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Age-dependent brain activation during forward and backward digit recall revealed by fMRI

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In this study, brain activation associated with forward and backward digit recall was examined in healthy old and young adults using functional MRI. A number of areas were activated during the recall. In young adults, greater activation was found in the left prefrontal cortex (BA9) and the left occipital visual cortex during backward digit recall than forward digit recall. In contrast, the activation in the right inferior frontal gyrus (BA 44/45) was more extensive in forward digit recall than in backward digit recall. In older adults, backward recall generated stronger activation than forward recall in most areas, including the frontal, the parietal, the occipital, and the temporal cortices. In the backward recall condition, the right inferior frontal gyrus (BA44/45) showed more activation in the old group than in the young group. These results suggest that different neural mechanisms may be involved in forward and backward digit recall and brain functions associated with these two types of recall are differentially affected by aging.

Keywords: Working memory; Short-term memory; Aging; Prefrontal cortex; fMRI

Introduction

Both forward and backward digit span recall have been widely used to assess short-term memory and working memory respectively in neuropsychological research and clinical evaluation (Folstein et al., 1975; Hedden and Gabrieli, 2004; Risberg and Ingvar, 1973; Wechsler, 1939, 1981, 1997). However, the neural mechanisms underlying digit span, especially the backward digit span, remain unclear. Some researchers suggested that backward digit span employs the same memory mechanism as forward digit span (i.e., both involve verbal representations) (Richardson, 1977), whereas other behavioral, neuropsychological, and optical imaging studies have suggested that backward digit span might involve a visuospatial process (Hoshi et al., 2000; Larrabee and Kane, 1986; Li and Lewandowsky, 1993, 1995; Rudel and Denckla, 1974). Recently, it has become more popular to assume that the backward recall task measures working memory (particular the executive function), and the forward digit recall is a short-term memory task (Anderson and Grady, 2001; Halpern et al., 2003; Hedden and Gabrieli, 2004).

For example, using optical tomography, Hoshi et al. (2000) observed that the backward digit span task was associated with more activation in the bilateral dorsolateral prefrontal cortex (DLPFC) than the forward digit span task. Based on earlier work that demonstrated the involvement of the right DLPFC in spatial tasks (McCarthy et al., 1996; Smith et al., 1996), Hoshi argued that the activation of the right DLPFC suggests the involvement of visuospatial processing in the backward digit span task. However, the activation of the right DLPFC is not exclusively linked to visuospatial processing. In fact, various functions have been associated with the right DLPFC (see Cabeza et al., 2000 for a review). For example, Manoach et al. (1997) found that in a non-spatial digit memory task unrelated to vision, an increase in memory load was accompanied by increased activation in the right DLPFC.

In a series of behavioral studies, Li and Lewandowsky (1993, 1995) investigated differences in processing forward and backward digit span tasks. They found that the addition of an inter-item arithmetic task, which separated the items by distracters and

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interfered with the association between the items but did not include any visuospatial information, disrupted the forward but not the backward recall. On the other hand, manipulating the level of visual similarity or spatial position (randomly or fixed) of the items, which changed visuospatial processing but did not influence the association between the items, affected the backward but not the forward recall. Therefore, Li and Lewandosky put forward a Dual Retrieval Processes Model (DRPM) in which the forward and the backward recall utilize different retrieval processes, the so-called associative forward recall and visual–spatial backward recall, respectively. These studies provided important evidence for differences between the forward and backward recall tasks at behavioral level. However, the question of whether different neural mechanisms are involved in these two types of digit recall task remains to be answered.

Understanding the neural mechanisms underlying the forward and the backward digit recall tasks has important implications, given the widespread use of digit span tasks as measures of short-term memory and working memory in clinical and research settings. For example, backward digit span impairment is central to the profile of impaired cognitive performance in schizophrenia (Stone et al., 1998). Furthermore, Simard and van Reekum (1999) found that the digit span test is one of the most sensitive memory tasks to assess the effects of some cognition-enhancing drugs for Alzheimer's disease. In aging research, some studies have suggested that the backward digit span is more sensitive to the effect of aging than the forward digit span. Carlesimo et al. (1994) also found a normal forward verbal span but a reduced backward verbal span in Alzheimer's patients they tested. The Mini Mental Status Examination (MMSE), a clinical test commonly used to evaluate mental status of older adults, includes the backward digit span instead of the forward digit span as one of its critical measurements of cognitive functions, particularly working memory and the executive function (Conklin et al., 2000; Folstein et al., 1975; Halpern et al., 2003; Jacqmin-Gadda et al., 1997; Stone et al., 1998; Wilde and Strauss, 2002).

In a more recent study, however, the link between aging and the backward digit span task has been challenged. Myerson et al. (2003) reanalyzed the forward and the backward digit span data used to form the norm of the Wechsler-III intelligence test. Across more than 60 years of adulthood, they found that the forward and the backward digit span tasks were similarly affected by aging. The differences between raw scores of these two types of digit span task remain remarkably constant across adulthood. Considering possible compensation for changes in memory function, the similarity in performance between the forward and the backward span tasks does not necessarily mean that there is no difference in the neural mechanisms supporting these two tasks during the aging process. Thus, we explored the neural basis of differences between the forward and backward digit recall tasks and the effects of aging on these two types of recall using functional MRI.

There are two related goals of the present study. The first is to use fMRI to investigate brain activities associated with the forward and backward digit recalls, to hopefully provide important insights into the differences between the mechanisms involved in these two types of digit recall tasks at the neural level. FMRI allows us to examine the activity of the entire brain during these memory tasks (Posner, 1998), making it advantageous over other imaging methods such as the optical tomography (Hoshi et al., 2000). The second goal of the current study is to examine whether there are age-related differences in brain activation associated with the forward and backward digit recall tasks, testing the hypothesis that aging differentially affects the brain mechanisms of these two tasks.

Materials and methods

Participants

Twenty right-handed healthy adults participated in this study after providing informed consent. All of them were native Chinese speakers. Half of the participants (five females) were older adults with a mean age of 63.7 ranging from 60 to 72 years and the other half (five females) were young adults with a mean age of 22.3 ranging from 19 to 27 years (see Table 1). The young and the old groups were matched in years of education. Each participant's health status was examined through an interview prior to the experiment. None of the participants had a history of neurological or psychiatric disorders. The older adults were also given the Mini Mental Status Examination (MMSE, Folstein et al., 1975) and all of them scored in the normal range (i.e., between 28 and 30).

Paradigm and procedure

All participants performed forward and backward digit recall trials when they were scanned. Both types of trials started with a fixation-cross displayed for 500 ms in the center of the screen. Subsequently, a series of digits (selected from 1 to 9 without repetition) were presented sequentially at the location of the fixation. To equalize the task difficulty for the young and old adults, we presented eight digits to the young participants at a rate of one digit per 500 ms (300 ms on, and 200 ms off), and five digits to the old participants at a rate of one digit per 800 ms (300 ms on, 500 ms off). After the last digit, a blank screen was displayed for 6 s, at which time the participants were required to look at the screen and covertly rehearse the digits continuously. Following this retention interval, a cue was presented to instruct the participants to recall the digits either in a forward or a backward order (Li and Lewandowsky, 1993, 1995). The participant was instructed to keep his or her head stationary and not to watch while writing the recalled digits on a sheet of paper. One author stood near the scanner and made the recording paper available after each trial. The cue lasted until the onset of the next trial's fixation-cross. The total time allocated to recall and rest was 29.5 s (see Fig. 1). Since all participants were able to finish the FR or BR task within 10 s, there was enough time (longer than 19.5 s) for the BOLD signal to recover to the baseline level.

An LCD monitor placed near the scanner bed was used to present the stimuli to the participants. The fixation-cross, the digits, and the cue to instruct participants to recall extended 2° × 2°, 2° × 2°, and

Table 1
Demographic and performance data

	Young	Old
N	10	10
Age (range)	19–27	60–72
Age (mean ± SD)	22.3 ± 2.5	63.7 ± 4.1
Male/female	5/5	5/5
Digit recall-forward, accuracy rate (% ± SD)	87.5 ± 9.0	95.0 ± 5.8
Digit recall-backward, accuracy rate (% ± SD)	85.0 ± 7.7	88.3 ± 9.0

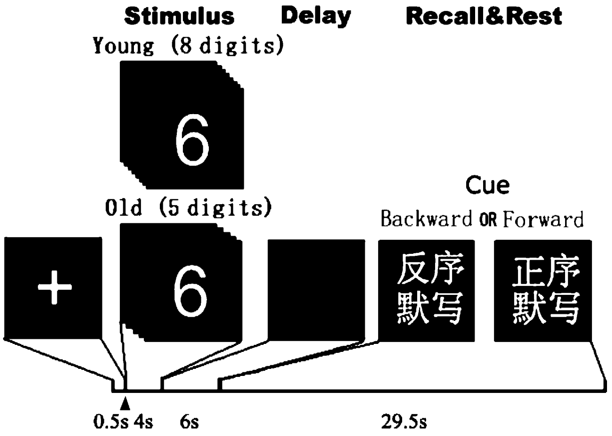

Fig. 1. The paradigm of forward and backward recall. The cue in Chinese indicates "Backward Recall" or "Forward Recall".

3° × 3° visual angle on the screen, respectively. The participants viewed the stimuli through a mirror placed above their eyes.

There were 12 trials (six were FR and the other six were BR trials) in each scanning session and the order of the FR and BR trials was randomized and counterbalanced across the participants. Two such scanning sessions was required of each participant, with approximately 2 min between sessions.

Data acquisition

Images were obtained with a 1.5-T Siemens Vision MR System (Siemens Medical Systems, Erlangen, Germany) equipped with echo planar imaging capability. A circularly polarized head coil was used, with foam padding to restrict head movements. Functional images were acquired with a T2*-weighted echo-planar imaging (EPI) sequence (TE = 51 ms, TR = 2 s, FOV = 24 cm) with 16 axial slices (thickness: 5 mm, slice gap: 1.25 mm, voxel size: 3.75 mm × 3.75 mm × 6.25 mm) that covered the whole brain. Corresponding high-resolution T1-weighted spin-echo (for anatomical overlay) and gradient-echo (for stereotaxic transformation) images were also collected. Each EPI scanning session lasted 8 min 6 s (243 images/slice). The first three images were discarded to account for the approach to steady state in the MR signal.

Data analysis

To derive activation maps corresponding to the different tasks, the fMRI data of our event-related study were analyzed in a manner similar to that in our previous published study (Zhang et al., 2004) using AFNI (Analysis of Functional NeuroImages, http://afni.nimh.nih.gov/afni/, Cox, 1996). First, the raw data were motion-corrected and normalized. After that, two types of epochs, one for the backward recall and the other for the forward recall, were extracted from the functional scanning sessions and averaged to derive the average epochs corresponding to backward and forward recall tasks, respectively, for each participant. Each averaged epoch was 20 time frames in length and resulted from 12 trials. Multiple regression analysis was then used to analyze the averaged data. In the multiple regression analysis, three memory phases were considered to contribute to the BOLD response in one epoch (FR or BR): stimulus (or encoding), delay (or active maintenance/rehearsal in the mind), and recall (or retrieval). Accordingly, three BOLD response models (stimulus, delay, and recall) were built by convolving the corresponding boxcar functions with the hemodynamic response function described by Glover (1999). A partial *F* test was used to determine the contribution of each phase and activation maps for the three phases in the forward or backward recall epoch were based on the *F* statistic results. Voxels showing reduced activation and those that did not reach statistically significant threshold ($P = 0.05$) were discarded. A minimum spatial cluster of four connected active voxels was then applied to these maps to eliminate isolated false activations. With the spatial clustering, the false positive level in this study was <0.0004 (estimated with the AlphaSim in AFNI). In the comparison of the results between the two tasks or the two groups, only activations corresponding to the recall phase were considered. Because, there were no procedural differences in the stimulus and delay phases between them.

The ROIs in this study included the prefrontal cortex (BA9), the gyrus frontalis inferior (GFi-BA44/45), the lobulus parietalis superior (BA 7), the lobulus parietalis inferior (LPi-BA 39/40), the supplementary motor area (BA 6), the occipital visual cortex (BA17/18/19), the gyrus temporalis medius (GTm-BA 21), the anterior cingulated gyrus (ACG-BA 32/24), and the medial temporal lobe (MTL), as these areas have been suggested to be involved in working memory (or short-term memory) or visuo-spatial tasks in many previous imaging studies (Cabeza and Nyberg, 2000; Hedden and Gabrieli, 2004; Li et al., 2004; Smith and Jonides, 1997; Zhang et al., 2004). These ROIs were all defined for each participant anatomically as follows. First, a set of ROIs corresponding to the regions listed above were defined in a standardized coordinate frame (Talairach and Tournoux, 1988). Subsequently, these masks were transformed onto coordinates corresponding to each participant's anatomic data and were slightly modified according to individual brain's sulci and gyri structures (Postle et al., 1999). These ROIs are task and activation independent. In each participant, the activated voxels in each ROI were collected and used to derive the activated volume and the time course of each task for further analysis.

The activated volumes in the anatomically defined ROIs were compared between the tasks (FR and BR) or the groups (young and old). In each group, the activated volume between the FR and the BR of each ROI were first compared (with *t* test) to ascertain which ROIs exhibited a significant task effect. The next step was to test the significance of the aging effect. Because potential differences in hemodynamic response properties between the young and the old participants may confound the results, a conservative approach of testing for the age-by-task interaction (D'Esposito et al., 2003; Logan et al., 2002) was used. Thus, a repeated-measures analysis of variance with a between-subject factor comparing age (young and old) and a within-subject factor comparing task (FR and BR) was conducted on the activated volume data for each ROI. In ROIs showing significant age-by-task interaction, a planed *t* test (independent sample *t* test) was applied to test whether the FR or the BR had a significant difference between the age groups. Finally, in order to test whether the activities in the regions with significant age-related difference are functionally relevant to the tasks in the older adults, a correlation analysis between brain activation and behavioral performance (Anderson and Grady, 2001) was performed. Specifically, we performed a correlation analysis between the activated volume and the accuracy in the ROIs exhibiting significant age-by-task interaction and a significant difference between the groups in at least one task (FR or BR).

To compare the BOLD response across different conditions based on the same set of relevant voxels, the FR and the BR activation maps were combined with a logical "OR" to generate a composite map. Activated pixels in the composite map within the anatomic ROIs were identified and average unit-epoch (20 time frames) time courses were extracted from these identified voxels for individual tasks and individual subjects. Accounting for the hemodynamic delay of the BOLD response (about 4–6 s), the BOLD signal in frames 8–10 were averaged and taken as the FR/BR signal, and the average signal in frames 1, 2, 19, and 20 was taken as the baseline signal. This approach of the BOLD signal analysis is similar to that used in our previous study (Zhang et al., 2004).

Results

Behavioral data

A repeated-measures analysis of variance (SPSS 10.0 statistical software package) with a between-subjects factor comparing age (young and old) and a within-subjects factor comparing task (FR and BR) was conducted on the recall accuracy data (see Table 1). The effects of neither the age nor the task were significant [$F(1,18) = 3.79$, ns ($P > 0.05$) for age, and $F(1,18) = 4.24$, ns for tasks]. There was no interaction between the age and the tasks [$F(1,18) = 0.875$, ns]. These results show that the performance accuracy was similar between the old adults and the young adults, suggesting that through the adjustment of the test parameters, the task difficulty was reasonably matched in these two age groups. Therefore, any differences between the groups found in the following imaging data are more likely due to the effects of aging than the differences in task difficulties.

fMRI data

Activated volume

For the predefined ROIs, the activated volume of each participant in each ROI for each task is given in Table 2. To examine the specific differences in activation between the forward and the backward digit recall tasks, the t test was used to compare the activated volume of a given ROI in each group (threshold $P < 0.05$). The results did not show any differences in activation between the forward and backward recall tasks during the stimulus and the delay phases of the memory trials. In contrast, in both young and old groups, significant differences in activated volume between the two tasks were only seen during the recall phase. More details regarding the activations during the recall phase are presented in the following sections.

Young adult group

Two ROIs exhibited larger activated volume in the backward recall task than in the forward recall task (see Fig. 2, Table 2). These two areas were both located in the left hemisphere. Specifically, they were the prefrontal area (BA9, $t = 2.506$, $P = 0.034$) and the occipital visual cortex (BA 17/18/19, $t = 3.031$, $P = 0.014$). In contrast, only the right gyrus frontalis inferior (GFi-BA 44/45) showed greater activated volume in the forward recall task than in the backward recall task ($t = -2.325$, $P = 0.045$).

Older adult group

In this group, the backward recall task elicited more extensive activation than the forward recall task in many cortical regions in both left and right hemispheres (see Table 2). These regions included: the DLPFC-BA 9 (left $t = 3.498$, $P = 0.007$; right $t = 2.689$, $P = 0.025$), the supplementary motor area-BA 6 (left $t = 4.519$, $P = 0.001$; right $t = 2.770$, $P = 0.022$), the lobulus parietalis superior-BA 7 (left $t = 3.344$, $P = 0.009$; right $t = 2.574$, $P = 0.030$), the lobulus parietalis inferior-BA 40/39 (left $t = 3.565$, $P = 0.006$; right $t = 2.974$, $P = 0.016$), the occipital visual cortex-BA 17/18/19 (left $t = 2.662$, $P = 0.026$), the gyrus temporalis medius-BA 21(left $t = 2.485$, $P = 0.035$; right $t = 2.656$, $P = 0.026$), and the gyrus frontalis inferior-BA 44/45 (left $t = 3.417$, $P = 0.008$). In contrast, no cortical region was more activated during the forward recall than during the backward recall in this group.

Test between groups

A repeated-measures analysis of variance with a between-subjects factor comparing age (young and old) and a within-subjects factor comparing task (FR and BR) revealed that there was a significant interaction (threshold $P < 0.05$) between the age group and the task in the right GFi-BA44/45 [$F(1,18) = 5.693$, $P = 0.028$; no main effect of group, $F(1,18) = 0.959$, ns; and no main effect of task, $F(1,18) = 0.107$, ns] (see Fig. 3B). This result suggests that in this ROI, there may be a genuine difference in brain activity between the age groups that cannot be attributed to a difference in hemodynamic response between these groups (Logan et al., 2002). A planned contrast t test (independent sample t test, threshold $P < 0.05$) between groups in this ROI revealed that the older participants exhibited more activation than the young participants in the right GFi-BA44/45 ($t = 2.436$, $P = 0.031$) (Fig. 3A) during the backward recall, while no significant difference was seen between the groups in the forward task.

In the older participants, there was a significant positive correlation (threshold $P < 0.05$) between the activated volume and the accuracy in the backward recall task ($r = 0.642$, $P = 0.045$) but not in the forward recall task ($r = 0.444$, ns) (Fig. 3C). The young participants showed no significant correlation either in the backward ($r = -0.387$, ns) or in the forward recall task ($r = -0.141$, ns).

BOLD signal change

Young adult group

The results of the BOLD signal change were similar to that of the activated volume (see Fig. 2 and Table 2). In the DLPFC-BA 9 (left $t = 3.412$, $P = 0.008$; right $t = 2.975$, $P = 0.003$) and the occipital visual cortex-BA 17/18/19 (left $t = 2.282$, $P = 0.048$; right $t = 2.479$, $P = 0.035$), the BOLD signal change during the BR task was significant higher than during the FR task. The opposite trend was marginally significant in the right GFi-BA 44/45 in the young participants ($t = -2.161$, $P = 0.059$). Additionally, in the lobulus parietalis superior-BA 7 (left $t = 2.878$, $P = 0.018$; right $t = 2.753$, $P = 0.022$) and the lobulus parietalis inferior-BA 40/39 (left $t = 4.115$, $P = 0.003$) and the left GFi-BA 44/45 (Broca area, $t = 2.291$, $P = 0.048$), the BOLD signal change was greater during the BR task than during the FR task.

Older adult group

In this subject group, the BOLD response analysis revealed the same pattern of results as the activated volume analysis (see Table

Table 2
The activated mean volume, the BOLD signal change, and the Talairach coordinates

ROIs (Brodmamn area)	Left									Right								
	Talairach's coordinate			Activated volume (mm^3)			BOLD signal change (%)			Talairach's coordinate			Activated volume (mm^3)			BOLD signal change (%)		
	x	*y*	*z*	FR	BR	*P*	FR	BR	*P*	*x*	*y*	*z*	FR	BR	*P*	FR	BR	*P*
Young																		
9	−37.3	26.7	30.0	448	1520	**0.034**	.44	1.43	**0.008**	35.2	31.3	31.0	607	1169	–	.79	1.44	**0.003**
32/24	−4.6	10.7	38.8	861	888	–	.93	1.14	–	5.0	13.6	37.9	686	747	–	.90	1.11	–
44/45	−47.9	14.0	16.2	2241	3278	–	.58	1.14	**0.048**	50.2	13.2	14.0	1863	659	**0.045**[a]	1.06	.89	0.059[b]
6	−13.5	−1.4	54.3	5221	5405	–	1.48	1.67	–	−13.7	2.9	54.6	2250	2461	–	1.05	1.35	–
7	−19.1	−60.6	43.1	1995	2874	–	.94	1.36	**0.018**	24.0	−53.8	43.1	1213	1652	–	.75	1.17	**0.022**
40/39	−40.4	−44.0	35.8	738	1846	–	.54	1.28	**0.003**	46.6	−35.2	32.5	149	545	–	.28	.54	–
17/18/19	−8.7	−74.1	9.8	1178	3032	**0.014**	.69	1.31	**0.048**	12.1	−72.3	10.3	1239	1942	–	.55	1.05	**0.035**
21	−53.1	−52.0	6.3	545	659	–	.58	.75	–	45.8	−51.6	5.5	343	457	–	.82	1.15	–
MTL	−26.6	−46.0	−5.4	88	220	–	.33	.49	–	25.6	−46.8	−4.4	150	439	–	.61	.81	–
Old																		
9	−36.3	27.8	30.7	523	1753	**0.007**	.81	1.49	**<0.001**	33.2	33.6	29.4	659	1529	**0.025**	.97	1.37	**0.008**
32/24	−4.2	10.5	36.8	369	941	–	1.18	1.48	**0.034**	3.7	9.6	36.6	229	606	–	.78	1.01	**0.039**
44/45	−47.6	13.2	15.7	1529	3454	**0.008**	1.00	1.40	**0.001**	47.2	13.8	14.2	1292	2206	–	1.15	1.41	**0.038**
6	−13.9	−1.7	54.8	3472	5722	**0.001**	1.26	1.66	**<0.001**	13.7	−2.6	55.3	2812	4482	**0.022**	1.22	1.49	**0.009**
7	−17.8	−59.0	42.9	2026	3652	**0.009**	1.22	1.70	**<0.001**	23.9	−55.7	43.1	1358	2382	**0.030**	1.18	1.50	**0.007**
40/39	−41.9	−42.9	35.5	1494	2540	**0.006**	1.13	1.59	**<0.001**	47.1	−35.8	33.3	782	1740	**0.016**	1.23	1.47	–
17/18/19	−10.4	−76.1	13.0	791	2707	**0.026**	.58	1.39	**0.001**	14.9	−75.2	13.0	853	2008	–	.70	1.40	**0.004**
21	−50.9	−45.8	2.7	484	1415	**0.035**	.92	1.22	**0.022**	48.4	−45.1	1.6	378	1494	**0.026**	1.07	1.39	–
MTL	−26.7	−29.6	−11.6	62	343	–	.46	.65	–	27.4	−28.8	−10.0	246	440	–	.61	.67	–

x,y,z: The mean coordinates of backward recall activated voxels centroid (The forward's are very similar to the backward in all ROIs.) in the standardized coordinate frame (Talairach and Tournoux, 1988).

–: Not significant.

[a] FR > BR.

[b] Marginally significant (FR > BR).

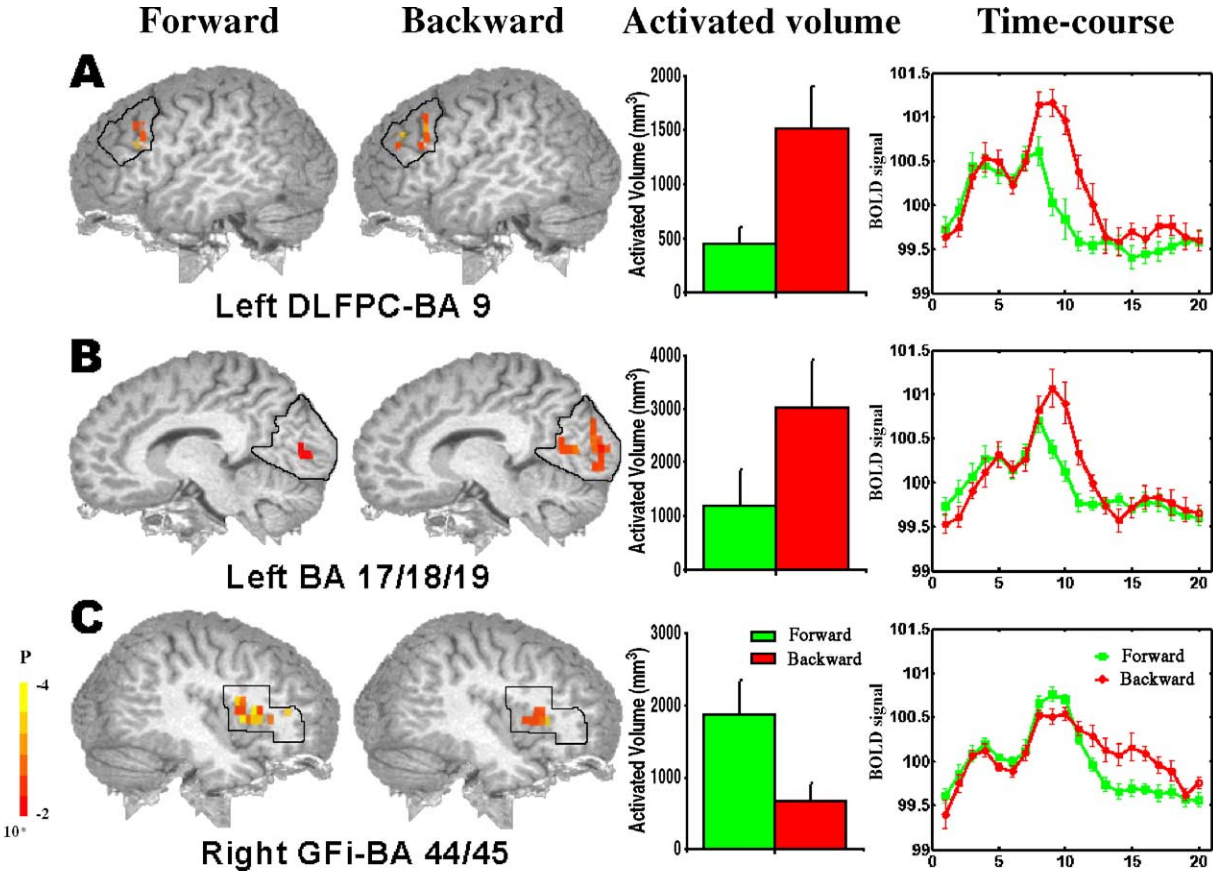

Fig. 2. The activated maps, the averaged activated volume, and the averaged time course of BOLD signal of the 3 areas [i.e., the left DLPFC-BA 9 (A), the left occipital visual cortex-BA 17/18/19 (B), and the right GFi-BA 44/45 (C)] with significant difference between the two tasks in young participants. From left to right, the first and second columns display the activation in the forward and backward recall task, respectively, in one young participant. The corresponding ROIs were demarcated with black lines. The third presents the averaged activated volume during the two tasks in the young group in corresponding ROI. Error bars represent the SE. The last column shows the averaged BOLD signal time course (y axis = BOLD signal; x axis = time frame). Each data point corresponds to the mean percent signal. Frames 8, 9, and 10 were taken as the response of the recall phase (accounting for appropriate hemodynamic lag). Error bars also represent the SE.

2). The backward recall task generally had greater BOLD signal change than the forward recall task in many cortical regions on both left and right hemispheres. These regions included: the DLPFC-BA 9 (left t = 7.078, P < 0.001; right t = 3.383, P = 0.008), the supplementary motor area-BA 6 (left t = 7.016, P < 0.001; right t = 3.322, P = 0.009), the lobulus parietalis superior-BA 7 (left t = 5.321, P < 0.001; right t = 3.513, P = 0.007), the lobulus parietalis inferior-BA 40/39 (left t = 7.248, P < 0.001), the occipital visual cortex-BA 17/18/19 (left t = 4.763, P = 0.001; right t = 3.825, P = 0.004), the gyrus temporalis medius-BA 21(left t = 2.774, P = 0.022), and the gyrus frontalis inferior-BA 44/45 (left t = 4.651, P = 0.001; right t = 2.425, P = 0.038). In contrast, no cortical region exhibited a larger response during the forward recall than during the backward recall in this group.

Test between groups

We found that there was a significant interaction between the age group and the task in the right GFi-BA 44/45 [F(1,18) = 10.44, P = 0.005; significant main effect of group, F(1,18) = 5.224, P = 0.035; and no main effect of task, F(1,18) = 0.500, ns]. The older participants showed more activation than the young participants in the backward recall task in the right GFi-BA44/45 (t = 3.696, P = 0.002) (Fig. 3D). In addition, no significant correlation between the accuracy in performing a given task and the BOLD signal change in either young or old group in the right GFi-BA44/45.

Discussion

The results of the present study show that both the forward digit recall and the backward digit recall tasks activated a network of brain areas in the frontal, the parietal, the temporal, and the occipital cortices. Furthermore, the results revealed interesting differences in brain activity associated with the forward digit recall and the backward digit recall. Responses in these regions of interests will be discussed in more detail and possible neural mechanisms underlying these two types of digit recall as well as any aging effect exhibited in these memory tasks will also be considered.

Comparison between the BR and the FR tasks in the young group

BR > FR in the visual occipital cortex

Both the activated volume and the BOLD signal response in the occipital visual cortex were greater when digits were recalled in

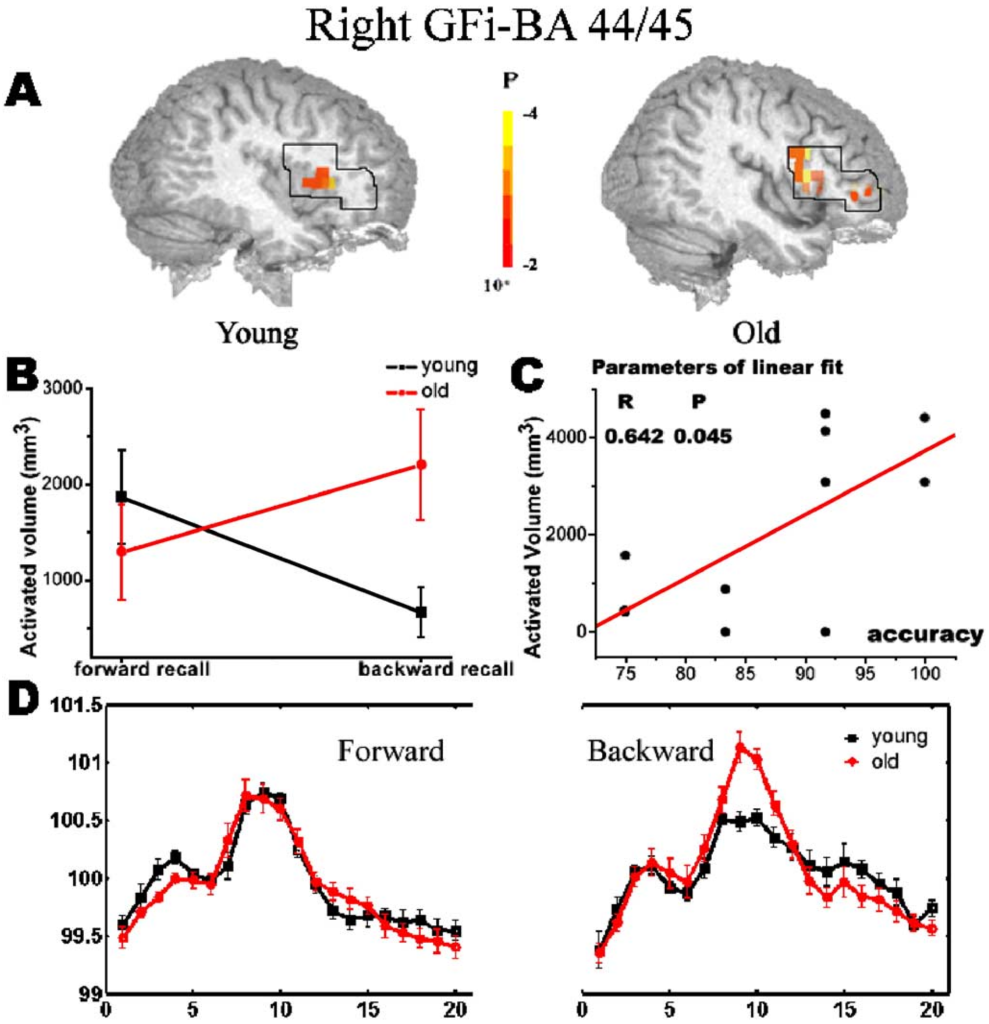

Fig. 3. Comparison of the activity in the right GFi-BA 44/45 between the young and the older group. (A) The activated map of the backward recall task in one old and young participant, the corresponding ROI is delineated in black. (B) Significant age-by-task interaction is found in the activated volume result. Error bars show the SE. (C) Significant positive correlation is found between the activated volume of the backward recall task and its accuracy rate. (D) The averaged time course of BOLD signal shows significant difference between the two groups in backward recall, but not in forward recall. Error bars represent the SE.

backward order than in forward order (see Fig. 2B). The occipital cortex is primarily involved in processing visuospatial information. The activation of the occipital visual cortex in memory tasks was also found in earlier neuroimaging studies by us and others (Heun et al., 2004; Li et al., 2004; Zhang et al., 2003). Using two convergent techniques (PET and TMS), Kosslyn et al. (1995, 1999) demonstrated that the occipital visual cortex (e.g., BA 17) was activated in visual mental imagery. Additionally, the BOLD signal change during the backward recall task was significantly higher than that during the forward recall task in the parietal lobe (BA 7 and BA 40/39). According to previous studies (e.g., Ganis et al., 2004; Trojano et al., 2002), the parietal cortex also plays a role in the visual mental imagery. Based on these studies and the fact that an identical visual cue (see Fig. 1) was presented during the forward and backward recall tasks in the present study, the greater activation in the occipital and the parietal cortices seen in the present study may indicate the usage of mental-imagery in the backward digit recall task. The present finding is also consistent with the finding of Paivio (1971) that the use of imagery greatly improved memory and with the idea that the backward recall may require the translation of a given serial order in the temporal domain into spatial coordinates, proposed by Rudel and Denckla based on their neuropsychological findings that patients with impairment of backward digit repetition had difficulties with spatial tasks and tasks that require correlational matching of serial and spatial orders (Rudel and Denckla, 1974). Although this idea was recently suggested again by Hoshi et al. (2000) based on results from their near-infrared optical tomography study, the current study provides more direct and definitive evidence supporting the possible involvement of the visuospatial processing or mental imagery in the backward digit recall.

BR > FR in DLPFC (BA9)

The present study reveals that DLPFC (BA9) was activated to a greater spatial extent and with a higher BOLD signal change in the backward digit recall task than in the forward recall task (see Fig. 2A). This finding is consistent with the view that backward recall taps into the executive process of working memory. In other words, recalling digits backward requires holding the digits in short-term memory and performing a mental manipulation on them (Anderson and Grady, 2001; Carlesimo et al., 1994; Halpern et al., 2003; Hedden and Gabrieli, 2004). Patients with impaired executive processes, such as Frontotemporal Dementia (FTD) could be normal in the forward digit span but impaired in the backward digit span. FTD patients generally have prefrontal pathology with intact occipital cortex (Arnold et al., 2000). In line with this important finding, the activation of the DLPFC found in the present study is unlikely an epiphenomenon. This result suggests that the DLPFC play an important role in the backward digit recall.

FR > BR in the right GFi (BA 45/44)

In the young adult group, the right GFi was significantly more activated during forward digit recall than during backward digit recall (see Fig. 2C). The right GFi has been found active in a number of episodic memory recall tasks (Lepage et al., 2000; Nyberg et al., 2002; Ragland et al., 2000; Wiggs et al., 1999). In addition, the right frontal regions have been reported to be more involved in retrieving the temporal order of memory items than the identity of memory items (Cabeza et al., 2000). Our finding of greater activation in the GFi during the forward recall is consistent with the Dual Retrieval Process model that a temporal order processing (i.e., temporal association between items) may be engaged in recalling digits in the order as they were presented (Li and Lewandowsky, 1993, 1995). However, other studies have suggested that the right GFi supports inhibition or monitoring during retrieval (Aron et al., 2004 for review; D'Esposito et al., 2000). Given the multiple possibilities, a concrete explanation for the increased activity observed in the right GFi in the forward recall remains an open question.

Neural basis of FR and BR processes

We found that the dominant active regions were different during the forward recall and backward recall tasks, which may suggest different underlying processes involved in these two tasks. This finding may be a piece of critical neural evidence supporting a cognitive model of dual processes, such as the model proposed by Li and Lewandowsky (1993, 1995) based on a series of behavior experiments. As argued by Tovee (1999), to claim one cognitive process is different from another, they should have different functional characteristics as well as anatomically distinct neural bases. In the present study, with neuroimaging measurements, we found that the brain regions that mediated backward recall are different to some extent from those mediating forward recall.

More specifically, our results strongly support the involvement of visual–spatial functions in the backward recall as specified in the DRPM (Li and Lewandowsky, 1995). That is, the dominant activation in the occipital and parietal cortices during the backward digit recall task suggests the engagement of visuospatial imagery processing when recalling digits in backward order. In contrast, the dominant activation in the right GFi (BA 44/45) in the forward recall task is consistent with the engagement of recalling the temporal association of items during the forward digit recall, as suggested by the DRPM.

The present study indicates that the DLPFC (BA 9) may play a special role in the backward recall, a finding that is not explicitly predicted by the DRPM (Li and Lewandowsky, 1995). However, the involvement of DLPFC in the backward recall is consistent with the predictions from the working memory model. A number of neuroimaging studies have found that the DLPFC may play an important role in tasks that involve the executive functions (Cabeza and Nyberg, 2000; D'Esposito et al., 2000 for review), such as manipulation of the information temporally stored in working memory (Postle et al., 1999) and coordinating the activities between the two slave systems (e.g., the phonological loop and the visuospatial sketchpad; Baddeley, 1992, 1996). Apparently, the backward digit recall task involves the executive functions in that the digits stored in working memory in the presented order need to be manipulated to reverse their temporal order. On the other hand, the information stored in the phonological loop and the visuospatial functions performed in the visuospatial sketchpad need to be coordinated as well (Baddeley, 2000; Owen et al., 1998). Thus, our data suggest that the executive control may be a critical component that underlies backward recall processes.

Comparing the brain activation pattern between the young and the older adults

In the older group, compared to the young group, there were more areas in both the left and the right hemispheres found to be more activated in the backward task than the forward task, but no region was found to be more activated in the forward task than in the backward task. These results suggest that aging may differentially affect the backward and the forward digit recall tasks.

Given that the activations in the right GFi (see Fig. 3B) showed significant interaction between the group (young and old) and the task (FR and BR), the observed activation difference of this brain area between groups cannot be solely attributed to general differences in hemodynamic response between the groups (D'Esposito et al., 2003; Logan et al., 2002) and the activation difference is task-specific to an extent. In this brain area, the older group had more activation than the young group only during the backward recall task, but there was not much difference between the groups during the forward recall task. These results suggest that the aging-related activation difference in the right GFi might be primarily due to the difference in the backward recall task. As mentioned earlier, the backward recall is a working memory task which needs the executive functions such as manipulation (Anderson and Grady, 2001; Conklin et al., 2000; Stone et al., 1998). Furthermore, the age-related changes are more apparent in the tasks demanding the executive functions (e.g., high level of attention and control process). In this condition, the task may recruit other brain regions that are not typically associated with the task for compensation or for adaptive coding in the older adults (Anderson and Grady, 2001; Buckner, 2004; Duncan, 2001). The present study showed more activation of the DLPFC (BA9) in the backward recall in the young adults, indicating that the backward recall may depend more heavily on the executive functions than the forward recall. Thus, the aging-related change of activation in the DLPFC may be associated with the backward recall task instead of the forward recall task.

The significant positive correlation between the fMRI activated volume and the performance accuracy in the older group but not in the younger group in the right GFi-BA 44/45 is consistent with previous studies (Rypma and D'Esposito, 2000; Stebbins et al., 2002) (Fig. 3C). For example, Stebbins et al. (2002) found that the spatial extent of fMRI activation in a memory task in the right inferior frontal gyrus was positively associated with memory recall performance in the older participants, while it was not significant in the younger participants. Many imaging studies have shown bilateral activation in elderly people and unilateral activation in young people performing the same task (Buckner, 2004; Reuter-Lorenz, 2002 for review). In line with these results, the data of Stebbins et al. (2002) and our results that the activated volume is positively correlated with the memory performance, suggest that, in addition to the increase of BOLD signal change (i.e., Grady et al., 2003), the increase of the spatial extent may reflect another aspect of aging for a demanding task. A similar view is held by Reuter-Lorenz et al. (1999) that "as people age, more units would be needed to supply the required capacity for a task".

The significant positive correlation between the cortical activity and performance accuracy suggests that activity in the GFi-BA 44/45 may be functionally relevant to the backward recall task in older adults. The discovery of additional and functionally important activity during the backward recall task in older adults is consistent with the compensation hypothesis that older people may recruit new cortical resources to compensate for the aging-related functional decrease (Cabeza et al., 2000; Grady et al., 2003; McIntosh et al., 1999). In the extreme case of brain damage, compensation, or as Duncan called it, adaptive coding, may also occur (Duncan, 2001). Other studies have reported that enhancement in one area is often accompanied with reduced activation in other areas (Logan et al., 2002), for example, in DLPFC and MTL, this was not observed in the present experiment. Another possible way to explain the present result is that older adults have weaker connections in a large-scale network (Cabeza et al., 2002; McIntosh et al., 1999) or reduction of the processing efficiency in these brain areas (Grady et al., 1992, 1998), so that these regions need to "work harder" or even use different strategies (Grady et al., 1998). Further studies on functional connectivity may help verify these possibilities.

DRPM to explain the aging effects

The working memory model seems to give a reasonable explanation for the present results. Can we also explain the findings, particularly the aging effect, in the framework of the DRPM (Li and Lewandowsky, 1995)? In the DRPM, backward recall relies heavily on visuospatial processing in the occipital visual cortex. However, it is generally considered that visual processing in the occipital cortex is not as sensitive to aging as the executive functions in the frontal lobe (Raz et al., 2004). Because DRPM does not have explicit descriptions of the role of the executive and the neural correlates (DLPFC) in backward recall, it does not directly predict the observed aging effect.

However, some previous studies have shown an aging effect in both the occipital and prefrontal cortices. In particular, Grady et al. (1994) found decreased activity in the visual cortex but increased activity in the PFC in a visual memory task in older people. Mental imagery is not restricted to visuospatial processing in the visual cortex, but also involves processes in other brain areas, depending on the nature of the imagery task. For example, working memory and the PFC are involved in some imagery tasks (Kosslyn et al., 2001; Mellet et al., 1998 for review). Based on the relationship between the behavioral performance of imagery tasks and the PFC volume in healthy adult participants (from 19 to 77 years), Raz et al. suggested that age-related deficits in performance of mental imagery tasks may stem in part from age-related PFC shrinkage and deterioration of working memory, but not from age-related slowing of sensorimotor reaction time (Briggs et al., 1999; Raz et al., 1999). With these considerations, an expanded DRPM may conceivably account for the aging effect on backward recall.

Clinical implications

Working memory is at the core of many cognitive functions and critical to general human intelligence (Baddeley, 1992, 1996; Wickelgren, 1997). Working memory impairments exist in many serious diseases such as dementia and schizophrenia (Albert, 1996; Gabrieli, 1996). Backward recall is widely used as a measurement of working memory and a subtest of MMSE for monitoring PFC function and detecting its changes, which are critical in the diagnosis of dementia and in the evaluation of efficacy of drug treatments and other interventions for aging and dementia (Carlesimo et al., 1994; Graf et al., 2001; Jonker et al., 2003; Nagaraja and Jayashree, 2001; Schneider et al., 1996; Simard and van Reekum, 1999).

PFC plays a critical role in many important and general cognitive functions, including executive control (Roberts, 1996), manipulation (D'Esposito et al., 2000), and general intelligence (Duncan et al., 2000). Consequently, the aging-related functional decline of PFC may produce a deficit in many cognitive functions. PFC pathologies have been found in dementia [frontal dementia (FD), frontotemporal dementia (FTD), and Alzheimer Disease (AD); Arnold et al., 2000]. Some neuropsychological studies have revealed executive deficits in Mild Cognitive Impairment (DeCarli et al., 2004; Griffith et al., 2003; Johnson et al., 2004; Ready et al., 2003) and that the executive dysfunction may facilitate early detection of AD (Chen et al., 2000, 2001; DeCarli et al., 2004).

Age-related changes of neurochemistry, volume, white matter (connections between neurons), and the function of PFC develop gradually throughout adulthood (Hedden and Gabrieli, 2004). Since heavier reliance on the PFC was shown in the backward recall than in the forward recall in older adults, the present results suggest that the backward digit span task may serve as a good assessment tool for older adults' working memory or executive functions.

In normal aging people, the differential aging effects associated with these two types of recall may be only evident at the neural level. Given the extensive neuronal compensation in the backward recall task, older subjects may not show a greater decline behaviorally in the backward digit span task (Myerson et al., 2003). However, even with similar performance, the age-related difference in the neural substrates between the forward recall and the backward recall may be detected with fMRI, as shown in this study. Other researchers have suggested that fMRI may be more sensitive than behavioral measurements (Hariri and Weinberger, 2003; Honey and Bullmore, 2004; Honey et al., 2004; Mattay and Goldberg, 2004; Wilkinson and Halligan, 2004), and fMRI has been used to investigate the biological basis of aging and dementia (Anderson and Grady, 2001; Buckner, 2004; Hedden and Gabrieli, 2004) and its use has been explored for the early detection of dementia (Bookheimer et al., 2000; Small, 2002). Thus, the paradigm used in the present study may have potential clinical applications as well.

Conclusions

In the present study, we examined and compared the neural correlates of backward digit recall to forward recall in healthy old and young adults in the entire brain using fMRI. Compared to the forward recall task, the backward recall task activated the left occipital visual region and the left PFC (BA9) more greatly, supporting the involvement of visuospatial processing (Hoshi et al., 2000; Larrabee and Kane, 1986; Li and Lewandowsky, 1995; Rudel and Denckla, 1974) and the central executive function (Carlesimo et al., 1994) in backward digit recall. The right GFi was found to be more activated in forward recall than in backward recall in young adults. The regions strongly activated in these two recall tasks showed little overlap, providing important neural evidence for a dual process model for these two types of recall. Our results also provide specific support for the view of the DRPM that the backward recall relies on visual–spatial processing (Li and Lewandowsky, 1995).

When brain activation patterns were compared across age groups, it was found that more regions, especially the frontal cortex, exhibited greater activation in the backward recall task than in the forward recall task in older adults. Moreover, the right GFi (BA 44/45) showed more activation during the backward recall in older adults than in young adults. This result suggests that backward digit recall is more affected by aging than forward recall at the neural level. These results may help to clarify the controversy on the specific role of the backward digit span in MMSE, as well as in the measurement of working memory functions. Furthermore, the fMRI paradigm used in the present study may be potentially adapted for clinical tests.

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References

Albert, M.S., 1996. Cognitive and neurobiologic markers of early Alzheimer disease. Proc. Natl. Acad. Sci. U. S. A. 93, 13547–13551.

Anderson, N.D., Grady, C.L., 2001. Functional imaging in cognitively intact aged people. In: Patrick, R.H., Charles, V.M. (Eds.), Functional Neurobiology of Aging. Academic Press, San Diego, pp. 211–222.

Arnold, S.E., Han, L.Y., Clark, C.M., Grossman, M., Trojanowski, J.Q., 2000. Quantitative neurohistological features of frontotemporal degeneration. Neurobiol. Aging 21, 913–919.

Aron, L., Robbins, T.W., Poldrack, R.A., 2004. Inhibition and the right inferior frontal cortex. Trends Cogn. Sci. 8, 170–177.

Baddeley, A.D., 1992. Working memory. Science 255, 556–559.

Baddeley, A.D., 1996. Exploring the central executive. Q. J. Exp. Psychol., A. 49, 5–28.

Baddeley, A.D., 2000. The episodic buffer: a new component of working memory? Trends Cogn. Sci. 4, 417–423.

Bookheimer, S.Y., Strojwas, M.H., Cohen, M.S., Saunders, A.M., Pericak-Vance, M.A., Mazziotta, J.C., Small, G.W., 2000. Patterns of brain activation in people at risk for Alzheimer's disease. N. Engl. J. Med. 343, 450–456.

Briggs, S.D., Raz, N., Marks, W., 1999. Age-related deficits in generation and manipulation of mental images: I. The role of sensorimotor speed and working memory. Psychol. Aging 14, 427–435.

Buckner, R.L., 2004. Memory and executive function in aging and AD: multiple factors that cause decline and reserve factors that compensate. Neuron 44, 195–208.

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

Cabeza, R., Anderson, N.D., Houle, S., Mangels, J.A., Nyberg, L., 2000. Age-related differences in neural activity during item and temporal-order memory retrieval: a positron emission tomography study. J. Cogn. Neurosci. 12, 197–206.

Cabeza, R., Anderson, N.D., Locantore, J.K., McIntosh, A.R., 2002. Aging gracefully: compensatory brain activity in high-performing older adults. NeuroImage 17, 1394–1402.

Carlesimo, G.A., Fadda, L., Lorusso, S., Caltagirone, C., 1994. Verbal and spatial memory spans in Alzheimer's and multi-infarct dementia. Acta Neurol. Scand. 89, 132–138.

Chen, P.J., Ratcliff, G., Belle, S.H., Cauley, J.A., DeKosky, S.T., Ganguli, M., 2000. Cognitive tests that best discriminate between presymptomatic AD and those who remain nondemented. Neurology 55, 1847–1853.

Chen, P.J., Ratcliff, G., Belle, S.H., Cauley, J.A., DeKosky, S.T., Ganguli, M., 2001. Patterns of cognitive decline in presymptomatic Alzheimer disease—a prospective community study. Arch. Gen. Psychiatry 58, 853–858.

Conklin, H.M., Curtis, C.E., Katsanis, J., Iacono, W.G., 2000. Verbal working memory impairment in schizophrenia patients and their first-degree relatives: evidence from the digit span task. Am. J. Psychiatry 157, 275–277.

Cox, R.W., 1996. AFNI: software for analysis and visualization of functional magnetic resonance neuroimages. Comput. Biomed. Res. 29, 162–173.

DeCarli, C., Mungas, D., Harvey, D., Reed, B., Weiner, M., Chui, H., Jagust, W., 2004. Memory impairment, but not cerebrovascular disease, predicts progression of MCI to dementia. Neurology 63, 220–227.

D'Esposito, M., Postle, B.R., Rypma, B., 2000. Prefrontal cortical contributions to working memory: evidence from event-related fMRI studies. Exp. Brain. Res. 133, 3–11.

D'Esposito, M., Deouell, L.Y., Gazzaley, A., 2003. Alterations in the bold fMRI signal with ageing and disease: a challenge for neuroimaging. Nat. Rev. Neurosci. 4, 863–872.

Duncan, J., 2001. An adaptive coding model of neural function in prefrontal cortex. Nat. Rev., Neurosci. 2, 820–829.

Duncan, J., Seitz, R.J., Kolodny, J., Bor, D., Herzog, H., Ahmed, A., Newell, F.N., Emslie, H., 2000. A neural basis for general intelligence. Science 289, 457–460.

Folstein, M.F., Folstein, S.E., McHugh, P.R., 1975. Mini-mental state. A practical method for grading the cognitive state of patients for the clinician. J. Psychiatr. Res. 12, 189–198.

Gabrieli, J.D., 1996. Memory systems analyses of mnemonic disorders in aging and age-related diseases. Proc. Natl. Acad. Sci. U. S. A. 93, 13534–13540.

Ganis, G., Thompson, W.L., Kosslyn, S.M., 2004. Brain areas underlying visual mental imagery and visual perception: an fMRI study. Cogn. Brain Res. 20, 226–241.

Glover, G.H., 1999. Deconvolution of impulse response in event-related BOLD fMRI. NeuroImage 9, 416–429.

Grady, C.L., Haxby, J.V., Horwitz, B., et al., 1992. Dissociation of object and spatial vision in human extrastriate cortex-age-related-changes in activation of regional cerebral blood-flow measured with [O-15] water and positron emission tomography. J. Cogn. Neurosci. 4, 23–34.

Grady, C.L., Maisog, J.M., Horwitz, B., Ungerleider, L.G., Mentis, M.J., Salerno, J.A., Pietrini, P., Wagner, E., Haxby, J.V., 1994. Age-related changes in cortical blood flow activation during visual processing of faces and location. J. Neurosci. 14, 1450–1462.

Grady, C.L., McIntosh, A.R., Bookstein, F., Horwitz, B., Rapoport, S.I., Haxby, J.V., 1998. Age-related changes in regional cerebral blood flow during working memory for faces. NeuroImage 8, 409–425.

Grady, C.L., McIntosh, A.R., Beig, S., Keightley, M.L., Burian, H., Black, S.E., 2003. Evidence from functional neuroimaging of a compensatory prefrontal network in Alzheimer's disease. J. Neurosci. 23, 986–993.

Graf, A., Wallner, C., Schubert, V., Willeit, M., Wlk, W., Fischer, P., Hariri, A.R., Weinberger, D.R., 2001. Imaging genomics. Br. Med. Bull. 65, 259–270.

Griffith, H.R., Belue, K., Sicola, A., Krzywanski, S., Zamrini, E., Harrell, L., Marson, D.C., 2003. Impaired financial abilities in mild cognitive impairment—a direct assessment approach. Neurology 60, 449–457.

Halpern, C., McMillan, C., Moore, P., Dennis, K., Grossman, M., 2003. Calculation impairment in neurodegenerative diseases. J. Neurol. Sci. 208, 31–38.

Hariri, A.R., Weinberger, D.R., 2003. Imaging genomics. Br. Med. Bull. 65, 259–270.

Hedden, T., Gabrieli, J.D., 2004. Insights into the ageing mind, a view from cognitive neuroscience. Nat. Rev., Neurosci. 5, 87–96.

Heun, R., Jessen, F., Klose, U., Erb, M., Granath, D.O., Grodd, W., 2004. Response-related fMRI of veridical and false recognition of words. Eur. Psychiatry 19, 42–52.

Honey, G., Bullmore, E., 2004. Human pharmacological MRI. Trends Pharmacol. Sci. 25, 366–374.

Honey, R.A.E., Honey, G.D., O'Loughlin, C., Sharar, S.R., Kumaran, D., Bullmore, E.T., Menon, D.K., Donovan, T., Lupson, V.C., Bisbrown-Chippendale, R., Fletcher, P.C., 2004. Acute ketamine administration alters the brain responses to executive demands in a verbal working memory task: an fMRI study. Neuropsychophamacology 29, 1203–1214.

Hoshi, Y., Oda, I., Wada, Y., Ito, Y., Yamashita, Y., Oda, M., Ohta, K., Yamada, Y., Tamura, M., 2000. Visuospatial imagery is a fruitful strategy for the digit span backward task: a study with near-infrared optical tomography. Brain Res. Cogn. Brain Res. 9, 339–342.

Jacqmin-Gadda, H., Fabrigoule, C., Commenges, D., Dartigues, J.F., 1997. A 5-year longitudinal study of mini-mental state examination in normal aging. Neurobiol. Aging 17, S55–S56.

Johnson, J.K., Vogt, B.A., Kim, R., Cotman, C.W., Head, E., 2004. Isolated executive impairment and associated frontal neuropathology. Dementia Geriatr. Cognit. Disord. 17, 360–367.

Jonker, C., Comijs, H.C., Smit, J.H., 2003. Does aspirin or other NSAIDs reduce the risk of cognitive decline in elderly persons? Results from a population-based study. Neurobio. Aging 24, 583–588.

Kosslyn, S.M., Thompson, W.L., Kim, I.J., Alpert, N.M., 1995. Topographical representations of mental images in primary visual cortex. Nature 378, 496–498.

Kosslyn, S.M., Pascual-Leone, A., Felician, O., Camposano, S., Keenan, J.P., Thompson, W.L., Ganis, G., Sukel, K.E., Alpert, N.M., 1999. The role of area 17 in visual imagery: convergent evidence from PET and rTMS. Science 284, 167–170.

Kosslyn, S.M., Ganis, G., Thompson, W.L., 2001. Neural foundations of imagery. Nat. Rev., Neurosci. 2, 635–642.

Larrabee, G.J., Kane, R.L., 1986. Reversed digit repetition involves visual and verbal processes. Int. J. Neurosci. 30, 11–15.

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

Li, S.C., Lewandowsky, S., 1993. Intralist distractors and recall direction: constraints on models of memory for serial order. J. Exper. Psychol., Learn. 19, 895–918.

Li, S.C., Lewandowsky, S., 1995. Forward and backward recall: different retrieval process. J. Exper. Psychol., Learn. 21, 837–847.

Li, Z.H., Sun, X.W., Wang, Z.X., Zhang, X.C., Zhang, D.R., He, S., Hu, X.P., 2004. Behavial and functional MRI study of attention shift in human verbal working memory. NeuroImage 21, 181–191.

Logan, J.M., Sanders, A.L., Snyder, A.Z., Morris, J.C., Buckner, R.L., 2002. Under-recruitment and nonselective recruitment: dissociable neural mechanisms associated with aging. Neuron 33, 827–840.

Manoach, D.S., Schlaug, G., Siewert, B., Darby, D.G., Bly, B.M., Benfield, A., Edelman, R.R., Warach, S., 1997. Prefrontal cortex fMRI signal changes are correlated with working memory load. NeuroReport 8, 545–549.

Mattay, V.S., Goldberg, T.E., 2004. Imaging genetic influences in human brain function. Curr. Opin. Neurobiol. 14, 239–247.

McCarthy, G., Puco, A., Constable, R.T., Krystal, J.H., Gore, J.C., GoldmanRakic, P., 1996. Activation of human prefrontal cortex during spatial and nonspatial working memory tasks measured by functional MRI. Cereb. Cortex 6, 600–611.

McIntosh, A.R., Sekuler, A.B., Penpeci, C., Rajah, M.N., Grady, C.L., Sekuler, R., Bennett, P.J., 1999. Recruitment of unique neural systems to support visual memory in normal aging. Curr. Biol. 9, 1275–1278.

Mellet, E., Petit, L., Mazoyer, B., Denis, M., Tzourio, N., 1998. Reopening the mental imagery debate: lessons from functional anatomy. NeuroImage 8, 129–139.

Myerson, J., Emery, L., White, D.A., Hale, S., 2003. Effects of age, domain, and processing demands on memory span: evidence for differential decline. Aging, Neuropsychol. Cogn. 10, 20–27.

Nagaraja, D., Jayashree, S., 2001. Randomized study of the dopamine receptor agonist piribedil in the treatment of mild cognitive impairment. Am. J. Psychiatry 158, 1517–1519.

Nyberg, L., Forkstam, C., Petersson, K.M., Cabeza, R., Ingvar, M., 2002. Brain imaging of human memory systems: between-systems similarities and within-system differences. Cogn. Brain Res. 13, 281–292.

Owen, A.M., Stern, C.E., Look, R.B., Tracey, I., Rosen, B.R., Petrides, M., 1998. Functional organization of spatial and nonspatial working memory processing within the human lateral frontal cortex. Proc. Natl. Acad. Sci. U. S. A. 95, 7721–7726.

Paivio, A., 1971. Imagery and Verbal Processes. Holt, Rinehart and Winston, New York.

Posner, M.I., 1998. The neuroimaging of human brain function. Proc. Natl. Acad. Sci. U. S. A. 95, 763–764.

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. U. S. A. 96, 12959–12964.

Ragland, J.D., Gur, R.C., Lazarev, M.G., Smith, R.J., Schroeder, L., Raz, J., Turetsky, B.I., Alavi, A., Gur, R.E., 2000. Hemispheric activation of anterior and inferior prefrontal cortex during verbal encoding and recognition: a PET study of healthy volunteers. NeuroImage 11, 624–633.

Raz, N., Briggs, S.D., Marks, W., Acker, J.D., 1999. Age-related deficits in generation and manipulation of mental images: II. The role of dorsolateral prefrontal cortex. Psychol. Aging 14, 436–444.

Raz, N., Gunning-Dixon, F., Head, D., Rodrigue, K.M., Williamson, A., Acker, J.D., 2004. Aging, sexual dimorphism, and hemispheric asymmetry of the cerebral cortex: replicability of regional differences in volume. Neurobiol. Aging 25, 377–396.

Ready, R.E., Ott, B.R., Grace, J., Cahn-Weiner, D.A., 2003. Apathy and executive dysfunction in mild cognitive impairment and in Alzheimer disease. Am. J. Geriatr. Psychiatry 6, 222–228.

Reuter-Lorenz, P.A., 2002. New visions of the aging mind and brain. Trends Cogn. Sci. 6, 394–400.

Reuter-Lorenz, P.A., Stanczak, L., Miller, A.C., 1999. Neural recruitment and cognitive aging: two hemispheres are better than one, especially as you age. Psychol. Sci. 10, 494–500.

Richardson, J.T.E., 1977. Functional relationship between forward and backward digit repetition and a non-verbal analogue. Cortex 13, 317–320.

Risberg, J., Ingvar, D.H., 1973. Patterns of activation in the grey matter of the dominant hemisphere during memorizing and reasoning. A study of regional cerebral blood flow changes during psychological testing in a group of neurologically normal patients. Brain 96, 737–756.

Roberts, A.C., 1996. Executive and cognitive functions of the prefrontal cortex. Philos. Trans. R. Soc. London, Ser. B 351, 1389–1395.

Rudel, R.G., Denckla, M.B., 1974. Relation of forward and backward digit repetition to neurological impairment in children with learning disabilities. Neuropsychologia 12, 109–118.

Rypma, B., D'Esposito, M., 2000. Isolating the neural mechanisms of age-related changes in human working memory. Nat. Neurosci. 5, 509–515.

Schneider, L.S., Farlow, M.R., Henderson, V.W., Pogoda, J.M., 1996. Effects of estrogen replacement therapy on response to tacrine in patients with Alzheimer's disease. Neurology 46, 1580–1584.

Simard, M., van Reekum, R., 1999. Memory assessment in studies of cognition-enhancing drugs for Alzheimer's disease. Drugs Aging 14, 197–230.

Small, G.W., 2002. Use of neuroimaging to detect early brain changes in people at genetic risk for Alzheimer's disease. Adv. Drug Delivery Rev. 54, 1561–1566.

Smith, E.E., Jonides, J., 1997. Working memory: a view from neuroimaging. Cogn. Psychol. 33, 5–42.

Smith, E.E., Jonides, J., Koeppe, R.A., 1996. Dissociation verbal and spatial working memory using PET. Cereb. Cortex 6, 11–20.

Stebbins, G.T., Carrillo, M.C., Desmond, J.E., Turner, D.A., Bennett, D.A., Glover, G., Gabrieli, J.D.E., 2002. Aging effects on memory encoding in the frontal lobes. Psychol. Aging 17, 44–55.

Stone, M., Gabrieli, J.D.E., Stebbins, G.T., Sullivan, E.V., 1998. Working and strategic memory deficits in schizophrenia. Neuropsychology 12, 278–288.

Talairach, J., Tournoux, P., 1988. Co-planer Stereotaxic Atlas of the Human Brain. Thieme, New York.

Tovee, M.T., 1999. Is face process special? Neuron 21, 1239–1242.

Trojano, L., Grossi, D., Linden, D.E., Formisano, E., Goebel, R., Cirillo, S., Elefante, R., Di Salle, F., 2002. Coordinate and categorical judgements in spatial imagery. An fMRI study. Neuropsychologia 40, 1666–1674.

Wechsler, D. (Ed.), 1939. The Measurement of Adult Intelligence. Williams and Wilkins, Baltimore.

Wechsler, D., 1981. Manual for the Wechsler Adult Intelligence Scale-Revised (WAIS-R). The Psychological Corporation, San Antonio, TX.

Wechsler, D., 1997. WAIS-III Administration and Scoring Manual. The Psychological Corporation, San Antonio, TX.

Wickelgren, I., 1997. Getting a grasp on working memory. Science 275, 1580–1582.

Wiggs, C.L., Weisberg, J., Martin, A., 1999. Neural correlates of semantic and episodic memory retrieval. Neuropsychologia 37, 103–118.

Wilde, N., Strauss, E., 2002. Functional equivalence of WAIS-III/WMS-III digit and spatial span under forward and backward recall conditions. Clin. Neuropsychol. 16, 322–330.

Wilkinson, D., Halligan, P., 2004. The relevance of behavioural measures for functional-imaging studies of cognition. Nat. Rev. Neurosci. 5, 67–73.

Zhang, D.R., Li, Z.H., Chen, X.C., Wang, Z.X., Zhang, X.C., Meng, X.M., He, S., Hu, X.P., 2003. Functional comparison of primacy, middle and recency retrieval in human auditory short-term memory: an event-related fMRI study. Cogn. Brain Res. 16, 91–98.

Zhang, D.R., Zhang, X.C., Sun, X.W., Li, Z.H., Wang, Z.X., He, S., Hu, X.P.L., 2004. Order memory for auditory digits and visual locations: an fMRI study. Hum. Brain. Mapp. 22, 280–289.