

Anterior prefrontal involvement in episodic retrieval reflects contextual interference

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Different patterns of prefrontal activation are commonly found in studies of episodic and source memory (typically anterior and lateral) compared to those found in studies of autobiographical memory (typically ventromedial). We investigated a proposal that the former pattern reflects contextual interference when retrieving events that occurred in similar contexts. We used virtual reality to simulate contextually varied life-like events, in which subjects received distinct objects from a number of people in a number of locations. We compared fMRI data from two experiments in which the number of events per context varied. The first experiment (Burgess, N., Maguire, E.A., Spiers, H.J., and O'Keefe, J. 2001. A temporoparietal and prefrontal network for retrieving the spatial context of lifelike events. *Neuroimage* 14, 439–453) involved 16 objects received from one of two people in one of two locations. The second experiment involved 20 objects, each received from a different person in a different location. The first experiment showed extensive bilateral activation of anterior and lateral prefrontal cortex, as well as a medial temporal and parietal network characteristic of both autobiographical and episodic memory. In the second study, the prefrontal activations were largely absent, while the medial parietal and temporal activations remained, and a ventromedial prefrontal area was additionally activated. Direct comparisons revealed large areas of significantly reduced activation in BA10, with lesser reductions in lateral prefrontal regions. We suggest that involvement of these prefrontal regions in episodic and source memory reflects the use of paradigms involving many events and few sources rather than any fundamental processing requirement of contextual retrieval in the absence of interference.

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Introduction

Episodic memory (Tulving, 1983), the recollection of events we have experienced in the past, has been considered in terms of two different types of information that might be retrieved (Burgess et al., 2001; Johnson et al., 1993)—the content of the event and the external context in which it occurs. Content refers to the change in the world that forms the event, while context is taken to mean the ongoing external circumstances relating to the event, such as the location, the time, the prevailing weather, and so on. Episodic recollection is often operationally defined by the ability to remember contextual information, while the content of an event can be recognised or “known” in the absence of any contextual information (Gardiner and Java, 1991; Yonelinas and Levy, 2002). There is a growing consensus that the medial temporal lobes (and the hippocampus in particular) provide the neural basis for episodic memory (Aggleton and Brown, 1999; Cohen and Eichenbaum, 1993; Kinsbourne and Wood, 1975; O'Keefe and Nadel, 1978; Scoville and Milner, 1957; Squire and Zola-Morgan, 1991), i.e. context-dependent memory for personally experienced events (Tulving, 1972, 1983). Evidence from neuroimaging (Cabeza et al., 2004; Maguire and Frith, 2003; Maguire et al., 2000, 2001; Piefke et al., 2003) suggests that autobiographical memory involves a temporal and parietal network consistent with this picture. In addition, it also involves a region of ventromedial prefrontal cortex which has been implicated in processing personal information (Gusnard et al., 2001; Johnson et al., 2002; Kelley et al., 2002).

Researchers interested in prefrontal contributions to memory have focused on a theoretical categorisation of memory, related to context-dependent memory, known as ‘source memory’. Source here refers to a combination of characteristics that together define the conditions under which a memory was acquired. This includes context and also the media and modalities by which the content was received (Johnson et al., 1993). Despite the close relationship between source memory and context-dependent episodic memory, source memory performance correlates with performance on ‘frontal’ tasks (Glisky et al., 1995; Schacter et al., 1984) and with frontal electrophysiological activity (Johnson et al., 1997) and is

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usually characterised as impaired by prefrontal damage (Schacter et al., 1984; Shimamura et al., 1990; Janowsky et al., 1989) rather than by medial temporal damage. Consistent with this difference, functional neuroimaging studies of source memory for laboratory-type stimuli reveal a different pattern of prefrontal activation than the autobiographical memory studies, see Gilboa (2004) for a review. Typically, anterior, dorsolateral, and ventrolateral prefrontal cortices are implicated in source memory studies (Henson et al., 1999; Rugg et al., 1999). While these prefrontal areas are unlikely to provide the storage sites for context-dependent memory, they clearly have an important role to play in the strategic organisation of retrieval (Christoff and Gabrieli, 2000; Dobbins et al., 2002; Henson et al., 1999; Rugg et al., 1999; Stuss and Benson, 1984), see Simons and Spiers (2003) for a review. Indeed, disconnection of the frontal and temporal lobes has been proposed as a cause of organic amnesia (Levine et al., 1998; Markowitsch, 1995; Warrington and Weiskrantz, 1982).

This paper concerns the nature of the prefrontal role in context-dependent memory. We focus on the intriguing differences between the patterns of prefrontal activation found in source memory compared to episodic recollection of autobiographical stimuli, despite the apparent operational similarity of testing these two processes. One potential explanation for these differing patterns (Burgess et al., 2001) is that prefrontal cortex is involved in selecting the correct event in the face of interference from several other events sharing a similar context. Source memory paradigms typically use a limited number of sources (such as 2 locations, 2 voices, or 2 lists presented at 2 different times), which is also typical of many laboratory tests of episodic or context-dependent memory. Real world episodic memories (or autobiography), on the other hand, tend to have richer and more distinct contexts, and thus the recall of episodic source or context involves the recall of a more unique set of information for each event.

Consistent with this interpretation, prefrontal cortex has been associated with interference (Henson et al., 2002; Incisa della Rocchetta and Milner, 1993; Smith et al., 1995) and competition (Sohn et al., 2003) in memory tasks. A previous experiment (Burgess et al., 2001) used controlled pseudorealistic events presented within a virtual environment (VE) to ensure a rich contextual element to the memoranda. During learning, subjects received a series of objects from one of two people in one of two locations. Between each event, the subject followed a marked route to the next location. Subjects were tested for their memory of the place and person associated with each object, as well as context-independent object recognition, in a forced choice recognition paradigm. Testing took place during fMRI scanning. In each test, subjects were presented with a pair of objects in a location containing a person and cued to indicate which object was associated with either (a) the person (context-dependent memory) or (b) the place (also context), or (c) which object was familiar (content/object familiarity), or (d) which was wider (perceptual control). Crucially, all 16 events involved reusing the same 2 characters and 2 locations due to limitations in the technology available at the time. Extensive activations were found in dorsolateral, ventrolateral, and anterior prefrontal cortex in context-dependent memory compared to object recognition, resembling those found in source memory studies. This finding suggests that contextual richness is not the causal difference between prefrontal involvement in source memory and autobiographical paradigms. By contrast, the repeated use of the same contexts leaves open the possibility that interference is the determining factor in lateral and anterior prefrontal involvement.

Here, we present an experiment using a similar paradigm to Burgess et al. (2001), in which subjects' memory is again tested for the context or content of events, but in which each event occurs in a unique context (i.e. involving a different person and place). We hypothesised that the pattern of prefrontal recruitment would be more like that found in autobiographical memory studies, while the recruitment of posterior areas would be largely unchanged from the previous study of Burgess et al. (2001). In addition, we included a condition in which the target object is re-presented with both contextual cues (place and person). This might be thought to aid more complete re-experiencing of the event or 'ecphory' compared to the individual contextual cues alone, possibly associated with episodic memory (Tulving, 1983). The number and duration of questions required to test memory for the contexts of the simulated events ruled out experimental designs in which interference was manipulated within a single session (see Materials and methods).

Materials and methods

The methodology of the present study was similar to that used by Burgess et al. (2001), including using the same MRI scanner and scanning parameters, see below. By increasing the number of locations and characters so that each event had a unique context, we reduced the amount of contextual interference. The previous study featured 16 events in only 2 locations involving 2 characters. By increasing the number of events to 20, we hoped to maintain a similar level of difficulty. The virtual town consisted of several buildings connected by roads and staircases (see Fig. 1a). The 20 locations in the town chosen to be the loci for events were selected to provide views that were as different from each other as possible.

The participants were 13 healthy right-handed male volunteers with ages ranging from 18 to 45 years (mean 26.9 years, SD 6.3 years). All gave informed written consent in the study which was approved by The National Hospital for Neurology and Neurosurgery and The Institute of Neurology Joint research ethics committee. Prior to scanning, participants practiced procedural aspects of the task, experiencing and answering questions on 3 trial events. For the main experiment (conducted in the MRI scanner), each participant started the experiment at the same location in the VE, from where a path was indicated by green markers. The participant followed the markers, controlling their movements using four keys (forward and back, and left and right turns), to the location of the first encounter, where 1 of 20 characters was waiting. When the participant approached within 5 virtual metres of the character, it stepped to one side (randomly chosen) and presented a large image of a common object on the other side (see Fig. 1b for an example). The subject was instructed to study the scene and remember the object, which person gave it to them, and in which place. After a self-paced study delay, they moved forward into the object, which caused it and its (now out of view) "owner" to disappear and the markers to the next location to appear. This process was repeated for a total of 20 events, after which the testing phase of the experiment and fMRI scanning took place.

Testing involved presentations of images taken from standard viewpoints of the event locations in the VE to standardise the stimuli used in the scanning phase of the experiment. The test images were composed from viewpoints typically seen by the subjects and consisted of 1 of the 20 characters in 1 of the 20 locations together with two of the presented objects (see Fig. 1c for an example). These pictures were used to ask 5 types of



Fig. 1. (a) A view of the virtual town from an elevated position, with roofs cut away, to show some of the extent and detail of the environment. This view was not experienced by subjects, who explored at ground level. (b) An example of an event during the exploration phase. After approaching the person, the view of the subject is frozen, and the person walks to one side. An object appears, at which time the subject is allowed to move again and, after self-paced study, moves forward to the object, which disappears. A trail of markers then appears, leading the subject to the next location. (c) An example of a test stimulus from the ‘Place’ condition. One of the objects was received in the location pictured; neither was associated with the person or with each other in other questions.

question about each event (see Table 1): “Place” (which object did the subject receive in this location); “Person” (which object was given by this person); “Object” (which object was received in the VE); “Bright” (which object was brighter in appearance); and “Both” (which object was associated with both the location and the person). Place, Person, and Both questions were intended to reveal activity associated with context-dependent memory,

which could be compared with Object questions (non-context-dependent recognition memory) and Bright questions (the perceptual control condition). The perceptual control question was different from the width question in the 2001 study because the images in the present study were of standard width. For the “object” question, the two objects comprised one previously presented object and a similar-looking foil object. For each event, 5

Table 1
The experimental conditions

Condition	Question	Details	Purpose
Bright (perceptual)	Which is the brighter object?	Both objects and person inconsistent with place and each other	Perceptual control for common task processes
Object	Which object was seen before?	Objects and person inconsistent with place and each other, one object was a novel foil	Object recognition memory
Person	Which object did this person give you?	Objects and person inconsistent with place, one object given by the person	Object–person association
Place	Which object did you receive in this place?	Objects inconsistent with person, one object consistent with location	Object–place association
Person and Place	Which object was given by this person in this place?	One object and person consistent with place	Object–place and person association

images were composed, one for each of the experimental conditions, and the task was always to indicate one of the two objects left or right with a button-press response. Each image was presented for 6 s followed by a 6-s period during which the screen was black. The order of presentation was a constrained random pattern, with 1 of each of the 5 question types presented in blocks, and each block of 5 containing no repeats of any object, person, or place. In total, the subject was in the scanner for the self-paced encoding phase (15–20 min), 20 min of fMRI data acquisition while answering the questions, and acquisition of the structural scan (10 min).

In creating the test stimuli for this study, as in Burgess et al. (2001), care was taken in the choice of foil objects never to duplicate novel associations between any pairing of the factors place, person, and object during testing. This was in order to minimise interference effects and to try and ensure that it was the original episode that was remembered rather than associations from the testing phase. Subjects were told that the only way to perform well on the task was to use their memory of the original event.

The equipment used to present the virtual environment and subsequent stimuli was a Pentium 3 500 MHz desktop PC with a 19" CRT monitor (for the training) and a P3 800 MHz notebook PC connected to MR-compatible projection equipment (during the experiment in the scanner). The VE was created using the tools and materials provided with the VR computer game "Deus-Ex" (Ion Storm, Austin, Texas), which is based on the Unreal 3D graphics and scripting engine (Epic Games, Inc, Raleigh, NC). At testing, stimuli were presented using the Cogent 2000 Matlab toolbox (Wellcome Department of Imaging Neuroscience: <http://www.vislab.ucl.ac.uk/Cogent>).

Image acquisition and data analysis

Functional imaging was performed during the memory-testing phase of the experiment. Both the acquisition and analysis took the same form as the previous (Burgess et al., 2001) study and used the same hardware and software. Data were acquired using a 2 T Siemens Magnetom VISION whole body MRI system (Siemens GmbH, Erlangen, Germany) equipped with a head volume coil. A structural MRI scan using a standard three-dimensional T1 weighted sequence was acquired from each subject. Functional T2*-weighted images were obtained using echo-planar imaging [echo time (TE) = 40 ms]. Volumes were acquired continuously for the whole head: 32 slices, each 3 mm thick, 3.17 s per volume. Image analysis was performed using SPM99 (Wellcome Department of Imaging Neuroscience: <http://www.fil.ion.ucl.ac.uk/spm>; Friston et al., 1995) in a standard manner. Briefly, the functional images were realigned (with each other) and coregistered with the structural scan. The images were normalised to a standard template (Montreal Neurological Institute) and spatially smoothed with a Gaussian filter (8 mm full width half maximum). For each subject, the fMRI time-series was high pass filtered (minimum cutoff period 65 s) and modelled as the weighted sum of regressors corresponding to effects of interest. All conditions were modelled in an event-related design, with event onsets defined as 2 s after the appearance of test stimuli on the screen. The timings were derived from logs produced by the Cogent toolbox. In addition, to control for visual and motor activity, regressors were created relating to the presence of a stimulus on the screen (6 s duration events) and to all motor responses (1 s events). All these

regressors were convolved with the canonical haemodynamic response function. Finally, the model also included regressors based on estimates of head movement obtained from the realignment procedure (to account for any second order effect of such movement remaining after realignment).

The parameters (i.e. the coefficients of the regressors) for the best fitting model were found and subjected to a random effects analysis. That is, for each voxel in the brain, single sample *t* tests were used to determine whether the contrast of parameter estimates between conditions (e.g., place minus object) was significantly different from zero. In addition, we examined the patterns of activation in the main effects for each condition compared to the background level of activation (which corresponds to all activation during the experiment not accounted for by the experimental regressors). As both experiments were modelled in the same way, comparisons could then be made between the two studies by performing a two-sample *t* test on the subject-level contrasts. This allowed us to discover which regions were significantly more or less active in the current study. Except

Table 2
Activations of interest found in Burgess et al. (2001)

	Brodmann area	Coordinates	Z score	Extent
<i>Place-Width</i>				
R vlpfc	47	30 24 -6	4.49	44
L vlpfc	47	-27 24 -9	4.03	40
L anterior pfc	10	-27 51 -3	4.41	68
R anterior pfc	10	30 57 3	4.03	31
R dlpc	9,44	54 30 30	4.31	55
L dlpc	9,44	-48 27 21	4.03	65
L frontal cortex	6	-36 15 57	3.63	8
L hippocampus		-21 -21 -9	3.57	3
POS, retrosplenial	17,18,23,29,30,31	-15 -60 18	5.49	895
<i>Place-Object</i>				
L anterior pfc	10	-27 54 -6	4.94	136
	10	-24 51 18	3.86	
R anterior pfc	10	24 60 6	4.49	110
L vlpfc	47	-42 24 -15	4.44	82
R vlpfc	47	33 24 -12	3.5	14
L dlpc	9,44	-42 21 39	4.12	109
	8	-27 27 54	3.45	
R dlpc	9	45 42 30	3.68	10
POS, retrosplenial	17,18,23,29,30,31	9 -66 48	5.20	831
<i>Person-Width</i>				
R dlpc	9,44	48 36 30	4.34	29
L dlpc	9,44	-48 30 33	3.6	7
		-45 24 24	3.25	10
R anterior pfc	10	30 57 3	4.05	35
L anterior pfc	"	-30 57 0	3.79	27
POS, retrosplenial	17,18,23,29,30,31	15 -63 27	5.33	635
<i>Person-Object</i>				
L dlpc	8	-39 12 48	4.94	26
	9,44	-42 27 36	3.93	19
R anterior pfc	10	24 60 0	4.04	95
L anterior pfc	10	-33 57 12	4.24	51
		-27 51 24	4.22	36
		-18 36 39	3.95	4
L vlpfc	47	-48 24 -9	4.19	28
POS, retrosplenial	7,23,31	6 -72 36	5.51	466

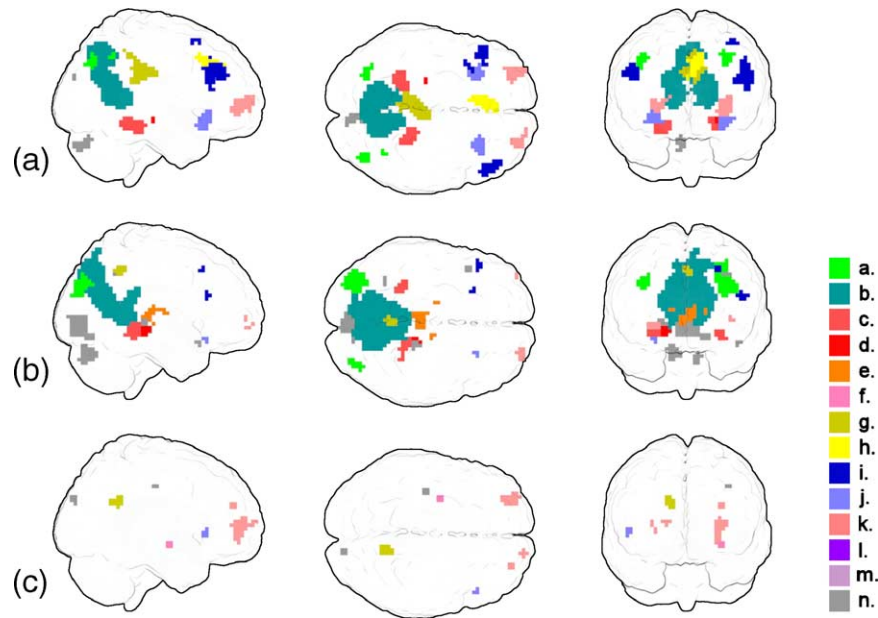


Fig. 2. Regional activations in the contrast of Place > Percept. (a) Burgess et al., 2001, (b) current study, (c) and activations significantly greater in the 2001 study at $P < 0.001$. Note reduced prefrontal activation in the current data relative to the 2001 study, significant in anterior PFC, posterior cingulate, and right ventrolateral PFC. (Color key: a. posterior parietal cortex; b. precuneus, parieto-occipital sulcus and retrosplenial cortex; c. parahippocampal gyrus; d. hippocampus; e. thalamus; f. caudate; g. midposterior cingulate cortex; h. anterior cingulate cortex; i. dorsolateral prefrontal cortex; j. ventrolateral prefrontal cortex; k. anterior prefrontal cortex; l. ventromedial prefrontal cortex; m. insula; n. regions not of interest in this analysis.). Percept here refers to the perceptual judgement control conditions (brightness in the current study, width in the 2001 study).

where indicated, the results we report exceed a threshold for statistical significance of $P < 0.001$, uncorrected for multiple comparisons in brain areas specified in our previous episodic and autobiographical studies (Burgess et al., 2001; Maguire, 2001). Only activations exceeding an extent threshold of 3 voxels are included in the figures and tables.

Results

Behavioural measures

Performance on the 4 memory tasks was broadly matched (the control task, 'bright', was not performance-assessed), and despite

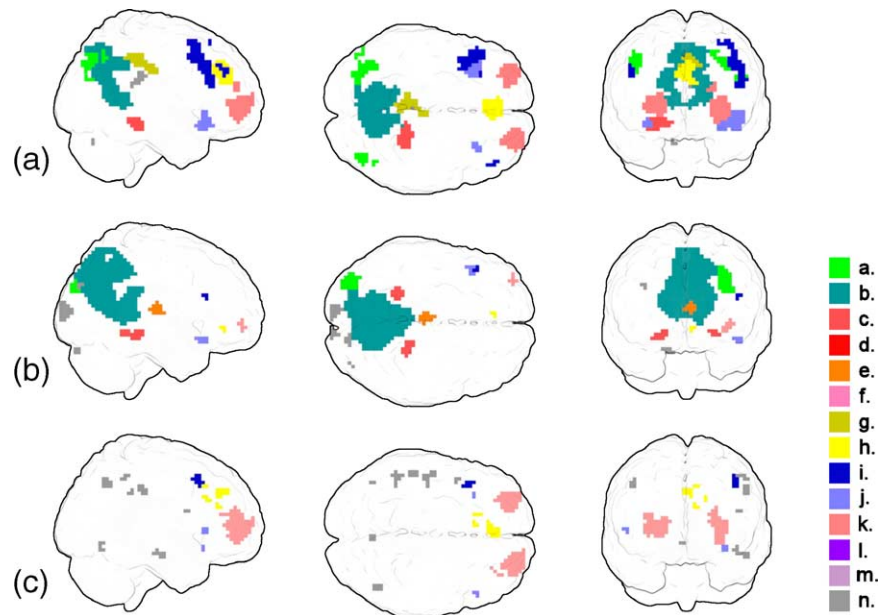


Fig. 3. Regional activations in the contrast of Place > Object in the 2001 study (a), current study (b), and significantly greater in 2001 (c). Note overall reduction in prefrontal activation (middle row, b) which is significant in bilateral anterior, left dorsolateral, bilateral ventrolateral PFC, and bilateral anterior cingulate (bottom row, c). For key, see Fig. 2 legend.

Table 3
Regional activations in the Place–Perceptual contrast

Location	Brodmann area	Coordinates	Z score	Extent
<i>Significant activations in current data</i>				
R vlpfc	47	30 24 -15	3.28	4
L dlpfc	8	-24 21 42	3.4	5
	45	-48 24 21	3.85	9
L + R anterior pfc	10	30 60 -6	3.48	9
	10	-39 57 0	3.24	3
R posterior cingulate	31	3 -48 42	3.59	15
POS	7,23,29,30,31	-9 -78 36	5.64	1476
R parahippocampal cortex and hippocampus	35	18 -30 -9	4.20	(subpeak)
R lingual gyrus	18	6 -84 -9	4.58	117
L + R posterior parietal	19	-33 -84 27	4.13	(subpeak)
	19	36 -81 36	3.76	27
L inf parietal lobule	40	-33 -54 39	3.64	3
L parahippocampal gyrus	37	-30 -39 -12	3.66	18
L thalamus	Mediodorsal/pulvinar	-6 -27 3	3.51	34
L + R thalamus	Ventrolateral	-15 -12 6	3.3	3
		15 -15 9	3.55	3
L temporal pole	38	-42 18 -18	3.66	5
L + R cerebellum		-9 -81 -33	3.62	18
		12 -75 -27	4.3	44
<i>Regions significantly more active in 2001 data</i>				
R vlpfc	47	51 24 0	3.47	7
L inf parietal gyrus	40	-36 -18 39	3.31	4
L + R anterior pfc	10	-30 54 6	4.31	54
	10	-27 45 21	3.39	6
	10	18 63 9	4.66	6
	10	30 51 9	3.48	6
R posterior cingulate	31	15 -51 27	3.78	25
R cuneus	18,19	18 -87 27	3.57	8
L putamen		-27 -6 -9	3.59	7

Legend for this and other tables of activations: pfc = prefrontal cortex; vlpfc = ventrolateral pfc; dlpfc = dorsolateral pfc; vmprfc = ventromedial pfc; POS = parieto-occipital sulcus, the commonly activated posterior region described in the text.

performing well, subjects were not at ceiling. Mean scores (with standard errors) were: Object – 85.5% (1.6%); Person – 89.5% (3.2%); Place – 88.5% (2.9%); Person and Place – 92.0% (1.9%). For comparison, the scores from (2001) were: Object – 88% (2%); Person – 80% (3%); Place – 79% (2%).

Imaging data

As the previous data from Burgess et al. (2001) were available to us, we were able to compare directly with the present study. The main difference between the studies is the substantially different pattern of frontal activations compared to largely similar regions of posterior activation and, specifically, a consistently greater involvement of lateral BA10 in the earlier study. As well as describing the activations found in the current study and the statistical comparison with the earlier one, a summary table is provided (Table 2), detailing the regions activated in the 2001 study for the main contrasts relevant to context-dependent memory (comparing the Place and Person conditions with the

Object and perceptual control conditions). The more posterior activations in the two studies are very similar for all the context-dependent memory conditions—a continuous strip of activation from the precuneus through retrosplenial cortex and extending to the parahippocampal region is present and highly significant in both studies.

Place–Bright

We consider first the contrast of Place with the perceptual control task. Fig. 2 shows the activations from the current study (middle row) below those from Burgess et al. (2001) and the regions which were significantly more active in the 2001 data (bottom row), colour coded to clarify the interesting regions, clearly showing a substantial reduction of prefrontal activation. We find small regions of activations in right ventrolateral PFC and posterior cingulate, left dorsolateral PFC, bilateral anterior PFC, bilateral thalamus, left parahippocampal gyrus, the left temporal pole and bilateral cerebellum, as well as the very large posterior activation found in all contrasts of both studies and well described in Burgess et al., 2001. Comparing between the two studies (lower parts of Table 3 and Fig. 2), bilateral anterior prefrontal (BA10), right ventrolateral prefrontal, and posterior

Table 4
Regional activations in the Place–Object contrast

Location	Brodmann area	Coordinates	Z score	Extent
<i>Significant activations in current data</i>				
L vlpfc	47	-42 21 -15	3.87	14
L dlpfc	45	-45 24 21	3.32	4
L anterior pfc	10	-33 54 -6	3.95	11
L anterior cingulate	24	-6 39 -6	3.98	4
POS	7,23,29,30,31	-6 -42 12	5.26	1852
L + R parahippocampal cortex	36	-24 -42 -12	3.4	15
	35	21 -33 -12	4.03	22
L thalamus	Mediodorsal	-3 -18 9	4.02	23
R cuneus	18	9 -99 15	3.32	10
R sup. occipital gyrus	19	36 -84 30	3.16	3
L middle occipital gyrus	18	-9 -93 9	3.96	39
R cerebellum		18 -87 -24	3.49	10
<i>Regions significantly more active in 2001 data</i>				
L + R anterior pfc	10	-24 51 -3	4.57	129
	10	21 54 3	4.69	109
	10	36 45 12	3.53	5
L dlpfc	8/9	-39 18 39	3.31	11
L + R vlpfc	47	51 24 3	3.61	5
	47	-33 21 -12	3.38	4
L + R anterior cingulate	9	0 39 36	3.83	22
	32	-6 36 21	3.14	3
	32	-6 21 39	3.41	3
	32	-15 21 30	3.4	4
L inferior frontal gyrus	13	-42 6 18	3.35	3
L + R inferior parietal	40	-48 -45 48	3.53	9
	40	-48 -39 36	3.34	3
	40	-51 -30 36	3.71	10
	40	45 -60 42	3.71	13
L middle temporal gyrus	21	-51 -12 -21	3.54	12
L fusiform gyrus	19	-42 -66 -12	3.25	3
R cerebellum		3 -66 -9	3.28	4

cingulate cortex are the only regions in this study to be significantly more active in 2001.

Place–Object

We consider next the contrast of Place with Object questions (see Table 4, upper, and Fig. 3, middle row). Activations were found on the left in anterior, ventrolateral, and dorsolateral prefrontal cortex, anterior cingulate, middle occipital gyrus, and the medial dorsal nucleus of the thalamus, in the right visual cortex, and bilaterally in parahippocampal gyrus, the parieto-occipital sulcus (POS), and the cerebellum. Again, there is much less prefrontal activation overall in the present experiment than in 2001 (see Table 2), most notably in bilateral anterior prefrontal cortex (BA10), but with smaller bilateral differences in ventrolateral PFC and anterior cingulate and inferior parietal cortex and left dorsolateral PFC (see Table 4, lower, and Fig. 3, bottom row).

Person–Bright

The Person–Bright contrast shows the same pattern as the contrasts above: reduced frontal and similar posterior activations,

Table 5
Regional activations in the Person–Perceptual contrast

Location	Brodmann area	Coordinates	Z score	Extent
<i>Significant activations in current data</i>				
R + L vlpfc	47	30 24 -15	3.49	10
	47	-27 24 -12	3.26	3
	45	-48 24 21	3.94	10
R + L anterior pfc	10	30 57 -6	3.76	19
	10	-36 54 3	3.72	11
POS	7,23,29,30,31	-3 -63 12	5.07	1163
L posterior cingulate	31	-3 -51 39	3.33	5
R substantia nigra		15 -15 -12	4.3	9
R + L middle occipital gyrus	18	33 -96 -3	4.11	9
	18	-30 -96 -3	3.9	12
R + L posterior parietal	39	39 -72 30	3.39	3
	39	-36 -69 24	4.46	123
L hippocampus/parahippocampal cortex/thalamus		-21 -27 -6	4.16	93
Thalamus	Medial nucleus	-3 -18 9	3.91	25
	Pulvinar	-3 -6 6	3.36	7
L lentiform nucleus		-15 -9 -3	3.85	14
		-21 -3 18	3.13	3
		-21 12 -9	3.77	11
L fusiform gyrus	37	-33 -36 -18	3.18	3
R + L cerebellum		27 -60 -30	3.93	56
		-36 -51 -27	3.48	5
		-12 -27 -39	4.3	31
		12 -78 -30	4.21	180
		-39 -66 -36	3.77	7
<i>Regions significantly more active in 2001 data</i>				
R + L anterior pfc	10	33 57 9	3.53	10
	10	-24 66 9	3.26	3
	10	-27 51 24	3.92	32
L superior frontal cortex	6	-6 24 63	3.79	9
R dlpc	9	33 45 36	3.43	5
R posterior parietal cortex	40	57 -54 42	3.84	15

Table 6
Regional activations in the Person–Object contrast

Location	Brodmann area	Coordinates	Z score	Extent
<i>Significant activations in current data</i>				
R + L anterior pfc	10	27 54 0	3.8	26
	10	-30 51 -6	3.89	24
L vmppfc	11	-3 33 -12	4.7	50
L vlpfc	47	-48 33 -3	3.31	5
POS	7,23,29,30,31	-15 -51 21	5.06	1473
L posterior parietal	19	-33 -81 36	3.32	6
	39	-45 -69 21	3.83	28
L + R caudate		15 12 9	3.64	12
		-18 0 18	3.54	12
R insula/putamen	13/47	36 24 -3	3.99	65
L insula	13/47	-24 21 -9	5.36	147
L superior temporal gyrus	22	-54 -45 21	3.58	7
L middle temporal gyrus	21	-54 -39 -9	3.57	11
L parahippocampal cortex	35/36	-21 -36 -15	4.09	16
L thalamus	Ventrolateral	-21 -24 12	3.5	4
L thalamus	Mediodorsal	0 -21 9	3.2	3
R cerebellum		15 -87 -33	3.76	10
		33 -78 -36	3.29	10
		33 -63 -27	3.74	8
<i>Regions significantly more active in 2001 data</i>				
R + L anterior pfc	10	24 57 3	3.75	38
	10	-24 48 18	3.56	8
	10	-30 57 6	3.62	9
R + L posterior parietal	40	57 -54 42	4.37	38
	40	-48 -42 51	3.81	19
	7	-15 -78 21	3.63	9
L cuneus	18	-21 -81 21	3.27	3
L parahippocampal gyrus	19	-18 -57 -9	3.65	5

with small activations in bilateral ventrolateral and anterior PFC, left posterior cingulate, the POS seen in all conditions, as well as bilateral posterior parietal cortex, middle occipital gyrus and cerebellum, and a cluster on the left encompassing parahippocampal cortex, hippocampus, pulvinar, caudate, and LGN (see Table 5 and Fig. 4). The comparison between the two datasets shows significantly less activation in the present study in bilateral anterior PFC (BA10), right dorsolateral PFC, a left superior frontal region in BA6, and a right posterior parietal cortex.

Person–Object

In the non-spatial contrast of Person with Object, we found activations in bilateral anterior PFC, insula, caudate and temporal cortex, and the extensive medial posterior activation we find in all these contrasts; in left ventrolateral and ventromedial PFC, posterior parietal cortex, parahippocampal gyrus, and mediodorsal and ventrolateral thalamus; and in the right cerebellum. Again, the prefrontal activations seen in the 2001 study are still present to some extent, but much reduced, while the posterior activations remain very similar in extent and intensity (see Tables 2 and 6 and Fig. 5). A notable difference in prefrontal cortex however is the presence of a much larger region of activation in ventromedial frontal cortex than in the Place–Object contrast of the present study, which again is absent in the 2001 data. Given the location of this activation, we also verified that it did not border on a region of signal loss. In comparing the two datasets, we find that

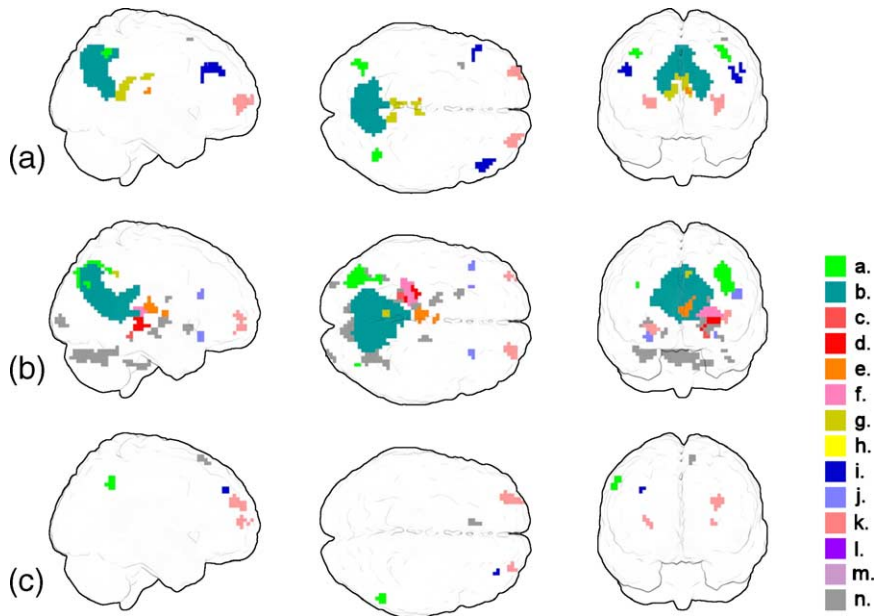


Fig. 4. Regional activations in the contrast of Person > Percept in the 2001 study (a), current study (b), and significantly greater in 2001 (c). Note significant reduction of activation bilaterally in anterior PFC and right dorsolateral PFC. For key, see Fig. 2 legend.

only bilateral anterior PFC, posterior parietal, and left parahippocampal gyrus are significantly more activated in the 2001 data.

Place and Person – [*Place + Person*] / 2

To test the hypothesis that two consistent contextual cues would have a super-additive effect compared to either place or person alone, we performed a contrast of Place and Person – [0.5 Place + 0.5 Person]. At the threshold of $P \leq 0.001$, we found activations in right perirhinal cortex (at 21 6 –33, $Z = 3.34$, 6 voxels), bilateral fusiform gyrus (–48 –60 –24, $Z = 3.57$, 15 voxels; 45 –57 –24,

$Z = 3.63$, 9 voxels), right precuneus (21 –75 42, $Z = 3.36$, 7 voxels), and also small clusters in left inferior occipital gyrus, inferior parietal lobule, and inferior temporal gyrus.

Object – *Bright*

The contrast Object – Bright was examined in comparison to the Object – Width contrast in the earlier study (see Table 7). We found activations in right dorsolateral PFC, bilateral posterior parietal cortex and fusiform gyrus, right lateral geniculate nucleus and substantia nigra, and bilaterally in the cerebellum. However,

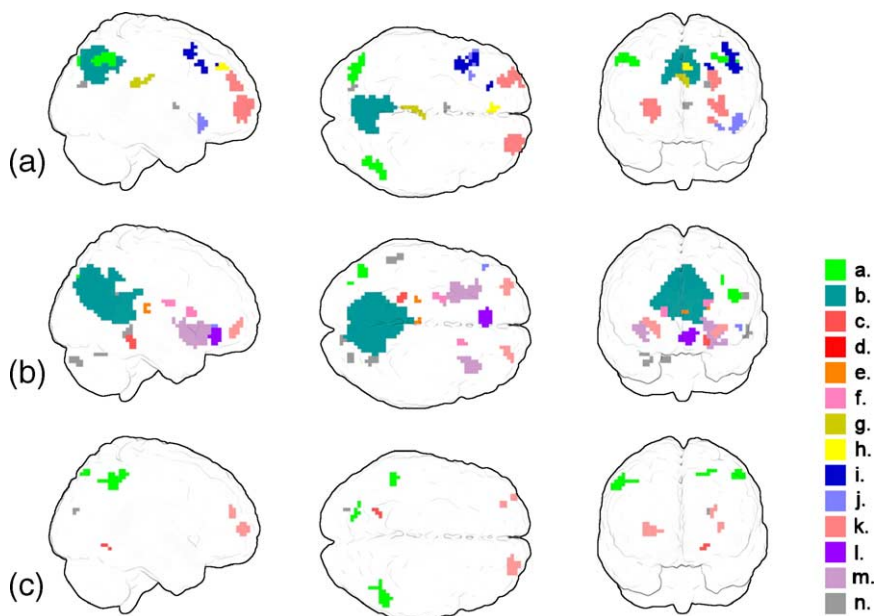


Fig. 5. Regional activations in the contrast of Person > Object in 2001 study (a), current study (b), significantly greater in 2001 (c). Note significant reduction of activation bilaterally in anterior PFC and left parahippocampal gyrus. For key, see Fig. 2 legend.

Table 7
Regional activations in the Object–Perceptual contrast

Location	Brodmann area	Coordinates	Z score	Extent
<i>Significant activations in current data</i>				
R dlpc	9	51 12 30	3.57	6
	46	42 51 9	4.19	24
L + R inferior occipital/ fusiform gyrus	9/46	45 27 12	4.18	94
	18/19/37	−27 −90 −3	4.74	166
		−36 −75 3	3.8	10
L + R posterior parietal	19	39 −81 −12	5.15	326
		33 −93 −3	3.42	11
	−24 −78 30	4.04	33	
	40	−39 −39 45	3.77	46
	7	−24 −66 51	3.67	30
R lateral geniculate nucleus	19	30 −72 36	4.38	49
	40	39 −39 39	4.13	139
R substantia nigra		27 −18 −6	3.51	25
L + R cerebellum		15 −15 −12	3.55	4
R lateral geniculate nucleus	19	−36 −39 −24	3.74	18
		−9 −78 −33	3.27	9
	−12 −72 −12	3.39	3	
R lateral geniculate nucleus	19	6 −75 −33	3.75	24
		3 −60 −39	3.75	8
<i>Regions significantly more active in 2001 data</i>				
L superior occipital gyrus	19	−33 −87 21	3.77	22
L middle occipital gyrus	19	−39 −81 3	4.85	82
R precuneus	19	30 −78 36	3.88	13
L + R inferior parietal lobule	40	42 −33 39	3.98	49
	40	−45 −45 45	3.9	35
L superior occipital gyrus	7	−24 −66 57	4.08	11
R middle temporal gyrus	37	45 −72 6	3.62	3

when we compare between the studies directly, we find no significant differences in prefrontal regions of interest, only differences in posterior regions of occipital, temporal, and parietal cortex.

Discussion

The purpose of this study was to investigate the reasons for the apparently differential prefrontal involvement in source memory paradigms and autobiographical recollection paradigms. Source memory typically activates anterior and ventro- and dorsolateral prefrontal cortex (Fletcher and Henson, 2001), whereas autobiographical memory typically activates only anterior medial frontal cortex (Maguire, 2001; Piefke et al., 2003). Specifically, we tested the hypothesis that in source memory paradigms the prefrontal activity is the result of contextual interference between the test events (Burgess et al., 2001).

In the earlier study of context-dependent episodic memory, we used virtual reality to create a limited number of rich contexts in which several events occurred (Burgess et al., 2001). Although that study had attempted to match the contextual richness of autobiographical memory, it failed to match the diversity of different contexts for each event. The results of that study showed a pattern of BA10, anterior cingulate, dorsolateral and ventrolateral prefrontal recruitment typical of source memory tests (i.e. memory for stimuli from a restricted set of

contexts), or tests of recollection using stimuli in a single context. In the current study, we increased the diversity between the contexts of the events, each having a distinct context. We had predicted that this would reduce the extent of prefrontal involvement, and this was indeed the case. Other than the increased number of places and characters in the present study, the new procedure is similar to our previous study, and this is reflected in the similarity of medial temporal/parietal activations associated with context-dependent memory in all the contrasts of both studies. This temporoparietal network was posited by Burgess et al. (2001) as a neural substrate for the storage of spatial and episodic memory, with prefrontal areas required for strategic aspects of retrieval including dealing with contextual interference between events.

Our results support the prediction that the prefrontal activations in the 2001 study resulted from contextual interference in all contrasts of context-dependent memory with either object familiarity or perceptual judgement and that there was clearly much less, or in many instances an absence of, significant activation in the aforementioned prefrontal regions. A direct statistical comparison between the two datasets showed that this difference was significant in the anterior prefrontal region of BA10 for all four of the context-dependent memory contrasts, with significant differences in lateral prefrontal region in some of these contrasts.

Our comparative analysis shows that activation in anterior BA10 was consistently reduced, confirming our prediction for this region, while activation in lateral PFC and anterior cingulate was reduced in some contrasts (mostly those involving place rather than person as a cue). This pattern suggests that even though the lateral PFC and anterior cingulate activations from the 2001 study appear largely reduced by our manipulation, there was still some sub-threshold activation in these regions. These results suggest that BA10 is the prefrontal region most involved in dealing with contextual interference. This may reflect a greater need for executive processes in such tasks, consistent with theories of frontal involvement in memory in which the lateral PFC regions are involved in the selection of candidate memory traces while anterior PFC exercises higher level control. Our results also predict that frontal patients would be less impaired in source memory experiments involving distinct sources for each event rather than many events from a few sources.

It should be noted that we were able to reduce interference but not eliminate it altogether—there is a limit to how distinct a series of events experienced over a short time in a virtual environment can be, and for reasons of experimental control, each event followed an identical pattern in terms of the actions of the subject. This may have inhibited holistic encoding; Brewer and Dupree (1993) found that memories for distinct actions are holistically encoded, whereas those for similar ones are not. However, this should have been much less of a problem using our realistic episodic stimuli than for many source memory paradigms. We also note that the task could be solved by elimination—i.e. by recollecting the context associated with the “incorrect” object and rejecting it rather than recognising the association between the “correct” object and the presented context. This does not present a problem of interpretation, however, as either strategy relies on the subjects’ context-dependent memory for the original episodes.

One interesting finding in the current study is the anterior ventromedial PFC activation in the person–object contrast,

which was not found in the same contrast in the 2001 experiment (though this difference is not statistically significant at $P = 0.001$). The same region has been implicated in temporal context confusion (Schnider et al., 2000; Schnider and Ptak, 1999) as well as in memory for autobiographical events (Cabeza et al., 2004; Maguire, 2001; Piefke et al., 2003). The fact that the activation was seen in the person–object contrast suggests that social relevance may play a particular part in the role of this region in memory. This view is consistent with neuroimaging studies implicating medial polar prefrontal cortex in both theory of mind (Fletcher et al., 1995) and imagining the actions of others (Ruby and Decety, 2001), though in both cases, the focus of activation was slightly superior to those we report here. The absence of such significant activation in the 2001 study may be due to the reduced distinctiveness in the events in that study—after repeated exposure to the same two characters, person-based responses may have habituated, while in the present study, a new character was associated with each event.

A number of theories have been proposed to account for prefrontal involvement in long-term memory including *post-retrieval processing* (Rugg et al., 1996), *descriptor*, and *verification* processes (Burgess and Shallice, 1996), supporting a specific *retrieval mode* (Nyberg et al., 1995), *monitoring* (Henson et al., 1999; Petrides et al., 1995), *retrieval effort* (Schacter et al., 1996), and *response conflict* (Botvinick et al., 1999). Our position is not inconsistent with these other accounts and may suggest one specific cause behind some of these more general effects in BA10 and, to a lesser extent, left ventrolateral PFC and anterior cingulate. For example, contextual interference may be one aspect contributing to retrieval effort and would provoke additional post-retrieval processing or monitoring, as well as response competition. Furthermore, it has been suggested that ventrolateral activity would be greater when retrieval cues are ambiguous (Petrides, 2002; Simons and Spiers, 2003), while dorsolateral activity could be related to selection amongst competing memories (Rugg et al., 1999). These factors certainly apply in this case—the use of the same contexts for several events in the 2001 study means that the contextual cues were both less well defined and would lead to more competing traces than in the present study. The study of confabulation has led to the proposal that ventromedial PFC plays a role in the disambiguation of events from different temporal contexts (Schnider and Ptak, 1999; Schnider et al., 2000). The strongest modulation of activation by contextual interference was in BA10. Recent theories of frontopolar cortex have postulated a high-level role in the evaluation of internally generated information (Christoff and Gabrieli, 2000) or as a “gatekeeper” between stimulus-oriented and stimulus-independent processing (Burgess et al., 2005). While these schemes do not directly address contextual interference in retrieval, they are broadly consistent in that there will be more internally generated information in the high-interference task. In fact, our BA10 activations are largely in the lateral part of the region, consistent with the gatekeeper model, which sees lateral BA10 as concerned with stimulus-independent processing. Our suggestion is that some of the frontal activity in episodic memory paradigms which use contextually impoverished stimuli is due to the effects of interference between similar contexts. These activations would not be seen if the episodic events used had more distinct contexts, as is the case with typical autobiographical stimuli.

Of course, there are clearly also other factors (unrelated to contextual interference) that modulate prefrontal activity—for example, greater involvement of dorsolateral PFC in free rather than cued recall (Fletcher et al., 1998). However, it also follows from our position that studies of episodic recollection using stimuli in restricted contexts may not reflect the set of typical processes involved in recollection of autobiographical experience, in which contexts are richer and more distinct. This view is consistent with a recent review of neuroimaging studies (Gilboa, 2004) in which a distinction is apparent between studies using lists of artificial stimuli and studies using autobiographical material.

Conclusion

We have shown that anterior and left ventrolateral prefrontal involvement in context-dependent memory for events can reflect interference between the events’ contextual cues. Our results imply that prefrontal involvement in source memory is largely driven by the use of paradigms involving many events and few sources rather than by any fundamental processing requirements of contextual retrieval in the absence of interference. This potentially accounts for some of the prefrontal activations found in prior studies using contextually impoverished stimuli, but not found in prior studies of autobiographical memory. In addition, the increased contextual richness of our paradigm may have contributed to ventromedial prefrontal activation similar to that previously found in studies of autobiographical memory. This is one way in which the VR paradigm may allow us to get closer to providing controlled but pseudorealistic autobiographical stimuli. We also found little super-additive effect of using multiple contextual cues compared to single cues, the exception being a small activation in the perirhinal cortex. One area for future research will be to simulate the variety of actions as well as contexts found in autobiographical memory. Another area will be to understand the lower-level processes involved in dealing with interference from similar contexts, in relation to current theories of prefrontal function.

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