

Load response functions in the human spatial working memory circuit during location memory updating

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Previous studies have emphasized that the dorsolateral prefrontal cortex is important for manipulating information in working memory, although activations in other frontal and parietal areas are commonly observed under the same conditions. We conducted an fMRI experiment to examine brain responses as a parametric function of memory updating, which is considered as an elemental process in working memory. In a variant spatial delayed-response task, human subjects performed updating operations over a 9-second delay period, during which they mentally transform the location of a memorized target in a 4 by 4 grid according to 3 to 12 instruction cues. Activity increased monotonically with increasing updating load in numerous cortical and subcortical regions including the rostradorsal premotor (rdPM), lateral precentral sulcus, lateral prefrontal, posterior associative, striatal and cerebellar areas. The rdPM and superior parietal were particularly sensitive to the updating manipulation. There were several main findings. First, updating spatial working memory involved mostly the same cortical and subcortical regions that were activated during maintenance of spatial information. Second, the updating load response functions of regions in the spatial working memory circuit showed a strong linear component. However, none shows significant increases in activity from 9 to 12 updating operations. Third, activity in the right rdPM and anterior inferior frontal gyrus correlated positively with working memory performance in the high updating load condition. Our findings suggest that updating and maintenance of spatial information may share similar processes and that the rostradorsal premotor cortex and anterior inferior frontal gyrus may be important for the success of tracking spatial information in working memory.

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Introduction

Working memory is commonly modeled as a system that supports the temporary maintenance and manipulation of information during complex cognitive tasks (Baddeley, 1986). It has been proposed that the underlying working memory network can be divided into specialized functional units. In particular, the dorsolateral prefrontal cortex (PFC) has been associated with manipulation processes of working memory and the ventrolateral PFC with maintenance and retrieval processes (D'Esposito et al., 1998; Owen et al., 1999; Petrides, 1994). Other cortical regions, especially the dorsal premotor and posterior parietal cortices, are also involved in working memory (see reviews by Collette and Van der Linden, 2002; Wager and Smith, 2003). It remains unclear whether these regions serve similar functions in working memory or whether they each have a specific function, such as maintenance, updating, shifting, inhibition, etc.

One useful approach to study the underlying neural substrates of working memory is to vary the task load parametrically. Numerous neuroimaging studies have used the *n-back* task, in which subjects are required to make judgments as to whether the current task item is the same as an item *n* back in the sequence. Various load response functions have been observed for the PFC including step (Cohen et al., 1997), linear (e.g., Braver et al., 1997), and invert-U shaped functions (Callicott et al., 1999; Jansma et al., 2004). However, the *n-back* paradigm is a complex working memory task involving not only manipulation processes (e.g., updating, reordering) but also maintenance processes (e.g., rehearsal, storage). Recent studies have examined the effect of load on simple maintenance by varying only the number of items to be remembered in delayed-recognition tasks. Some have found a linear increase in activity in the dorsolateral prefrontal cortex with increasing maintenance load during the delay period (Linden et al., 2003; Rypma et al., 2002), while others have found decreased or leveled activity at high maintenance load (Leung et al., 2004). Similar patterns of load-dependent activity for working memory maintenance have also been observed in the dorsal premotor and posterior associative areas (Leung et al., 2004; Linden et al., 2003; Todd and Marois, 2004; Xu and Chun, 2006).

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The present study aimed to examine responses in the spatial working memory circuit as a parametric variation in memory updating load while keeping the maintenance load minimum and unchanged. Memory updating has been considered an elemental executive operation in working memory (Baddeley, 1996; Miyake and Shah, 1999). It refers to the operation of adjusting the current contents in working memory to adapt new information (Morris and Jones, 1990), for example, updating the current product during a sequence of mental arithmetic operations. We were particularly interested in the lateral PFC, posterior parietal cortex, and dorsal premotor cortex as these regions have been implicated to play important roles in spatial working memory (e.g., Awh et al., 1999; Courtney et al., 1998; Leung et al., 2002). We expected activity to increase with the number of updating operations in brain areas that are sensitive to manipulation processes in working memory. Conversely, we expected to find no or minimum variation of activity in areas that are specialized for maintaining information in working memory since only one item was required to be remembered at any point of time in the updating conditions.

Methods

Subjects

Fourteen right-handed healthy adults (6 females and 8 males, aged 21–32 years, mean age=24) were recruited from the Yale University community, none with a history of drug abuse and psychiatric and neurological disorder according to self-report. All subjects gave informed consent to the protocol that was reviewed and approved by the Institution Review Boards of both Yale University School of Medicine and State University of New York at Stony Brook.

Data from one subject were excluded due to excessive motion during scanning. A total of 13 data sets were used in the final data analysis.

Working memory updating task

We implemented a variant of the spatial delayed-response task to incorporate the updating manipulation. Our design was modified

from previous studies (Hanakawa et al., 2002; Sawamoto et al., 2002). Fig. 1 shows a sample trial for each updating condition and a timeline of task events. Each trial began with a fixation period of 4.5 s followed by a 1-second presentation of a visual stimulus (a red dot) in one of the cells of a 4×4 grid which served as the starting target position. This was followed by a mental updating period of 9 s during which a series of arrows in 4 possible directions (up, down, left, right) were displayed sequentially. Each arrow indicated to which of the four neighboring cells the target should be mentally moved. At the end of the updating period, a testing stimulus (a blue "X") was displayed for 1 s and the participants made button presses to indicate whether or not it matched the final target position. The chance for a match and a non-match response was 50/50. The correspondence between the two fingers and match/non-match responses was counterbalanced across participants. The initial target stimulus and the testing stimulus were presented in all 16 possible locations at equal chance. The arrow series were generated pseudorandomly with no regular patterns, repeating patterns, or patterns that would confine the mental target within a local area. Only a few series contained three arrows of the same direction in a row. There were also no immediate back and forth arrows (e.g., a left arrow right after a right arrow).

The number of updating operations was manipulated by varying the total number of instruction cues (0, 3, 6, 9, and 12 arrows) during the 9-s mental updating period. In trials with less than 12 arrows, bars without arrowheads were displayed to equate visual stimulation across conditions (e.g., 12 bars were displayed during the updating period of the 0-arrow trials). Each arrow or bar was displayed for 250 ms and the interstimulus interval was 450 ms. Each trial was 15.5 s long and the intertrial interval was 11.5 s. There were 10 trials per run (2 trials per condition) and a total of 8 runs. The order of the updating conditions was counterbalanced across runs and subjects.

Working memory control task

In addition to the updating task, each subject performed a working memory control task after completing the memory

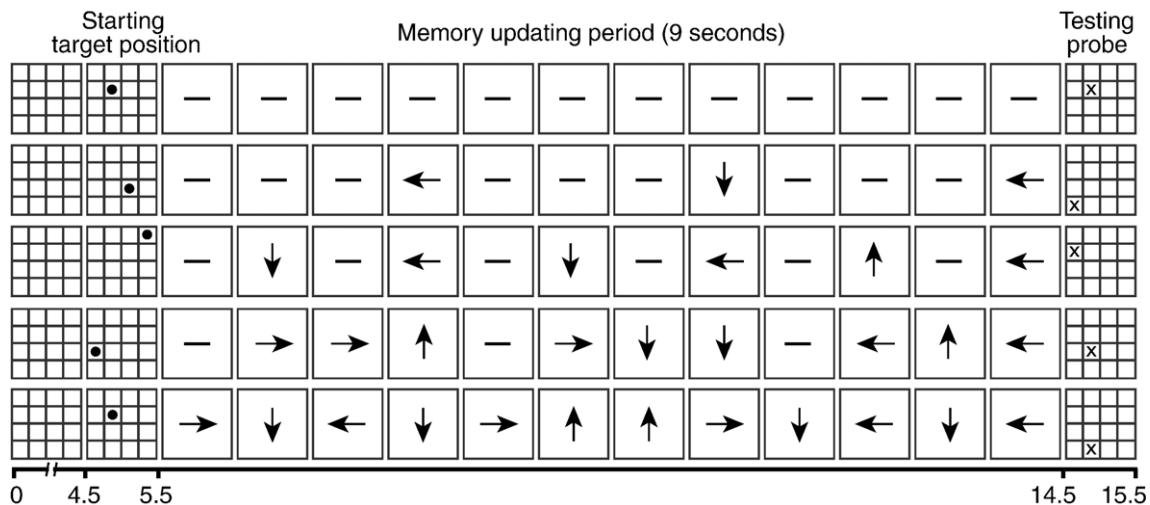


Fig. 1. A schematic drawing of the spatial working memory updating task conditions. Sample trials that required 0, 3, 6, 9, and 12 updating operations are shown. Arrows were used as the instruction cues and bars the fillers. Each arrow/bar was presented for 250 ms with a 450 ms gap between two stimuli. The bottommost row shows the timeline of task events in seconds. The intertrial interval was 11.5 s (not shown).

updating runs. At the beginning of each trial, 4 dots (targets) were simultaneously displayed on the grid at 4 different locations to serve as the working memory set. Following a 9-s blank delay period (without grid, arrows, or bars), a testing stimulus was displayed at either one of the four target locations or a new location. The subjects made button presses to indicate whether or not the testing dot matched the location of one of the four target locations. The timing of task events and other parameters was the same as the updating task (see above). Each subject completed one run with 12 trials. This task was used for comparison purposes and to determine brain activations in response to a challenging working memory task without any explicit updating or other manipulation demands.

Imaging procedures

Whole brain images were acquired using a 3 T system (Trio, Siemens AG, Erlangen, Germany). Conventional T1-weighted sagittal images were collected for slice localization. Twenty-four axial-oblique slices (5 mm) were prescribed parallel to the anterior–posterior commissural line. T1-weighted structural images were obtained with a 300 ms repetition time (TR), a 2.5 ms echo time, a 60° flip angle (FA), a 22 cm × 22 cm field of view (FOV), and a matrix size of 256 × 256. Functional images were acquired with the same slice selection and a TR of 1500 ms, TE of 30 ms, FA of 80°, matrix size of 64 × 64, and a FOV 22 × 22 cm using T2*-sensitive gradient-recalled single shot echo-planar pulse sequence. Each subject was scanned for 8 functional runs of the updating task (180 image volumes/run) and 1 run of the memory control task (216 image volumes). High-resolution anatomical images were also obtained (MPRAGE sequence, 176 sagittal 1 mm thick slices, TR=2530 ms, TE=3.52 ms, FA=7°, matrix=256 × 256).

Image processing and analysis

SPM2 was used for image processing and constructing individual and group contrast maps (Wellcome Department of Imaging Neuroscience, University College London, London, UK). The first 8 images were discarded from each functional run. Functional images were corrected for different times of slice acquisition followed by a 6-parameter rigid body motion correction. Runs with images that have motion greater than 3 mm in the *x*, *y* or *z* direction or more than 1.5° of pitch, yaw or roll were eliminated from further analysis. Images were realigned with reference to the first image of the middle run. Functional images were co-registered with in-plane anatomical as well as high-resolution anatomical images, segmented (gray and white matter), and were then normalized to a Montreal Neurological Institute (MNI) gray matter template using a 12-parameter affine registration following by nonlinear transformation (Friston et al., 1995a). The image volumes were resampled to 3 × 3 × 3 mm voxel size. Images were subsequently smoothed in the spatial domain with a Gaussian filter of 8 mm at full-width at half maximum. The data were also high-pass filtered with 1/128 Hz cutoff frequency to remove low-frequency signals (e.g., linear drifts).

Two kinds of statistical design were applied to analyze data from each individual. First, a standard design was constructed for each data set, using the general linear model (GLM). For each updating condition, the onset times of the cue, updating, and probe events were defined and the durations of the events at 1, 6, and 2 scan steps, respectively. Each event was convolved with a canonical

hemodynamic response function and entered as regressors in the model (Friston et al., 1995b). For each individual, *t*-tests were performed to examine both simple main effects of each updating load condition and differences between the higher updating load conditions and the 0-arrow (0-load) condition. Beta weights (or estimated parameters) of each condition of interest were used in the *t*-test calculations. Second, a parametric design was constructed for each data set, including unweighted covariates for the onset times of the task events of each condition and covariates weighted by the corresponding updating load levels (0, 3, 6, 9, 12) as linear regressors. Both correct and incorrect trials were included in these analyses to determine the overall effect of updating load.

For the whole group, random effects analyses were conducted to test for statistical differences between conditions of interest (e.g., 6-arrow vs. 0-arrow) using the corresponding contrast values from each individual. The contrast values of a condition were the weighted sum of the beta weights from the single subject analysis. *T*-values for group comparisons were calculated using one-sample *t*-test. Final group statistics were corrected by false discovery rate (FDR) (Genovese et al., 2002).

Regions of interest (ROIs) were defined as spheres (radius = 10 mm) with the center at the peak coordinates of the activation clusters obtained from the group composite maps of updating load using the parametric analysis. Two control regions (primary motor and visual cortices) were selected anatomically. We used the MarsBar Matlab toolbox (Brett et al., 2002) (<http://marsbar.sourceforge.net>) to extract ROI data from each individual. Time-courses were collapsed across trials for each task condition, of which the average percent signal change for each time point was calculated relative to the baseline. Baseline was the average of the first three images of a trial. Repeated measures analysis of variance (ANOVA) was applied to determine the updating load effect and linearity of load response function for each ROI. Error trials were removed from these tests. Linear regression was applied to determine the correlation between the average percent signal change of an ROI during the updating period and working memory performance (hit rate–false alarm rate) in the 12-arrow condition.

Results

Behavioral results

The average accuracy for each updating condition was 99, 92, 82, 88, and 78% and reaction time was 987, 1017, 1006, 1103, and 1098 ms from the 0- to 12-arrow conditions. The average accuracy was 92% and reaction time was 1128 ms for the memory control condition. Difference in performance between the updating conditions was significant for accuracy ($F(4,48)=9.60, p<0.001$), but not for reaction time ($F(4,48)=1.25, p>0.05$). Post hoc *t*-tests showed that accuracy in conditions that require 3 or more updating operations was lower than the condition with 0 number of updating operations (all comparisons with $p<0.05$). The recognition rate (hit rate–false alarm rate) decreased from 0.97 to 0.58 ($F(4,48)=8.75, p<0.0001$) as false alarm rate increased with increasing number of updating operations.

Spatial working memory circuit: maintenance versus updating

Results from the memory control task revealed widespread cortical and subcortical activations during the delay period (Fig.

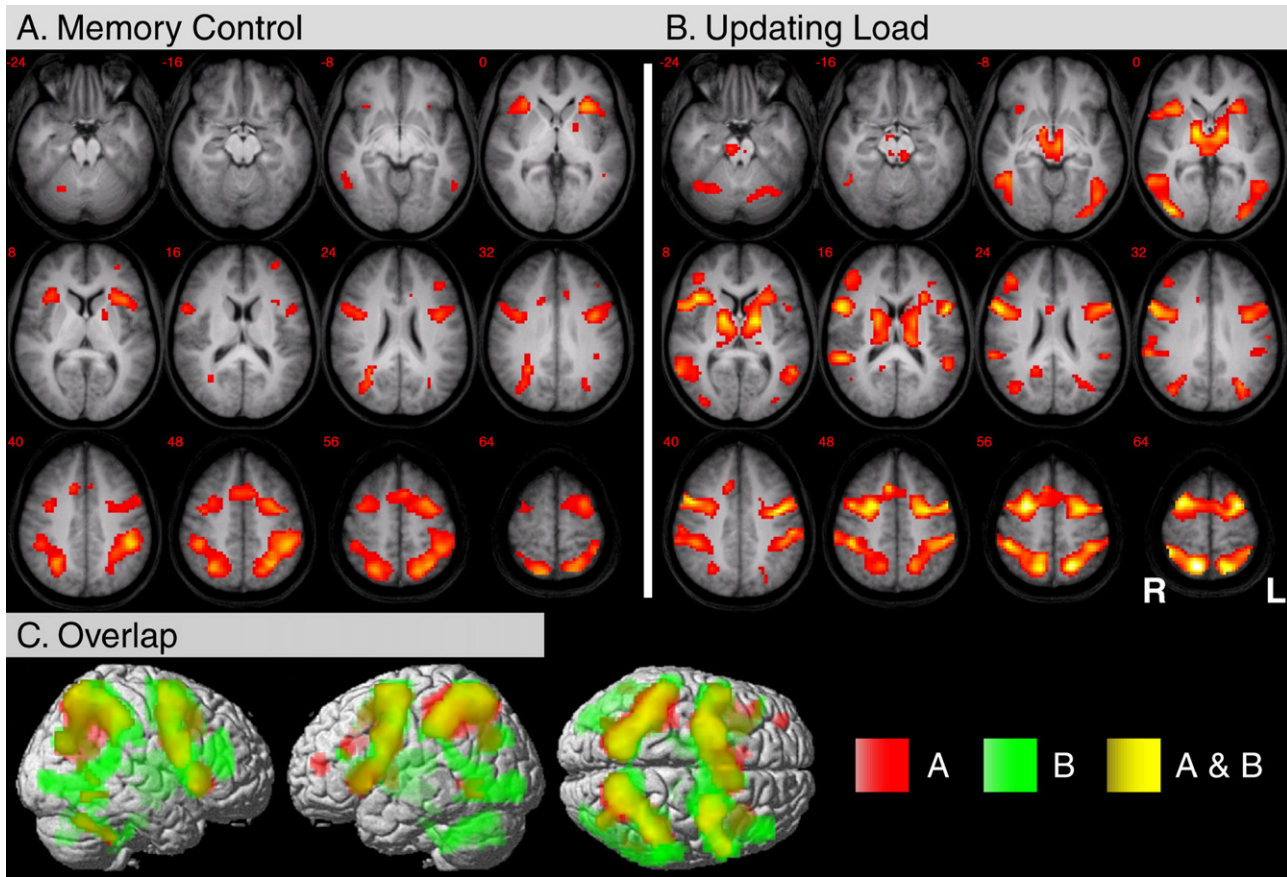


Fig. 2. (A) Group composite maps showing activations during the delay period of the memory control task. (B) Group composite maps showing activations as a parametric function of load during the updating period of the updating tasks. In both panels A and B, the color scale from red to yellow represents t -values ranging from 0 to 10. Activations were overlapped on the mean anatomical image of the 13 subjects in both panels A and B. (C) Overlapped results from panels A and B on a rendered single subject template. Threshold is $p < 0.005$, uncorrected and cluster filter 6 contiguous voxels. L—left hemisphere, R—right hemisphere.

2A). Table 1 shows a list of activation peaks in clusters of 6 or more contiguous voxels ($p < 0.03$, corrected). In particular, activations were evident in the inferior parietal lobe (IPL), superior parietal lobe (SPL), intraparietal sulcus (IPS), rostradorsal premotor area (rdPM), lateral precentral sulcus (pre-CS), insula, pre-supplementary motor area (pre-SMA) and inferior frontal gyrus (IFG). The rdPM activation was anterior to the junction of superior frontal sulcus (SFS) and pre-CS as shown in previous studies of spatial working memory (e.g., Courtney et al., 1998). Most regions showed bilateral activation. Activations were also found in the left middle frontal gyrus (MFG), right cerebellum, left lenticular nucleus (putamen) and right temporo-occipital junction (TOJ) at a lower threshold ($p < 0.05$, corrected).

Many of the same areas were modulated by the number of updating operations as revealed by the results from the parametric analysis (Fig. 2B). Table 2 shows a list of activation peaks in clusters of 6 or more contiguous voxels ($p < 0.005$, corrected). Several regions, particularly in the right hemisphere, showed more extensive activations in response to the updating load manipulation in comparison to the memory control task. These regions were the right rdPM, SPL (extending to the precuneus), lateral prefrontal areas (MFG and IFG), and the bilateral lenticular nuclei (extending to the thalamus), temporo-parietal junction (TPJ), middle temporal gyrus (MTG), and middle occipital gyrus (MOG). See Fig. 2C to visualize the amount of

overlap between activations that varied as a parametric function of updating load and activations that were observed during the delay period of the memory control task.

Updating load response function: voxel-based analysis

Regions in the spatial working memory circuit exhibited different levels of sensitivity to the updating load. Fig. 3 shows the group composite maps for the 3-arrow to 12-arrow updating conditions in contrast with the 0-arrow condition ($p < 0.005$, uncorrected; cluster filter of 6 voxels). These results showed that the load-dependent activations for updating were not simply due to sensory stimulation from the presentation of arrows/bars during the updating period. Our data showed that the bilateral rdPM, SPL and IPS are active even at the lowest updating load and activity in these regions increased with increasing number of updating operations. Responses in the lateral pre-CS, IPL, TPJ, MOG, and lenticular nuclei were above threshold when the number of updating operations was 6 or above. In addition, the insula, lateral prefrontal areas (right IFG and MFG) and MTG showed suprathreshold activation in the 9- and 12-arrow updating conditions. The anterior PFC (aPFC, BA 10), dorsal MFG (BA 9), and mediadorsal PFC were activated during the response period of the task (not depicted in the figures).

Table 1
Regions activated during the delay period of the memory control task

Lobe	Region	BA	Cluster size	Talairach coordinates			T	Z
				x	y	z		
Left parietal	IPL	40/2	859	-45	-36	40	7.38	4.45
	SPL/IPS	7		-30	-56	50	7.06	4.36
	SPL	7		-21	-61	56	6.10	4.04
Right parietal	IPL	40	97	45	-36	43	5.72	3.90
	SPL	7	438	18	-67	59	6.01	4.01
	SPL/IPS	7		30	-59	44	6.29	4.11
	SOG	19		33	-66	28	4.75	3.50
Left frontal	Insula/IFG		266	-30	20	-1	6.29	4.11
	IFG	44		-48	9	8	4.75	3.50
	rdPM	6/8	270	-30	-1	47	5.76	3.92
	pre-CS ^a	6/44	93	-39	1	28	5.73	3.90
	MFG	46/10	7	-33	47	6	4.38	3.32
	MFG ^b	46	21	-39	30	21	4.01	3.13
Right frontal	Insula/IFG	47	88	30	23	-4	5.17	3.68
	rdPM	6/9	187	39	-4	42	5.02	3.62
	pre-CS	6/44		39	1	25	4.73	3.49
Medial frontal	pre-SMA	6/32	107	-9	14	46	4.97	3.59
	ACC	32/24		12	19	35	4.50	3.38
Subcortical	Cblm		6	24	-62	-20	4.13	3.20
	Lent nuc ^b		20	-18	0	6	3.55	2.88
Occipital	TOJ/MOG ^b	37	10	50	-56	-5	3.43	2.81

Peak activations from random effects analysis are listed with a threshold of $p < 0.03$, FDR corrected, and cluster filter of 6 contiguous voxels. BA—Brodmann's area, IPL—inferior parietal lobe, SPL—superior parietal lobe, IPS—intraparietal sulcus, SOG—superior occipital gyrus, IFG—inferior frontal gyrus, rdPM—rostrorodorsal premotor cortex, pre-CS—precentral sulcus, MFG—middle frontal gyrus, pre-SMA—pre-supplementary motor area, ACC—anterior cingulate cortex, Cblm—cerebellum, Lent nuc—lenticular nucleus, TOJ—temporo-occipital junction, MOG—middle occipital gyrus.

^a Cluster at $p < 0.025$, FDR corrected.

^b Cluster at $p < 0.05$, FDR corrected.

Updating load response function: ROI analysis

Results from the extracted ROI data confirmed that the updating load response functions of the spatial working memory circuit are mostly linear. Fig. 4 shows the average timecourses of selected regions in the working memory circuit (see Table 2). The characteristics of timecourses included both transient responses to target presentation and probe presentation and sustained effects during the updating period. Areas such as the occipital gyrus (OG) showed a stronger transient effect relative to most frontal areas. During the updating period, responses dropped near the baseline for the 0-arrow condition (without updating operations) while responses increased monotonically from the 3-arrow condition to the 12-arrow condition. Fig. 5 (left) illustrates the load-dependent activity in the frontal and parietal areas as a function of the number of updating operations. The average percent signal change during the updating period of each updating condition was calculated using scans 8 to 12 (6.5–12.5 s after the target presentation) to correct for delay in hemodynamic response. Load-dependent activity for updating was also observed in the temporal, occipital and subcortical regions (Fig. 5, right). The load response functions of brain regions in the spatial working memory circuit had a strong linearity component as determined by repeated measures of

ANOVA ($p < 0.005$). Similar effects were not observed for the control regions including the motor and visual cortices. Although most regions in the spatial working memory circuit showed monotonic increases in activity from 0 to 9 updating operations (Figs. 4 and 5), further increases in activity from 9 to 12 updating operations were insignificant even with the error trials excluded from analysis. Paired t -tests showed that the latter increase was only approaching significance in the right rdPM ($p = 0.08$) and right MFG ($p = 0.06$).

We also examined whether the rdPM, SPL and lateral prefrontal areas (IFG and MFG) are related to the success of spatial working memory updating in the most demanding condition (12 updating operations). This was to test a more stringent hypothesis that responses in these cortical areas linearly correlate with individual differences in spatial working memory performance. Working memory performance was measured in recognition rate (hit rate–false alarm) (see Behavioral results). Linear regression analysis showed significant correlation between individual performance and responses in the right rdPM ($R^2 = 0.32$, $F = 5.17$, $p = 0.04$) and right

Table 2
Regions modulated by the updating load

Lobe	Region	BA	Cluster size	Talairach coordinates			T	Z
				x	y	z		
Left parietal	SPL	7	410	-21	-56	55	9.41	4.96
	IPL	40		-39	-38	52	6.58	4.20
	IPL	40		-48	-33	43	6.53	4.19
Right parietal	SPL/PCu	7	452	12	-58	64	11.96	5.45
	IPL	40		42	-41	57	8.70	4.80
Left frontal	rdPM	6	502	-27	3	58	9.14	4.90
	Pre-CS	9/6		-45	-1	39	8.55	4.76
	IFG	44/6		-50	7	16	7.91	4.60
Right frontal	rdPM	8	767	27	3	52	9.67	5.02
	IFG	44		56	10	16	8.60	4.78
	Insula/IFG	13/45		42	18	5	7.79	4.57
	Pre-CS	9/6		48	5	36	7.50	4.49
Medial frontal	IFG	46/45	11	39	38	6	5.28	3.73
	MFG	46	7	42	36	20	5.01	3.61
	pre-SMA/ACC	6/32	22	9	20	43	6.54	4.16
	Temporal	STG	39	25	-53	-52	11	6.54
TPJ		22		-50	-40	21	4.82	3.53
TPJ		22	159	53	-40	16	6.84	4.29
MTG		21		59	-52	5	6.02	4.01
MTG		37/21		45	-50	-5	5.66	3.88
Occipital	SOG	39/19	19	-30	-65	31	5.60	3.85
	MOG	19	65	-36	-84	2	5.42	3.78
	MOG	19		-45	-67	-4	5.31	3.74
	OG	19	39	39	-81	4	7.77	4.56
Subcortical	Lent nuc		556	-18	-5	9	8.20	4.68
	Lent nuc			18	-5	11	7.21	4.40
	SNr			12	-6	-2	7.67	4.54
	Th			-12	-20	15	5.49	3.81
	Cblm	14		-36	-42	-31	5.55	3.84
	Cblm	16		-24	-62	-22	5.14	3.67
	Cblm	7		36	-59	-20	4.99	3.60

Peak activations from random effects analysis are listed with a threshold of $p < 0.005$, FDR corrected, and cluster filter of 6 contiguous voxels. TPJ—temporo-parietal junction, STG—superior temporal gyrus, SNr—substantia nigra, Th—thalamus. See other abbreviations in Table 1.

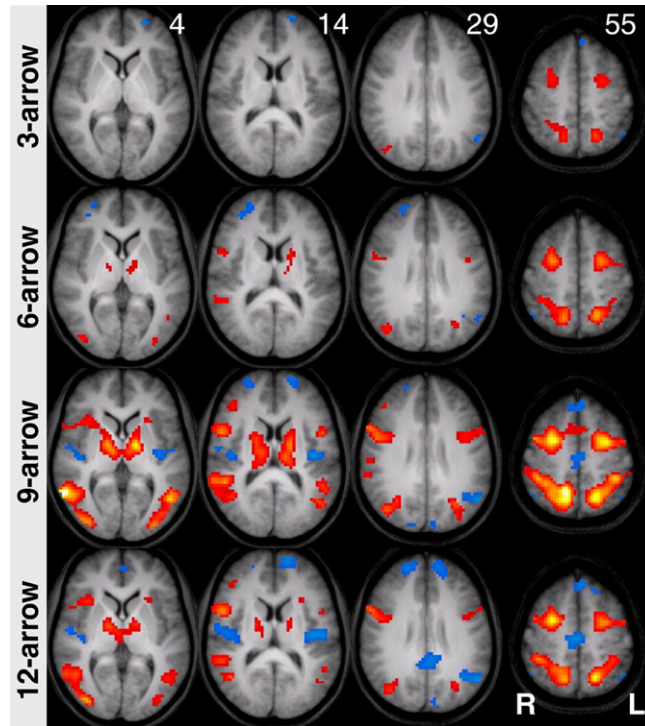


Fig. 3. Group composite maps showing activations during the updating period of the 3-, 6-, 9-, and 12-arrow conditions in contrast with the 0-arrow condition. The rdPM and SPL showed heightened activation even in the 3-arrow condition while the lenticular nuclei, pre-CS, and lateral prefrontal areas showed increases in activity at higher load conditions. Threshold is $p < 0.005$, uncorrected and cluster filter 6 contiguous voxels. L—left hemisphere, R—right hemisphere. Z-coordinates (mm) of the slices are displayed at the top.

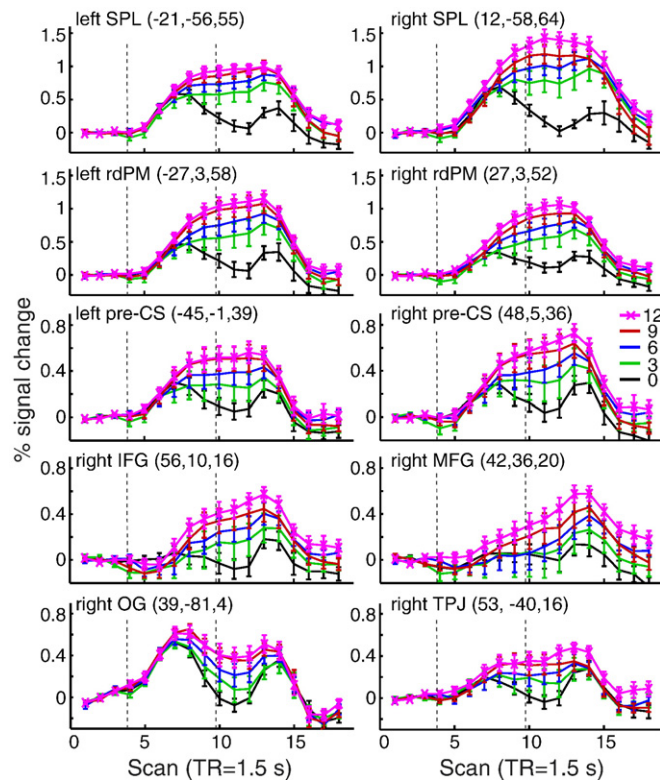


Fig. 4. Timecourses depicting average percent signal change in ROIs during the updating tasks. The x-axis represents time in scans (1.5-s steps). Talairach coordinates of the center of the ROIs are shown in parentheses. The two vertical lines bound the portion of the trial during which updating operations are required. Line colors represent the task conditions of different number of updating operations: 0—black, 3—green, 6—blue, 9—red, and 12—magenta.

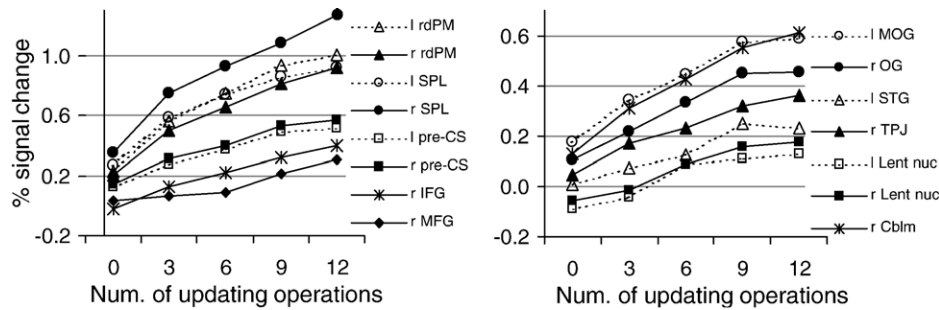


Fig. 5. Load response functions. Responses in cortical and subcortical regions in the spatial working memory circuit increased monotonically with increasing number of updating operations. See Table 1 and Table 2 for abbreviations.

anterior IFG ($x=39, y=38, z=6$) ($R^2=0.35, F=5.97, p=0.03$) during the updating period (Fig. 6, top). In contrast, responses in the right MFG and SPL did not correlate with the recognition rate (Fig. 6, bottom).

Discussion

The present study provides novel data on responses of the neural substrates underlying spatial working memory as a parametric function of updating load while keeping the maintenance load minimum. A network of frontal, parietal, occipito-temporal and subcortical (striatum and dorsal cerebellum) regions showed monotonic increases in activity with increasing number of operations performed to update the location of one memorized target. Most regions that showed updating load-dependent activity were also activated in the working memory control task. Our results indicated that the rdPM and SPL are sensitive to the updating manipulation; they were activated at the lowest updating load condition with 3 operations. In addition, our results showed that the rdPM and anterior IFG correlate with individual dif-

ferences in spatial working memory performance. These findings suggest that the rdPM and anterior IFG may be important for the success of tracking spatial information in working memory.

Prefrontal cortex

The “process specific” model hypothesizes that the dorsolateral PFC is selectively involved in manipulation processes whereas the ventrolateral PFC is involved in maintenance (and retrieval) processes in working memory (Owen et al., 1999; Petrides, 1994). However, the present findings demonstrated that both dorsolateral PFC (e.g., right MFG) and ventrolateral PFC (e.g., bilateral IFG/insula) are modulated by the updating operations. Our data further showed that activity in the anterior portion of IFG, but not MFG, correlates with spatial working memory performance. The other parts of the IFG/insula were also more strongly modulated by the updating demand in comparison to the MFG, as revealed by the group statistical results. Importantly, both dorsolateral and ventrolateral prefrontal areas were activated in the memory control task. Our data thus support that maintenance and

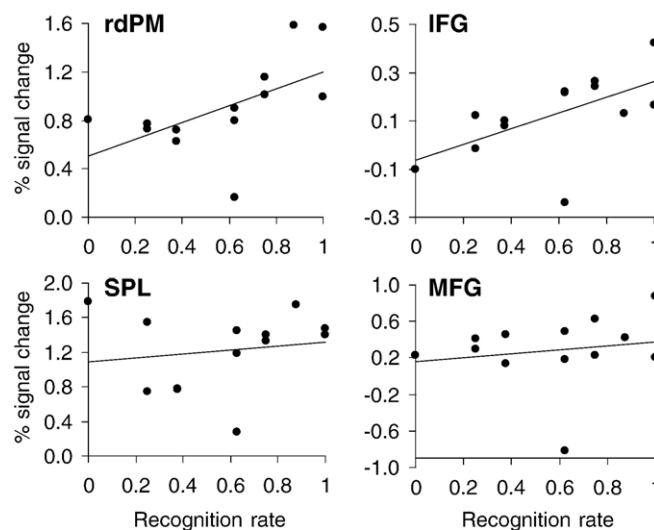


Fig. 6. Scatter plots depicting the correlation between the average percent signal change during the updating period and working memory performance in the 12-arrow updating condition. Each dot represents data from one subject. The x-axis represents recognition rate (hit rate–false alarm rate). The y-axis represents percent signal change from baseline in the anterior IFG ($x=39, y=38, z=6$), rdPM ($x=27, y=3, z=52$), MFG ($x=42, y=36, z=20$), and SPL ($x=12, y=-58, z=64$). Responses in the anterior IFG and rdPM significantly correlated with performance while MFG and SPL did not. See Table 1 and Table 2 for abbreviations.

manipulation processes are integrated within the lateral prefrontal areas (Goldman-Rakic, 1987). Similar results were reported in neuroimaging studies using a running span design in the verbal domain (Postle et al., 2001; Salmon et al., 1996). However, previous studies have found greater activations in the dorsolateral PFC relative to the ventrolateral PFC in an alphabetization task (Postle et al., 1999) and in a continuous attentional switch task (Garavan et al., 2000). The additional dorsolateral PFC activity may be a result of the greater mental demand since these latter tasks required additional cognitive processes (e.g., retrieval and reordering) and manipulation of multiple items in working memory. A recent study also did not find functional dissociation along the dorsoventral axis of PFC, but did find scattered dissociation in responses to manipulation (anterior MFG and inferior frontal junction) in comparison to maintenance (dorsal premotor cortex) of target color and orientation in working memory (Mohr et al., 2006). The apparent discrepancy in findings between studies may be due to differences in maintenance load and, in addition, the type and number of manipulation operations required by the task.

The right MFG showed a linear load response function for updating in the present study. This was different from our previous spatial working memory study, in which we manipulated the number of spatial locations to be remembered and found poor recognition performance (~66% accuracy) and a reduction in MFG activity at high maintenance load (4 locations) (Leung et al., 2004). It is likely that our subjects may have just reached their limit in updating capacity since their performance was lower in the 12-arrow condition than the other conditions. In addition, it is unlikely that the activity will increase any further even with a higher updating load since the increases in activity from 9 to 12 updating operations were not significant for the prefrontal areas and other areas that we have examined. Nevertheless, the activity in several regions appeared to have reached an asymptote earlier than some other regions (e.g., compare right MFG with right OG in Figs. 4 and 5). This potentially reflects that the right lateral PFC together with the right rdPM and SPL (see below) is involved in supporting spatial working memory of larger processing loads than other regions (e.g., OG and TPJ). Previous studies have implicated that the dorsolateral PFC is involved in executive processes that help holding more information in verbal working memory (Rypma et al., 2002) and object working memory (Linden et al., 2003).

Dorsal premotor cortex

While the premotor cortex has been traditionally considered as a higher order motor region for motor preparation, planning and sequencing, more recent studies have consistently demonstrated that portions of the dorsal premotor cortex are activated in cognitive tasks (see Picard and Strick, 2001). It has been demonstrated that the premotor cortex shows functional specialization along the rostro-caudal axis, where cognitive operations (e.g., attention) involve the rostral portion and motor operations (e.g., preparation) involve the caudal portion (see Boussaoud, 2001). The dorsal premotor activation associated with spatial working memory is near the junction of SFS and pre-CS (BA 6/8) (Courtney et al., 1998; Rowe et al., 2000; Simon et al., 2002), which is usually rostral and dorsal to the functionally defined frontal eye fields (FEF) (Koyama et al., 2004; Paus, 1996). In contrast, the caudal premotor area including FEF has been related to motor preparation in several fMRI studies of

spatial working memory (Curtis et al., 2004; Simon et al., 2002; Toni et al., 1999).

Our findings corroborate the notion that the rdPM is involved in spatial working memory. In an elegant experiment, Tanaka et al. (2005) have demonstrated that the dorsal premotor cortex (here we called rdPM) has a critical role in updating spatial information. They found that repetitive transcranial magnetic stimulation (rTMS) of the rdPM interrupted updating operations in the spatial domain but not in the verbal domain (Tanaka et al., 2005). It has been shown that activations in the rdPM are not due to motor control (Hanakawa et al., 2002) or motor preparation *per se* (Simon et al., 2002). However, others have found that the rdPM was predominantly involved in maintenance rather than manipulation of working memory in a task requiring reordering of spatial memoranda (Postle et al., 2000). Since eye movements were not monitored in the present study, it cannot be ruled out that the premotor activations may also reflect small gaze shifts during the updating period. However, distinguishable activations in the rdPM and FEF have been identified respectively with spatial working memory and saccadic eye movements in previous fMRI studies that directly compared the two (see Courtney et al., 1998; Hanakawa et al., 2002).

Attentional load-dependent activity has been observed in the rdPM during visual tracking of multiple moving targets in an fMRI study (Culham et al., 2001). Although the targets were always visible in the visual tracking task, this task may require spatial working memory to distinguish and monitor the motion of multiple targets among non-target distractors. Alternatively, our updating task may modulate the attentional network as visual cues (arrows) were presented to guide updating the mental representation of the target location in working memory. It has been demonstrated that the two cognitive systems may share underlying neural circuits (e.g., LaBar et al., 1999). Covert spatial attention has been implicated to play a role in the maintenance of spatial information (Awh and Jonides, 2001) and target selection in working memory (Griffin and Nobre, 2003; Lepsien et al., 2005).

Other cortical and subcortical areas in the spatial working memory network

Besides rdPM and lateral PFC, updating load-dependent functions were observed in many other regions including the posterior parietal cortex (SPL and IPS) and the lateral pre-CS. Both regions are frequently reported in neuroimaging studies of attention (Corbetta, 1998) and working memory (Smith and Jonides, 1999). Aside from a role in spatial attention, the involvement of posterior parietal cortex in cognitive control has been recognized (see review by Corbetta et al., 2002). In a set of experiment, Medendorp and colleagues show that the posterior parietal cortex is involved in monitoring target locations (Medendorp et al., 2003) and, perhaps more importantly, in integrating target and effector information for guiding movements (e.g., reaching a target) (Beurze et al., 2006; Medendorp et al., 2005). Indeed, studies showed that right parietal neglect patients have selective deficits in remembering target locations (Husain et al., 2001; Pisella et al., 2004), which is needed for the later preparation and planning of delayed responses.

The pre-CS activation in the present study is in the inferior frontal junction (IFJ), an area considered to serve as a general mechanism in cognitive control by recent neuroimaging studies (Derrfuss et al., 2004). IFJ and anterior insula are commonly activated during tasks involving cognitive control, especially during response inhibition

(Konishi et al., 1999) and mental set switch (Nagahama et al., 2001). Both the posterior parietal cortex and pre-CS showed greater activation in correspondence to rejecting negative probes at more familiar locations than the less familiar locations (Leung and Zhang, 2004). A recent study also showed that the pre-CS is activated during face/house memory updating (Roth et al., 2006). Perhaps memory updating is the shared basic process among the more complex cognitive control tasks (e.g., the Stroop task).

Substantial load-dependent activations for updating were observed in subcortical regions (e.g., lenticular nucleus of the basal ganglia and the dorsal cerebellum). Accumulating evidence demonstrates that the basal ganglia and cerebellum are actively involved in cognitive processes (see reviews by Houk and Wise, 1995; Middleton and Strick, 2000). For example, neuroimaging studies have shown that the caudate nucleus is active during temporary maintenance of spatial information beyond motor preparation in spatial working memory tasks (Simon et al., 2002). Others have also found activations in the lenticular nucleus during covert shifts of spatial attention (Gitelman et al., 1999). Furthermore, recent neurocomputational models have implicated that a network of frontal and striatal regions forms the neural basis of working memory and that a key function of basal ganglia is working memory updating (O'Reilly and Frank, 2006). Our results thus provided empirical evidence supporting that the basal ganglia (lenticular nuclei) are involved in updating spatial working memory. Since eye movements were not monitored in the present study, additional evidence is clearly needed to delineate the functional relationship between the subcortical systems and the cortical systems during working memory and eye movement control.

In summary, findings from the present study extended previous research by showing load-dependent activity in a widespread network of cortical and subcortical regions in correspondence with updating spatial representations in working memory. In addition, we found that responses of the right rdPM and anterior inferior frontal gyrus are closely related to individual differences in spatial working memory performance. While the switch between visual cues and their representations may contribute to some of the observed effects, we show that, by keeping the maintenance load minimum, the regions in the spatial working memory circuit are modulated by the number of updating operations in a rather linear manner. The close correspondence between our findings using a working memory updating task and previous findings using an attentional tracking task (Culham et al., 2001) provides additional evidence that spatial attention and working memory may share underlying neural substrates. Future experiments will need to differentiate between memory updating, attentional/visual tracking, and reordering operations.

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