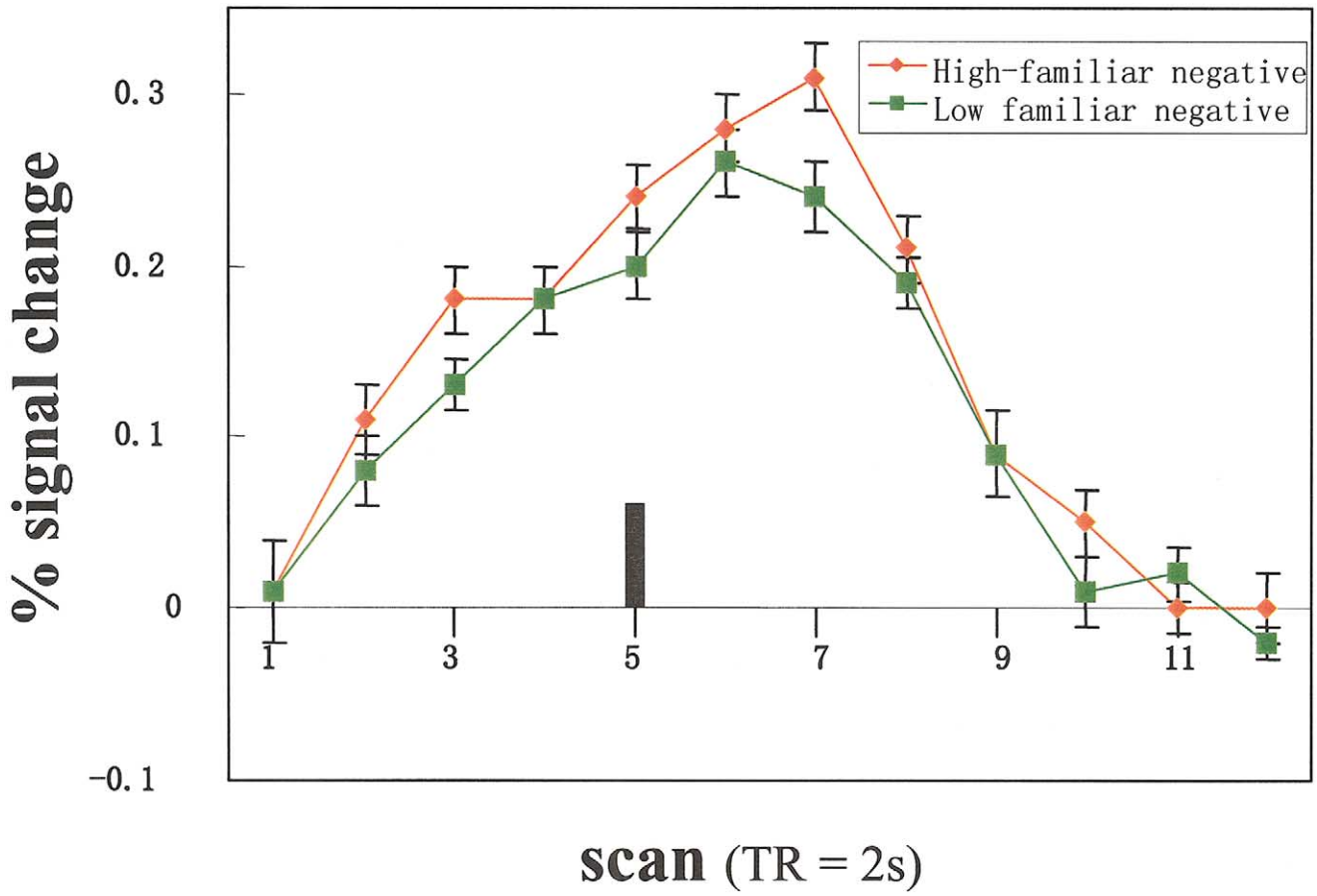

Fig. 4. Time series for area left BA44/45. The orange line (diamonds) is for the High-familiar negative responses and the green line (squares) for the Low-familiar negative responses.

The High-familiar negative trials had significantly greater activity than the Low-familiar negative trials at the seventh scan [$t(7) = 1.85$, $P = 0.05$, one-tailed]. There was no difference between the two types of negative trials in the other ROAs except in the cingulate BA32, which showed a similar pattern as BA44/45 [$t(7) = 1.76$, $P = 0.06$, one-tailed].

Discussion

In the Sternberg task, responses to negative probes are significantly slower than to positive probes. Corresponding to this behavioral index of increased cognitive processing, we found in the present working memory selection task that multiple frontal areas showed greater activity when participants made correct negative responses relative to when they made correct positive responses. As revealed by the time series results, the increased frontal activation had its origin in the test stage when participants were accessing information in working memory and evaluating it against the probe. The time series results also showed that these frontal areas were active in both the negative and the positive trials, only more so in the former than in the latter. In contrast, no brain area was significantly more active in the positive trials than in the negative trials. We also found that when participants rejected a negative probe, an area of BA44/45 in the left inferior frontal gyrus showed more activation if the familiarity of the probe was high than if it was low. This replicates the results from D'Esposito et al. (1999) and several other studies mentioned in the introduction, indicating that left ventrolateral PFC activity increases when familiar negative probes have to be disregarded, relative to when negative probes are not familiar. It should be noted, however, that the ventrolateral PFC area (−46, 14, 23) we found is superior to the region (−48, 21, 9) reported by Jonides et al. (1998). It is unclear whether this reflects subject sampling differences or differences between the two studies in the processes recruited for the different tasks used.

One implication from the current pattern of results is that when participants were making responses, they engaged the same set of brain areas for positive and negative responses, although to different degrees. There was no area only involved in making positive or negative responses. This is consistent with predictions from cognitive models of the

Sternberg task. The exhaustive serial search model of Sternberg (1966) proposes that regardless of the final response made, the same comparison process between the probe item and the memory set items is carried out until the target set is exhausted. The comparison process may be prolonged in the negative trials due to a more stringent criterion for making a negative response.

Similar predictions can be derived from more recent models for the Sternberg paradigm (Jones and Anderson, 1987; Ratcliff, 1978). For example, the diffusion model of Ratcliff (1978) asserts that in the response stage, the probe is compared in parallel with traces of the memory set items. Each item is assumed to have one separate trace composed of a large number of features. Each comparison will produce either a positive or a negative outcome if the match or mismatch between features of the probe and that of a memory trace is above a certain threshold. A positive response is made when participants find one comparison finishes with a positive outcome, and a negative response is made when each and every comparison finishes with a negative outcome. The response time difference between positive and negative trials is captured in this model in that while a positive response can be made when any of the multiple comparison processes returns with a positive outcome, a negative response cannot be issued until all comparisons end with a negative outcome. Therefore, according to the diffusion model, negative responses may be produced more slowly than are positive responses, but the same kind of processes are engaged in making the two types of response (see note, for how the diffusion model accounts for the set-size effect[2]).

The finding that multiple frontal areas are involved in the relatively simple response phase of our task and that these same areas are found in other tasks and task phases (e.g., Duncan and Owen, 2000) suggests that individual frontal areas are unlikely to be identified exclusively with particular phases of tasks, such as encoding, maintenance, and response (see also Ranganath et al., 2003). Task phases need to be further decomposed into more elementary component processes to better characterize the functional organization of the frontal cortex. This approach is illustrated by two recent studies. Raye et al. (2002) found that a process as simple as refreshing, i.e., thinking about a just-seen item, activated an area of DLPFC area (BA9), an area that has often been proposed to be engaged by complex manipulating of information in working memory (D'Esposito et al., 1999). Johnson et al. (2003) found activation in right prefrontal cortical area BA9 when participants noted whether an item had been presented previously (in this case, immediately before or no longer ago than 36 s). Both "refreshing" and "noting" are component processes or simple cognitive operations characterized in the Multiple Entry Modular Memory framework (MEM; Johnson, 1992). According to MEM, such basic operations contribute to executive and mnemonic functions involved in working memory, long-term memory, and other higher order cognitive functions (Johnson and Hirst, 1993; Johnson and Reeder, 1997) that are usually associated with prefrontal cortex (Stuss and Benson, 1986; Shallice, 1988).

In view of this component processes approach, the access and evaluation phase of our task may be broken down into several basic operations. When the probe is presented, to decide if it was in the target set, participants need to activate an agenda[3] to remember, refresh the probe representation during evaluation, rehearse the information in the working memory set, and note the relationship between the probe and individual items in the memory set. These component processes in MEM (Johnson, 1992), activated agendas, refreshing, rehearsing, and noting, would be involved both in making positive responses and in making negative responses. Presumably, for negative trials, these processes may be recruited to a larger extent, relative to positive trials. For example, there may be a difference in "duty cycle" between trial types, where processes (i.e., neural assemblies) are active for a longer period of time and produce a greater signal in negative trials than in positive trials.

Based on prior findings, we suggest that in our study, right BA10 may be involved in engaging an agenda to retrieve/evaluate, or a retrieval mode (Lepage et al., 2000), left BA9 in the refreshing operation (Raye et al., 2002), right BA9/46 in the noting operation (Johnson et al., 2002), and left BA44/45 in rehearsing (Smith and Jonides, 1999). Of course, other regions are likely involved as well in circuits subserving some or all of these operations, but it is notable that, in our study, only frontal regions showed significantly different activation for negative and positive trials.

Of these areas, the left BA44/45 area is particularly interesting in that it showed different levels of activation not only for the negative and the positive responses, but also for the High-familiar negative and the Low-familiar negative responses, as did in the D'Esposito et al. (1999) and related studies. If this area subserves rehearsal, why does it differentiate between the two types of negative trials? We speculate that when lure probe familiarity is high but does not yield a quick match with the memory set, one way to overcome such interference is to enhance relevant representations by rehearsing the target set. This possibility is easier to envision in the diffusion model than in the Sternberg model. In the Sternberg model, scanning is com-

[2] The Sternberg model explains the set size effect with an exhaustive serial search process. In the diffusion model, as there are more items to be remembered, the encoded representation of the target set is subject to more noise. Therefore, although the probe is compared against all items in the target set in parallel, the comparison process slows down as noise increases, hence the set size effect.

[3] In the MEM framework (Johnson and Hirst, 1993), agendas are well-learned or assembled-on-line routines consisting of a set of more elementary cognitive operations. When activated, the operations will unfold to achieve a specific processing goal.

pulsorily exhaustive for any given set size. In the diffusion model, comparison is based on a continuous accumulation of information. Rehearsal could influence information accumulation by increasing the activation of the target representation. That is, rehearsing (like refreshing) is a way to "bias" relevant information (e.g., Miller and Cohen, 2001).

Interference also tends to increase ACC activity. For example, in a recent fMRI study, Druzgal and D'Esposito (2001) asked their participants to remember one to four faces over an 8-s delay and then presented them with a test face. Participants decided if the test face matched any of the remembered face(s). Like our study, they also found greater activity in anterior cingulate (BA32) for negative trials (which they called "non-matching" trials) relative to positive trials (which they called "match" trials). They identified this BA32 activity with conflict monitoring, a function generally associated with the anterior cingulate (e.g., Botvinick et al., 2001). They reasoned that conflict could be involved in the Sternberg paradigm, in two possible ways. One possibility is that, when making negative responses, participants may have to overcome a general positive response bias because negative responses involve more stringent response criteria. The other is that irrelevant features shared between the probe and the memory set items may prime a positive response that competes with the correct negative response on negative trials. Either way, greater conflict would be present in the negative trials than in the positive trials. This conflict monitoring explanation seems a reasonable account for our anterior cingulate activation. In addition, our result that the cingulate also had a tendency to activate more in the High-familiar negative trials than in the Low-familiar negative trials is consistent with this interpretation because interference from inappropriate familiarity should produce a greater degree of conflict.

Recently, Jonides et al., (2002) reanalyzed data from the D'Esposito et al. (1999) study. In a contrast between the "Recent negative" trials and "Non-recent negative" trials, they identified a region of ACC showing greater activation for Recent negative trials, $P < 0.09$. The P value we found for ACC activity in the contrast of High-familiar vs. Low-familiar negative trials was 0.06. This similarity suggests a small but consistent ACC activation associated with greater interference (Jonides et al., 2002).

Our WMST task is similar to the directed-forgetting paradigm that has previously been used in memory research (Bjork, 1978, 1989; Zacks and Hasher, 1994; Golding and MacLeod, 1998). A basic finding from this line of research is that when subjects are instructed to forget information, the representation of the to-be-forgotten information is made inaccessible but can resurface at later times under suitable circumstances, suggesting the information had been inhibited rather than "lost." In our task, when the subjects were asked to focus on the relevant letters, they were essentially instructed to forget the other irrelevant letters. Therefore, the distractor set may have been inhibited following the cue display. Such inhibition could lead to delayed processing of the probe item in the High-familiar negative trials since probes on Low-familiar trials were not subject to inhibition.

Behaviors in patients with PFC lesions have long been associated with disruption of inhibition (Luria, 1966; Knight et al., 1981; Shimamura, 1995; Chao and Knight, 1998). Findings from neuroimaging studies, for example, with the Stroop task, are consistent with the idea that PFC plays a critical role in inhibitory functions (Bench et al., 1993; Carter et al., 1995; Taylor et al., 1997; Leung et al., 2000). Our finding of greater PFC activity for the High-familiar negative trials than for the Low-familiar negative trials is consistent with such a view. However, although direct inhibition of irrelevant information is a candidate mechanism for interference resolution, an alternative to active suppression of irrelevant information is a frontally mediated activation ("biasing") of relevant information (Kimberg and Farah, 1993; Miller and Cohen, 2001; Johnson et al., 2002).

Finally, it should be noted that Druzgal and D'Esposito (2001) reported more activity in left DLPFC for match (positive) than for mismatch (negative) trials, which is opposite to our finding of greater activity for negative trials than for positive trials. Thus the conditions (e.g., stimuli, specific task requirements) under which activity is greater for positive or for negative trials in PFC during the test phase of Sternberg-type tasks remains to be determined.

Acknowledgments

This research was supported by National Institute on Aging Grant AG15793 and National Institute of Health Grant MH62196.

References

Bench, C.J., Frith, C.D., Grasby, P.M., Friston, K.J., Paulesu, E., Frackowiak, R.S., Dolan, R.J., 1993. Investigations of the functional anatomy of attention using the Stroop test. Neuropsychologia 31, 907–922.

Bjork, R.A., 1978. The updating of human memory, in: Bower, G.H. (Ed.), The Psychology of Learning and Motivation, (Vol. 12). Academic Press, New York.

Bjork, R.A., 1989. Retrieval inhibition as an adaptive mechanism in human memory, in: Roediger IIIH.L., Craik, F.I.M. (Eds.), Varieties of Memory and Consciousness: Essays in Honour of Endel Tulving, Lawrence Erlbaum, Hillsdale, NJ, pp. 309–330.

Botvinick, M.M., Braver, T.S., Barch, D.M., Carter, C.S., Cohen, J.D., 2001. Conflict monitoring and cognitive control. Psychol. Rev. 108, 624–652.

Buckner, R.L., Koutstaal, W., Schacter, D.L., Dale, A.M., Rotte, M., Rosen, B.R., 1998. Functional-anatomic study of episodic retrieval. II. Selective averaging of event-related fMRI trials to test the retrieval success hypothesis. Neuroimage 7, 163–175.

Carter, C.S., Mintun, M., Cohen, J.D., 1995. Interference and facilitation effects during selective attention: an H^2O^{15} PET study of Stroop task performance. Neuroimage 2, 264–272.

Chao, L.L., Knight, R.T., 1998. Contribution of human prefrontal cortex to delay performance. J. Cogn. Neurosci. 10, 167–177.

D'Esposito, M., Postle, B.R., Ballard, D., Lease, J., 1999. Maintenance versus manipulation of information held in working memory: an event-related fMRI study. Brain Cogn. 41, 66–86.

Druzgal, T.J., D'Esposito, M., 2001. A neural network reflecting decisions about human faces. Neuron 32, 947–955.

Duncan, J., Owen, A.M., 2000. Common regions of the human frontal lobe recruited by diverse cognitive demands. Trends Neurosci. 23, 475–483.

Forman, S.D., Cohen, J.D., Fitzgerald, M., Eddy, W.F., Mintun, M.A., Noll, D.C., 1995. Improved assessment of significant activation in functional magnetic resonance imaging (fMRI): use of a cluster-size threshold. Magn. Reson. Med. 33, 636–647.

Friston, K.J., Holmes, A.P., Worsley, K.J., Poline, J.P., Frith, C.D., Frackowiak, R.S.J., 1995. Statistical parametric maps in functional imaging: a general linear approach. Hum. Brain Mapp. 2, 189–210.

Funahashi, S., Bruce, C.J., Goldman-Rakic, P.S., 1989. Mnemonic coding of visual space in the monkey's dorsolateral prefrontal cortex. J. Neurophysiol. 61, 331–349.

Fuster, J.M., Alexander, G.E., 1971. Neuron activity related to short-term memory. Science 173, 652–654.

Golding, J.M., MacLeod, C.M. (Eds.), 1998. Intentional Forgetting: Interdisciplinary Approaches. Lawrence Erlbaum, Mahwah, NJ.

Goldman-Rakic, P.S., 1987. Circuitry of primate prefrontal cortex and regulation of behavior by representational memory. in: Plum, F (Ed.), Handbook of Physiology, Vol. 5, Section 1: The Nervous System. American Physiological Society, Bethesda, MD.

Jha, A.P., 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. 12), 90–105.

Johnson, M.K., 1992. MEM: mechanisms of recollection. J. Cogn. Neurosci. 4, 268–280.

Johnson, M.K., Hirst, W., 1993. MEM: memory subsystems as processes, in: Collins, A.F., Gathercole, S.E., Conway, M.A., Morris, P.E. (Eds.), Theories of Memory, Lawrence Erlbaum, East Sussex, England, pp. 241–286.

Johnson, M.K., Raye, C.L., Mitchell, K.J., Greene, E.J., Anderson, A.W., 2003. fMRI evidence for an organization of prefrontal cortex by both type of process and type of information. Cerebr. Cortex 13, 265–273.

Johnson, M.K., Reeder, J.A., 1997. Consciousness as meta-processing, in: Cohen, J.D., Schooler, J.W. (Eds.), Scientific Approaches to Consciousness, Lawrence Erlbaum, Mahwah, NJ, pp. 261–293.

Johnson, M.K., Reeder, J.A., Raye, C.L., Mitchell, K.J., 2002. Second thoughts versus second looks: an age-related deficit in reflectively refreshing just-activated information. Psychol. Sci. 13, 64–67.

Jones, W.P., Anderson, J.R., 1987. Short- and long-term memory retrieval: a comparison of the effects of information load and relatedness. J. Exp. Psychol. Gen. 2, 137–153.

Jonides, J., Badre, D., Curtis, C., Thompson-Schill, S.L., Smith, E.E., 2002. Mechanisms of conflict resolution in prefrontal cortex, in: Stuss, D.T., Knight, R.T. (Eds.), Principles of Frontal Lobe Function, Oxford University Press, London.

Jonides, J., Marshuetz, C., Smith, E.E., Reuter-Lorenz, P.A., Koeppe, R.A., 2000. Age differences in behavior and PET activation reveal differences in interference resolution in verbal working memory. J. Cogn. Neurosci. 12, 188–196.

Jonides, J., Smith, E.E., Marshuetz, C., Koeppe, R.A., Reuter-Lorenz, P.A., 1998. Inhibition in verbal working memory revealed by brain activation. Proc. Natl. Acad. Sci. USA 95, 8410–8413.

Kimberg, D.Y., Farah, M.J., 1993. A unified account of cognitive impairments following frontal lobe damage: the role of working memory in complex, organized behavior. J. Exp. Psychol. Gen. 122, 411–428.

Knight, R.T., Hillyard, S.A., Woods, D.L., Neville, H.J., 1981. The effects of frontal cortex lesions on event-related potentials during auditory selective attention. Electroencephalogr. Clin. Neurophysiol. 52, 571–582.

LePage, M., Ghaffar, O., Nyberg, L., Tulving, E., 2000. Prefrontal cortex and episodic memory retrieval mode. Proc. Natl. Sci. Acad. 97, 506–511.

Leung, H.C., Gore, J.C., Goldman-Rakic, P.S., 2002. Sustained mnemonic response in the human middle frontal-gyrus during on-line storage of spatial memoranda. J. Cogn. Neurosci. 14, 659–671.

Leung, H.C., Skudlarski, P., Gatenby, J.C., Peterson, B.S., Gore, J.C., 2000. An event-related functional MRI study of the Stroop color word interference task. Cerebr. Cortex 10, 552–560.

Luria, A.R., 1966. Higher Cortical Functions in Man. Basic Books, New York.

Miller, E.K., Cohen, J.D., 2001. An integrative theory of prefrontal cortex function. Annu. Rev. Neurosci. 24, 167–202.

Poline, J.B., Worsley, K.J., Evans, A.C., Friston, K.J., 1997. Combining spatial extent and peak intensity to test for activations in functional imaging. Neuroimage 5, 83–96.

Postle, B.R., Berger, J.S., D'Esposito, M., 1999. Functional neuroanatomical double dissociation of mnemonic and executive control processes contributing to working memory performance. Proc. Natl. Acad. Sci. 96, 12959–12964.

Postle, B.R., Berger, J.S., Goldstein, J.H., Curtis, C.E., D'Esposito, M., 2001. Behavioral and neurophysiological correlates of episodic coding, proactive interference, and list length effects in a running span verbal working memory task. Cogn. Affect. Behav. Neurosci. 1, 10–21.

Ranganath, C., Johnson, M.K., D'Esposito, M., 2003. Prefrontal activity during working memory and episodic long-term memory. Neuropsychologia 41, 378–389.

Ratcliff, R., 1978. A theory of memory retrieval. Psychol. Rev. 85, 59–108.

Raye, C.L., Johnson, M.K., Mitchell, K.J., Reeder, J.R., Greene, E.J., 2002. Neuroimaging a single thought: dorsolateral PFC activity associated with refreshing just-activated information. Neuroimage 15, 447–453.

Rypma, B., Berger, J.S., D'Esposito, M., 2002. The influence of working memory demand and subject performance on prefrontal cortical activity. J. Cogn. Neurosci. 14, 721–731.

Rypma, B., D'Esposito, M., 1999. The roles of prefrontal brain regions in components of working memory: effects of memory load and individual differences. Proc. Natl. Sci. Acad. 96, 6558–6563.

Rypma, B., Prabhakaran, V., Desmond, J.E., Glover, G.H., Gabrieli, J., 1999. Load-dependent roles of frontal brain regions in the maintenance of working memory. Neuroimage 9, 216–226.

Shallice, T., 1988. From Neuropsychology to Mental Structure. Cambridge University Press, New York.

Shimamura, A., 1995. Memory and frontal lobe function. in: Gazzaniga, M.S. (Ed.), The Cognitive Neurosciences. MIT Press, Cambridge, MA.

Smith, E.E., Jonides, J., 1999. Storage and executive processes in the frontal lobes. Science 283, 1657–1661.

Sternberg, S., 1966. High-speed scanning in human memory. Science 153, 652–654.

Stuss, D.T., Benson, D.F., 1986. The Frontal Lobes. Raven Press, New York.

Talairach, J., Tournoux, P., 1988. Co-Planar Stereotactic Atlas of the Human Brain. Thieme Medical, New York.

Taylor, S.F., Kornblum, S., Lauber, E.J., Minoshima, S., Koeppe, R.A., 1997. Isolation of specific interference processing in the Stroop task: PET activation studies. Neuroimage 6, 81–92.

Van Selst, M., Jolicoeur, P., 1994. A solution to the effect of sample size on outlier elimination. Q. J. Exp. Psychol. A Hum. Exp. Psychol. 47A, 631–650.

Zacks, R.T., Hasher, L., 1994. Directed ignoring: inhibitory regulation of working memory, in: Dagenbach, D., Carr, T.H. (Eds.), Inhibitory Processes in Attention, Memory, and Language, Academic Press, San Diego, CA, pp. 241–264.

Zhang, X., Johnson, M.K., 2001. Enhanced distractor activation does not increase selection difficulty in working memory. Paper presented at the Annual Meeting of the Midwestern Psychological Association, Chicago, IL.