

SUSTAINED AND TRANSIENT NEURAL MODULATIONS IN PREFRONTAL CORTEX RELATED TO DECLARATIVE LONG-TERM MEMORY, WORKING MEMORY, AND ATTENTION

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ABSTRACT

Common activations in prefrontal cortex (PFC) during episodic and semantic long-term memory (LTM) tasks have been hypothesized to reflect functional overlap in terms of working memory (WM) and cognitive control. To evaluate a WM account of LTM-general activations, the present study took into consideration that cognitive task performance depends on the dynamic operation of multiple component processes, some of which are stimulus-synchronous and transient in nature; and some that are engaged throughout a task in a sustained fashion. PFC and WM may be implicated in both of these temporally independent components. To elucidate these possibilities we employed mixed blocked/event-related functional magnetic resonance imaging (fMRI) procedures to assess the extent to which sustained or transient activation patterns overlapped across tasks indexing episodic and semantic LTM, attention (ATT), and WM. Within PFC, ventrolateral and medial areas exhibited sustained activity across all tasks, whereas more anterior regions including right frontopolar cortex were commonly engaged in sustained processing during the three memory tasks. These findings do not support a WM account of sustained frontal responses during LTM tasks, but instead suggest that the pattern that was common to all tasks reflects general attentional set/vigilance, and that the shared WM-LTM pattern mediates control processes related to upholding task set. Transient responses during the three memory tasks were assessed relative to ATT to isolate item-specific mnemonic processes and were found to be largely distinct from sustained effects. Task-specific effects were observed for each memory task. In addition, a common item response for all memory tasks involved left dorsolateral PFC (DLPFC). The latter response might be seen as reflecting WM processes during LTM retrieval. Thus, our findings suggest that a WM account of shared PFC recruitment in LTM tasks holds for common transient item-related responses rather than sustained state-related responses that are better seen as reflecting more general attentional/control processes.

Key words: prefrontal cortex, sustained/transient, declarative long-term memory, attention, working memory, cognitive control

Functional neuroimaging of human declarative (episodic and semantic) long-term memory (LTM) has revealed commonalities among recruited brain regions across a wide array of tasks, preferentially involving prefrontal cortex (PFC) (Cabeza and Nyberg, 2000). A hypothesis is that PFC regions similarly engaged in episodic and semantic LTM tasks may be related to working memory (WM) operations and cognitive control processes (Wagner, 1999, 2001). In line with such a proposal, direct comparisons of brain activity associated with LTM and WM tasks have consistently demonstrated overlapping PFC activations (Cabeza and Nyberg, 2000; Braver et al., 2001; Cabeza et al., 2002; Ranganath et al., 2003, 2004, 2005; Nyberg et al., 2003). However, other functional neuroimaging studies have revealed overlap in neural activity between visual attention (ATT) tasks and different memory tasks, i.e. episodic recognition (Cabeza et al., 2003), verbal working memory (Coull et al., 1996; LaBar et al., 1999) and spatial working memory (see Awh and Jonides, 2001 for a review). In particular, a close

relationship has been established between WM and ATT with regard to common fronto-parietal engagement, which implicate shared cognitive mechanisms (Desimone and Duncan, 1995; Awh and Jonides, 2001). Hence, it remains unclear to what extent findings of commonly recruited prefrontal areas during different LTM tasks may reflect WM processes or more basic attentional mechanisms related to maintaining an attentive state of "readiness" throughout task performance.

Previous such cross-function investigations of regional activation similarities have typically relied on *either* blocked or event-related paradigms that provide measures of task-induced activity that differ regarding the timescale of the neural responses they account for. Mixed designs that *combine* blocked and event-related functional magnetic resonance imaging (fMRI) procedures can dissociate the relative contributions of temporally independent neural modulations (Düzel et al., 1999; Donaldson and Buckner, 2001; Visscher et al., 2003), by separating responses that are sustained throughout the task from responses that are

transient in nature (i.e., stimulus-synchronous) (c.f., Düzel et al., 1999).

Sustained responses are thought to subserve state-related processing, putatively induced by task instructions to direct behaviour in a context-relevant manner during the entire task. Two key component processes that may elicit sustained neural modulations are top-down attentional biasing and cognitive control. First, some sustained responses likely support the maintenance of an enhanced level of alertness and attentional focus throughout task performance (Posner and Petersen, 1990; Coull, 1998). Second, certain processes such as maintaining the relevant task set is likely shared by many cognitive tasks (Wagner, 2001; Braver and Barch, 2002), and such processes may be termed task-general WM processes.

Transient responses reflect mechanisms that support item-related processing *per se*. Item processes may involve components such as stimulus coding, retrieval control during memory search (Wagner, 2001; Buckner, 2003), response selection (Thompson-Schill et al., 1999) as well as motor execution.

Common prefrontal activations may reflect either sustained or transient neural responses. Here we used “mixed” event-related/blocked fMRI procedures to index sustained and transient blood-oxygen-level-dependent (BOLD) signal changes during four cognitive tasks, episodic yes/no recognition, semantic classification, 2-back WM, and sustained ATT. For sustained brain activity, a primary aim was to investigate whether state-related responses would generalize across episodic and semantic LTM tasks. Furthermore, in an attempt to examine the presumably shared cognitive mechanisms underlying overlapping sustained responses, we conducted additional analyses of regions exhibiting common sustained activity during the LTM tasks in relation to sustained responses elicited during WM and ATT tasks. Patterns of sustained activity increases common to all tasks might reflect general attentional processes. Sustained activity associated with the LTM and WM tasks, but not the ATT task, might reflect task set and preparatory processes to ensure context-appropriate processing once a stimulus item is presented. Moreover, some sustained responses were expected to differentiate WM and ATT from LTM tasks because the latter required no item processing in-between test items (inter-stimulus intervals – ISIs – varying between 3-24 sec), whereas active on-line processing was continuously required during the ATT and WM tasks.

For transient brain activity, the LTM and WM tasks were contrasted with the ATT task to isolate item-specific mnemonic processes from visual and motor activity. We expected some transient frontal responses to generalize across all memory tasks, including dorsolateral PFC (DLPFC) activity

(Courtney et al., 1997; Cabeza et al., 2002). Other frontal responses were expected to be recruited in a task-specific manner; with differential activity in right ventrolateral PFC (VLPFC) for episodic memory, left VLPFC for semantic memory, and premotor cortex for WM (Nyberg et al., 2002).

MATERIALS AND METHODS

Subjects

Fourteen healthy adults volunteered to participate in the experiment, one of which had to be excluded from further analysis due to technical problems with the data acquisition. Of the remaining 13 subjects (5 male, 8 female; mean age: 28 years, range: 22-41 years), the behavioural data from one subject was incomplete, with only three out of four functional sessions completed. This subject was included in all statistical analyses, except for region of interest (ROI) time course analyses. Thus, the random-effects analyses were based on 13 subjects, and the ROI time course analyses were based on 12 subjects. Subjects gave written informed consent. All were right-handed and had normal or corrected-to-normal visual acuity. None of the subjects had a history of neurological or psychiatric illness. The study was approved by the local ethics committee at the Karolinska Hospital.

Task Procedures

Before the subjects were placed in the scanner, they were presented with a study list of 40 words with the instruction to memorize as many as possible during two successive presentations of the same list (2.5 sec/word). For each subject, 12 of the studied words were randomly chosen as targets for the subsequent recognition tests in the scanner. Subjects were given instructions regarding all task procedures and performed a short pre-scan practice run to ensure that task instructions were properly understood.

Each of the four functional runs included four task conditions, each represented in task blocks of 90 sec. The task blocks were separated by resting blocks (25 sec) during which subjects were instructed to rest while fixating a small circle that was constantly displayed at the centre of the screen. Functional runs were initialized after the presentation of a visual prompt (10 sec), followed by another visual prompt (2.5 sec) instructing the subjects to “REST”, and subsequently the small circle was shown for 25 sec. After this initial rest period, the first task was initiated by the presentation of a visual prompt (2.5 sec) that informed subjects of which task was to be performed (Figure 1). The prompts initializing respective task were: RECOGNITION (episodic

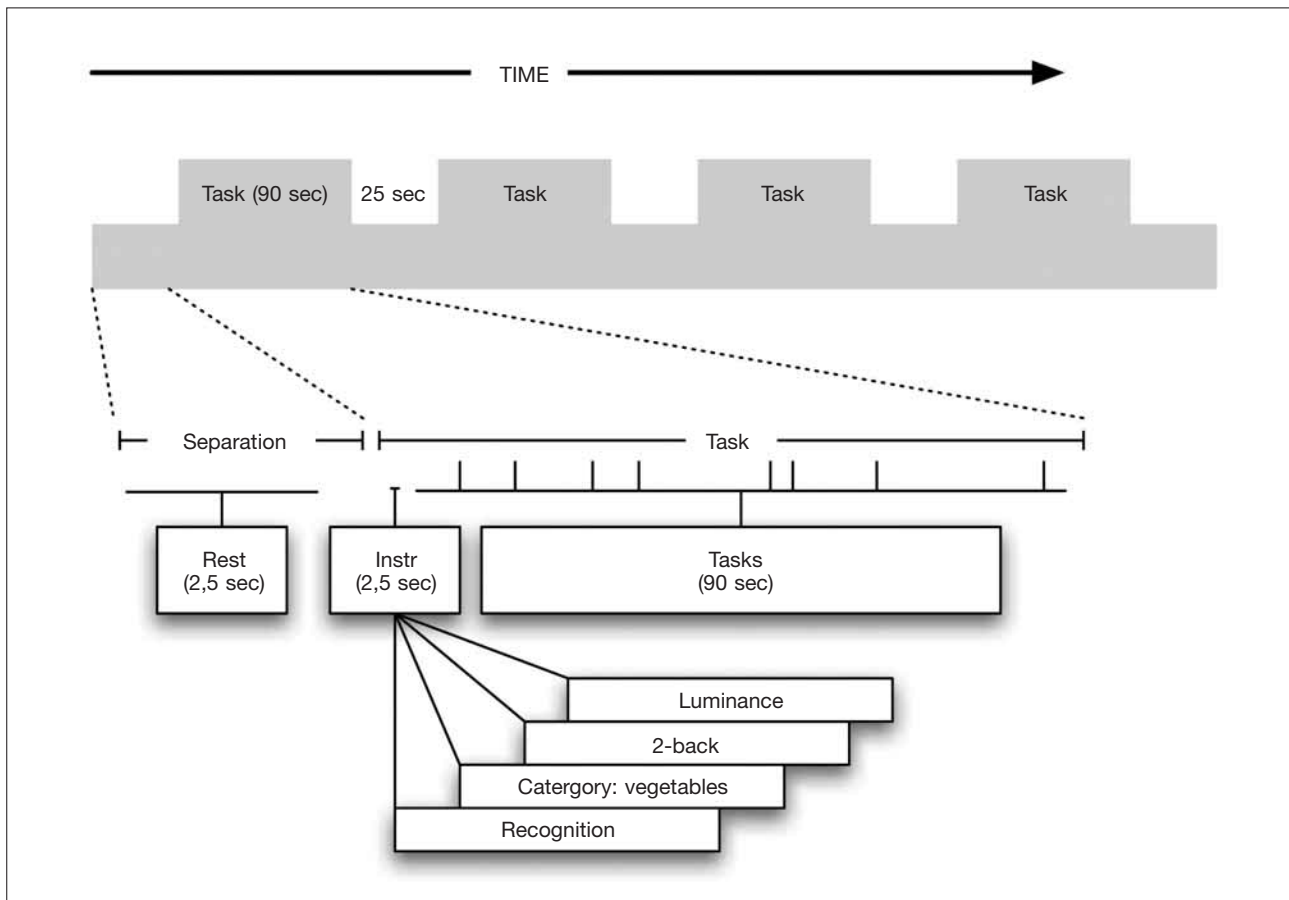


Fig. 1 – Schematic illustration of the mixed blocked/event-related functional magnetic resonance imaging (fMRI) paradigm used in the present study. In each functional run, the four task blocks were separated by resting blocks. A task instruction initiated each task block, within which individual items were intermixed with fixation gaps of varying time duration.

task), CATEGORY, and the specific category target, e.g. VEGETABLES (semantic categorization task), 2-BACK (WM task), and LUMINANCE (ATT task). The order of the four task conditions within each functional run was counterbalanced across runs within subjects and across subjects. Task conditions were also counterbalanced across subjects such that each condition followed every other condition equally often.

The visual stimuli (black letters on white background) were presented using the ERTS software (J. Beringer, BeriSoft Cooperation, Frankfurt, Germany, 1987) and projected onto a screen positioned at the foot end of the scanner bore. Subjects comfortably viewed the screen through a mirror attached to the head coil. An MRI-compatible response box was attached to the right-hand of the subjects and used to record task performance (reaction times – RT – and accuracy).

Experimental Tasks

The study included four conditions: episodic LTM retrieval, semantic LTM retrieval, WM, and sustained ATT. The tasks used identical stimuli (visual presentation of single words), with the exception of the sustained ATT task (which included a single letter string). Across memory

tasks, each task block included 8 individual items, each presented for 2.5 sec in a jittered manner. Word items were intermixed with a fixation cross-hair at the centre of the screen of pseudorandom duration. The cross-hair was continuously displayed throughout each task condition, with single words shown just below. Task conditions were identical with respect to behavioural response (key-press ‘yes/no’), except for the ATT task (key-press ‘yes’ only). The item-type ratio in the memory tasks was 3/8 for trials requiring a “yes”-response and 5/8 for trials requiring a “no”-response. This disproportionate relation between items was due to the particular nature of 2-back paradigms, where the two first items by necessity produce “no”-responses. The ATT task required subjects to respond “yes” at each of eight instances of target detection (see below).

For the episodic retrieval task, we used a “yes/no” recognition paradigm that required subjects to press a specified “yes” button with the index finger of the right hand each time they recognized the presented word as “old” (i.e., part of a pre-scan study list), and to press a specified “no” button with the ring finger of the right hand to indicate that the word was “new” (i.e., not part of the pre-scan study list). To assess semantic retrieval we used a category classification task. The

task required subjects to decide whether each presented word was a subordinate concept of a specific target category or not (the category-instance used as target was visually presented at the start of a semantic task block). Subjects were instructed to press “yes” each time they identified a word as a subordinate of the target category and to press “no” if the word did not fit the category. Different category instances were used for each of the four semantic task blocks. The non-category words used were members of a single category semantically close to the target category (e.g., fruit vs. vegetables). For the WM condition a 2-back task paradigm was used (Kirchner, 1958). Subjects were instructed to press “yes” each time they thought the presented word was the same as the word presented two items earlier in the sequence, and to press “no” each time it was not. We used a vigilance paradigm (Mackworth, 1957) to assess sustained ATT, during which subjects were instructed to maintain focal ATT at six black lettered X’s in a row (XXXXXX) that were continuously displayed for the duration of the task. At jittered intervals the luminance of the stimulus was slightly dimmed for 400 msec and the subjects were required to press a button with the index finger each time they perceived a stimulus dimming. This stimulus change occurred 8 times in each ATT task block. By using a very subtle change in luminance, the sustained attention/vigilance demand was kept high.

MR Image Acquisition

Structural T1-weighted images (TR/TE/flip = 24 msec/6 msec/35°, $.9 \times 1.5 \times .9$ mm³ voxel size) and functional echo-planar images (pixel size = 3.4×3.4 mm², TE = 40 msec) with BOLD contrast were acquired on a General Electric Signa Echo Speed 1.5T MR scanner. Each echo-planar image volume comprised 25 slices (thickness = 5 mm, slice gap = .5 mm) covering the whole brain except for the most inferior part of the cerebellum. The echo-planar image acquisition sessions consisted of 194 volumes acquired continuously with a repetition time (TR) of 2.5 sec. Four sessions were performed in each subject and each session was preceded by four “dummy” scans to allow for T1 equilibrium effects. The duration of each functional run was 8 min and 5 sec. Four runs were acquired per subject with 5-10 minutes in between.

Data Analysis

Behavioural task performance was analyzed to assess differences in difficulty across the four task conditions by considering accuracy and RT measures.

Functional imaging data were pre-processed in several steps prior to statistical analyses using the

SPM99 software package (<http://www.fil.ion.ucl.ac.uk/spm/spm99.html>). Image realignment to the first volume was performed using a truncated sinc interpolation. Subsequent to realignment, all image volumes were corrected for variability in slice timing acquisition, normalized to an approximate Talairach space (Talairach and Tournoux, 1988) as defined by the SPM99 T1-weighted MNI template, and finally smoothed with an isotropic 10-mm, full-width, half-maximum (FWHM) Gaussian kernel.

In mixed blocked/event-related designs the regressors modelling item-related responses will invariably be correlated to some degree with their corresponding state-related regressors. A high degree of correlation implies a low parameter estimation efficiency (Otten et al., 2002; Visscher et al., 2003). In this study, we sought to minimize the degree of correlation between item and state regressors by introducing a jittering of the intervals between consecutive items within each state block. The ISIs were pseudorandomized between 3 and 28 sec according to an approximate Poisson distribution (i.e., for 61% of the items, the ISI was 3 sec, for 30% of the items, the ISI was 15 sec, and only for a minority of items, ISIs were 20-25 sec long) such that the correlation between item and state-related regressors did not exceed .6. This degree of correlation allows a reasonably efficient estimation of item- and state-related activity, while at the same time not compromising the test properties.

Sustained and transient effects were separately modelled in the framework of the general linear model (GLM) (Friston et al., 1995) as implemented in SPM. In detail, item-related transient responses were modelled as regressors containing delta functions representing onset of stimulus whereas state-related sustained responses were modelled with a boxcar function (Friston et al., 1998). For the ATT task, the item regressor represented the onsets of the luminance change, the duration of which matched that of stimulus presentations in the memory tasks. Both regressor-types were convolved with a canonical hemodynamic response function. All data were low-pass filtered (temporal Gaussian kernel, FWHM = 4 sec) as well as high-pass filtered (cut-off frequency = .002 Hz) by including low frequency regressors in the GLM as covariates of no interest.

Applying the GLM to the data resulted in least square estimates of all regressors on a subject-specific level averaged across the four sessions. Effects of interest were calculated as linear combinations of the individual regressors and stored as subject-specific contrast images. All statistical inferences were based on contrast images (statistical parametrical maps, SPMs) from all thirteen subjects that were entered into a second-level model (one sample t-tests) for each effect of interest, yielding a random effects analysis (Holmes and Friston, 1998).

SPMs were generated for both sustained (state) and transient (item) neural activity changes in all task conditions. Statistically significant BOLD signal changes were identified for each task condition relative to rest (sustained effects) and relative to ATT (transient effects). For the transient effects different item response-types (i.e., hits, misses, correct rejections, and false alarms) were collapsed within each task condition and analyzed together. Unless otherwise specified, the False Discovery Rate (FDR) correction for multiple comparisons (Genovese et al., 2002), thresholded at $p < .05$, was used, and extent threshold was set to 8 voxels. To identify common responses across sets of task conditions, we performed conjunction analyses (Friston et al., 2005; Nichols et al., 2005) using a threshold of $p < .001$ uncorrected. This method, referred to as “the Minimum Statistic compared to the Conjunction Null” (Nichols et al., 2005), differs from prior methods of conjunction analysis by asserting that all contrasts involved were individually significant at the predefined threshold. The analytical strategy for common sustained effects was to identify activated regions for the LTM tasks, and then relate these to WM and/or ATT. First, a conjunction was performed on the semantic and episodic LTM tasks. Next, the resulting activation map was used to formally assess the relative degree of overlapping sustained activity across tasks. Centred at each peak coordinate identified from the LTM conjunction, a sphere with an 8-mm radius was created. Within each of these common LTM regions we examined the magnitude of sustained activity elicited during the WM and ATT task, respectively (reported peak activations were thresholded at $p < .05$ FDR corrected). In addition, a small volume correction (SVC) procedure was used to formally identify the number of activated voxels within an 8 mm sphere (comprising 257 voxels) of the peak foci of the LTM conjunction with respect to the WM and ATT tasks (a threshold of $p < .05$ FDR corrected was used for identification of voxels activated above baseline). For the assessment of transient effects relative to ATT, each activation map was inclusively masked with the main effect of corresponding memory condition relative to baseline, thresholded at $p < .001$ uncorrected, in order to ensure that task-induced transient increases were not caused by relative decreases during the ATT task. For common memory-related transient effects, we performed a conjunction of the three memory tasks relative to ATT, and inclusively masked the overall activation map with the main effect of each memory task relative to baseline, thresholded at $p < .001$ uncorrected. To illustrate the temporal profiles of sustained and transient activity changes, time course data was extracted, averaged across individuals and plotted for a number of relevant regions (8-mm-radius-spheres centred at peak foci) that were identified from selected contrasts.

RESULTS

Behavioural Data

Accuracy across the four tasks was consistently high, and ranged from .85, SD = .11 (episodic task) to .98, SD = .03 (ATT task). In general, performance was less accurate on the LTM tasks (semantic task: .87, SD = .07) than the WM (.96, SD = .05) and ATT tasks. A repeated-measures analysis of variance (ANOVA) of the accuracy data revealed that the differences were significant [$F(3, 12) = 14.5$; $p < .001$]. Pairwise *post-hoc* comparisons showed that subjects performed significantly worse on the semantic task relative to ATT ($p < .001$) and WM ($p < .001$), respectively. The episodic task was also associated with significantly less accurate performance relative to ATT ($p < .007$) and WM ($p < .015$). There was no difference in accuracy between the two LTM tasks. Performance accuracy was also equivalent between the ATT task and the WM task. An ANOVA on mean RTs revealed significant differences between the tasks [$F(3, 12) = 52.6$; $p < .001$]. The fastest RTs were produced during the WM task, which was associated with a significantly faster response than all other tasks (mean = 1215 msec, SD = 514, all pairwise *post-hoc* comparisons relative WM yielded p values $< .001$), whereas the ATT task was associated with a reliably slower response as compared to all other tasks (mean = 1592 msec, SD = 159 msec, all pairwise *post-hoc* comparisons relative ATT showed p values $< .001$). RTs did not differ between the episodic and semantic memory tasks (episodic task: mean = 1370 msec, SD = 468 msec; semantic task: mean = 1418 msec, SD = 485 msec, $p = .7$).

Neuroimaging Data

Blocked and event-related fMRI signal change was used to examine sustained and transient neural responses associated with episodic memory, semantic memory, WM, and sustained ATT. Positive, as well as negative BOLD signal changes (relative to resting baseline for sustained responses and relative to ATT for transient responses) are reported in separate sections.

Sustained BOLD Increases

Brain regions associated with sustained processing in each task are shown in Figures 2a-2d and peak foci are listed in Table I. As can be seen from Figure 2, the activity pattern was quite similar for the LTM tasks, albeit with more extensive activation for semantic memory. Direct contrasts showed that there were no significant differences between episodic and semantic memory tasks ($p > .05$). A conjunction analysis, where the resulting activation map was inclusively masked

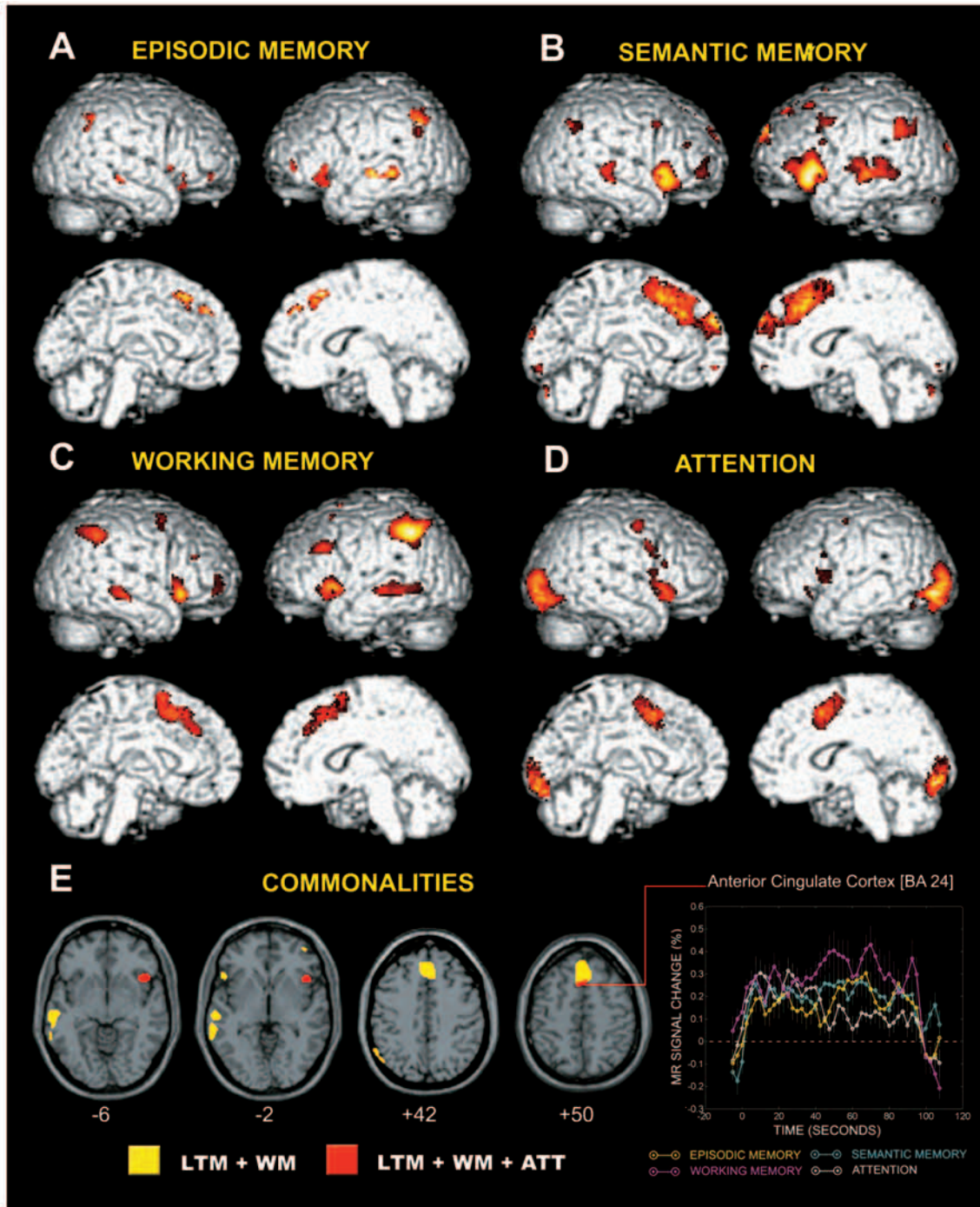


Fig. 2 – Sustained response increases during (a) episodic memory, (b) semantic memory, (c) working memory, and (d) attention, relative to baseline. Statistical parametric maps are superimposed on lateral and medial rendered views of the brain (for coordinates see Table I). Figure 2a was thresholded at $p < .001$ uncorrected; Figures 2b-2d were thresholded at $p < .05$ false discovery rate (FDR) corrected, extent threshold $a-d > 8$ voxels. (e) To visualize the overlaps in sustained activity between long-term memory (LTM), working memory (WM) and attention (ATT), we performed conjunction analyses of the LTM tasks and the main effects of WM and ATT, respectively (thresholded at $p < .001$ uncorrected). Overlapping sustained response increases for episodic and semantic LTM, WM, and ATT are mapped on horizontal sections of a canonical brain (z-coordinates are given for each section). Yellow areas denote regions that showed significant sustained increases across both LTM and WM tasks, but not ATT. Red areas indicate regions that were associated with significant sustained increases across all four tasks including ATT (for coordinates, see Table II). Average time course is depicted for a common dorsal anterior cingulate cortex (ACC)/pre-supplementary motor area (pre-SMA) region (MNI-coordinates; $x = 2, y = 24, z = 50$).

with both LTM main effects, showed that overlapping activity increases were located in several distinct PFC subregions including bilateral mid-VLPFC (BA 47/45), frontopolar cortex (BA

10) and medial PFC including the pre-supplementary motor area (pre-SMA) (BA 6) and a caudal portion of the dorsal anterior cingulate cortex (ACC) (BA 32). In addition, regions in

TABLE 1
Brain regions showing sustained neural response increases relative to baseline for semantic memory, episodic memory, working memory, and attention

Episodic memory		Semantic memory		Working memory		Attention	
Region	BA	MNI	Region	BA	MNI	Region	BA
	x	y	z	x	y	z	t
<i>Frontal cortex</i>							
Medial frontal gyrus/ACC/pre-SMA	8/6/32	2	26	47	5.47	Medial frontal gyrus/ACC/pre-SMA	8/32
L Inferior frontal gyrus	9	6	48	31	4.44	Dorsomedial frontal gyrus	9/10
L Anterior middle frontal gyrus	47	-49	25	-10	5.39	Ventromedial frontal gyrus	11
R Inferior frontal gyrus	10/44	-48	45	0	5.19	L Inferior frontal gyrus	47/45
R Frontal operculum/Insula	45	53	14	3	5.66		44/45
R Anterior middle frontal gyrus	47	34	25	-11	4.69	L Superior frontal gyrus	8
	47/10	46	48	-7	4.23	L Middle frontal gyrus	9
<i>Temporal cortex</i>							
L Middle temporal gyrus	21	-65	-35	-2	6.22	R Inferior frontal gyrus	47
L Superior temporal gyrus	38	-46	19	-13	5.43	R Middle frontal gyrus	9
R Middle temporal gyrus	21	55	-29	-4	4.37		46
<i>Working memory</i>							
<i>Frontal cortex</i>							
Medial frontal gyrus/ACC/pre-SMA	6/32	-8	10	46	7.07	R Anterior middle frontal gyrus	10/47
L Middle frontal gyrus	8	-4	31	35	5.37		9/10
L Inferior frontal gyrus	6/8	-51	27	28	7.84		21
R Inferior frontal gyrus	47	-32	18	53	4.06		22
R Middle frontal gyrus	47/45	-48	13	-2	7.39		22
	6	44	21	-8	7.31		40
	46	34	11	55	4.39		40
	10	46	34	20	4.17		19
		38	56	-4	4.76		18
<i>Temporal Cortex</i>							
L Superior temporal gyrus	22	-55	8	-2	6.86		17/18
L Middle temporal gyrus	21	-61	-41	-3	6.63		19
R Middle temporal gyrus	21	51	-31	-2	5.96		18
<i>Parietal cortex</i>							
L Inferior parietal lobule	40	-46	-48	47	7.93		19
L Superior parietal lobule	7	-38	-61	53	6.35		18
R Inferior parietal lobule	40	46	-46	43	5.59		17/18
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TABLE II
Brain regions showing overlapping sustained response increases relative to baseline across semantic and episodic long-term memory tasks, and responses during working memory and attention within an 8 mm radius from long-term memory foci

Region	BA			LTM			t*			Working memory						Attention								
	x	y	z	x	y	z	x	y	z	x	y	z	t	P	K	SVC	x	y	z	t	P	K	SVC	
<i>Frontal cortex</i>																								
Medial frontal gyrus/ACC/pre-SMA	8/6/32	2	34	38	6.78	-2	34	36	5.24	.002	109	-	-	-	-	-	-	18	50	3.93	-	-	-	-
	6/32	4	24	50	6.76	8	22	48	4.76	.000	188	-	-	-	-	-	4	18	-	-	-	-	-	8
L Inferior frontal gyrus	47/45	-52	20	0	5.93	-48	14	-2	7.39	.001	159	-	-	-	-	-	-	-	-	-	-	-	-	-
	47	-48	22	-8	5.76	-48	14	-2	7.39	.002	118	-	-	-	-	-	-	-	-	-	-	-	-	-
R Inferior frontal gyrus	47	50	16	0	5.70	44	22	-8	7.31	.003	89	-	-	-	-	-	52	18	-6	5.01	.001	139	-	
	47	44	18	-10	5.58	44	22	-8	7.31	.001	122	-	-	-	-	-	42	20	-6	5.32	.001	128	-	
R Middle frontal gyrus	10/47	44	54	-2	4.24	44	54	-2	4.28	.007	44	-	-	-	-	-	-	-	-	-	-	-	-	-
	10/46	42	54	8	3.80	42	54	6	4.50	.011	28	-	-	-	-	-	-	-	-	-	-	-	-	-
<i>Temporal cortex</i>																								
L Middle temporal gyrus	21	-64	-46	-4	5.99	-62	-42	-6	6.63	.002	100	-	-	-	-	-	-	-	-	-	-	-	-	-
	21	-66	-34	-4	5.26	-66	-34	-4	5.19	.002	101	-	-	-	-	-	-	-	-	-	-	-	-	-
	21	-64	-24	-6	5.00	-64	-24	-6	3.87	.005	61	-	-	-	-	-	-	-	-	-	-	-	-	-
<i>Parietal Cortex</i>																								
L Supramarginal gyrus	40/39	-60	-60	32	4.69	-60	-58	32	3.82	.010	29	-	-	-	-	-	-	-	-	-	-	-	-	-
L Inferior parietal lobule	40	-50	-68	40	4.01	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

Note. Coordinates are in MNI space. ACC = anterior cingulate cortex; pre-SMA = pre-supplementary motor area; BA = approximate Brodmann's area; LTM = long-term memory. Asterisk after t denote averaged t-value across episodic and semantic tasks. SVC = small volume correction analyses; P = cluster-level p-values and K = no. of significant voxels within 8 mm-spheres (= 257 voxels) centered at common LTM peak foci. Activation threshold $p < .001$ uncorrected for the LTM conjunction, and $p < .05$ FDR corrected for working memory and attention, respectively, extent threshold = 8 voxels.

temporal and parietal cortex exhibited LTM-general sustained increases (Table II). The findings of state-related frontal engagement corroborate previous findings of sustained activity patterns in studies using mixed blocked/event-related fMRI designs (Donaldson et al., 2001; Burgund et al., 2003; Velanova et al., 2003), which have shown state-related activity increases in very similar structures.

The coordinates from the conjunction analysis of the LTM tasks were used to create 8-mm-spheres surrounding the peak foci to examine whether these regions also were activated during the WM and ATT tasks. This analysis showed that most of the regions associated with LTM were also engaged during the WM task (Table II). A subset of the frontal regions that were commonly activated for the LTM and WM tasks were also activated during the ATT task (Table II) (Figure 2e). These were located in right VLPFC and ACC/pre-SMA and shared a similar sustained activation profile (Figure 2e). Conversely, none of the memory-general regions located in posterior cortices were significantly activated in the ATT task.

Conjunction analyses were done to verify the above results of task commonalities. For the analysis of common regions across all four tasks as well as the analysis of regions that were engaged during the memory tasks but not the ATT task, consistent results were obtained. The only exception was that the conjunction analysis suggested that the left VLPFC region was commonly engaged during all four tasks and not specific to the memory tasks.

Sustained BOLD Signal Decreases

Brain regions showing relative decreases in sustained BOLD responses (or state-related deactivations) compared with rest, are presented in Figures 3a-3d. As can be seen, the pattern varied substantially across conditions with only a few significant decreases for the LTM tasks, whereas extended decreases were noted for the WM and ATT tasks, involving practically the whole brain. For both the WM and ATT task, the strongest decreases were located in posterior brain areas.

To investigate commonalities in sustained activity decreases across all task conditions we conducted a conjunction analysis for all main effects relative to baseline, where we inclusively masked the resulting overall deactivation pattern with each main effect. Overlapping decreases were found in medial posterior cortices in the vicinity of the parieto-occipital sulcus, including the cuneus, precuneus and the occipital gyrus, as well as the posterior cingulate gyrus (Figure 3e). These findings converge with numerous previous studies that have reported similar task-induced decreases relative to low-level baselines (Shulman et al., 1997; McKiernan et al., 2003).

Transient BOLD Signal Changes

Figures 4a-4c and Table III shows transient activity increases for the LTM and WM tasks relative to ATT. Distinct increases were seen in regions that previously have been associated with these forms of memory. The episodic memory task was associated with increased activity in right VLPFC (BA 47) and left middle temporal cortex (BA 21) extending into medial portions of the temporal lobe (Figure 4a). The semantic memory task was associated with increases in left VLPFC (BA 45) and left lateral occipito-temporal cortex (Figure 4b). The transient activation pattern for the WM task included distinct increases in left DLPFC (BA 9), right premotor (BA 6), and medial parietal cortex (BA 7) (Figure 4c). A conjunction of the LTM and WM tasks relative to ATT, inclusively masked with the main effect of each memory task *versus* baseline, revealed that common transient increases were located in several discrete regions (see Figure 4d), including left posterior DLPFC in the middle frontal gyrus near the inferior frontal junction rostral to the precentral gyrus (BA 44/9), a small area in left VLPFC (BA 47), and left superior parietal cortex (BA 7) (for coordinates see the figure captions to Figure 4d).

Transient decreases relative to the ATT condition were seen for all tasks, showing the most pronounced effects for the WM task, including several posterior visual regions. As transient decreases were not of primary concern for the present purposes, these results will not be further discussed.

DISCUSSION

A mixed blocked/event-related fMRI design was used to dissociate sustained and transient responses associated with four different cognitive tasks. For the state-related component, a primary goal was to compare common patterns of sustained neural activation during episodic and semantic LTM tasks with that of WM and ATT. Across all four tasks right VLPFC (BA 47) and medial PFC (BA 6/32) demonstrated sustained recruitment. The engagement of these regions during the attention/vigilance task and during ISIs in the three memory tasks could relate to the apprehension of upcoming events and the operation of a common ATT network (Pashler et al., 2001). Vigilance typically activate right frontal areas (Cohen et al., 1988; Pardo et al., 1991). Right VLPFC and ACC/pre-SMA have been associated with task preparation and ATT in cueing paradigms (Gitelman et al., 1999; Luks et al., 2002; Brass and von Cramon, 2002; Curtis et al., 2004), and ACC is typically considered as part of an anterior attentional network (Posner and Petersen, 1990). Here it should be noted, though, that the

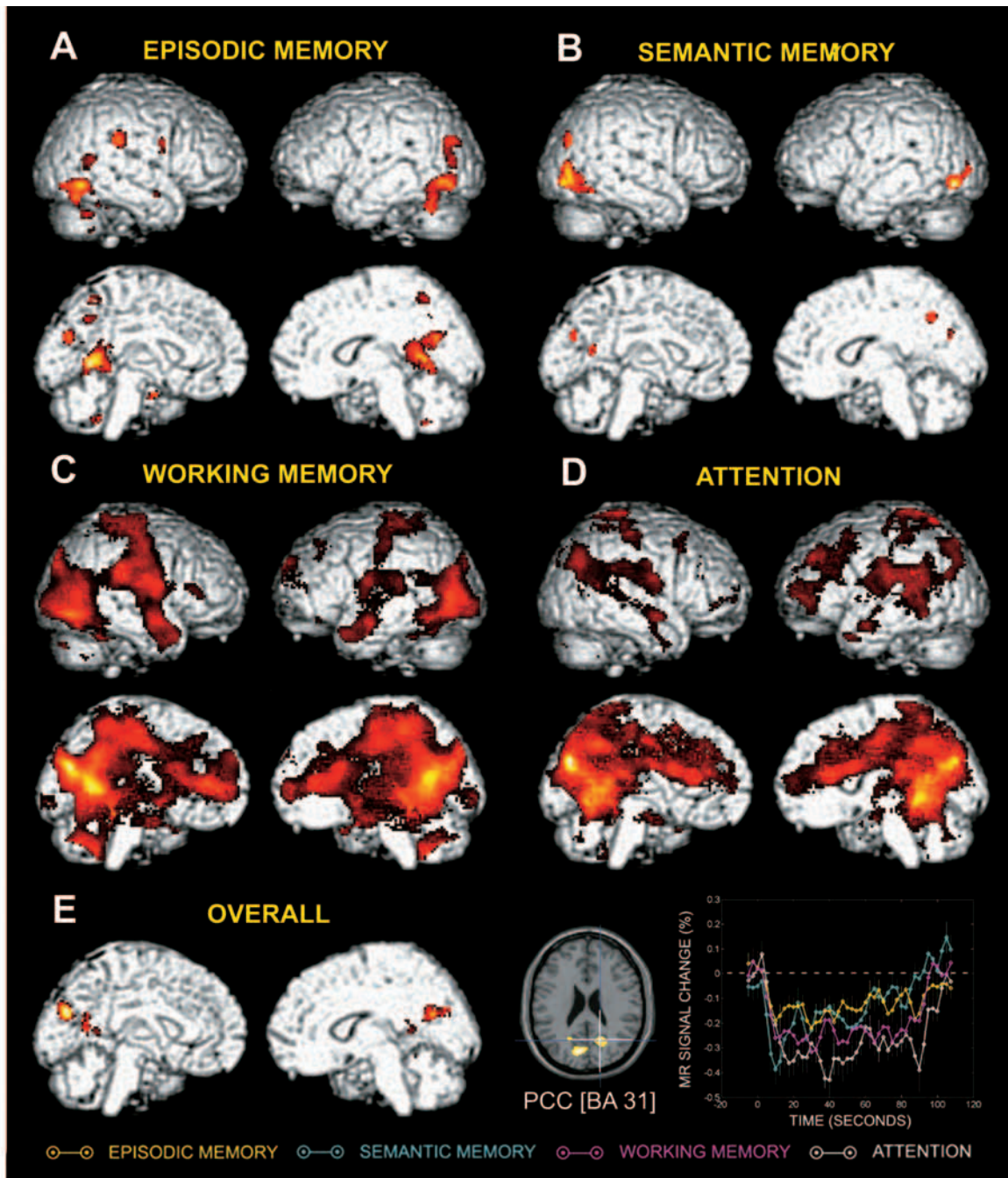


Fig. 3 – (a) Regions associated with sustained response decreases during episodic memory relative to baseline included bilateral posterior cingulate gyrus (BA 29/30/23, MNI-coordinates: x, y, z ; $-10, -48, 10$ and $8, -44, 17$), right lingual gyrus (BA 19; $22, -60, -2$), right fusiform gyrus (BA 18; $38, -68, -20$), bilateral middle occipital gyrus (BA 19; $-46, -66, -8$ and $50, -62, -10$), left parahippocampal gyrus (BA 34; $-30, -2, -26$), left middle temporal gyrus (BA 39; $-42, -76, 28$), right superior temporal gyrus (BA 22; $56, -56, 12$), right middle temporal gyrus (BA 21; $60, 0, -18$), right inferior parietal cortex (BA 40; $68, -32, 30$), precuneus (BA 7; $-6, -58, 38$), right inferior frontal gyrus/precentral gyrus (BA 44/6; $48, 4, 26$) and bilateral cerebellum ($-38, -58, -28$ and $30, -54, -46$). (b) Sustained response decreases during semantic memory relative to baseline were observed in bilateral middle occipital gyrus (BA 19/37; $-36, -74, -10$ and $38, -70, -10$), precuneus (BA 7; $16, -58, 42$ and BA 18; $-2, -74, 26$) and left posterior cingulate gyrus (BA 23; $-18, -58, 14$). (c) Sustained response decreases during WM relative to baseline were observed in the parieto-occipital sulcus/precuneus (BA 18; $-8, -74, 24$), left posterior cingulate gyrus (BA 29/30; $-12, -50, 8$), left parahippocampal gyrus (BA 35/36; $-28, -36, -14$), left inferior frontal gyrus (BA 11/47; $-40, 34, -16$), bilateral cerebellum ($-12, -54, -46$ and $12, -54, -48$), ACC (BA 24/32; $-4, 38, 12$), left precentral gyrus (BA 6; $-60, -2, 12$), left postcentral gyrus (BA 3/1; $-46, -20, 60$) and right posterior cingulate gyrus (BA 23; $10, -24, 23$). (d) Sustained response decreases associated with attention relative to baseline were found in left parieto-occipital sulcus (BA 18/19; $-6, -78, 28$), left middle temporal gyrus (BA 39; $-30, -60, 10$), left superior temporal gyrus (BA 21/38; $-40, 10, -30$), bilateral cerebellum ($-18, -50, -42$ and $26, -50, -42$), right parahippocampal gyrus (BA 28; $-16, -14, -14$), bilateral precentral gyrus (BA 4; $-16, -34, 74$ and $20, -30, 74$), right postcentral gyrus (BA 3/1; $26, -40, 74$), bilateral parietal cortex (BA 7; $-16, -58, 68$ and $14, -52, 72$), bilateral hippocampus ($-36, -18, -16$ and $44, -6, -22$) and left middle temporal gyrus ($-56, 0, -18$). Figures 3a, 3c, 3d were thresholded at $p < .05$ false discovery rate (FDR) corrected, Figure 3b was thresholded at $p < .001$ uncorrected, extent threshold > 8 voxels. (e) Overlapping sustained decreases common to all tasks relative to baseline were observed in the parieto-occipital sulcus/precuneus/cuneus (BA 18/19), bilateral precuneus/posterior cingulate gyrus (BA 31 and BA 30/29). Common sustained decreases were revealed by a conjunction analysis for all main effects relative to baseline ($p < .05$ FWE corrected), where the overall deactivation pattern was inclusively masked with each main effect (thresholded at $p < .001$ uncorrected), extent threshold > 8 voxels. Time courses are shown for an area in posterior cingulate cortex (PCC, BA 31; MNI-coordinates: x, y, z ; $18, -62, 24$).

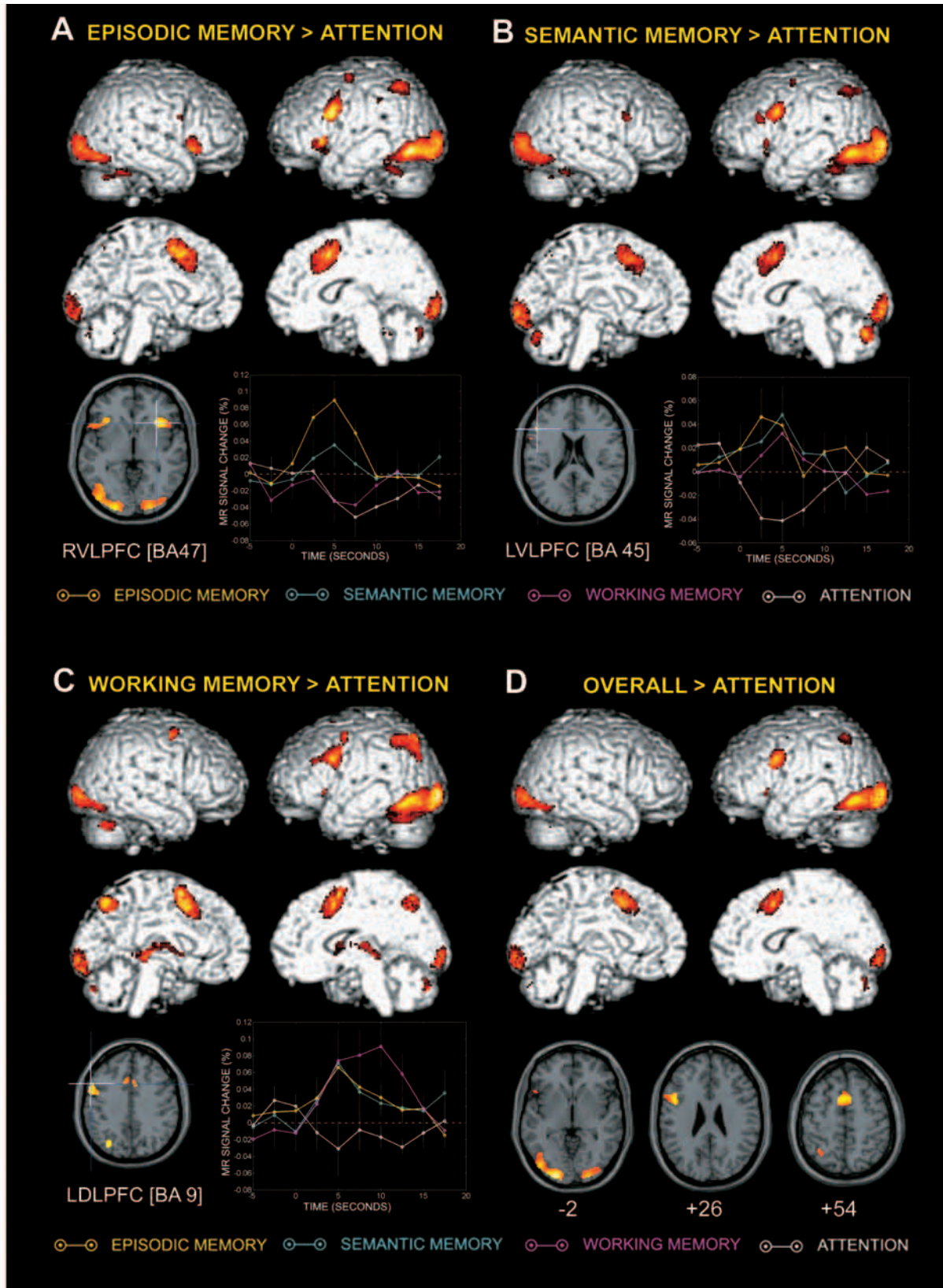


Fig. 4 – (a) Transient response increases for episodic memory relative to attention. Time courses depicted for the right inferior frontal gyrus (BA 47; MNI-coordinates: x, y, z; 32, 20, -2). (b) Transient response increases for semantic memory as compared to attention. Time courses plotted for a left inferior frontal region (BA 45; -48, 22, 20). (c) Transient response increases for working memory as compared to attention. Time courses plotted for a left middle frontal region (BA 9; -54, 14, 38). All activations were thresholded at $p < .05$ false discovery rate (FDR) corrected relative to the attention condition, and inclusively masked with the main effect of the corresponding memory condition relative to baseline, thresholded at $p < .001$ uncorrected, extent threshold > 8 voxels. For coordinates see Table III. (d) Overlapping transient response increases across all memory tasks relative to attention were found in bilateral middle occipital gyrus (BA 19; -42, -68, -10 and 40, -72, -12) and cuneus (BA 18; -24, -96, 0 and 24, -94, 0), anterior cingulate cortex (ACC)/pre-supplementary motor area (pre-SMA) (BA 32/6; -4, 8, 52), left inferior/middle frontal gyrus (BA 44; -46, 6, 30, and BA 44/9; -44, 16, 26), left superior parietal cortex (BA 7; -32, -58, 50), medial cerebellum (6, -80, -34) and left inferior frontal gyrus (BA 47; -50, 18, 2). Activations are overlaid on horizontal sections of a canonical brain (z-coordinates are given for each section).

TABLE III
Brain regions showing transient neural response increases relative to attention for episodic memory, semantic memory, and working memory

Episodic memory	BA	MNI			
		x	y	z	t
<i>Frontal cortex</i>					
Medial frontal gyrus/ACC/pre-SMA	6/32	10	10	48	7.99
	6	-6	6	54	7.78
L Frontal operculum/Insula	47	-32	26	-2	5.93
L Inferior frontal gyrus	47	-46	18	2	5.37
L Middle frontal gyrus	44	-46	8	28	7.89
	45	-42	18	22	7.11
L Middle frontal/Precentral gyrus	6/4	-28	-8	62	3.81
R Frontal operculum/Insula	47	32	20	-2	8.75
R Middle frontal gyrus	44	48	8	26	3.44
<i>Temporal cortex</i>					
R Fusiform gyrus	37	34	-50	-22	5.15
<i>Parietal cortex</i>					
L Superior parietal lobule	7	-32	-56	52	6.97
L Inferior parietal lobule	40	-40	-38	38	3.44
<i>Occipital cortex</i>					
L Middle occipital gyrus	19	-40	-68	-8	10.07
R Middle occipital gyrus	19	38	-72	-12	7.06
<i>Cerebellum</i>					
Medial cerebellum		8	-78	-34	4.87
R Cerebellum		34	-64	-32	4.03
<i>Semantic memory</i>					
<i>Frontal cortex</i>					
Medial frontal gyrus/ACC/pre-SMA	32/24	10	12	46	7.16
	8/6	-2	24	48	6.50
L Middle frontal gyrus	44/6	-48	6	30	6.68
	45	-48	22	20	6.50
L Inferior frontal gyrus	47	-50	18	2	5.41
L Middle frontal/Precentral gyrus	6/4	-30	-8	60	3.64
R Inferior frontal gyrus	45	46	14	24	5.28
<i>Temporal cortex</i>					
R Fusiform gyrus	37	36	-50	-22	5.43
<i>Parietal cortex</i>					
L Superior parietal cortex	7	-32	-60	52	5.69
<i>Occipital cortex</i>					
L Cuneus	18	-24	-98	2	9.96
R Cuneus	18	28	-94	4	7.07
<i>Cerebellum</i>					
R Cerebellum		36	-62	-32	3.17
<i>Working memory</i>					
<i>Frontal cortex</i>					
Medial frontal gyrus/ACC/pre-SMA	6/8	4	10	56	7.28
	32	8	12	42	6.56
L Middle frontal gyrus	44/9	-44	6	30	6.19
	9	-54	14	38	5.94
L Middle frontal/Precentral gyrus	6	-40	-2	50	4.62
L Inferior frontal gyrus	47	-48	18	-2	3.82
R Middle frontal/Precentral gyrus	6	34	0	56	6.02
<i>Parietal cortex</i>					
L Precuneus	19	-32	-74	40	6.39
L Inferior parietal lobule	40	-36	-54	48	6.03
Medial precuneus	7	-6	-62	48	4.77
<i>Occipital cortex</i>					
L Cuneus	18	-26	-96	-2	7.49
R Cuneus	18	24	-96	2	5.59
<i>Cerebellum</i>					
Medial cerebellum		4	-82	-34	5.70
R Cerebellum		38	-64	-32	5.61
<i>Other structures</i>					
Thalamus		8	-20	6	4.24
Caudate nucleus		8	8	0	3.72

Note. Coordinates are in MNI space and correspond to peak activations in each condition relative to attention, thresholded at $p < .05$ FDR corrected, and inclusively masked with corresponding main effect relative to baseline, thresholded at $p < .001$ uncorrected; extent threshold > 8 voxels. BA = approximate Brodmann's area; ACC = anterior cingulate cortex; pre-SMA = pre-supplementary motor area.

conjunction analysis suggested that bilateral VLPFC regions were engaged across all tasks.

Frontal sustained activity that were common for LTM and WM tasks, in the absence of significant effects during ATT, were located in right frontopolar cortex (BA 10), and a midline area (BA 8/6/32), rostral to the task-general medial site. An effect was also seen in left VLPFC (BA 47/45), although the conjunction analysis indicated that this region was also engaged during the ATT task. This pattern of sustained activity may represent information about the task context, e.g., instructions, (Pettersson et al., 2003) that is necessary to maintain on-line in an active state during the temporal gaps between items in the memory tasks (Cohen et al., 1996). Such ISIs were missing in the ATT task, where a single item was constantly displayed. Activity in right frontopolar cortex and ACC has consistently been noted during episodic retrieval (Cabeza and Nyberg, 2000; Lepage et al., 2000), and such activity has been interpreted as reflecting instantiation and maintenance of a neurocognitive set underlying episodic retrieval (Tulving et al., 1994; Nyberg et al., 1995; Lepage et al., 2000). The present finding of sustained frontopolar and ACC activity during episodic memory retrieval is consistent with this view (c.f., Cabeza et al., 2002), but the fact that such activity was also seen for the semantic and WM tasks indicates a more general functional role. Indeed, frontopolar activation has been associated with WM tasks (Braver and Bongiolatti, 2002; Cabeza et al., 2002; Nyberg et al., 2002), semantic monitoring tasks (MacLeod et al., 1998), and tasks of cognitive branching (Koechlin et al., 1999). A recent study by Sakai and Passingham (2003) also associated activity in the anteriormost region of the frontal lobes with preparatory processes during the period between task instruction and the first memory items to be retained in WM. Furthermore, in a previous fMRI study using mixed blocked/event-related design to explore the functional anatomy and temporal dynamics underlying controlled episodic retrieval (Velanova et al., 2003), a similar set of regions showed sustained activity as in the present study (frontopolar, medial frontal, and parietal cortices).

A striking observation was the extensive decreases in sustained activity, relative to rest, during the WM and ATT tasks (c.f., Shulman et al., 1997; McKiernan et al., 2003). That this effect was much stronger for WM and ATT than the LTM tasks, is likely related to the prolonged high levels of focused ATT and intensive processing demands in the former tasks (c.f., Ghatan, 1995). That is, in contrast to LTM tasks where processing demands diminished during ISIs, WM and vigilance tasks were characterized by continuous processing throughout the entire duration of the task. The most profound cerebral consequence of this persistency in effortful cognitive processing is seemingly

widespread regional decreases in neural activity. These apparent task-selective deactivations might be related to the differential operation of a *default mode of brain activity* (Fransson, 2005; Gusnard and Raichle, 2001; Raichle et al., 2001), during ISIs of the LTM tasks. Under resting conditions, neural activity has been revealed in an extensive brain network, including precuneus/posterior cingulate cortex, lateral parietal cortex, and the parieto-occipital sulcus (Raichle et al., 2001). This pattern might reflect a default mode of brain activity that involve processes such as spontaneous thought (Christoff et al., 2004), self-reflection and monitoring of internal states and the external environment (Shulman et al., 1997; Gusnard et al., 2001). Our findings could reflect the reinstatement of the default mode in the comparatively process vacant ISIs during the LTM tasks. Hence, when item-independent brain responses in the LTM tasks were contrasted with rest, where the default mode should be the main process, this activity was cancelled out. By contrast, in WM and ATT, when there was continuous item-processing throughout the tasks, the default mode was likely disabled. Therefore, when compared with rest, brain regions related to the default mode appeared as deactivated. It should also be noted that selective deactivations were observed in visual areas for the 2-back WM task. Since decreases in visual areas are not part of the “default mode network”, these deactivations may reflect a more active suppression of brain activity and processing in regions not engaged in WM maintenance rather than a more passive disengagement related to the default mode. A complementary interpretation as to the relative absence of sustained decreases in the semantic memory-rest comparison is that the default mode during rest predominantly involves conceptual processing. Accordingly, semantic retrieval and resting conditions have been shown to activate similar regions when contrasted with non-semantic tasks (Binder et al., 1999). In a similar vein, default-mode activity has been related to episodic memory processing (Greicius et al., 2004). Taken together, increased and decreased sustained brain activity can be interpreted in terms of control signals that promote top-down biasing of task-relevant *versus* irrelevant processing pathways (Desimone and Duncan, 1995; Ghatan et al., 1998; Miller and Cohen, 2001; Braver and Barch, 2002).

In addition to the sustained effects, transient stimulus-synchronous increases were seen for all tasks. These activations generally occurred in areas distinct from the sites of sustained responses, which provide additional evidence that state- and item-related brain activity can be dissociated. One transient activation that was common to all memory tasks was located in left posterior DLPFC (BA 44/9). It is striking that this response was transient as DLPFC often is implicated in relation to representing and maintaining task context

(Cohen et al., 1996; MacDonald et al., 2000; Curtis and D’Esposito, 2003). In contrast, our results implicate that this region is concerned with item-specific processing. Left posterior DLPFC has shown event-related modulations in previous studies; in the context of episodic retrieval and enhanced control demand (Velanova et al., 2003), retrieval across WM and episodic memory tasks (Cabeza et al., 2002), and transient control during task-switching (Braver et al., 2003). Such activations may reflect general retrieval-control processes (Wheeler and Buckner, 2003) and retrieval from LTM may generate an active representation, similar to that produced during updating of WM-contents (Courtney et al., 1997).

Moreover, differential transient responses were noted for all three memory tasks. Such effects could reflect actual recovery of domain-specific information from episodic, semantic and WM, respectively. For the episodic task, a salient transient effect was observed for right PFC (BA 47). This region has previously been suggested to be part of a network subserving episodic *retrieval mode* (Nyberg et al., 1995; Lepage et al., 2000). The present observation that this region was associated with item-related processing appears inconsistent with this suggestion and more coherent with interpretations of right prefrontal activity in terms of post-retrieval monitoring (Rugg et al., 1996) and/or cue specification (Henson et al., 1999). However, it is possible that subjects initiated a retrieval mode only when items (i.e., retrieval cues) were presented rather than trying to maintain it across the task block. If true, the fairly long intervals between some cues could have contributed to this behaviour (i.e., participants returned to the default mode in-between test items). For the WM task, transient increases were observed in DLPFC (BA 9), premotor areas (BA 6), and precuneus (BA 7). This pattern is consistent with previous findings from WM studies (Cohen et al., 1997; Nyberg et al., 2002; for a review, see Smith and Jonides, 1997). The specific WM task that we used, 2-back, involves several different item-processes that can be related to the observed transient effects, including temporal coding of items (Cohen et al., 1997) and updating functions (Collette and Van der Linden, 2002). The semantic task was associated with transient activations in left VLPFC and left lateral occipito-temporal cortex, which is in keeping with numerous previous studies of semantic memory (Martin, 2001; Thompson-Schill, 2003). One candidate function of left VLPFC is to guide controlled semantic retrieval (Wagner et al., 2001). As our semantic task required the participants to classify items that belonged to conceptually related categories (e.g., fruit-vegetables), this account is consistent with the present observations. It should be noted that the pattern observed for semantic memory largely overlapped those for the episodic and WM tasks,

which may reflect a task-general verbal processing/semantic component (Braver et al., 2001). A point of consideration concerns the fact that the analyses of transient effects were based on items associated with *both* correct and incorrect responses, which might have affected the results. However, since the differences in accuracy between conditions were small and relatively few items were used, it is unlikely that this procedure should have had any significant effect on the activation data.

In summary, the present findings present a complex and equivocal picture with respect to a WM account of common PFC activations in episodic and semantic LTM tasks. The subset of overlapping regions that were attributed to more general attentional processes included bilateral, but predominantly right, VLPFC and a posterior part of ACC/pre-SMA. These regions may mediate top-down attentional biasing and vigilance related to the apprehension of upcoming events to be acted upon. Regarding the sustained state-related effects, the patterns of commonalities in frontal engagement that differentiated the three memory tasks from the ATT task involved ACC and frontopolar areas. These regions, which were common to LTM and WM, constitute candidate regions for which a WM account of frontal LTM-activity might apply. However, these specific activation sites are not generally attributed to WM maintenance processes. Instead, in previous work, these regions have been considered a signature of retrieval mode (Lepage et al., 2000), indicating a more generic functional role of the neural circuitry underlying retrieval mode in episodic memory tasks. Frontopolar cortex and ACC/pre-SMA activity have also been linked to anticipatory task preparation and the representation of intention (Sakai and Passingham, 2003; Lau et al., 2004). Collectively, these functional accounts indicate that the sustained state-related effects that were common to WM and LTM may reflect cognitive control processes related to task set in a way that is not dependent on WM maintenance.

Given that overlapping sustained activity changes may reflect general control signals that govern task-relevant processing, a possibility is that a WM account of frontal LTM activity holds for transient activity changes. The region in posterior DLPFC (BA 44/9) that was found to be equally activated across all memory tasks may represent WM processes that coordinate the active retrieval of information from episodic and semantic LTM, which tentatively generalize across a wide range of cognitive tasks. As was discussed above, left posterior DLPFC has shown item-related modulations in previous studies, and Courtney et al. (1997) noted that "activation of the same areas by both long-term retrieval and working memory is consistent with the idea that retrieval produces an active representation of the recalled material much

like the active representation of material held during working memory delay" (p. 610).

In conclusion, studies employing decomposition of overlapping and specific neural responses across multiple tasks into sustained *versus* transient modulations promises to provide a better understanding of the multifaceted relation between PFC subregions and component processes underlying human memory.

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