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Dissociable contributions of the mid-ventrolateral frontal cortex and the medial temporal lobe system to human memory

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Although the prefrontal cortex and regions of the medial temporal lobe are commonly co-activated in neuroimaging studies, their precise respective contributions to human memory remain unclear. In this event-related fMRI study, conditions requiring volunteers to simply look at pictures of abstract art were compared with conditions in which they were explicitly instructed to remember similar stimuli for later recognition. Looking, with no explicit instruction to remember, was associated with significant increases in signal intensity in the medial temporal lobe in 19 of the 20 volunteers scanned, but not in a region of the mid-ventrolateral prefrontal cortex that has previously been implicated in memory encoding and retrieval. Behavioral data collected outside the scanner on the same task revealed that recognition of these stimuli was, however, above chance. When the task instructions were changed to encourage the volunteers to remember the stimuli, significant increases in signal intensity were observed bilaterally, in the mid-ventrolateral frontal cortex, but there was no concomitant increase within the medial temporal lobe region. Moreover, behavioral data collected outside the scanner confirmed that recognition of these stimuli was significantly improved relative to the 'just look' trials. These results suggest that the mid-ventrolateral frontal cortex and the medial temporal lobe region make dissociable contributions to human memory that correspond closely to 'top–down' and 'bottom–up' notions of cognitive control, respectively.

Introduction

For many years, it has been known that medial temporal lobe damage in humans produces profound memory impairments, while patients with frontal lobe lesions often perform normally on many standard tests of memory (Lee et al., 2000a; Petrides, 1994). The pattern that has emerged from functional neuroimaging studies in healthy volunteers is quite different, with increases in activity reported in medial temporal and frontal lobe areas during many different memory tasks (Buckner et al., 1995, 1999; Fletcher and Henson, 2001; Lee et al., 2000a). One region that has been consistently activated is the mid-ventrolateral frontal cortex which, in humans, lies below the inferior frontal sulcus and includes Brodmann areas 45 and 47 (Brodmann, 1909). Activity in this region has been reported during spatial, verbal and pattern working memory tasks (Owen et al., 1996a, 2000; Stern et al., 2000) but also during episodic memory tests of encoding and retrieval (Fletcher et al., 1998; Lee et al., 2000b; Owen et al., 1996b). The medial temporal lobe structures, including the hippocampus, are also frequently activated during tests of both episodic (Ryan et al., 2001; Schacter et al., 1999) and working memory (Cabeza et al., 2002; Monk et al., 2002; Ranganath and D'Esposito, 2001; Stern et al., 1996). In short, while individual studies have reported memory-related activity in the medial temporal lobe system or the mid-ventrolateral frontal cortex, the picture emerging from the imaging literature as a whole is of frequent co-activation across the two regions (Buckner et al., 1999).

In neuropsychological studies, medial temporal lobe damage frequently impairs simple recognition memory performance, even when the vaguest sense of familiarity should be sufficient to generate a correct response (Owen et al., 1995; Wheeler et al., 1995). Frontal lobe patients are generally unimpaired on such tasks but have difficulties when internally generated intentions or goals are required to generate a response (Lee et al., 2000a; Petrides and Milner, 1982; Wheeler et al., 1995). Such evidence suggests that an important factor for understanding the functional relationship between the mid-ventrolateral frontal cortex and the medial temporal lobe system may be the extent to which a volunteer explicitly intends to remember or retrieve a given stimulus and the changes in attentional control that may be consequent upon such an intention. The role of intention has been investigated previously in memory by comparing intentional encoding tasks with so-called 'incidental' memory tasks (Buckner et al., 2001; Stark and Okado, 2003; Wagner et al., 1998; Otten et al., 2001; Fletcher et al., 2003), although in both cases, activity in the mid-ventrolateral frontal cortex has been reported. However, in many incidental tasks, an intention is still involved, but it is directed away from explicit memorization (e.g., to judging whether words are in uppercase or lowercase letters; Buckner et al., 2000, 2001).

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In this study, event-related functional magnetic resonance imaging (fMRI) was used to explicitly test the hypothesis that mid-ventrolateral frontal cortex activity, but not medial temporal lobe activity, will vary according to the degree to which the intention to encode or retrieve information is modulated by a prior instruction cue, all other factors being held constant. Volunteers were instructed on random trials either to just look at pictures of abstract art or to try and remember them for later test. Recognition was examined by asking, on random trials, whether they remembered seeing specific pictures previously. In a fourth condition, volunteers were instructed to passively re-view stimuli shown previously. It was predicted that medial temporal lobe activity would be observed during all experimental conditions when compared to rest, while activity in the mid-ventrolateral frontal cortex would only be observed when volunteers specifically intended to remember or retrieve the stimuli following a specific instruction to do so.

Methods

An initial pilot experiment was conducted to test two aspects of the imaging paradigm: (i) whether explicitly asking volunteers to try and remember stimuli for later recognition lead to improved memory performance compared to when they were asked to simply look at similar stimuli and (ii) whether looking at a single presentation of a stimulus was sufficient to yield significant memory for that stimulus. In both the behavioral pilot study and the functional neuroimaging study, a series of colorful abstract paintings that were neither well known, nor contained easily recognizable objects, were collected and randomly assigned to four experimental conditions (Fig. 1). In the interests of brevity, the two conditions in which the volunteers were asked to simply look at the paintings (without any instruction to remember or recall) will henceforth be referred to as low-intention. The two conditions in which the volunteers were asked explicitly to remember or make a recognition judgement about the paintings will be referred to as high-intention.

In all conditions, each trial consisted of an instruction presented for 1.5 s. which was followed by a 0.4-s delay and then the presentation of an abstract painting for 3 s. Trials were separated by an inter-trial interval of 0.4 s. In the low-intention encoding condition, the instruction was ‘look at this’. The volunteer’s task was just to look at the painting that followed. In the high-intention encoding condition, volunteers received the instruction ‘remember this’. They were told that the task was to remember the painting that followed for possible later recognition. In the high-intention recognition condition, the instruction was ‘have you seen this?’ Here, the volunteer was required to decide whether or not the painting had been seen before. A fourth condition, referred to as low-intention re-viewing was designed to control for the fact that paintings in the high-intention recognition condition were viewed more than once and to examine, as far as is possible, recognition memory in the absence of a specific instruction. In this condition, volunteers were asked to re-view stimuli (with the instruction ‘look at this’)

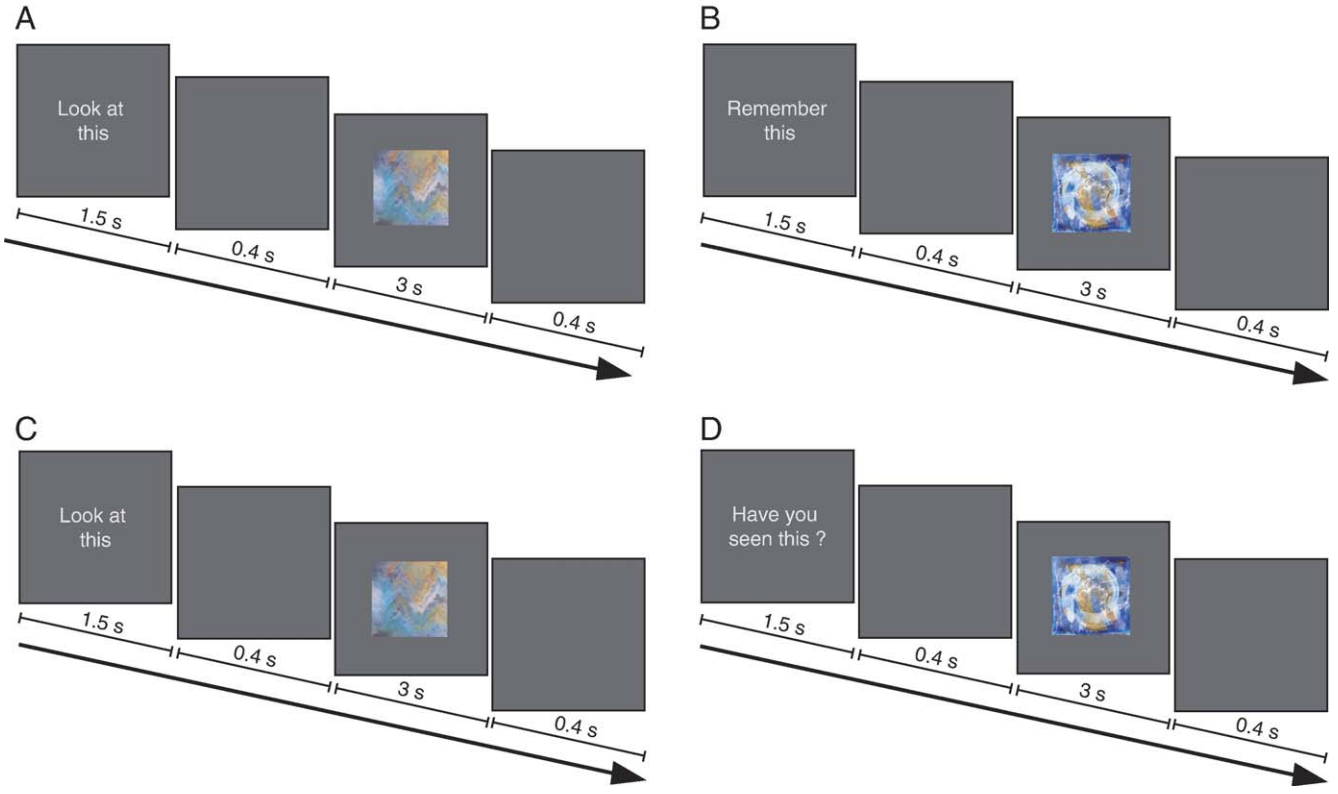

Fig. 1. Example trials illustrating the four experimental conditions. On each trial, participants were given an instruction followed by an experimental stimulus. (A) Low-intention encoding. Before each painting, participants were given the instruction ‘look at this’. (B) High-intention encoding. Before each painting, participants were given the instruction ‘remember this’. (C) Low-intention re-viewing. As in the low-intention encoding condition, participants were given the instruction ‘look at this’. However, in the low-intention re-viewing condition, the painting was shown for the second or third time. (D) High-intention recognition. Before each painting, participants were given the instruction ‘have you seen this?’

that had been shown previously in the low-intention encoding condition.

Behavioral pilot study

Volunteers

Nineteen right-handed volunteers participated in the pilot study (9 male, 10 female, 18–33 years of age).

Stimuli and task parameters

Volunteers were instructed to try to remember 54 paintings (high-intention encoding). Eighteen of these paintings were presented only once, 18 were presented twice and a further 18 three times each. Each of these 54 paintings was shown subsequently, and volunteers were asked for each, 'have you seen this?' (high-intention recognition of intentionally encoded stimuli). Volunteers were also instructed to look at a separate set of 54 paintings (low-intention encoding). Eighteen of these paintings were presented only once, 18 were presented twice and a further 18 three times. Each of these 54 paintings was shown subsequently, and volunteers were asked for each, 'have you seen this?' (high-intention recognition of low-intention encoded stimuli). A further 108 paintings, not shown previously, were also used in the high-intention recognition condition and served as foils for the paintings that were presented in the low- and high-intention encoding conditions.

The volunteers pressed a button with their index finger to indicate that they had seen the painting before. A second button was pressed with the middle finger if volunteers decided that the painting had not been seen before.

All trials were presented randomly with the following constraints: Paintings that were repeated always re-occurred within the next 19–26 trials. There were no more than three trials with the same instruction (i.e., trial type) in a row.

The entire experiment was divided into three 'self-contained' experimental blocks of equal length (145 trials), to allow the volunteers to rest periodically. In each block, the first trial was excluded from the analysis. Additionally, the first 10 trials of the high-intention recognition condition were excluded from the analysis because it was obvious that most of these paintings had to be new.

Functional neuroimaging study

Volunteers

Twenty-one right-handed healthy young adults (13 male, 8 female, 18–31 years of age) participated in the imaging study. One volunteer was excluded from all analyses because of excessive motion during scanning. The study received ethical approval from the Central Oxford Research Ethics Committee.

Stimuli and task parameters

The procedure was identical to the pilot study described above except for the following changes. Volunteers were instructed to try to remember 30 paintings, each presented once for encoding (high-intention encoding). Each of these paintings was shown subsequently, following the instruction, 'have you seen this?' (high-intention recognition of high-intention encoding stimuli). A further 10 paintings, not shown previously, were also used in the high-intention recognition condition and served as foils.

Volunteers were also instructed to look at a separate set of 30 paintings (low-intention encoding). Ten of these paintings were presented only once, the remaining 20 being re-presented two times each (low-intention re-viewing of low-intention encoding stimuli). Sixty non-events were presented in which the screen was blank for 5.3 s.

In all conditions, except the non-event condition, responses were made. Volunteers pressed two buttons simultaneously with their index and middle fingers during the presentation of the paintings in the low-intention encoding, low-intention re-viewing and high-intention encoding conditions. In the high-intention recognition condition, volunteers indicated whether or not they had seen a painting before with the middle or index finger of the right hand, respectively.

Volunteers performed a practice which consisted of 170 trials in the scanner before they carried out the actual fMRI experiment.

Image acquisition and analysis

fMRI scanning was carried out at the Centre for Functional Magnetic Resonance Imaging of the Brain (FMRIB), Oxford, UK on a 3-T MRI system driven by a Varian Unity Inova console and equipped with an Oxford Magnet Technology magnet, a Siemens body gradient coil and a bird-cage radio-frequency head coil built by Enzo Barberi (Robarts Research Institute, Canada). An In Focus LP1000 projection system (Unicol engineering, Oxford, UK) was used to project the stimuli onto a white screen located at the foot end of the scanner bed. Volunteers viewed this screen via a pair of prism spectacles (Wardray-Premise engineering, Surrey, UK). Volunteers' responses were made using 2 specified buttons ('left' and 'right') on a 4 button response box held in the right hand. Foam padding was used to immobilize volunteers within the MRI head coil.

For functional data, an echo planar imaging (EPI) pulse sequence was implemented to acquire T2*-weighted image volumes with blood oxygen level-dependent (BOLD) contrast. Each volume consisted of 21 slices with a voxel size of 3 4 5 mm (TR = 3 s, TE = 30 ms, flip angle of 90°, FOV: 256 256 mm, matrix size: 64 64). A map of the magnetic field was acquired and then used to correct for distortion to the EPIs resulting from inhomogeneities in the field (Cusack and Papadakis, 2002; Jezzard and Balaban, 1995). This procedure has been shown to improve anatomical localization and increase the power of group studies by achieving better spatial registration between the data from different volunteers (Cusack et al., 2003). The field map was always acquired directly before or after the acquisition of the functional data to ensure that the head position of the volunteer was maximally comparable. A high-resolution T1 structural scan was acquired (voxel size: 1 1 3 mm) either during the same scanning session or on a different day.

SPM99 software was used for preprocessing and statistical analyses (www.fil.ion.ucl.ac.uk/spm). The first five volumes of the EPIs were discarded due to T1 saturation effects. After realignment of the data slice-timing correction was carried out. The field map information was used to correct for distortions in the phase-encode directions of the EPIs using an SPM toolbox (Cusack et al., 2003; Cusack and Papadakis, 2002). The EPIs were normalized by using a masked EPI to EPI template normalization (Brett et al., 2001) and smoothed with a 12-mm Gaussian kernel for the group analyses and a 6-mm Gaussian kernel for single volunteer analyses.

A general linear model was applied to the functional data of each participant (Friston et al., 1995). The model included

covariates for sustained neuronal responses elicited during high-intention encoding, high-intention recognition of previously presented paintings, high-intention recognition of new paintings, low-intention encoding, low-intention re-viewing of paintings shown for the second time, low-intention re-viewing of paintings shown for the third time and non-events. The onsets of events were at the time the instruction was shown. The duration of the events was the whole-trial duration (5.3 s). A boxcar function convolved with a canonical hemodynamic response was used to model these events. Additionally, six motion parameters derived during realignment were used to correct for residual movement artefacts. A high-pass filter with a cut-off of 200 s was employed to correct for low-frequency drifts in BOLD-signal. Parameter estimates for each covariate were calculated from the least mean squares fit of the model to the data.

Planned contrasts were carried out on parameter estimates of the covariates of interest against parameter estimates of covariates of suitable control conditions: 'low-intention encoding' versus 'non-events', 'low-intention re-viewing of paintings' (shown for the second and third time) versus 'non-events', 'high-intention encoding' versus 'non-events', 'high-intention recognition' versus 'non-events', 'high-intention encoding' versus 'low-intention encoding', 'high-intention recognition of previously presented paintings' versus 'low-intention re-viewing of paintings shown for the second time'. The resulting contrast images were entered into one one-sample *t* test per contrast to permit inferences about condition effects across volunteers (i.e., random effects analyses). Additionally, single volunteer analyses were performed. All statistical tests were corrected for multiple comparisons and thresholded using the false discovery rate (Genovese et al., 2002). Unless otherwise indicated, the threshold was $P = 0.05$. In the group analyses, activations are only reported if they include more than 10 activated voxels.

In order to compare differential changes in activity between the medial temporal lobe region and the mid-ventrolateral frontal cortex across the four conditions, a supplementary region of interest (ROI) analysis was conducted. Accordingly, planned contrasts were conducted on parameter estimates of the covariates of interest for each of the four experimental conditions against parameter estimates of covariates of the non-event control condition for each volunteer. To identify the ROI, an SPM map was made for the random effects analysis of the sum of all four experimental conditions compared to the non-event condition. This map was thresholded at $P < 0.05$ in order to yield several candidate regions activated by the experimental conditions. The mid-ventrolateral frontal cortex was identified using published co-ordinates (41, 20, 0 and 37, 20, 3) from a meta-analysis of previous studies (Duncan and Owen, 2000). The nearest local maxima were identified from the current data set (36, 18, 0 and 36, 22, 2) and a 7-mm radius sphere was drawn around these coordinates using the MARSBAR tool (Brett and others, 2002; http://marsbar.sourceforge.net). Using the same comparison between all the experimental conditions and the non-event random effects map, the largest peak of activity within the medial temporal lobe was identified in both hemispheres (22, 30, 0 and 20, 30, 2). Given the size of this region, a sphere of 5-mm radius was drawn around each peak using the MARSBAR tool. For both the frontal and temporal lobe regions, the same spheres were used for all participants. Data were extracted for each participant for the contrasts between each of the four experimental conditions and the non-event control condition and an ANOVA with the factors 'region of interest' (ventrolateral prefrontal cortex versus medial temporal lobe), 'intention' (high-intention condition versus low-intention) and 'type of task' (encoding versus recognition) was carried out.

Results

Behavioral pilot study

Accuracy data were transformed into *d'* measures for each of 19 volunteers (Macmillan and Creelman, 1991) (also see Table 1). This provides a measure of performance that is independent of response bias. Higher values correspond to better performance. Data were then averaged over participants. The resulting values in the low-intention encoding condition were 2.24 (one repetition), 2.70 (two repetitions) and 3.02 (three repetitions). The resulting values in the high-intention encoding condition were 2.53 (one repetition), 2.95 (two repetitions) and 3.21 (three repetitions). A two-way repeated measures analysis of variance was conducted comparing type of encoding (low-versus high-intention) with repetitions (1–3 repetitions). There was a significant main effect of type of encoding ($F_{(1,18)} = 6.74$, $P < 0.02$), with high-intention encoding leading to better recognition than low-intention encoding. The main effect of repetition was also significant ($F_{(2,36)} = 44.16$, $P < 0.0001$), confirming that repetition of the paintings during encoding enhanced performance at the recognition stage. There was no significant interaction between the two factors ($F_{(2,36)} = 0.42$, $P = 0.66$), confirming that repetition of the stimuli during low- and high-intention encoding had a similar effect on performance. In general, performance at recognition was well above chance for both low- and high-intention encoded paintings, even following a

Table 1
Hits, misses, false alarms (FA) and correct rejections (CR) in the behavioral pilot study and the fMRI study

		Hits						Misses						FA	CR
		HI1	HI2	HI3	LI1	LI2	LI3	HI1	HI2	HI3	LI1	LI2	LI3		
A	S	15.6	17.1	17.6	14.1	16.0	16.9	2.4	0.9	0.3	3.9	2.2	1.0	7.0	70.9
	M	18	18	18	18	18	18	18	18	18	18	18	18	78	78
B	S	27.1	–	–	–	–	–	2.9	–	–	–	–	–	0.4	9.6
	M	30	–	–	–	–	–	30	–	–	–	–	–	10	10

HI1, high intention encoding, picture shown once; HI2, high intention encoding, picture shown twice, HI3, high intention encoding, picture shown three times, LI1, low intention encoding, picture shown once; LI2, low intention encoding, picture shown twice, LI3, low intention encoding, picture shown three times; A, results of the pilot experiment; B, results of the fMRI experiment; S, average scores, averaged over all participants; M, maximum score. Note that in the fMRI experiment the volunteers were only asked to indicate whether or not they had seen a picture that was presented once in the high intention encoding condition.

Table 2
Peak increases in activity in the contrasts 'low-intention encoding–non-events' and 'low-intention re-viewing–non-events'

Region	*T*	*X*	*Y*	*Z*	*P*
Low-intention encoding–non-events					
Right premotor cortex (BA 9/6)	4.21	52	10	38	0.004
Paracentral lobule (BA 24)	10.98	2	10	52	0.000
Left premotor cortex (BA 6/4)	6.53	46	2	52	0.000
Left postcentral gyrus (BA 1 /2)	9.39	50	28	58	0.000
Left hippocampal region	6.36	22	28	4	0.000
Right hippocampal region	5.85	20	30	2	0.000
Cingulate gyrus (BA 29)	7.29	0	44	4	0.000
Right intraparietal sulcus (BA 7)	4.72	30	60	48	0.002
Left intraparietal sulcus (BA 7)	4.23	24	64	48	0.004
Right extrastriate cortex /fusiform gyrus (BA 19)	12.03	38	72	14	0.000
Right striate cortex (BA 17)	12.74	14	94	6	0.000
Right striate/extrastriate cortex (BA 18/17)	13.85	16	102	4	0.000
Low-intention re-viewing–non-events					
Left superior frontal gyrus (BA 10)	4.27	28	60	2	0.004
Left superior frontal gyrus (BA 10)	3.31	34	48	30	0.028
Left gyrus frontalis medialis (6/32)	9.92	4	10	52	0.000
Right premotor cortex (BA 6/44)	3.12	44	8	34	0.040
Left middle frontal gyrus/precentral sulcus (BA 6)	4.66	40	0	58	0.002
Left precentral gyrus (BA4)	5.80	40	26	66	0.000
Left postcentral gyrus (BA 1)	5.68	50	28	58	0.000
Left hippocampal region	4.59	22	30	6	0.002
Right hippocampal region	3.03	24	30	4	0.048
Right intraparietal sulcus (BA 7/40)	4.44	32	62	50	0.003
Left precuneus/inferior parietal lobule (BA 7/40)	5.29	28	64	46	0.001
Right extrastriate cortex/fusiform gyrus (BA 19)	11.46	38	72	14	0.000
Right striate cortex (BA 17)	11.10	14	94	6	0.000
Right extrastriate cortex (BA 18)	13.07	16	102	4	0.000

Stereotaxic coordinates (*X*, *Y*, *Z*) are shown in MNI space (template of the Montreal Neurological Institute), as well as *t* values (*T*) and significance levels (*P*).

single presentation of the stimuli (one-tailed *t* tests tested against '0', $t_{(18)}$ 15.19, $P < 0.0001$).

Functional neuroimaging study

The constraints of the experimental paradigm meant that it was not possible to collect any behavioral data during the low-intention memory condition. However, the data that was available (see Table 1) showed that, as in the behavioral pilot study, the volunteers performed better than chance during high-intention recognition of high-intention encoding paintings (d⊭ 2.87; one-tailed *t* test tested against '0', $t_{(19)} = 17.89$, $P < 0.0001$).

When low-intention encoding was compared to the non-events, significant increases in signal intensity were observed in the parahippocampal gyrus/hippocampus bilaterally (Table 2, Figs. 2 and 3). In contrast, no significant activity was observed in the mid-ventrolateral frontal cortex (Fig. 2). Signal intensity changes were also observed in occipital regions extending from striate to extrastriate cortex, in motor and premotor cortices (including the supplementary motor area) and in frontopolar cortex.

When low-intention re-viewing and non-events were compared (Table 2, Figs. 2 and 3), a similar pattern emerged. Thus, significant signal intensity changes were observed in the parahippocampal gyrus/hippocampus bilaterally, while no significant activity was observed in the mid-ventrolateral frontal cortex (Fig. 2). Additional changes were observed in frontopolar cortex and right premotor cortex (BA 6/9).

In contrast, when high-intention encoding was compared to low-intention encoding, significant signal intensity changes were observed in the mid-ventrolateral frontal cortex, but not in the parahippocampal gyrus/hippocampus (Table 3, Fig. 2). Additional activity was observed in the left dorsolateral frontal cortex (DLPFC), frontopolar cortex, anterior cingulate cortex, the banks of the intraparietal sulcus, bilaterally, and in several visual areas (Table 3).

When high-intention recognition was compared to low-intention re-viewing, a similar pattern emerged (see Table 3, Fig. 2): While the mid-ventrolateral frontal cortex was activated bilaterally, no significant difference in activity was observed in the medial temporal lobe region. In addition, activity was observed in the left DLPFC, frontopolar cortex, anterior cingulate, and intraparietal sulcus.

A supplementary whole brain analysis was carried out to establish whether signal intensity changes in the parahippocampal gyrus/hippocampus were similar, or different, in the low- and high-intention memory conditions. When both high-intention encoding and high-intention recognition were compared to non-events, bilateral parahippocampal gyrus/hippocampus activation was observed that was very similar to that observed in the low-intention conditions described above (Fig. 3).

The ROI analysis of the observed ventrolateral frontal and medial-temporal peaks was conducted to explore the relationship between activity changes in these areas across the four experimental conditions (Fig. 4). Analysis of variance revealed significant main effects of ROI ($F_{(1,19)} = 15.94$, $P < 0.05$) and intention ($F_{(1,19)} = 23.18$, $P < 0.05$) and a significant interaction between the two factors ($F_{(1,19)} = 18.55$, $P < 0.05$), confirming that the

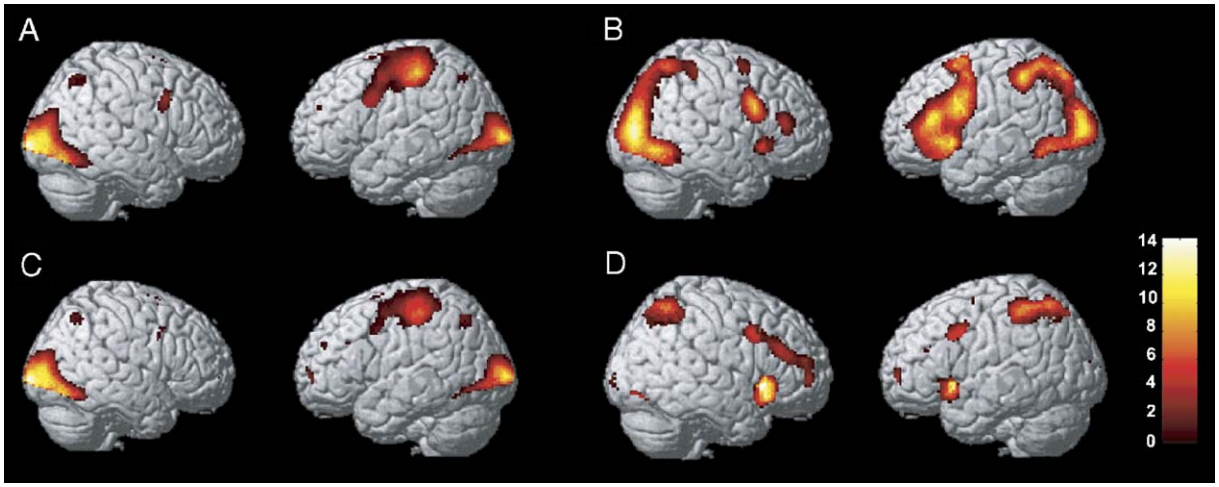

Fig. 2. Regions of increased activity during the low- and high-intention conditions. fMRI activity observed in the contrasts 'low-intention encoding–non-events' (A), 'high-intention encoding–low-intention encoding' (B), low-intention re-viewing–non-events' (C) and 'high-intention recognition–low-intention re-viewing' (D) in group analyses using one-sample *t* tests corrected for multiple comparisons ($P < 0.05$, FDR corrected). Activation maps were rendered onto the canonical T1-weighted brain image of SPM 99.

response to a specific intention was significantly different in the mid-ventrolateral frontal cortex and the medial temporal lobe region. There was no main effect of the type of task ($F_{(1,19)} = 0.04$, $P > 0.05$) or interaction between type of task and any other factor. Therefore, data from the high-intention encoding and recognition conditions were combined for each ROI, as were the data from the low-intention encoding and re-viewing conditions, and post hoc contrasts conducted. These contrasts clearly revealed that the source of the significant interaction term was the reduced activity in the low-intention conditions in the ventrolateral ROIs (see Fig. 4), which differed significantly from that in the same region during the high-intention conditions ($t(19) = 6.57$; $P < 0.05$) as well as from that in the medial temporal lobe ROIs in both the high-intention ($t(19) = 5.47$; $P < 0.05$) and the low-intention conditions ($t(19) = 5.25$; $P < 0.05$). Supplementary contrasts confirmed that, in the ventrolateral frontal cortex, activity in neither the low-intention encoding condition ($t(19) = 1.74$; $P > 0.05$) nor the low-intention recognition condition ($t(19) = 1.83$; $P > 0.05$) differed significantly from zero.

Single-volunteer analyses were then conducted in order to localize activity in the parahippocampal gyrus/hippocampus more precisely and to investigate whether signal intensity changes in this region were present in the majority of the volunteers. As activity in this region was observed in all conditions where paintings were presented (Fig. 3), these conditions were combined to maximize statistical power. The

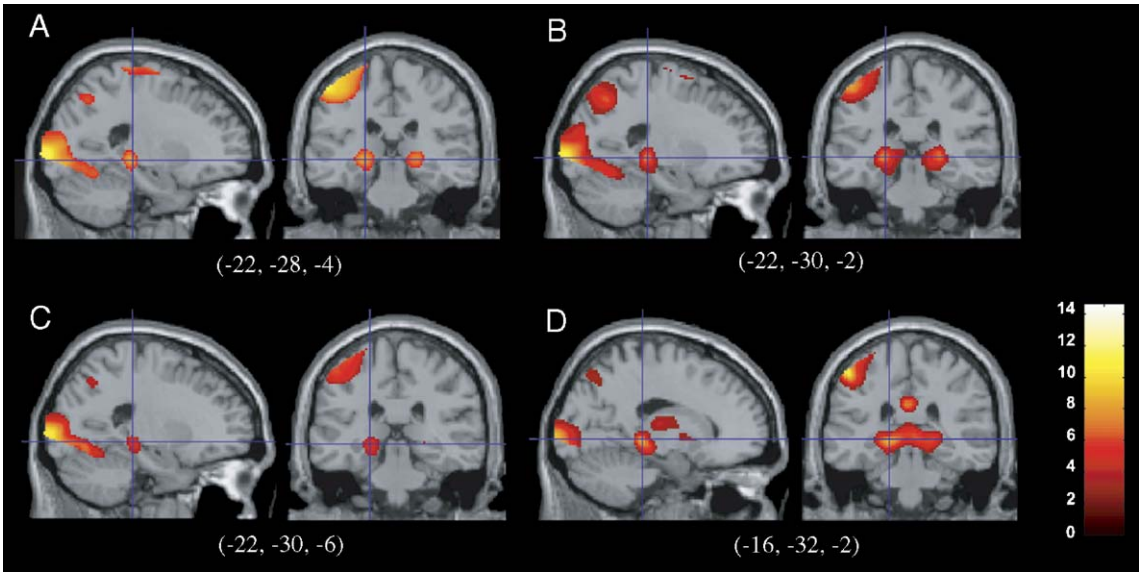

Fig. 3. Regions of increased activity in the parahippocampal gyrus/hippocampus. fMRI activity observed in the contrasts 'low-intention encoding–non-events' (A), 'high-intention encoding–non-events' (B), 'low-intention re-viewing–non-events' (C) and 'high-intention recognition–non-events' (D) in group analyses using one-sample *t* tests corrected for multiple comparisons ($P < 0.05$, FDR corrected). Activation maps were overlaid onto a normalized T1-weighted image. In coronal slices, the left hemisphere is on the left of the panel. The crosshairs locate peak activity in the left parahippocampal gyrus/hippocampus whose MNI coordinates are shown underneath each panel.

Table 3
Peak Increases in activity in the contrasts 'high-intention encoding–low-intention encoding' and 'high-intention recognition–low-intention re-viewing'

Region	*T*	*X*	*Y*	*Z*	*P*
High-intention encoding–low-intention encoding					
Right mid-DLPFC (BA 46)	5.34	52	36	18	0.001
Left inferior frontal sulcus/mid-DLPFC (BA 45/46)	9.51	50	32	18	0.000
Right VLPFC (BA 47)	4.01	38	20	0	0.005
Left VLPFC (BA 47)	5.51	34	18	2	0.000
Left medial frontal gyrus (BA 6/8)	7.11	6	16	54	0.000
Right inferior frontal gyrus (BA 44/6)	6.24	52	10	28	0.000
Right basal ganglia	3.06	16	6	6	0.026
Left premotor cortex (BA 6)	8.34	46	4	28	0.000
Right middle frontal gyrus (BA 6)	3.38	28	2	62	0.015
Right fusiform gyrus (BA 37)	9.70	38	56	18	0.000
Left intraparietal sulcus (BA 7)	7.15	26	62	50	0.000
Left extrastriate cortex (BA 19/37)	9.13	44	60	12	0.000
Right intraparietal sulcus (BA19/39)	7.78	28	74	30	0.000
Right extrastriate cortex (BA 19/18)	7.95	36	82	8	0.000
Left extrastriate cortex (BA 19/18)	9.10	24	84	22	0.000
High-intention recognition–low-intention re-viewing					
Left frontopolar cortex (BA 10)	3.31	30	60	2	0.031
Right frontopolar cortex (BA 10)	4.84	42	52	16	0.004
Right mid-DLPFC (BA 46)	3.99	50	42	18	0.011
Left mid-DLPFC (BA 46)	3.17	48	36	24	0.038
Anterior cingulate (BA 32)	5.47	2	36	24	0.003
Left mid-DLPFC (BA 46)	3.04	50	32	26	0.045
Right mid-DLPFC (BA 46)	4.18	52	32	28	0.009
Right VLPFC (BA 47)	8.18	32	24	6	0.001
Medial frontal gyrus (BA 8/32)	5.48	4	28	42	0.003
Medial frontal gyrus (BA 6)	5.82	0	20	48	0.002
Left VLPFC (BA 47)	6.26	30	16	8	0.002
Left premotor cortex (BA 9/6)	3.99	52	10	40	0.011
Left superior frontal sulcus (BA 6)	3.03	30	2	64	0.046
Globus pallidus	8.48	12	4	2	0.001
Posterior cingulate gyrus (BA 23)	6.67	0	26	30	0.002
Left intraparietal sulcus (BA 40/2)	6.34	42	40	56	0.002
Right intraparietal sulcus (BA 7/4)	5.59	30	56	56	0.002
Left intraparietal sulcus (BA 7)	6.42	24	60	52	0.002
Right precuneus (BA 7)	4.25	16	70	50	0.008
Right extrastriate cortex/fusiform gyrus (BA 19)	3.02	36	72	14	0.046
Left precuneus (BA 7)	4.33	8	74	46	0.007
Right extrastriate cortex (BA 19)	3.74	30	78	12	0.016
Extrastriate cortex (BA 18)	5.83	6	86	8	0.002
Left extrastriate cortex (BA 19)	2.98	24	94	14	0.050

Stereotaxic coordinates (*X*, *Y*, *Z*) are shown in MNI space (template of the Montreal Neurological Institute), as well as *t* values (*T*) and significance levels (*P*).

individual functional maps were overlaid on high-resolution structural MR images acquired for each volunteer (see Methods section). These images were co-registered to the EPIs and normalized using the same parameters that were utilized for the EPI normalization. Significant parahippocampal gyrus/hippocampal system activation was clearly evident in 19 of the 20 volunteers (Fig. 5). In the remaining volunteer, activation was observed, but at a lower (non-significant) threshold (P = 0.1, FDR corrected). Although the activated area included the hippocampus in many volunteers, in many cases, the peak coordinate of activity was located within the parahippocampal gyrus, somewhat medial and superior to the body of the hippocampus itself.

Activity in the mid-ventrolateral frontal cortex was also investigated further by analyzing the single volunteer data. Since mid-ventrolateral frontal cortex activation was similar in the high-intention encoding and high-intention recognition group comparisons, these conditions were combined and compared to the combined low-intention conditions. Fourteen out of 20 volunteers showed significant activation in this region (Fig. 6). In 3 of the remaining volunteers (non-significant), activation was observed at a lower threshold (P = 0.1, FDR corrected).

It is important to acknowledge the fact that, although the high-intention recognition and low-intention re-viewing conditions were matched as closely as possible, they differed both in terms of the responses given and the type of encoding episode associated with each. The low-intention condition required a simple button press, while the high-intention recognition condition required a choice reaction. In addition, the volunteers had been asked to encode the stimuli that were shown during high-intention recognition condition, while they had not been asked explicitly to remember the stimuli that were shown during low-intention re-viewing. However, with respect to the mid-ventrolateral frontal cortex and the parahippocampal gyrus/hippocampus, the pattern of results observed during the recognition conditions was closely replicated during the corresponding encoding conditions. In both encoding conditions, the stimuli had not been encountered before and the responses were matched, suggesting that neither of these factors contributed significantly at recognition.

Discussion

In this study, a novel memory paradigm was used to demonstrate that activity in the mid-ventrolateral frontal cortex, but not the medial temporal lobe system, increases when volunteers have an intention to encode or retrieve information about a stimulus following a specific instruction to do so, all other factors being held constant. In contrast, activity in the parahippocampal

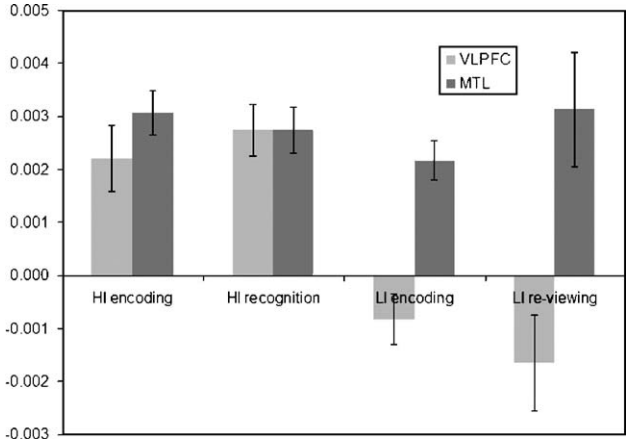

Fig. 4. Contrast values of the contrasts high-intention encoding (HI encoding) versus non-events, high-intention recognition (HI recognition) versus non-events, low-intention encoding (LI encoding) versus non-events and low-intention re-viewing (LI re-viewing) versus non-events in regions of interest in the mid-ventrolateral prefrontal cortex (VLPFC) and the medial temporal lobe (MTL). Error bars show the standard error of the mean.

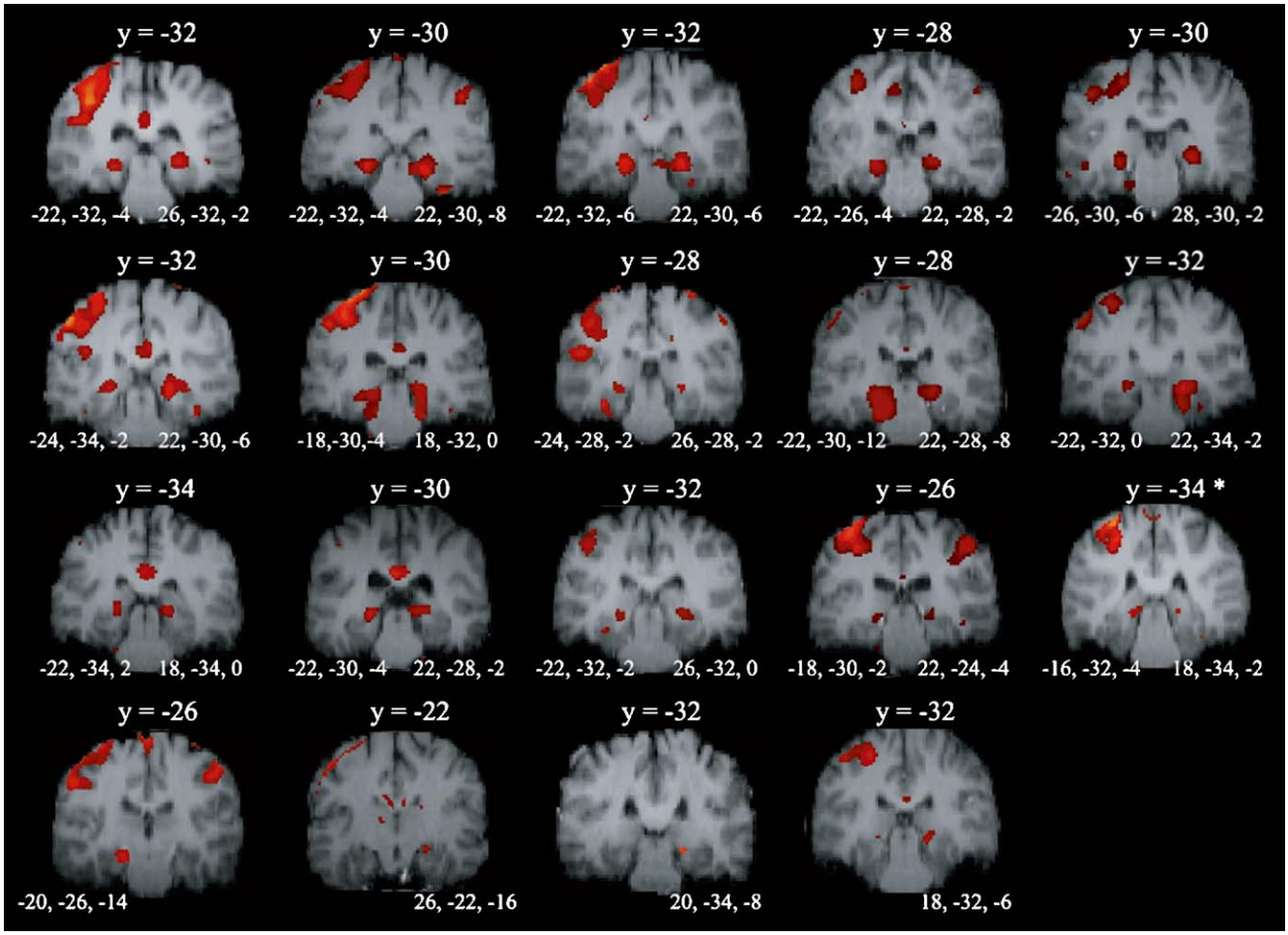

Fig. 5. fMRI activity in the parahippocampal gyrus/hippocampus in individual volunteers. Single volunteer activity in the contrast 'all experimental conditions – non-events'. All 19 volunteers presented here showed significant activation in the parahippocampal gyrus/hippocampus ($P < 0.05$, FDR corrected). Activations were overlaid onto high-resolution T1-weighted brain images of each volunteer that were co-registered to the EPI's and normalized. The left hemisphere is on the left of the panel. For each volunteer the *y*-coordinate of the presented slice is shown above the figure. Underneath the coordinates of the peak activity in the parahippocampal gyrus/hippocampus are presented. All coordinates are in MNI space.

gyrus/hippocampus increased in all of the experimental conditions, including those in which no explicit memory instruction was given (see Fig. 4).

Behavioral data from the pilot experiment confirmed that the condition in which no explicit instruction to remember the stimuli was given, nevertheless, resulted in delayed recognition that was well above chance, even for stimuli that were presented only once during the low-intention encoding condition. Furthermore, repetition of the paintings, without any instruction to remember, significantly improved performance at recognition, again suggesting that the stimuli were attended to and that this alone induced some level of behaviorally relevant mnemonic processing. The results of the functional neuroimaging study clearly demonstrated that the parahippocampal gyrus/hippocampus was significantly active during the low-intention encoding condition, whereas the mid-ventrolateral frontal cortex was not, suggesting that, in the absence of any previously cued intention to remember, memory is mediated primarily by the medial temporal lobe system. Similar results were observed at recognition; that is, re-viewing of stimuli that had been presented previously, with no explicitly cued intention to remember, resulted in significant signal intensity changes in the parahippocampal gyrus/hippocampus, but not in the mid-ventrolateral frontal cortex. These results suggest again, that the conscious experience of familiarity that may lead to successful recognition even in the absence of any explicit instruction to retrieve items from memory, is preferentially mediated by the medial temporal lobe system and not by the mid-ventrolateral prefrontal cortex. This notion concurs closely with the assumptions of relational memory processing accounts of hippocampal system function, which assume that "the hippocampal system provides the critical machinery for binding together the various elements encountered in our interaction with the environment; and it does this binding automatically and obligatorily, in the sense that no strategic intervention is necessary" (Cohen et al., 1999). Similarly, Martin (1999) has noted that the "medial temporal lobe is automatically engaged whenever an event is attended to and volunteers engage in the type of processing that spontaneously occurs in response to a particular type of stimulus."

Given such a fundamental role in memory processing, it is notable that relatively few functional neuroimaging studies have reported significant increases in signal intensity in the medial temporal lobe region compared, for example, to the mid-ventrolateral frontal cortex. It has been suggested that the involvement of the medial temporal lobe system in relatively automatic (or 'bottom–

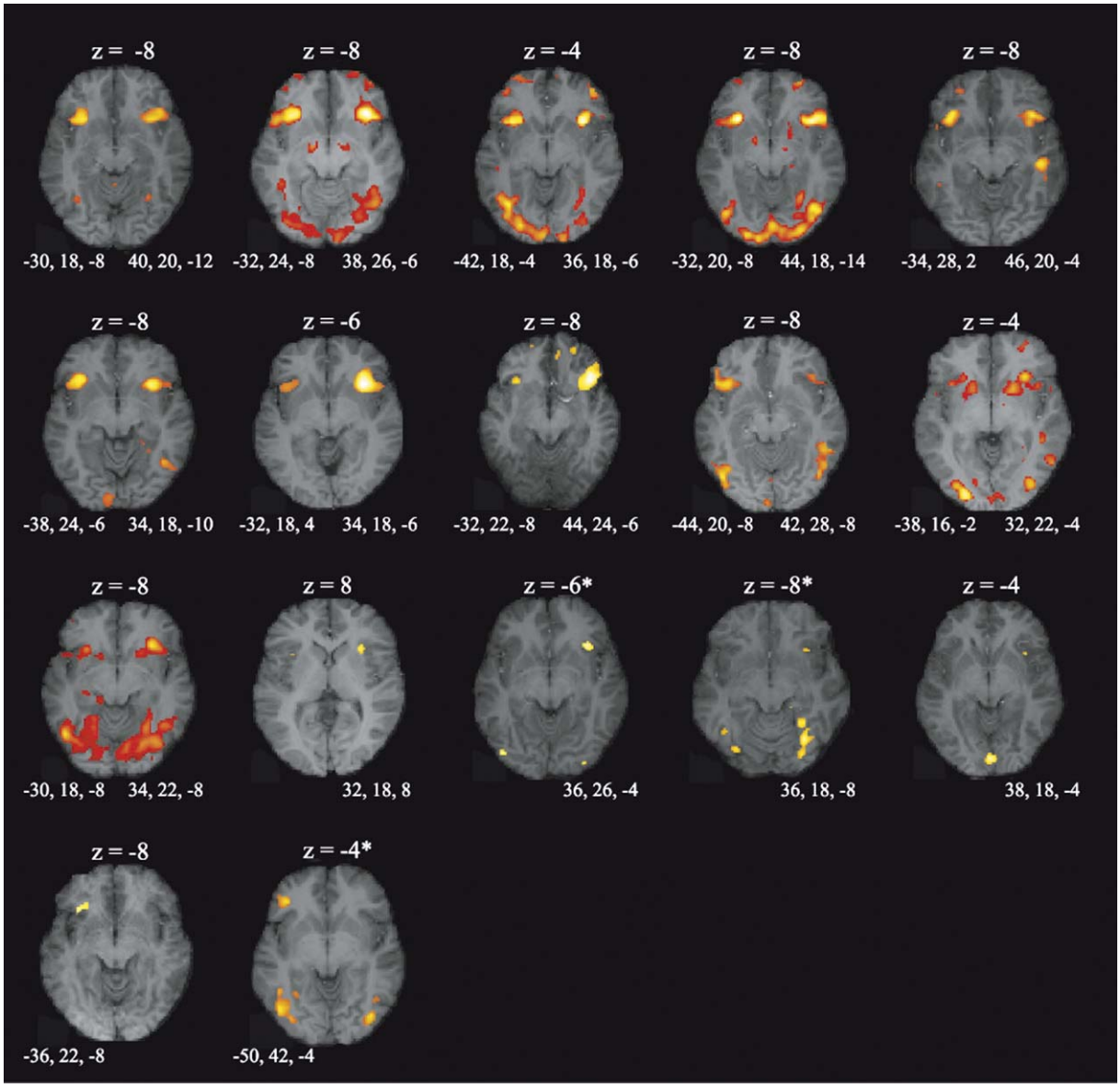

Fig. 6. fMRI activity in the mid-VLPFC in individual volunteers. Single volunteer activity in the contrast 'all high-intention – all low-intention conditions'. Data from 14 volunteers showed significant activation in the mid-VLPFC ($P < 0.05$, FDR corrected). Additionally, data of 3 volunteers are shown (*) for whom mid-VLPFC activity was observed at a lower threshold ($P < 0.1$, FDR corrected). Activations were overlaid onto high resolution T1-weighted brain images for each subject that were co-registered to the EPI's and normalized. The left hemisphere is on the left of the panel. For each volunteer the z-coordinate of the presented slice is shown above the figure. Underneath the coordinates of the peak activity in the mid-VLPFC are shown. All coordinates are in MNI space.

up') memory processes may effectively 'cancel out' activity when experimental and control conditions are compared directly (Martin, 1999). For similar reasons, Stark and Squire (2001), have argued that resting conditions are inappropriate baselines for fMRI studies of memory, particularly with respect to detecting medial temporal lobe activity, as they can reduce, eliminate, or even reverse the sign of activity in this region. The current findings confirm that this is not necessarily the case; in fact, compared to non-events (effectively a resting baseline), significant medial temporal lobe activity was observed during passive viewing of visual stimuli even at the single subject level in 19 of the 20 volunteers scanned.

What the present results also demonstrate, however, is that when the task instructions (but not the stimuli) at encoding and recognition are changed to encourage additional intentional (or 'top–down') control of mnemonic processing, no significant changes are observed in medial temporal lobe activity, despite marked improvements in memory performance. In contrast, significant bilateral increases in signal intensity were observed in the mid-ventrolateral frontal cortex when the volunteers intended to encode and make decisions about the stimuli following an explicit instruction to do so.

The idea that the frontal cortex is important for intended actions is not a new one, although the precise nature of this involvement has been neither behaviorally, nor anatomically, well specified. As early as 1922, Bianchi (1922) suggested that the frontal lobes are involved in controlling behavior, while the neuropsychological literature throughout the last century is filled with descriptions of frontal lobe patients that imply an impairment of intended actions. For example, deficits in planning (Owen et al., 1990; Shallice,

1982, 1988), the temporal structuring of behavior (Fuster, 1997), monitoring or manipulation in working memory (Owen, 1997; Petrides, 1994) and the control of behavior by context (Cohen and Servan-Schreiber, 1992) have been described, all of which imply a disorder of intended actions, yet all of which also lack testable, well-specified components. The current results confirm that even simply changing a task instruction from 'look' to 'look and remember' is sufficient to elicit a robust change in activity within the mid-ventrolateral region of the prefrontal cortex.

Although this study was specifically designed to investigate the functions of the mid-ventrolateral frontal cortex by using encoding and recognition within episodic memory as a means by which to increase the demand on intentional processing, previous functional neuroimaging studies in humans have reported activity in this region during many other types of cognitive task. For example, the mid-ventrolateral frontal cortex has been activated in tasks that require the selection, comparison and judgement of stimuli held in short-term and long-term memory (Petrides, 1994), during stimulus selection (Rushworth et al., 1997), when the specification of retrieval cues is required (Dobbins et al., 2002), during the 'elaboration encoding' of information into episodic memory (Henson et al., 1999; Wagner et al., 1998) and when judgements of word meaning are required (Kapur et al., 1994). In fact, activity in this region has been reported frequently during tasks that appear to make no direct demands on memory at all, including reversal learning (Cools et al., 2002), inhibition (Konishi et al., 1999), extra-dimensional set-shifting (Nakahara et al., 2002; Hampshire and Owen, in press) and task switching (Dove et al., 2000). While each of these tasks has unique requirements that undoubtedly contribute to differences in the overall pattern of activity reported, they all require the self-initiated, conscious (i.e., intentional) selection of appropriate responses, often in the absence of external cues.

Broadly speaking, the findings from lesion studies in the monkey also suggest that the mid-ventrolateral frontal cortex makes a polymodal contribution to a variety of different tasks that require the initiation and execution of intended actions. In the macaque, the mid-ventrolateral frontal cortex lies below the sulcus principalis on the inferior convexity and comprises areas 12 or 47/12 and 45 (Carmicheal and Price, 1994; Petrides and Pandya, 1994). Lesions of the ventrolateral frontal cortex, but not the more dorsal cortex surrounding the sulcus principalis, cause impairments in non-spatial delayed-matching-to-sample for single items (Mishkin and Manning, 1978; Passingham, 1975), spatial and non-spatial delayed alternation (Mishkin et al., 1969), the learning of arbitrary stimulus–response associations (Gaffan, 1994; Petrides, 1994; Murray and Wise, 1997) switching attention to behaviorally relevant aspects of the world (e.g., Dias et al., 1996), and even impair object matching when the sample and the match are simultaneously present and there is no delay component (Rushworth et al., 1997). Thus, once a simultaneous version of the task has been relearned, the imposition of a delay between sample and match poses no more of a problem for a monkey with a ventrolateral frontal lesion than it does prior to surgery (Rushworth et al., 1997). Electrophysiological data from the monkey also support a role for this region in the initiation of a variety of explicit cognitive processes. For example, Sakagami and Niki (1994) trained monkeys to either make or withhold a response depending on which stimulus they were shown. On some blocks of trials, the relevant dimension of the stimulus was its color, on other trials, it was its position or shape. Ventrolateral neurons appeared to encode the stimulus dimension of current interest to the monkey. Similarly, Rao et al. (1997) identified neurons ventral to the principal sulcus, that encoded either, or both, the location and the identity of stimuli presented in a novel delayed response procedure. Remarkably, some neurons adapted flexibly as the emphasis of the task changed during its various stages. Thus, once a target object's identity was no longer relevant many of the 'what-and-where' cells no longer coded for object identity but switched to code for object location. This finding suggests that the response of ventrolateral prefrontal 'memory cells' is flexible, i.e., they can code different stimulus attributes at different times according to task demands. In other words, they will respond to a stimulus, irrespective of its modality and whenever there is an explicit requirement and an associated intention to do so. Finally, Li et al. (1997) taught monkeys a conditional response task and recorded from ventrolateral cells, while they learned to associate each of learned responses with a new cue. Ventrolateral neurons were particularly modulated during the process of learning the selection rule associated with each of the novel stimuli.

In summary, the current results bring together much previous literature and suggest that, in both humans and in non-human primates, the mid-ventrolateral frontal cortex plays a crucial role in intended thoughts and actions. What is less clear is whether the precise cognitive and neural mechanisms by which this involvement occurs can be specified any more clearly, beyond this basic operational description. One likely possibility is that the ventrolateral frontal cortex acts by biasing or 'tuning' attentional processing between competing representations in modality-specific posterior regions in order to maintain their relevance to current behavioral goals. Such a view is anatomically plausible given the strong bidirectional connections between many posterior cortical association areas and the mid-ventrolateral frontal region, which, in turn, is closely interconnected with the entire lateral prefrontal cortex (Petrides, 1994). Moreover, a frontal module with such properties has been proposed recently (O'Reilly et al., 2002; Frank et al., 2004; see also, Dehaene et al., 1998), although in those computational models, the critical region was defined rather more generally as the 'lateral prefrontal cortex'. Flexible tuning of task-relevant variables within the mid-ventrolateral frontal cortex is also consistent with accounts of prefrontal function that emphasize its importance in switching (Cools et al., 2002; Konishi et al., 1999; Nakahara et al., 2002; Dove et al., 2000; Hampshire and Owen, in press) and the 'top–down' modulation of attention (e.g., Owen et al., 1991, 1993; Knight, 1994; Desimone and Duncan, 1995; Dias et al., 1996). Compromising such a function would be expected to affect a wide variety of tasks but particularly any behavior (e.g., an action or a thought), that derives from the subject's plans and intentions (Petrides, 1994).

In this light, the apparent incongruity between the results of neuropsychological investigations in patients and the findings of many functional neuroimaging studies in healthy volunteers can be more clearly understood. For example, many episodic memory tasks can be performed adequately in a number of different ways; on the basis of judgments of relative familiarity or through the willed (i.e., intentional) recollection of encoded information (Jacoby and Dallas, 1981; Mandler, 1980). Information about stimulus familiarity may be sufficient to allow many patients with frontal lobe damage, or more specifically, damage to the mid-ventrolateral frontal cortex, to generate correct responses in the absence of more specific information about the actual content of the remembered information. The common observation that

patients with frontal lobe lesions can perform perfectly well on certain tasks which undoubtedly tap episodic and working memory processes (e.g., Owen et al., 1995; for review, see Wheeler et al., 1995), is entirely consistent with this suggestion. In contrast, an extensive neuropsychological literature from patients with damage to the medial temporal lobe structures confirms that such patients are often impaired at relatively simple memory tasks that can be solved on the basis of stimulus familiarity, including those that require only single item recognition (e.g., Kimura, 1963; Milner, 1968; Owen et al., 1995; Piggott and Milner, 1993). The fact that the mid-ventrolateral frontal cortex and the medial temporal lobe system are commonly co-activated in functional neuroimaging studies suggests that, in healthy volunteers performing at optimal levels, both regions will be recruited routinely for most memory tests, whether or not they are both absolutely necessary for successful performance.

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