Functional MRI evidence for a role of frontal and inferior temporal cortex in amodal components of priming

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Summary
Changes in human brain activity associated with repetition priming during word generation were characterized across a series of neuroimaging and behavioural studies. Repetition priming was consistently observed behaviourally as a decrease in response latency for repeated items, and was found for both visually and aurally cued word-generation tasks. Brain imaging using whole-brain functional MRI identified neural correlates of these effects. The principal effect of priming was to reduce neural activity within regions that were already being used to perform the word-generation tasks. Repeated word generation in response to visual cues was correlated with anatomically selective reductions in activity within the left frontal cortex along the inferior frontal gyrus and inferior temporal regions and, to a lesser degree, in specific earlier visual regions. These reductions were reversed when new items were presented, indicating that they were item-specific. Repeated word generation in response to aural cues also showed anatomically selective activity reductions within the left frontal and inferior temporal regions, indicating that
these activity reductions were not dependent on the perceptual modality of the cue. The auditory cortex showed minimal repetition-related reductions. The presence of activity within left frontal regions that decreases as a function of item repetition for both visual and auditory cues suggests that these reductions may underlie an amodal repetition-priming effect existing at processing stages involving lexical/semantic search and access. The surprising finding that activity reductions in the inferior temporal cortex can be linked to repetition of either visual or auditory cues further suggests that these regions may be modulated in a top-down fashion during repetition priming, independent of (or in parallel with) stimulus-driven perceptual processes. Taken collectively, the data converge on a neural correlate of lexical/semantic priming. Amodal lexical/semantic processes, which may be triggered initially by modality-specific cues, proceed via an interaction between frontal and posterior brain regions. These interdependent regions show activity reductions that correlate with facilitated task performance when items are repeated.

Introduction
Brain imaging methods based on PET and functional MRI (fMRI) have been used recently to characterize the regions involved in word-retrieval tasks and to determine how the level of activity within these regions may change when items are repeated. Both PET and fMRI studies have shown that word-retrieval tasks that depend on meaning-based (semantic) decisions or phonological decisions are most often accompanied by increased activation in several spatially and functionally diverse regions (for reviews, see Wise *et al.*, 1991; Petersen and Fiez, 1993; Warburton *et al.*, 1996; Binder *et al.*, 1997; Cabeza and Nyberg, 1997). In addition to increased activation in modality-specific brain regions

involved in the initial perception of the stimuli used to cue task performance (e.g. activation in the visual cortex in the case of visually presented words or other items), word-retrieval tasks often activate regions of the left inferior frontal gyrus at or near Brodmann areas (BA) 44, 45 or 47, sometimes extending in an anterior and dorsal direction along the border of the prefrontal and motor cortex (BA 44 or 6). Activations in the anterior cingulate, right lateral cerebellum and left temporal cortex are also commonly observed.

These regions play some role in operating on and/or maintaining higher-level verbal representations. However, the specific role is unclear at present and may relate to aspects of phonology, lexical representations and/or their integration with semantics; subregions within the larger networks probably provide separate processing contributions. What is clear is that, across a wide range of tasks that demand elaboration upon verbal and semantic representations, this network of higher-level regions that includes the frontal cortex is consistently activated and is largely independent of the specific modality of the cue (e.g. Chee *et al.*, 1999) or even whether the cue is a picture or visual word (e.g. Vandenberghe *et al.*, 1996). Moreover, these regions can be modified by experience. When subjects retrieve the same words repeatedly or make the same semantic meaning-based decision on multiple occasions, activity within these regions is attenuated (Raichle *et al.*, 1994; Demb *et al.*, 1995).

The observation that these regions can be modified by experience is particularly critical for the understanding of human memory. Behavioural indices, such as response latency and accuracy, have shown that when items are repeated during semantic or lexical retrieval (or decision tasks), performance on the repeated items is faster, more accurate, and/or biased—a phenomenon referred to as repetition priming. Expanding beyond the early studies of Raichle and colleagues and Demb and colleagues, mentioned above, numerous studies have shown that brain regions that are active during the initial performance of a semantic or lexical retrieval task are less active after repeated exposures to the items (Squire *et al.*, 1992; Raichle *et al.*, 1994; Buckner *et al.*, 1995a; Demb *et al.*, 1995; Blaxton *et al.*, 1996; Gabrieli *et al.*, 1996; Schacter *et al.*, 1996). These reductions may reflect a neural correlate of repetition priming (Ungerleider, 1995; Schacter and Buckner, 1998; Wiggs and Martin, 1998). Repetition-related reductions have been observed in the frontal cortex and in the other regions mentioned above, as well as in earlier visual regions associated with perceptual processes.

Recent investigations have focused on understanding which specific brain regions show priming-related activity reductions and what kinds of task processes are correlated with these reductions. These explorations are, in part, motivated by the behavioural observation that repetition-priming effects can be reduced, but are typically not eliminated, when the perceptual characteristics of a repeated item are changed between study and test. For example, priming effects are often reduced when an item is presented first in the visual and then in the auditory modality, or when characteristics of an item within a given modality are altered (Roediger and McDermott, 1993; Schacter *et al.*, 1993). Behavioural observations indicating that priming may often, to a greater or lesser degree, survive changes in the specific perceptual format of the stimulus suggest that priming involves both form-specific and non-specific or amodal mechanisms (Kirsner *et al.*, 1989; Rajaram and Roediger, 1993), possibly involving processes occurring at multiple stages in a processing hierarchy (Roediger *et al.*, 1999) and/or multiple brain regions within processing subsystems (Schacter and Tulving, 1994). Perceptual processing regions that are sensitive to the perceptual format of a stimulus and higher-level, conceptual processing regions that are relatively less influenced by the precise perceptual instantiation of a word or concept may both benefit from item repetition. That is, repetition priming may modify activity both within relatively early brain regions involved in perceptual processes and in regions occurring later in the hierarchy of processing, at more conceptual stages that promote lexical and semantic access. Anterior brain regions, including the left frontal cortex discussed above, provide a prime candidate for regions likely to be involved in conceptual aspects of repetition priming; more posterior modality-specific regions in the visual or auditory cortices may be involved in perceptual aspects of priming.

In the present study, two related questions were explored using functional neuroimaging techniques: (i) to what extent are brain regions that are believed to be involved in amodal (conceptual) processing modulated by repetition priming? (ii) to what extent are brain regions that are believed to subserve modality-specific processes modulated by repetition? These questions were addressed in a series of fMRI studies using both visually and aurally cued tasks. All of these studies involved word-generation tasks that have been used previously with PET. Because these word-generation tasks can cause motion artefacts when overt speech is employed, we adopted a covert procedure in which subjects generate words silently. Accordingly, a series of behavioural studies outside the MRI environment was also conducted to characterize the behavioural correlates of repetition priming in these covert tasks, and to build confidence that the paradigms imaged using fMRI yielded robust repetition-priming effects under covert word-generation procedures.

Methods
Overview
Subjects performed word-generation tasks within the MRI environment or outside the MRI environment, in a behavioural setting typical of cognitive psychological studies. Cues to guide word generation (most often the beginnings of words or word stems) were presented in blocks. A given block consisted either entirely of new items (cues that were never previously presented in the experiment) or entirely of repeated

Table 1 *Overview of studies*

Study	Type	n	Stimuli	Modality	Task	Response mode
1a	Beh	12	Word stems	Visual	Word completion	Overt
1b	Beh	12	Word stems	Visual	Word completion	Overt and covert
1c	fMRI	8	Word stems	Visual	Word completion	Covert
2a	Beh	12	Word stems	Visual	Word completion	Overt
			Nouns	Visual	Verb generation	Overt
2b	fMRI	8	Word stems	Visual	Word completion	Covert
			Nouns	Visual	Verb generation	Covert
3a	Beh	12	Word stems	Auditory	Word completion	Overt
3b	Beh	12	Word stems	Auditory	Word completion	Overt and covert
3c	fMRI	12	Word stems	Auditory	Word completion	Covert

Beh = behavioural study; n = number of subjects participating in substudy.

items (cues that were presented previously, in earlier blocks of the experiment). Within the MRI environment, brain activity was indirectly measured using an fMRI sequence sensitive to blood oxygenation level-dependent contrast (Kwong *et al.*, 1992; Ogawa *et al.*, 1992); all word generation was performed covertly. In the behavioural setting, voice onset latencies of word generation were measured to provide a behavioural index of repetition priming. Critically, in the behavioural setting both covert and overt word-generation procedures were used to determine their comparability.

Methods that are general to all of the studies are described first, followed by the methods and results pertaining specifically to each of the five behavioural and three fMRI studies. Table 1 provides an overview of the studies, including the type of study (behavioural or fMRI), the nature of the stimuli, the presentation modality, the word-generation task performed and the response mode (overt, covert or both). As indicated in Table 1, the studies were organized into three sets of experiments and subexperiments: experiments 1a–c focused on visual word-stem completion, experiments 2a–b compared visual word-stem completion with visual verb generation, and experiments 3a–c examined auditory word-stem completion.

Subjects

All subjects were native speakers of English between the ages of 18 and 37 years. The number of participants included in the three fMRI experiments were as follows: eight in fMRI experiment 1 (six males); eight in fMRI experiment 2 (four males); and 12 in fMRI experiment 3 (six males). All fMRI subjects were right-handed, as assessed using the Edinburgh Handedness Inventory (Lezak, 1995). For the behavioural studies, 12 naive subjects between the ages of 18 and 35 years served in each study. Informed consent was obtained prior to scanning or testing in a manner approved by the Human Studies Committee of the Massachusetts General Hospital.

Behavioural methods

Visual stimuli were presented using a PowerMacintosh (Apple Computer) connected to a Sharp 2000 colour LCD projector.

For fMRI, stimuli were projected onto a screen attached to the head coil through a collimating lens. For the auditory study, subjects wore a custom-modified headphone connected to an amplifier outside the MRI suite. Sounds were presented by the PowerMacintosh computer and fed directly into the amplifier. In the behavioural setting, stimuli were displayed on a 17-inch AppleVision monitor. Voice onset latencies were recorded through a CMU button box (Carnegie Mellon University, Pittsburgh, Pa., USA). Sounds were presented using AppleDesign Powered Speakers (Apple Computer).

MR imaging methods

Scans were acquired on a 1.5 T General Electric scanner fitted with an echo-planar imaging upgrade (Advanced NMR systems, Wilmington, Mass., USA). Whole-brain imaging was performed using the standard General Electric quadrature head coil.

Subjects lay in the scanner with the head snugly surrounded by a pillow and cushions within the head coil to reduce movement. The scanning procedure involved first collecting anatomical images and adjusting the echo-planar shim (Reese *et al.*, 1995). This non-functional portion of the session (~30 min) was directly followed by eight to 10 functional runs of 3.5 min each (<1 h 30 min).

Two relevant anatomical images were collected, including: (i) a sagittal localizer image [conventional T_1-weighted spoiled gradient echo (SPGR) sequence, 60 contiguous 2.8 mm slices) and (ii) an echo-planar T_1-weighted inversion recovery image aligned to the functional runs [TI (inversion time) = 1200 ms, 1.563×1.563 mm in-plane resolution].

Functional runs involved scanning over 16 or 17 transverse slices (7 mm, skip 1 mm between slices, 3.125×3.125 mm in-plane resolution) aligned to the plane intersecting the anterior and posterior commissures. The resulting 12.8 or 13.6 cm range of imaging was sufficient to image the entire brain, including the cerebellum, in almost every subject. Between 105 and 128 images per slice were acquired using a T_2^*-weighted asymmetrical spin echo sequence designed to reduce contributions from large vessels [TE (echo time) = 70 ms, 25 ms offset] (Baker *et al.*, 1993). A set of four or more sequential images were generated and discarded before

the critical image acquisition was begun in order to allow saturation of T_1.

Generation of individual subject activation maps

All fMRI runs for an individual subject were averaged vertically, such that each time-point was the average of that same time-point across runs. For example, if six runs were collected from a subject, the images acquired at the 8 s time-point in each of the six individual runs were averaged to yield one set of images at 8 s, each image representing the mean of the six contributing images.

Runs averaged within a subject were used to construct a statistical activation map based on the non-parametric Kolmogorov–Smirnov statistic (Press *et al.*, 1992). Either all task blocks were compared with fixation blocks, or the task blocks of novel items were directly compared with blocks of repeated items (similar to Buckner *et al.*, 1998*a*, *b*; Wagner *et al.*, 1998). Statistical maps were displayed using a pseudocolour scale superimposed on the high-resolution EPI (echo-planar imaging) T_1-weighted inversion recovery image, which was acquired in-plane and aligned to the functional activation runs.

Generation of group activation maps in Talairach space

Each individual subject's data were transformed into the stereotaxic space of the Talairach and Tournoux atlas (Talairach and Tournoux, 1988) using procedures described previously (Buckner *et al.*, 1998*a*, *b*). Once in atlas space, data were averaged across subjects. First, the interpolated SPGR images were averaged to yield a mean anatomy image. Secondly, the functional runs were averaged and used to construct activation maps in a manner identical to that used for individual subjects. In this instance, however, the interpolated and averaged SPGR images were used as an anatomical underlay.

Identification of peaks in standardized atlas coordinates and time-course generation

Coordinates of activation peaks were determined using an automated peak detection algorithm. Peaks were defined as the location of voxels (i) showing significant activation ($P < 0.0001$), (ii) showing more significant activation than neighbouring voxels, and (iii) occurring within a cluster of at least five significant voxels. These procedures have been set so as to identify few false positives in control data sets using the logic of Zarahn and colleagues (Zarahn *et al.*, 1997; see also Buckner *et al.*, 1998*b*). The location of the most significant voxel was selected in instances in which peaks were identified within 8 mm of each other. However, because of uncertainties in any statistical-threshold procedure owing to coloured-noise properties such as motion, the time-

course of the signal change was characterized for all peaks of theoretical interest to determine whether the signal change followed the task paradigm (Binder and Rao, 1994).

Regions were defined around these peaks using a second automated procedure to track the signal change within that region over time. For this procedure, all contiguous significant voxels within 12 mm of the peak location were included in a 3D volume. Mean signal intensity within this volume was calculated for each image over the averaged functional runs, yielding a time-course for the signal change. The time-course was corrected for linear drift and temporally smoothed with a 6 s Hanning filter. The time-course was then scaled to percentage signal change.

Individual experiments and results
Experiment 1a: visually cued overt word-stem completion

Repetition-priming effects were examined in an overt visually cued variant of the word-stem completion task. Subjects were presented visually with three-letter word stems, one at a time (e.g. 'gre_' or 'pur_'), and were instructed to generate aloud the first English language word completion that came to mind (e.g. 'green' or 'purple'). Word stems were selected from a pool of 288 unique three-letter word stems that had at least five English word completions. Word stems were presented centrally in white-on-black letters, in 36-point Geneva font. The stimulus duration was 2.0 s, with 2.5 s between the onsets of stimuli. Behavioural testing was conducted in experimental runs in which blocks of multiple stimuli were presented sequentially and repeatedly, across a given run (12 stimuli in each 30 s block). Each block contained stimuli that were presented in a different random order each time. The stem-completion blocks were separated by a 30 s period of visual fixation. In this manner, a series of word-stem completion blocks was performed with items within the blocks having been exposed for differing numbers of repetitions across blocks. In the first block the word stems were new (NEW), in the second they were repeated once (REP1), in the third they were repeated twice (REP2), etc. for a total of five blocks. Six runs were conducted for each subject. This paradigm is identical to fMRI experiment 1c except that, in the behavioural study, subjects responded overtly to each word-stem cue.

Experiment 1a: results

Clear repetition-priming effects were observed (Fig. 1). The mean reaction time for NEW word-stem completions (the first block) was 902 ms. Responding became progressively faster across repetitions, decreasing to 726 ms by the final block. A repeated measures ANOVA (analysis of variance) performed on the mean voice onset latencies for the five blocks showed a highly significant effect of repetition [$F(4,44) = 16.57$, $P < 0.0001$].
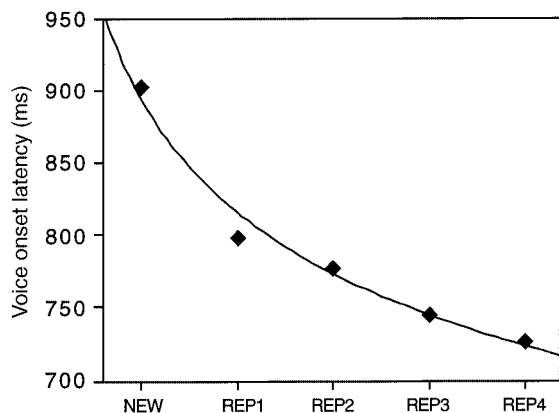
Fig. 1 Overt visual word-stem completion. Repetition priming in experiment 1a was revealed as a speeded response across blocks when items were repeated. Mean voice onset latency is plotted for each block as a diamond. NEW = block of items comprising entirely word stems that were not previously presented; REP1 = block of items where all stems were previously presented once; REP2 = items previously presented twice, etc. The line is the best log fit for the data.

Fig. 2 Overt and covert visual word-stem completion. Repetition priming in experiment 1b was again revealed as a speeded response across blocks. Mean voice onset latency is plotted for each block as a diamond, similar to Fig. 1. The filled diamonds indicate overt task blocks; open diamonds indicate covert task blocks. The lines are the best log fit for the data, with the initial latency for the covert blocks estimated from the PRE block (all items NEW). Overt and covert repetitions gave a similar increase in speed of responding.

Examination of participants' response stereotypy revealed that, on average, subjects provided the same completions to the stems on 87% of the trials (SD = 0.09, range = 0.72–0.98; calculated as the sum of the most frequently repeated responses for each item). Furthermore, in this experiment and all subsequent behavioural experiments, significantly greater decreases in response times were found for those items where subjects provided the same response to the repeated cues than for those occasional items where they generated a novel response to the repeated cues (and which showed response times similar to those of never-presented NEW items). This suggests that priming depended on repetition of both the cue and the lexical/conceptual processes involved in generating the response.

Experiment 1b: visually cued overt and covert word-stem completion

In order to determine whether covert word-stem completion would yield repetition-priming effects similar to those of overt word-stem completion, a behavioural study was conducted using a within-subjects design in which, across runs, subjects generated words either overtly or covertly (three runs of each kind). For the covert runs, subjects did not speak aloud during the initial repetition blocks but silently generated a single-word completion for each cue as it was presented. The response was then switched to overt production after four item repetitions so that the repetition-priming effect could be assessed. As in the subsequent fMRI studies, which also involved covert rather overt word generation, the instructions to participants were specific, requiring subjects to covertly generate a response for each item that was presented.

In addition, to allow the estimation of voice-onset latencies for the new items in the covert runs, prior to the first block
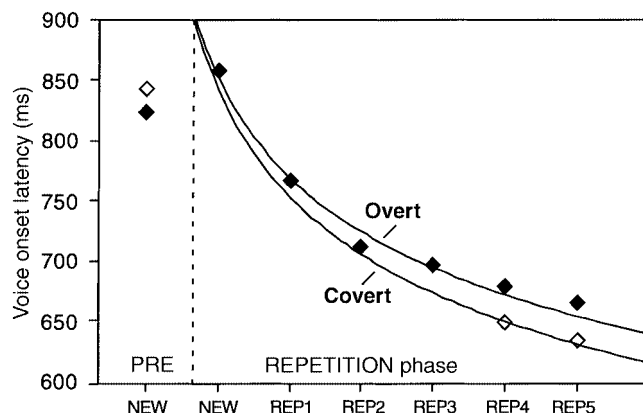
an additional set of new items was presented. For this prerepetition block, subjects responded overtly for both overt and covert word-production runs. This allowed estimation of the beginning of the voice-onset latency for subjects during the covert word-production runs but without participants ever overtly producing items in the critical covert blocks. Similarly, the final block (REP4) was performed overtly for both the overt and covert word-production runs, allowing the effect of item repetition to be assessed in both instances. For all runs (both overt and covert), participants were instructed, via a visual cue presented immediately before each block, whether the block was to be 'spoken' or 'silent'. The basic question was: would runs involving covert word production show the same item-repetition effects as those involving overt word production? Finally, a final overt block of repeated items (REP5) was added as a further control so that subsequent learning could be assessed in the covert blocks following the adoption of an overt response.

Experiment 1b: results

Again, clear repetition-priming effects were observed for overt word production (Fig. 2). Importantly, item repetition effects were also clearly observed for covert production; there was little difference between the covert and overt runs. The mean reaction time for completions to the NEW word-stems was 858 ms for the overt runs and was estimated to be 842 ms for the covert runs (based on the PRE repetition block). In the overt condition, responding became progressively faster across repetitions, reducing to 677 ms by the fourth repetition block. As shown in Fig. 2, covert repetition yielded a similar repetition-priming effect, decreasing to 649 ms by the fourth repetition. The final, overt fifth repetition block yielded only slightly faster latencies for

Table 2 *Selected foci of activation across studies*

Region	Exp 1c: vis stem			Exp 2b: stem + verb			Exp 3c: aud stem		
	x	*y*	*z*	*x*	*y*	*z*	*x*	*y*	*z*
Task conditions greater than low-level control									
L frontal	−34	9	34	−37	9	37	−40	6	34
L operculum	−28	22	12	−28	28	12	−28	22	9
L inferior temporal	−37	−55	−18	−50	−58	−12	−43	−52	−12
SMA/preSMA	0	0	56	−6	3	65	−3	−3	59
	6	9	56	0	16	65	3	13	50
R cerebellum	12	−65	−31	15	−68	−34	12	−68	−21
	34	−65	−21	43	−62	−21	28	−58	−21
NEW greater than REPEATED									
L frontal				−43	9	34	−43	6	25
L operculum				−43	34	3	−34	31	3
L inferior temporal				−43	−33	−9	−56	−43	0
				−53	−52	−9			
				−43	−46	−6			

Selected Talairach and Tournoux (1988) coordinates (*x*, *y*, *z*) are given for areas of greatest significance and generalization across studies. All coordinates listed designate regions of highly significant activation. A full list of coordinates is available upon request from the authors. SMA = supplementary motor area; vis = visual; aud = auditory; L = left; R = right.

both the overt and covert runs, indicating that the majority of the repetition-priming effect had been attained for both procedures.

A repeated measures ANOVA performed on the mean voice-onset latencies for the overt blocks, and including only the items from the repetition phase (i.e. items that were the same across the blocks, or the conditions NEW, REP1, REP2, REP3, REP4 and REP5 from Fig. 2) showed a highly significant overt repetition effect [$F(5,55) = 19.91$, $P < 0.0001$]. Importantly, a similar analysis for the covert blocks also showed an effect of repetition [considering only the PRE-NEW and REP4 blocks, $F(1,11) = 124.96$, $P < 0.0001$; considering PRE-NEW, REP4 and REP5, $F(2,22) = 84.47$, $P < 0.0001$].

Thus, by all measures used, the covert procedure yielded a repetition-priming effect that was robust and comparable with that of the overt production procedure. These findings suggest that (i) participants are generating words during the covertly cued blocks, and (ii) the processes underlying repetition priming occur under covert conditions.

Experiment 1c: fMRI of visually cued word-stem completion

The basic task paradigm was a covert variant of the word-stem completion task as used in behavioural experiments of the repetition-priming effect, and also as previously used with PET (Squire *et al*., 1992; Buckner *et al*., 1995a; Schacter *et al*., 1996) and fMRI (Buckner *et al*., 1996a; Ojemann *et al*., 1998) studies. Two types of fMRI run were studied. In the first six runs for each participant, 30 s blocks of word-stems were presented with all new items in each block. The goal of these runs was to determine the functional–anatomical brain regions recruited during the word-stem completion task,

independently of item-specific repetition-priming effects. The TR (repetition time) was set to 2.0 s. The second type of run was identical to that of experiment 1a, and comprised the final four runs for each participant. For these runs, the same set of word-stem cues was presented repeatedly across a series of five blocks. The TR was set to 3.0 s. The overall presentation parameters were identical to those of experiment 1a, except that the participants performed covert word-stem completion as described in experiment 1b.

Word-stem completion was contrasted with a low-level reference task in which subjects simply visually fixated on a centrally presented cross-hair. Fixation occurred for 30 s before and after each block of word-stem completion.

Experiment 1c: results
Main effect of task

A network of brain regions was active during word-stem completion when compared with fixation, confirming results from prior PET and fMRI studies (Buckner and Tulving, 1995; Ojemann *et al*., 1998) (Fig. 3, Table 2). This network included statistically significant activations within the visual cortex extending from medial regions that are likely to lie within the striate cortex to extrastriate regions to regions within the inferotemporal cortex; these extrastriate activations extended further in the anterior direction in the left than in the right hemisphere. Multiple frontal regions were active, including a dorsal frontal region within the inferior frontal gyrus near BA 6 and/or 44 and a ventral frontal (prefrontal) region within and lateral to the opercular cortex (at or near BA 44 and/or 45). Along the medial wall of the frontal cortex, activations were noted in supplementary motor area, extending into the anterior cingulate. The right lateral cerebellar cortex also showed prominent activation.
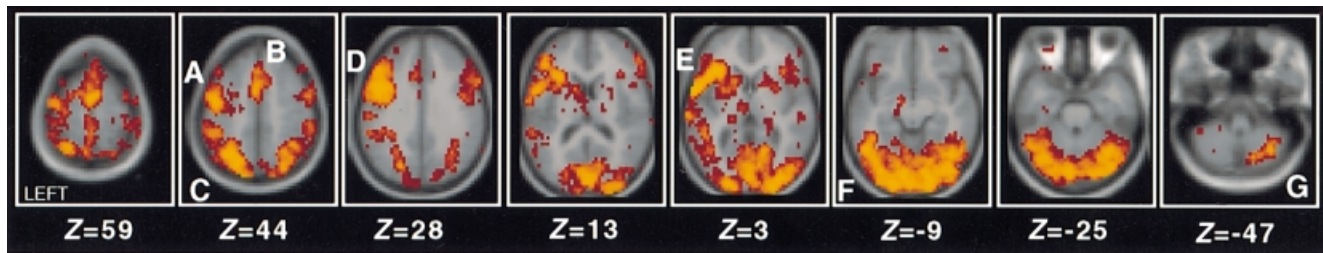
Fig. 3 fMRI of visually cued word-stem completion. Data from experiment 1c show the pathway of brain regions activated during word-stem completion when compared with fixation. Sections were taken horizontally; the inferior–superior level is given below each section based on the plane in the Talairach and Tournoux atlas (Talairach and Tournoux, 1988). Coloured voxels are all significant (threshold = $P < 0.001$); increasing significance is revealed by increasing colour intensity. A pathway of regions is activated, including left frontal regions along the inferior frontal gyrus (A, D and E), the supplementary motor area extending into the anterior cingulate (B), the lateral parietal cortex (C), the visual striate cortex extending into the extrastriate cortex and inferior temporal cortex (F), and the right lateral cerebellum (G).

A complete list of all active regions, their coordinates in Talairach and Tournoux atlas space (Talairach and Tournoux, 1988) and their significance can be obtained from the first author.

Repetition effects

To determine the correlates of repetition priming, the mean fMRI signal intensity was tracked across the new and repeated item blocks for a subset of regions that were activated by the task during initial runs (in which no items were repeated). The findings are shown in Fig. 4. Multiple regions, including those within the visual extrastriate cortex and the two regions within the left inferior frontal gyrus, decreased significantly for the repeated compared with the new items. Thus, the first three studies converge to demonstrate related correlates of repetition priming. Experiments 1a and 1b clearly revealed decreases in response latency as a function of repeated performance of the word-stem completion task, and the present experiment showed that these decreases were accompanied by reductions in the level of neural activation observed in specific regions of the pathway that is activated during word generation.

However, the present experiment contained two confounding factors. First, it is possible that the gradual reduction in fMRI signal that we observed for the left frontal regions partly or entirely derives from non-specific factors, such as fatigue, that are unrelated to item repetitions. Secondly, examination of the time-course of the fMRI signal revealed a signal undershoot that caused shifts in the baseline that could account for part or all of the signal reductions (e.g. the component labelled b in Fig. 4).

Confidence in the item-specific nature of the effects that we observed would be increased if it could be shown that (i) the reductions were specific to the particular sets of items that were repeated and did not generalize to new (not previously presented) items, and (ii) similar magnitudes and patterns of reduction occur under conditions in which multiple new blocks of items are included at the beginning of the runs, such that the fMRI signal undershoot would be stable

before presentation of the first repetition block. The first of these aims was addressed in experiment 2a, in which participants received both a modified version of the visual stem-completion paradigm and performed an additional verb-generation task (described below) in a behavioural setting; the second aim was addressed in experiment 2b, in which both the modified visual stem-completion and verb-generation paradigms were presented during functional imaging. Moreover, because new and repeated item blocks were examined within the same fMRI runs in experiment 2b, the separate item types could be compared directly in order to reveal the complete anatomy showing repetition-related modulation. It was not possible to perform this analysis in the present experiment.

Experiment 2a: overt visually cued word-stem completion and verb generation

Word-stem completion

In the modified visual word-stem completion paradigm, voice-onset latencies were examined when words were generated in response to visually presented word stems in a total of four runs. Each run comprised blocks of items that were repeated from previous blocks (similar to experiments 1a–c) but, in addition, they also included blocks of items at the beginning and the end of the run that were entirely new (never previously presented). Specifically, each run began with two blocks of new items, then items from the second block were repeated four times, after which there were two further blocks of new items (i.e. runs followed the following structure: NEW, NEW, REP1, REP2, REP3, REP4, NEW, NEW). The block length was decreased to 16 s and included seven items per block (stimulus duration = 1.5 s with 2.3 s between stimulus onsets). The key question was: will response latencies for the two blocks of new items at the conclusion of each run be similar to the response latencies for new items at the beginning of the run? If, as expected, response latencies abruptly increased upon changing from the repetition phase of the run to the presentation of new items, this finding
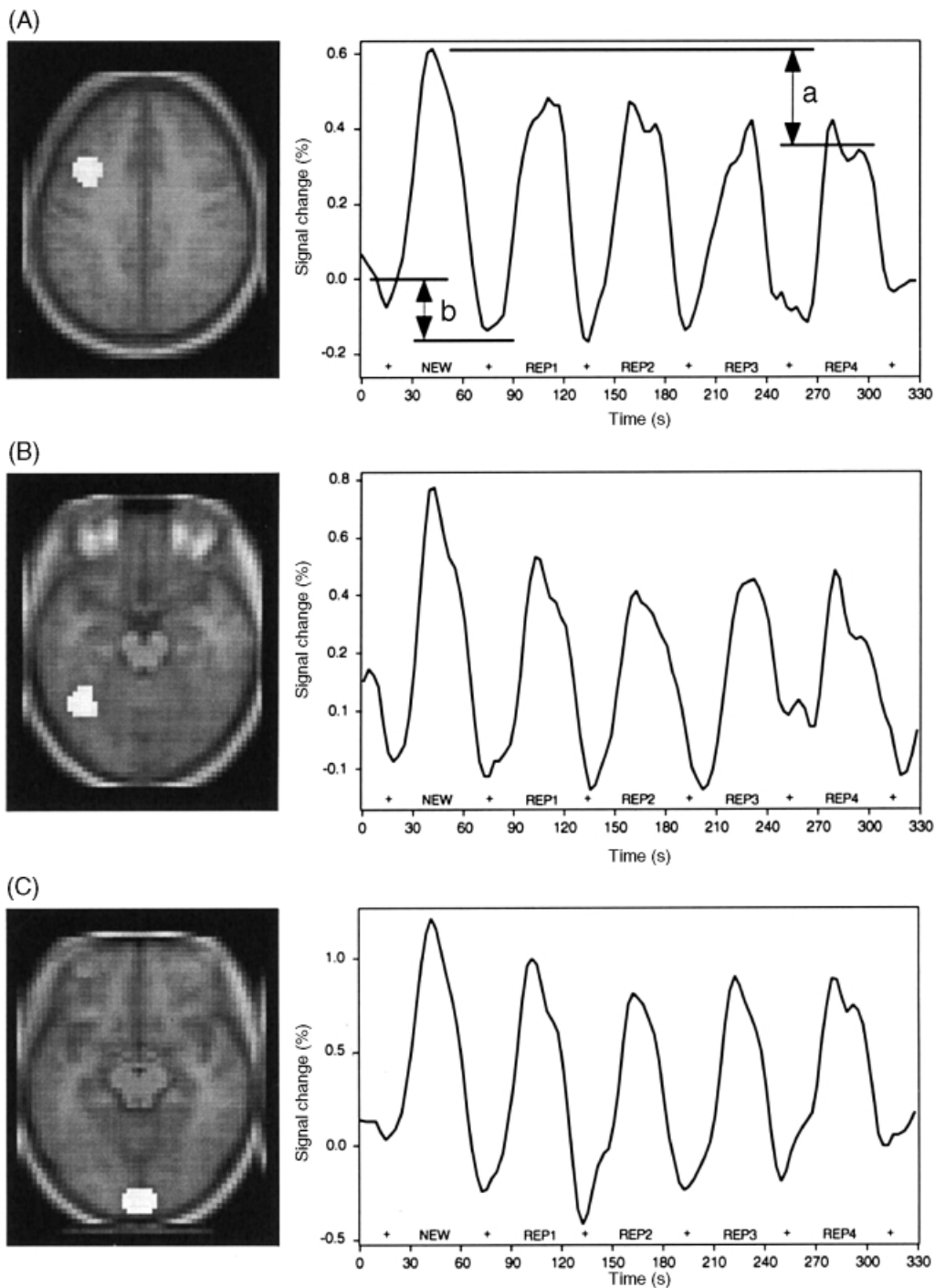
Fig. 4 fMRI signal changes for theoretically important regions. (**A**) A region within the left inferior frontal gyrus (–34, 9, 34). (**B**) An extrastriate region extending into the inferior temporal gyrus (–37, –55, –18). (**C**) A region at or near the striate cortex (lingual gyrus; 0, –93, –9). In each panel, the horizontal image to the left shows the area of the region in one plane. Regions were defined in three dimensions (see text). The time-course to the right shows the signal intensity over time for the region. Signal intensity is in percentage change and the positions of the task blocks are indicated at the bottom of the graph. Labels indicate word-stem completion task blocks. NEW indicates new items; REP1, REP2, REP3 and REP4 indicate blocks with items presented previously as described in the text and similar to Figs 1 and 2; + indicates fixation. In all three regions, signal intensity decreased with increasing repetition, as shown for the frontal region (a). However, a possible confounding factor existed in that the baseline signal was also changed between blocks during the fixation baseline (b).

would provide evidence for the item-specific nature of the behavioural facilitation effects we observed.

Verb generation

The observation in experiment 1c of repetition-related decreases in brain activation in amodal processing regions, particularly the left prefrontal cortex along the inferior frontal gyrus, suggests that the word-generation task reveals neural correlates of facilitated task processing in regions that are involved in higher-level aspects of lexical or semantic response generation and selection. However, in visually cued word-stem completion, retrieval occurs under conditions in which the stimulus cue (the three-letter word stems) provides comparatively direct perceptual support for word retrieval (but note that, because the word stems all allowed multiple completions, some selection as well as generation is clearly necessary). Examination of a task in which the stimulus cue does not provide any direct perceptual support for the response to be retrieved, and in which the relationship between the cue and the word to be generated is strictly semantic or conceptual in nature, would allow generalization of the findings from the stem-completion task. Investigating such a task would also establish more firmly that the repetition-related reductions that we observed are associated with repeated semantic, conceptual or lexical processing. A suitable task for these purposes is verb generation, which has been used previously in PET studies (e.g. Petersen *et al.*, 1988; Wise *et al.*, 1991; Raichle *et al.*, 1994; Warburton *et al.*, 1996). In the verb-generation task, participants are shown nouns (e.g. 'dog') and are asked to generate a verb that might be associated with the noun (e.g. 'walk' or 'bark').

As for visually presented word stems, the effects of repeated generation of verbs (action words) associated with nouns were assessed in an identical behavioural study that paralleled the word-stem study in design. All subjects performed both visual word-stem completion and verb generation, counterbalanced for order across subjects.

Experiment 2a: results
Word-stem completion

From Fig. 5 it is clear that the effects of repetition in the visual word-stem completion task were largely specific to the sets of repeated items: the mean voice-onset latencies for the first new blocks were very similar to one another (1002 and 1008 ms, respectively). These latencies were also similar to the concluding blocks of new items within each run (1029 and 1016 ms, respectively). Only the blocks in which the items were repeated showing systematically decreasing response times, decreasing to 870 ms by the fourth repetition. A repeated measures ANOVA, performed on the mean voice onset latencies in which only the blocks from the phase where there was repetition of the same items were considered, showed a significant effect of repetition [$F(4,44) = 8.63$,
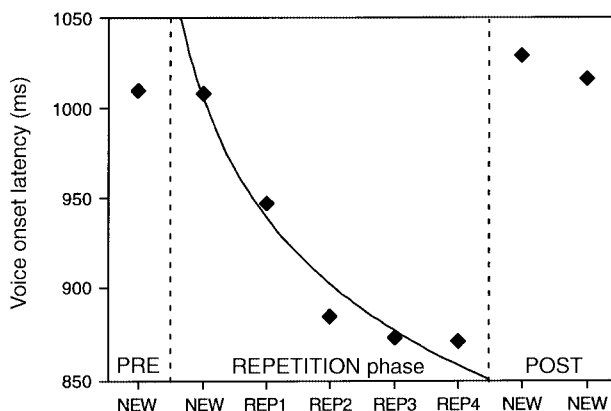

Fig. 5 Repetition priming for visual word-stem completion in the modified block design of experiment 2a. The NEW item blocks in the PRE phase showed similar mean onset latencies. During the REPETITION phase the response times decreased, revealing a behavioural correlate of priming. Critically, in the POST phase, when NEW items were again introduced, the response time increased to a level indistinguishable from that for the PRE phase, suggesting the repetition-priming effects were item-specific. The line is a log fit to the data acquired during the REP phase.

$P < 0.0001$]. In contrast, an ANOVA comparing the mean voice-onset latency for the first two NEW blocks versus that for the last two NEW blocks, provided no evidence of a global or 'item-independent' within-run practice or fatigue effect [$F(3,33) < 1$]; a similar conclusion could be drawn from a focused comparison of the average of the first two new blocks against the average for the last two new blocks [$F(1,11) < 1$]. These comparisons indicate that the effects of repetition in the visual stem-completion task are item-specific, i.e. observed when the particular stems are repeated, rather than as function of prolonged or additional performance of the task.

As in the previous experiments, participants' responses showed a high level of stereotypy (mean = 86%, SD = 0.08, range = 0.73–0.97) .

Verb generation

Repetition effects in the verb-generation task were clearly present, and paralleled the pattern observed for the word-stem completion task (Fig. 6). Response times were longer for new items for which participants were required to generate an appropriate verb for the first time (mean voice-onset latencies of 1267 and 1253 ms for the PRE NEW and NEW items, respectively), but decreased with repeated performance of the task, decreasing to 998 ms by the fourth repetition. A repeated measures ANOVA performed on the mean voice-onset latencies for the blocks from the repetition phase, in which the same items were presented repeatedly (i.e. conditions NEW, REP1, REP2, REP3 and REP4), revealed a significant effect of repetition [$F(4,44) = 38.83$, $P < 0.0001$]. Plotting the number of repetitions against the mean response time revealed that, as for the word-stem completion
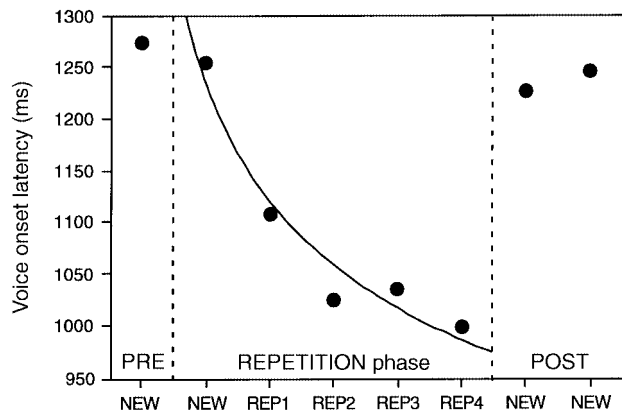
Fig. 6 Repetition priming for visual verb generation in experiment 2a. The pattern of response was very similar to that found for word-stem completion in Fig. 5. However, response times during verb-generation were slightly longer.

task, performance facilitation was well described by a power function (Fig. 6).

As found for the visual word-stem completion task, Fig. 6 shows that these decreases in response times were specific to the particular items that were repeated. The two measurements where new nouns were presented following the repetition blocks (POST) were accompanied by a clear increase in response latency, with response times (1226 and 1246 ms) that were very similar to the initial response times (1267 and 1253 ms). There was no difference in the average latency of responding to NEW items at the beginning of the runs versus NEW items at the conclusion of the runs [comparing all four blocks of NEW items, $F(3,33) < 1$; comparing the average of the first two NEW blocks against the average of the last two NEW blocks, $F(1,11) < 1.8$].

Consideration of participants' responses showed that the level of response stereotypy during the repetition phase was again considerable (mean = 84%, SD = 0.08, range = 0.67–0.96)

Experiment 2b: fMRI of covert visually cued word-stem completion and verb generation

Functional imaging was performed during covert tasks that were similar in format to those described in the behavioural experiment 2a. Both word-stem completion and verb generation were examined in separate runs. Prior to each run, specific instructions were given to perform all task blocks covertly. Ten functional runs (five for each task) were acquired per subject, each run consisting of 16 interleaved 16 s blocks (TR = 2 s). The ordering of which sets of runs came first (word-stem completion or verb generation) was counterbalanced across subjects. This design allowed several analyses beyond those possible in experiment 1c. First, each type of block (NEW or REP) could be independently compared with the same fixation blocks. Secondly, the NEW and REP blocks could be directly compared with each other to identify directly those regions that are modulated by item

repetition. Thirdly, the repetition effects could be examined after a baseline state had been established, following the signal undershoot as observed in experiment 1c and many prior fMRI studies. The signal rebound could be examined for the NEW item blocks following REP blocks to determine whether the repetition-related effects were indeed item-specific.

Experiment 2b: results
Main effect of task for word-stem completion
Consistent with experiment 1c, a network of brain regions was again activated by word-stem completion (all NEW words), as contrasted with the low level-fixation control (Fig. 7, Table 2). These activations were located within multiple left frontal and prefrontal regions (along the inferior frontal gyrus), the visual striate and extrastriate cortex extending into the inferior temporal cortex, and the right lateral cerebellum, among others. For reasons that are not clear, these data contained more noise of high spatial frequency (note the speckled appearance of the data in Fig. 7).

Main effect of task for verb generation
The findings from verb generation were extremely similar to those from word-stem completion. All of the activations generalized, including left prefrontal activation extending from both the inferior (near BA 44 and/or 45) and dorsal portions of the inferior frontal gyrus (BA 44 and/or 6) into more anterior prefrontal regions, including BA 47. Surprisingly, there were few differences between the word-stem completion and verb-generation tasks (Fig. 7A and B). On the one hand, this suggests that the present findings are reliable across independent data sets from different tasks. On the other hand, word-stem completion and verb generation are different in terms of task demands (for discussion, see e.g. Buckner *et al.*, 1995*b*). It is thus noteworthy that the two tasks activate similar anatomical regions, as revealed by bold-contrast fMRI. In the present study, however, a powerful means of comparing the word-stem completion and verb generation tasks was not available to address directly whether there were relatively subtle differences in the anatomical regions recruited by these two tasks. This is because the between-task comparison would be across runs. Results of this comparison were explored but yielded no notable differences. For purposes of further comparison of the repetition-priming effect, given that they were so similar, the two data sets were pooled in order to generate the best estimate of the repetition-priming effects. All effects noted were present and were very similar in both of the two data sets when they were considered separately.

Repetition effects
To address the question of repetition priming, regions in the left frontal cortex (centred on $x = -37$, $y = 9$, $z = 37$), the
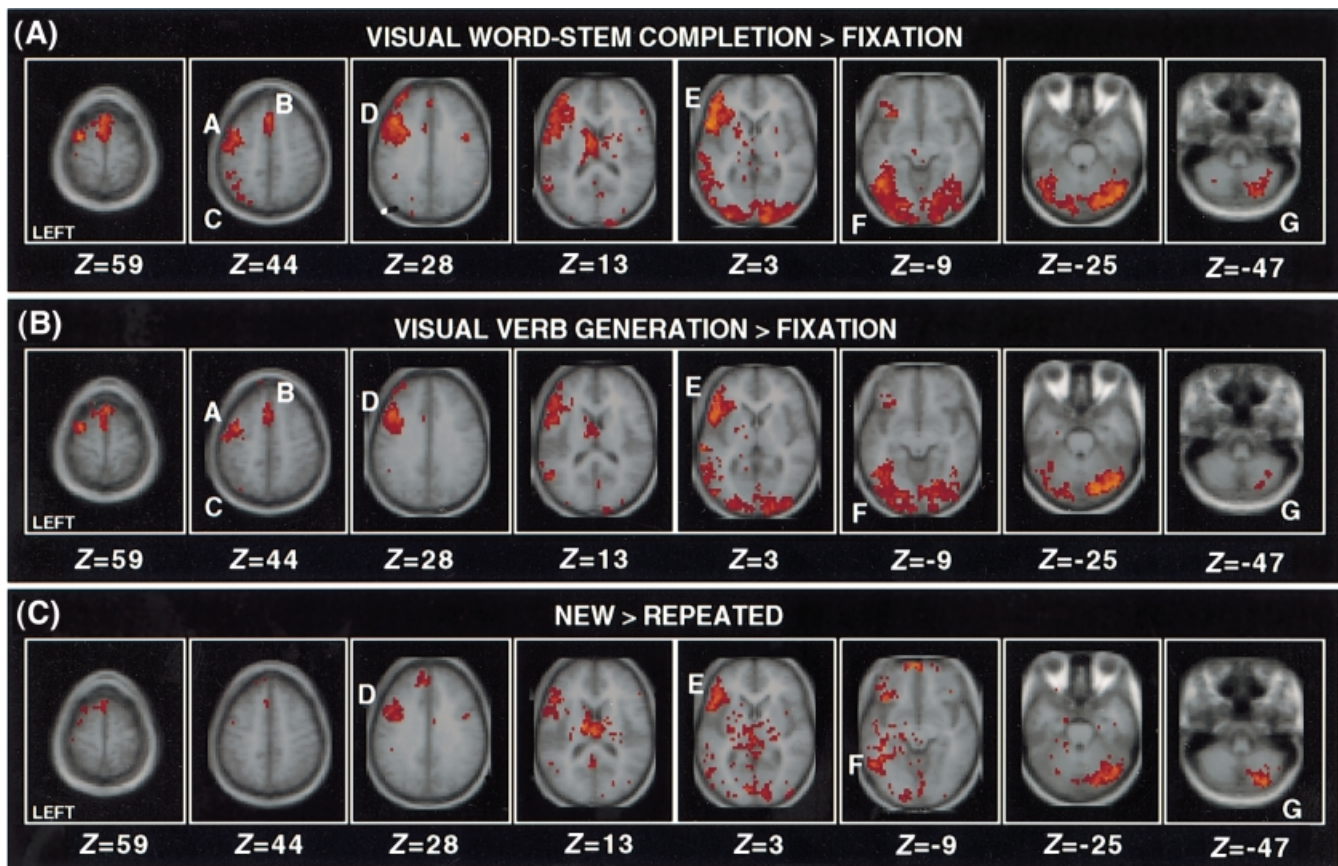
Fig. 7 fMRI of visually cued word-stem completion and verb generation. Data from experiment 2b show the pathway of brain regions activated during (**A**) word-stem completion compared with fixation, (**B**) verb generation compared with fixation and (**C**) for the repetition-priming effect in which all NEW item blocks were directly compared with all OLD item blocks. The format and colour scale are the same as in Fig. 3 with the threshold set to $P < 0.0001$. **A** and **B** reveal highly similar patterns of activation, which were also quite similar to those of experiment 1c (Fig. 3). A subset of activated regions showed repetition-priming effects as revealed in **C**. The most prominent included the left inferior frontal gyrus (labelled D and E) and the visual extrastriate regions extending into inferior temporal cortex (labelled F).

inferior temporal cortex (centred on $x = –50$, $y = –58$, $z = –12$) and the lingual gyrus at or near the primary visual cortex (centred on $x = –12$, $y = –99$, $z = –12$) were examined for regional signal intensity change over time (Fig. 8). All regions showed an effect of item repetition, with a qualitative decrease in magnitude as the repetitions increased. The signal intensities increased abruptly upon presentation of NEW items in the last two blocks, establishing that the signal reductions were related to item-specific factors, consistent with the behavioural repetition-priming effects observed in experiment 2a.

Statistical activation maps from the direct comparison between the NEW item blocks and REP item blocks revealed the network of brain regions showing priming-related reductions (Fig. 7C). Two notable findings emerged. First, confirming the observations from the regional analyses above, the left frontal and visual extrastriate regions extending into the inferior temporal cortex showed significant signal modulation between NEW and REP items, exhibiting greater activity during the NEW item blocks. Secondly, the network of regions showing significant reductions comprised only a

subset of those regions activated by the task when compared with fixation. That is, a subset of regions activated by the word-stem and word-generation tasks showed significantly reduced activation in association with item repetition although, qualitatively, most regions showed some degree of modulation. The regions showing robust signal reductions included the left frontal and inferior temporal regions but, consistent with prior PET and fMRI studies, did not include regions at or near the primary motor cortex or many of the visual regions activated during the task. However, unlike our previous study using randomly intermixed event-related trials (Buckner *et al.*, 1998*a*), the present study did reveal significant left-lateralized signal modulation at or near the primary visual cortex, perhaps reflecting a form of perceptual priming or decreased attention to items in the repeat blocks.

In general, the blocked-task paradigm used in the present study showed a subtle degree of repetition-related modulation in almost all of the time-courses that were examined. Moreover, blocked-trial modulation was also observed in the last new trial block in the POST repetition period within many regions, the second NEW trial block showing a signal
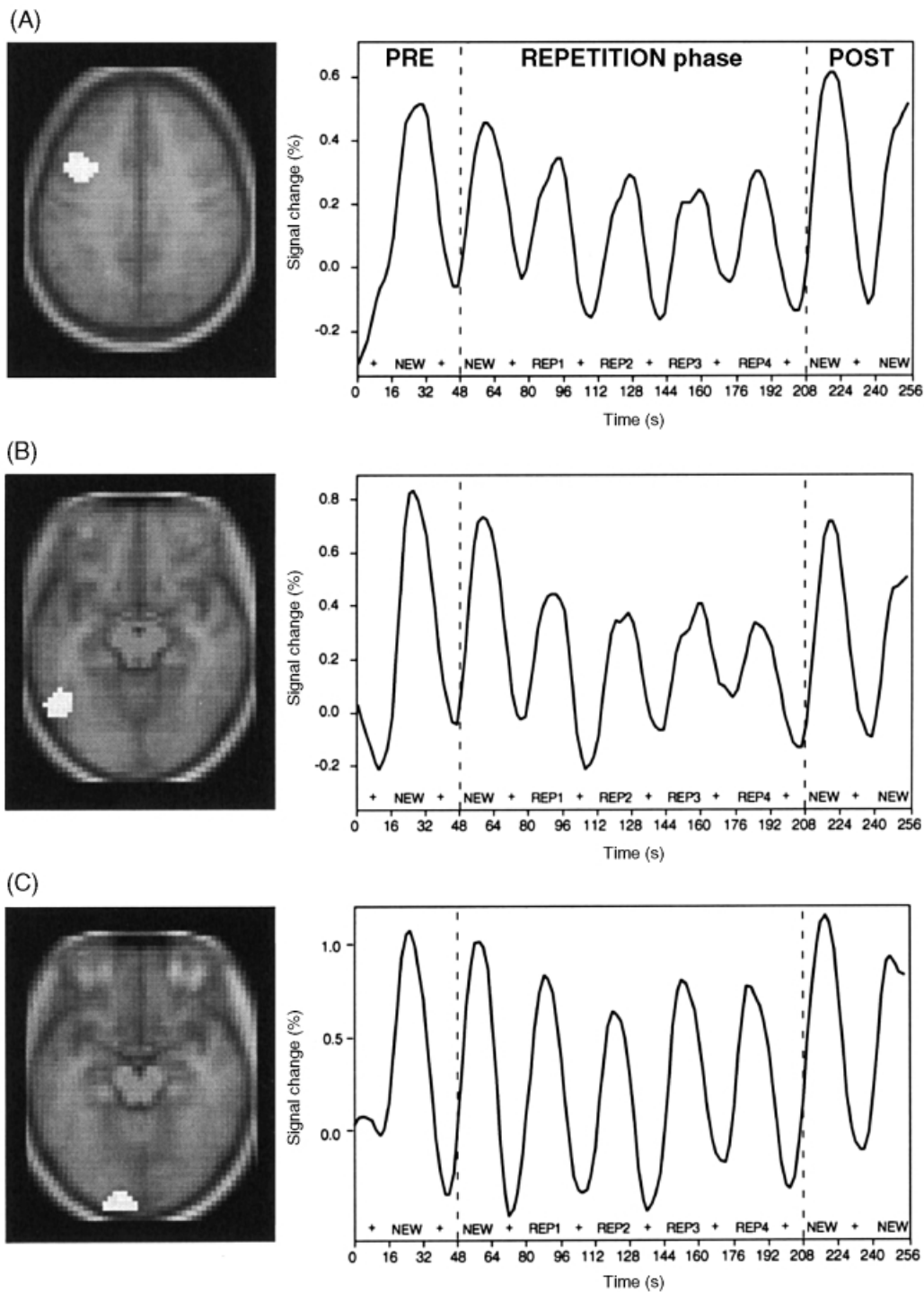
Fig. 8 fMRI signal changes in experiment 2b for three separate regions [**A**, left inferior frontal gyrus (–37, 9, 37); **B**, fusiform/inferior temporal gyrus (–50, –58, –12); **C**, lingual gyrus (–12, –99, –12)]. The time-course of regional signal change is shown in a format similar to that of Fig. 4. Clear effects of item repetition were observed during the REP phase. Importantly, the effects were not due to a shift in baseline, as the extra NEW block in the PRE phase allowed the baseline signal to reach a steady state (seen best in the lingual gyrus region). Furthermore, following the last repetition block (REP4), the signal change increased in the NEW blocks during the POST phase, suggesting that the effects were, in part, item-specific.

reduction relative to the first (Fig. 8). This fMRI signal reduction for new item blocks paralleled the numerical trends in the behavioural findings in all but one of the POST blocks

tested (Figs 5, 6, 9 and 10). The tentative conclusion, which will need to be explored further, is that two separate effects may exist: a non-specific blocked factor that perhaps relates
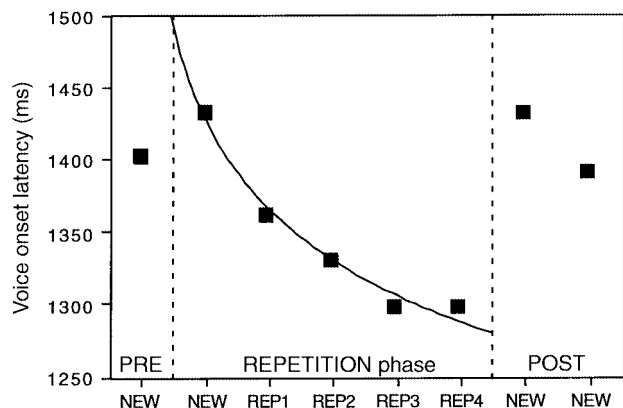
Fig. 9 Repetition priming for auditory word-stem completion. Data are shown for the auditory variant of word-stem completion of experiment 3a. The pattern of responding was very similar to that found for visual word-stem completion (Fig. 5) and verb generation (Fig. 6).
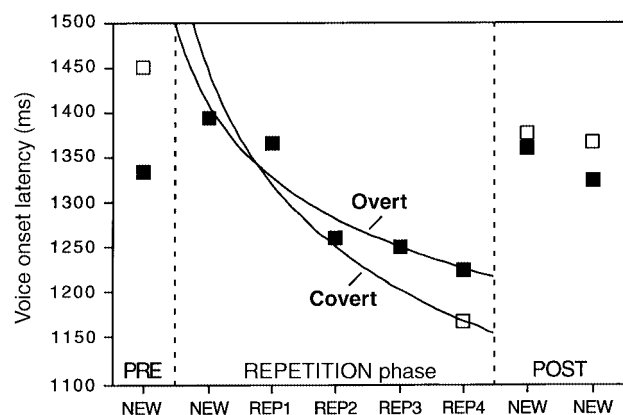

Fig. 10 Overt and covert auditory word-stem completion. Behavioural data from experiment 3b replicate the overt testing procedure of experiment 3a (Fig. 9) and extend the observation of a repetition-priming effect to a covert production procedure. Filled squares indicate overt blocks; open squares indicate covert blocks. As with the visual cues, the aurally cued task showed clear repetition-priming effects with covert production.

to the subjects' anticipation of trials and general arousal level (possibly related to the participants' adoption of a general task 'set,' in which the 'set' subtly changes for blocks comprising repeated items relative to blocks comprising entirely new items), and an item-specific factor.

An open question concerns the degree to which activity reductions reflect facilitation of (i) amodal, non-specific processes relating to lexical/semantic search and access or (ii) perceptual processes dependent on the modality and form of the cue. For regions such as those in the frontal cortex that have been associated with higher-level lexical and semantic processes, the strong hypothesis would be that reductions occur in these regions independent of cue modality. However, for other regions, such as the region in the inferior temporal cortex, the predictions are less clear. On the one hand, the inferior temporal cortex is contiguous with visual regions late in the ventral visual processing pathway, and

activity reductions may reflect perceptual aspects of the task. On the other hand, auditory word processing tasks have activated these regions, suggesting that their role may be related to lexical/semantic aspects of the task and, hence, reflect amodal processes (Price *et al.*, 1996; Binder *et al.*, 1997; Buchel *et al.*, 1998). To explore which of these possibilities best characterizes activity reductions related to frontal and inferior temporal priming, a series of further studies was conducted using auditory cue presentation. The hypothesis was that auditory cues would show repetition-priming effects and that brain regions that showed overlapping repetition-priming effects between visually and auditorily cued word-stem completion would reflect amodal processes relating more to conceptual processes than to perceptual processes.

Experiment 3a: auditorily cued overt word-stem completion

Experiments 3a–c examined auditorily cued word-stem completion (e.g. Bassili *et al.*, 1989; Schacter and Church, 1992) in a paradigm structured in the same manner as experiment 1c (16 s blocks). In this instance, however, all word stems (single syllables) were presented aurally (e.g. the sound 'pur' or 'tray') and participants generated completions based on the sounds (e.g. 'perfect', 'trait'). The goal of these studies was to generalize findings from the word-generation tasks outside the domain of purely visual stimulus presentation and to determine which brain regions involved in word generation were activated independently of cue modality and which were selective for cue modality. Experiments 3a and 3b were behavioural studies involving overt word generation and both overt and covert word generation respectively; experiment 3c involved fMRI imaging during covert performance of the auditorily cued word-generation task.

Possible auditory word-completion stems were selected using the Oxford Psycholinguistic Database. An initial pool of items was compiled such that all stems were unique and had at least five English language phonetic completions. A word corresponding to each stem was recorded in a male voice using MacRecorder and then edited (using SoundEdit Pro) to include only the first syllable. A normative study with 40 participants, aged 16–26 years, showed that the average correct completion rate for the 147 stems eventually selected, under untimed presentation conditions, was 88%.

The word stems were presented in five runs, preceded by a brief practice block. Each run consisted of eight blocks, each block comprising seven trials. The nature of the task blocks followed a pattern directly parallel to that of the visual word-stem completion and verb-generation tasks of experiment 2a. The actual presentation duration of the auditory word stems varied somewhat, depending on the item (i.e. the stems were self-terminating), with a stimulus presentation rate of one word stem every 2.29 s. Subjects

visually fixated on a central fixation point during the entire run to reduce eye movements.

Experiment 3a: results

The average voice onset latencies for overtly generated items on the auditory cued task are shown in Fig. 9. The pattern is very similar to that previously observed for both visually cued word-stem completion and visually cued verb generation: responses to the NEW items at the outset of the runs (1403 and 1433 ms) were slower than those to the REP items, response latencies decreasing to 1298 ms by the fourth repetition but returning to the initial levels (1432 and 1390 ms) when entirely NEW items were once again presented. A repeated measures ANOVA, considering only items from the repetition phase that were the same across the blocks (i.e. NEW, REP1, REP2, REP3, REP4), revealed a highly significant effect of repetition [$F(4,44) = 11.22$, $P < 0.0001$]. Examination of the response times for the four blocks of NEW items also showed a trend towards an overall effect of block [$F(3,33) = 2.88$, $P = 0.5$]; however, from Fig. 9 it can be seen that this outcome primarily reflected relatively longer response latencies for the second and third NEW blocks relative to that for the first and last NEW blocks. Consistent with this, a focused comparison contrasting the mean for the first two blocks of NEW items in each run against the mean for the last two blocks of NEW items revealed no effect [$F(1,11) < 1$].

Consideration of participants' responses showed a considerable level of response stereotypy, with an average of 75% of the items repeated (SD = 0.13, range = 0.54–0.91).

Experiment 3b: auditorily cued overt and covert word-stem completion

The purpose of this experiment was to ensure that covert auditory stem completion also resulted in repetition priming. The experimental procedure was identical to that of experiment 2a except that, for some of the runs, participants responded covertly rather than overtly. The covert runs followed the same general pattern as the overt runs in the visually cued task: an initial 'estimation' of the novel completion rate provided by a preobservation, then silent (covert) production until the fourth repetition, which was spoken, and ending with two blocks of new items, both requiring spoken responses. Each subject had two runs in which responding was entirely overt and three runs involving a covert response. As in the visually cued word-stem completion paradigm, participants were instructed, immediately before each block (via the presentation of a visual cue), whether the block was to be 'spoken' or 'silent.'

Experiment 3b: results

Clear priming effects of repetition on auditory word-stem completion were again observed (Fig. 10). For the overt runs,

considering only the items from the repetition phase that were the same across the blocks (i.e. NEW, REP1, REP2, REP3, REP4), response latencies decreased from 1393 ms on the first presentation to 1224 ms on the fourth repetition [$F(4,44) = 3.88$, $P = 0.009$]. Most importantly, a similar decrement was observed for runs in which participants responded covertly, the estimated response latency for the PRE baseline items of 1449 ms decreasing to 1168 ms by the fourth repetition [$F(1,11) = 27.96$, $P = 0.0003$]. Response latencies to NEW items during the POST phase were similar to those for NEW items in the PRE phase, with similar increases in response times for the new items observed in runs that were preceded by overt or by covert response generation, thereby showing, in both instances, that the reduction in voice onset latencies was specific to the particular items that were presented.

The average level of stereotypy for the overt runs was very similar to that observed for the previous auditory stem-completion experiment, in which participants responded overtly for all runs (mean response stereotypy of 77%, SD = 0.14, range = 0.51–0.96).

Experiment 3c: fMRI of covert auditorily cued word-stem completion

Functional imaging was performed during covert word generation, using procedures similar in format to behavioural experiment 3a and similar in terms of fMRI format to experiment 2b. Again, prior to each run specific instructions were given to perform all task blocks covertly, in this instance blocks of auditorily cued word-stem completion. Five functional runs were acquired per subject, each run consisting of 16 interleaved 16 s blocks (TR = 2 s). Within all runs, word-stem completion blocks followed the same order as in experiment 2a (NEW, NEW, REP1, REP2, REP3, REP4, NEW, NEW), and regularly alternated with blocks of visual fixation (odd numbered blocks). Stimulus duration varied during task blocks, with 2.3 s between onsets (seven items per block).

Experiment 3c: results
Main effect of task

Multiple brain regions forming a network were active during auditory word-stem completion when compared with visual fixation (Fig. 11A, Table 2). Many of these regions had also been found to be activated during the visual word-stem completion and verb-generation tasks, including the left inferior frontal gyrus near the border of BA 6 and/or 44 extending ventrally into the inferior prefrontal cortex at or near BA 44, 45 and/or 47 near the frontal operculum. Activations were again noted in the supplementary motor area and the right lateral cerebellum.

Quite distinct from the visual tasks, however, the auditory variant showed extremely robust activation in the bilateral
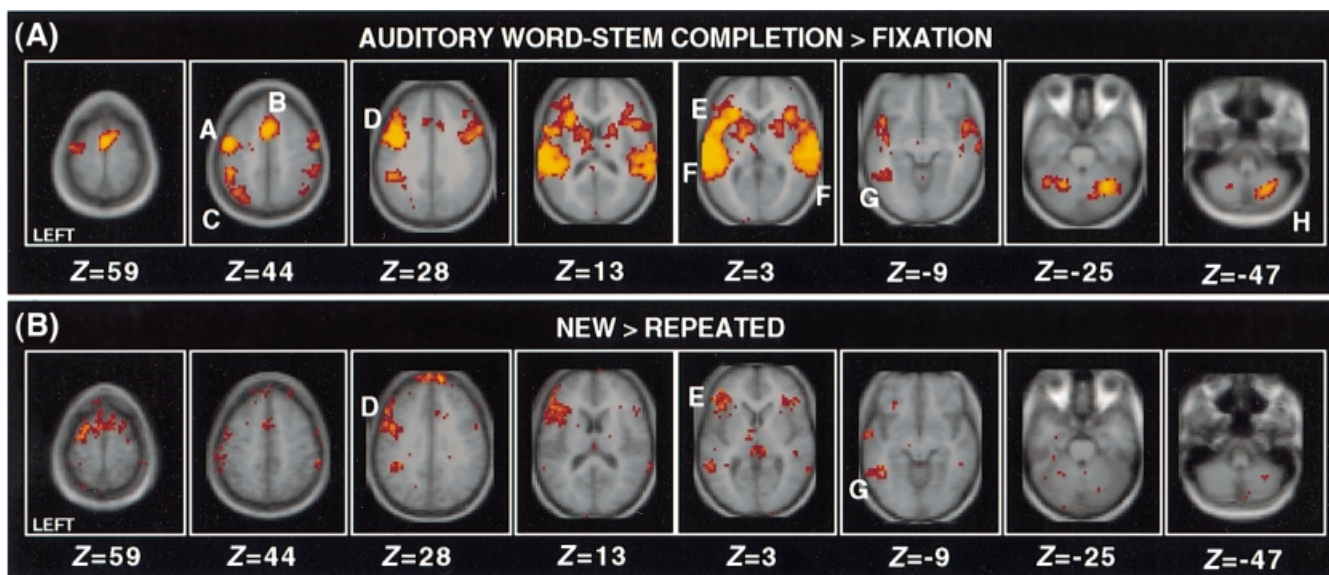
Fig. 11 fMRI of aurally cued word-stem completion. Data from experiment 3c show the pathway of brain regions activated during (**A**) auditory word-stem completion compared with fixation, and (**B**) for the repetition-priming effect in which all NEW item blocks were directly compared with all OLD item blocks. The format and colour scale are the same as in Figs 3 and 7. A pathway of brain regions is activated overlapping in part with those observed during experiments 1c and 2b including activation of the left inferior frontal gyrus (labelled A, D and E) and a limited region of the inferior temporal gyrus (labelled G). Activation of the visual cortex is largely absent; in fact it is decreased (see Fig. 13). The auditory cortex is robustly activated bilaterally (labelled F). The repetition-priming effect (**B**) is again present in the left frontal cortex and also within the left inferior temporal cortex.

auditory cortex. This activation was detected in spite of the loud sound of the scanner, which may have interacted with the word stems, consistent with earlier observations (Binder and Rao, 1994).

Regions in the visual cortex extending into the inferior temporal cortex and parahippocampal gyrus showed two opposing effects that existed in spatially distinct regions. By and large, the visual cortex was either silent or had reduced activation compared with fixation (Fig. 12). Such reductions are distinct from those observed during item repetition. In this instance, the reductions are in relation to fixation and not relative to an active task baseline with an elevated activity level due to task demands. The reductions here probably (although not definitively) reflected a cross-modal suppression effect: strong activation in the auditory cortex may have been suppressing activity in certain visual regions (Haxby *et al.*, 1994; Kawashima *et al.*, 1995; Buckner *et al.*, 1996*b*; for review, see Shulman *et al.*, 1997). The visual regions showing activity reductions were extremely similar in spatial location to those previously observed with PET during auditory word presentation (Buckner *et al.*, 1996*b*).

The second effect observed in the putative visual cortex was surprising: a region in the inferior temporal cortex near the fusiform gyrus ($x = -43$, $y = -52$, $z = -12$) was increased in activation and spatially distinct from nearby regions of signal decrease that extended into the parahippocampal cortex and posteriorly into the visual extrastriate regions. The time-course of activation of this inferior temporal region, which is quite similar in location to the region showing activity reductions in the visually

cued tasks, is shown in Fig. 13. Thus, auditory word-stem completion increases activity within certain regions of the inferior temporal cortex in addition to a more widespread and general suppression effect across many regions of the ventral visual processing pathway. The clear opposing effects of the auditory word-stem completion task on the separate occipital-temporal regions shows that they are functionally dissociable regions (Fig. 12). The inferior temporal region behaved as an amodal processing region.

Repetition effects

In a parallel analysis of the visual word-stem completion studies, regions in the left frontal cortex (centred on $x = -40$, $y = 6$, $z = 34$), the inferior temporal cortex site of activation increase (centred on $x = -43$, $y = -52$, $z = -12$) and the superior temporal gyrus at or near the primary auditory cortex (centred on $x = -62$, $y = -18$, $z = 12$) were examined for regional signal intensity change over time (Fig. 13). Both the frontal and inferior temporal regions showed strong effects of item repetition similar in profile and magnitude to those observed in the earlier studies using visual cues. For both regions, the reductions in signal intensity were reversed upon presentation of NEW items, again indicating that the signal reductions related to item-specific factors. By contrast, the region near the primary auditory cortex showed no change that was associated with item-specific repetition effects. Thus, despite the finding that regions at or near the primary auditory cortex were the most robustly activated (in terms of both statistical significance
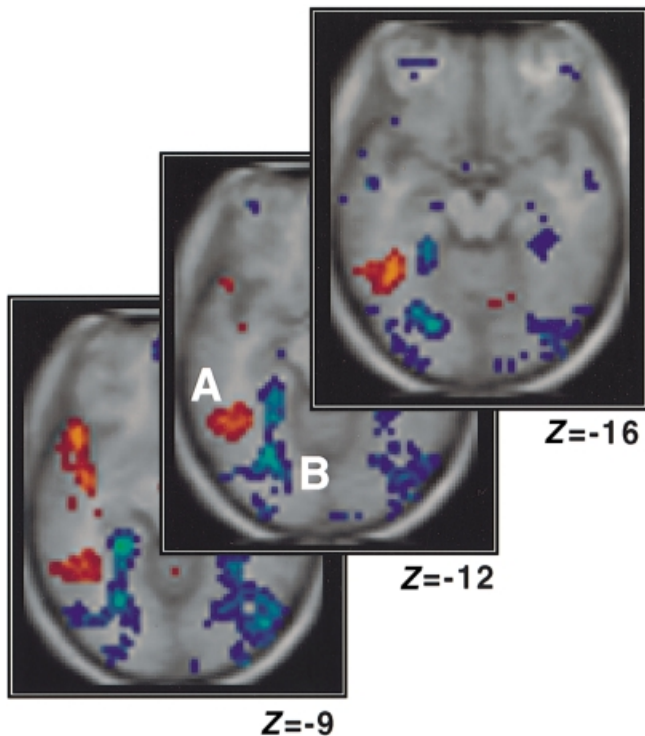
Fig. 12 More detailed fMRI images obtained during auditory word-stem completion. The behaviour of regions along the ventral visual processing pathway extending into the inferior temporal cortex from experiment 3c is revealed. Horizontal images show both the increases (red/yellow) and decreases (blue/green) in activation; the level of the horizontal section is indicated at the bottom. The threshold is set to $P = 0.001$; increasing colour intensity indices increasing significance. Note the clear opposing behaviour of the more posterior and anterior regions. The more posterior regions (B) show clear reductions in activation consistent with a cross-modal suppression effect. By contrast, the more anterior region (A; $x = -43$, $y = -52$, $z = -12$) is significantly activated by the task in a manner similar to that of the frontal cortex.

and percentage signal change), these regions showed little or no modulation in relation to repetition priming. Direct comparison of the NEW with the REP item blocks confirmed all of these findings (Fig. 11B).

General discussion

The present series of studies explored the effects of item repetition during a variety of lexical/semantic word-generation tasks. Tasks included visually cued word-stem completion, visually cued verb generation and aurally cued word-stem completion. In all instances, behavioural measurements of voice onset latency demonstrated that repetition of items decreased response latency (repetition priming). Reductions in response latency followed a stereotypic pattern that was predicted well by a power function. Blood oxygenation level-dependent-contrast fMRI measurements revealed that repetition of items was associated with decreased activity levels within specific brain regions

that were activated by the tasks in their unprimed states, including the left frontal cortex near the inferior frontal gyrus and also the inferior temporal cortex. All correlates of item repetition were reversible upon presentation of novel items, indicating that the effects were item-specific. Taken collectively, the present findings support a neural correlate of repetition priming: repeated exposure to an item leads to facilitated (speeded) processing of that item, which correlates with anatomically selective reductions in brain activity (see also Squire *et al.*, 1992; Raichle *et al.*, 1994; Buckner *et al.*, 1995a; Demb *et al.*, 1995; Blaxton *et al.*, 1996; Gabrieli *et al.*, 1996; Schacter *et al.*, 1996; for review see Schacter and Buckner, 1998).

The observation of close parallels between the patterns of behavioural facilitation (indexed by voice-onset latencies) and the patterns of neural activation (anatomically selective reductions) as a function of repetition across three types of tasks—visually cued word-stem completion, visually cued verb generation and aurally cued word-stem completion—focuses attention on the commonalties of the tasks and the similar processes involved. All three tasks required the selection and retrieval of a word that met certain constraints. The nature of the constraints differed for the three tasks—primarily orthographic and phonological for visually presented word-stems, phonological for aurally presented word-stems, and semantic, conceptual or associative for verb generation. However, in each instance, a number of alternative responses were possible, and the participant needed to 'select' and 'retrieve' one of those responses (Thompson-Schill *et al.*, 1997).

All three tasks activated a network of shared regions, including the ventral and dorsal regions of the left inferior frontal gyrus (BA 44/45/47 and 6/44), which are thought to be involved in operating on and/or maintaining higher-level verbal representations (i.e. semantic, lexical or phonological information). Decreases in brain activity in these frontal regions may provide neural evidence for a relatively 'non-specific' or 'amodal' component that has been repeatedly documented in behavioural studies of repetition priming (e.g. Rajaram and Roediger, 1993) and that may also partially underlie the facilitation of conceptual processing, in which the cue that is provided during initial exposure shows no overlap of perceptual information from study to test, but requires the retrieval of a specific word or concept (e.g. Bassili *et al.*, 1989; Blaxton, 1989; see also Demb *et al.*, 1995; Gabrieli *et al.*, 1996).

This emphasis on amodal components of the word-stem completion task may seem surprising, particularly given that word-stem completion priming, studied in its conventional form, shows a strong perceptual component, as evidenced by significant modality effects (Roediger and McDermott, 1993; Schacter, 1994). However, in all previous studies of word-stem completion priming, the study and test task did not match, and the stimuli did not repeat directly. For example, Rajaram and Roediger (Rajaram and Roediger, 1993; see also Squire *et al.*, 1992; Buckner *et al.*, 1995a) showed
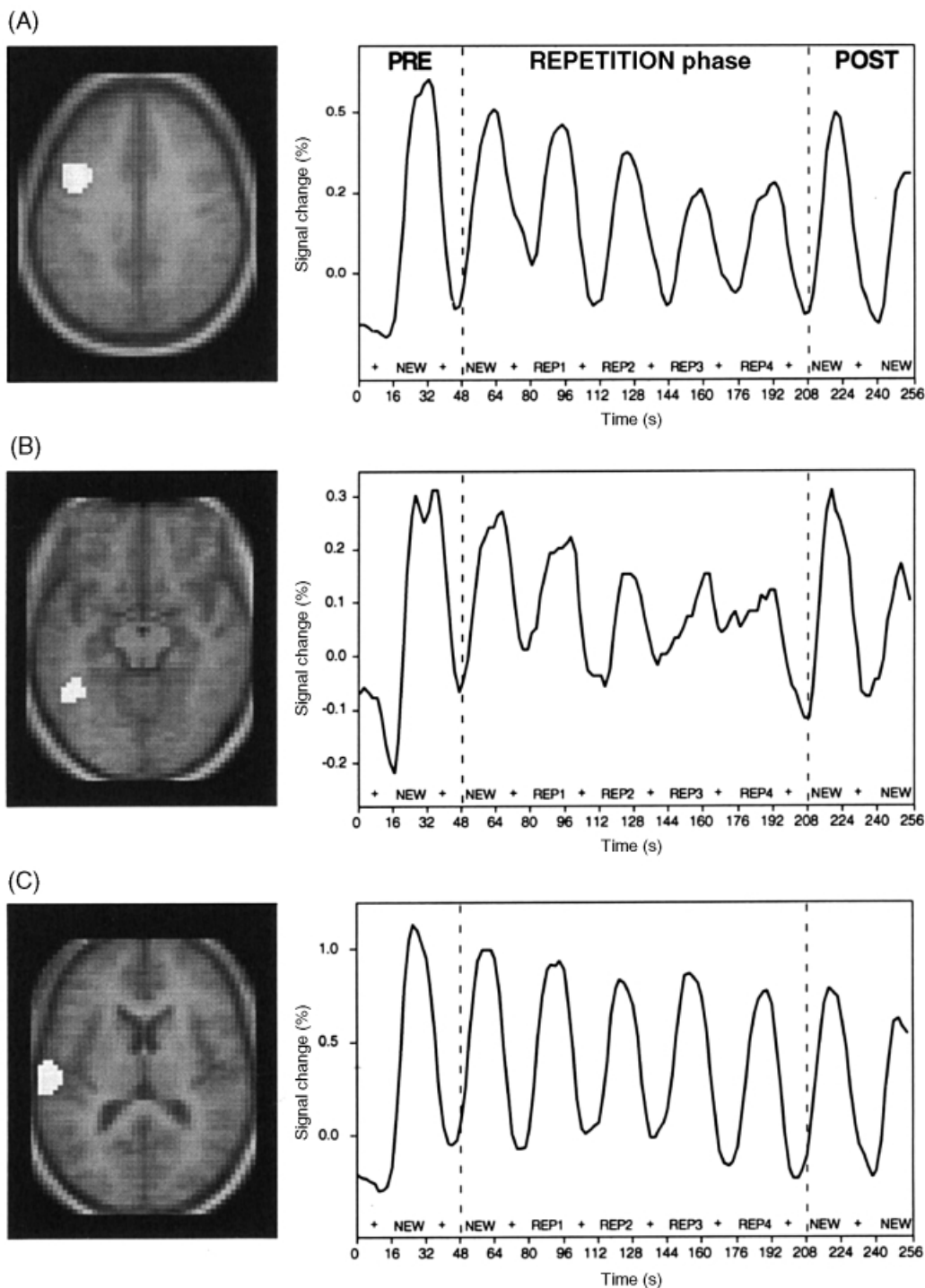
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Fig. 13 fMRI signal changes in experiment 3c for three separate regions similar to those shown in Figs 4 and 8. The time-course of regional signal change is shown. In this instance a region near the primary auditory cortex [superior temporal gyrus (–62, –18, 12), shown in **C**] was selected rather than the primary visual cortex, which was not activated in the auditory variant. Again, clear effects of item repetition were observed during the REP phase for the region within the left inferior frontal gyrus (–40, 6, 34) (**A**) and for left inferior temporal cortex (–43, 52, –12) (**B**). Following the last repetition block (REP4), the signal change increased in the NEW blocks during the POST phase, suggesting that the effects were, in part, item-specific in a manner similar to that seen in the visual task variants.

complete words at study (e.g. 'basket'), at which time subjects rated how much they liked the meaning of the word. At test, word-stem completion was used to assess priming (e.g.

complete 'bas_'). In our variant, we repeated directly both word-stem cues (e.g. 'bas_') and the task (subjects were always attempting to complete word-stems), thereby holding

constant the conceptual, lexical, and semantic retrieval demands across repetitions and never actually presenting the full (visual or auditory) form of the word.

It is thus not surprising that results from our variant of the word-stem completion task were similar to those elicited by other tasks that directly repeat lexical/semantic retrieval demands and traditionally show conceptual priming effects (e.g. the abstract/concrete classification task as studied by Demb *et al.*, 1995 and the verb-generation task studied by Raichle *et al.*, 1994). In this regard, the methods and results of the present study also help to refocus theoretical interpretations of perceptual versus conceptual priming. A complex task such as word-stem completion is not exclusively open to influences in either perceptual or conceptual processing; by repeating higher-level lexical/semantic retrieval components of the task, it appears that strong conceptual priming effects can be enhanced. However, full interpretation of this finding, and the precise extent to which the effects of word-stem completion under conditions such as those used here are more conceptual in nature than those for a typical word-stem completion task, will have to await more complete behavioural analysis.

Differences were noted between the auditory and visual variants of the tasks, which suggested regions that were more related to perceptual processes. The visual variants, as expected, showed robust activity increases in the primary and association visual cortex, whereas the auditory variant showed a robust bilateral increase near the primary auditory cortex extending into the auditory association cortex. Importantly, repetition-priming effects were observed in several of these modality-specific regions, including regions near the primary visual cortex ($x = -12$, $y = -99$, $z = -12$). The finding of a reduction in activity in the primary visual cortex came as a surprise because event-related fMRI studies of object repetition have shown that the level of primary visual cortex activation is preserved in the face of repeated presentations (Buckner *et al.*, 1998*a*). Although further research will need to determine the specific task factors that account for this difference, one possible explanation is that the blocked testing procedure allows participants to anticipate repeated items not on an item-by-item basis, because items were newly randomized on each presentation, but for the entire block of items, such that subjects were aware that all of the items would be new or that all would be repetitions. This awareness may have in some manner altered attentional or other aspects of processing. It should be noted, however, that the inferior frontal gyrus and the inferior temporal activity region reductions generalize across both blocked and event-related testing procedures, and across covert and overt procedures. Thus, there were highly reproducible findings in these regions, and these are the focus of the remaining discussion.

Of particular theoretical importance was the finding that a region in the left inferior temporal cortex was activated by word-stem completion regardless of the cue modality and, furthermore, this region had reduced activity in response to

item repetition for both visual and auditory cues. Thus, despite being contiguous with regions in the ventral visual processing stream, this inferior temporal region behaved in all respects like an amodal or non-specific processing region. The most parsimonious explanation for this is that the region was driven, in part, by top-down modulation, possibly interdependent with prefrontal activity. The two regions showed similar repetition-priming effects, and the prefrontal cortex provides a conduit by which repetition of an auditory cue could influence inferior temporal cortex activity. Previously, regions in the inferior temporal cortex showing item-related activity reductions have been associated with facilitation in visual perceptual processes (for reviews, see e.g. Schacter and Buckner, 1998; Wiggs and Martin, 1998). The present findings suggest that a partial revision of this explanation is necessary, at least for certain tasks and for certain regions within the inferior temporal cortex.

Consistent with this idea and with our results, Badgaiyan and colleagues recently reported a PET study of auditory word-stem completion priming in which subjects heard a series of words and were then scanned during primed and unprimed auditory stem completion (Badgaiyan *et al.*, 1999). They found that there was decreased blood flow during primed compared with unprimed auditory stem completion performance in a region of the extrastriate cortex (BA 19). This was similar to one of the previous PET studies of visual stem completion priming that exhibited priming-related blood flow reductions (Squire *et al.*, 1992; Buckner *et al.*, 1995*a*; Schacter *et al.*, 1996; Backman *et al.*, 1997). Although this region was posterior to the region in the inferior temporal cortex that showed repetition-related reductions in the present study (stereotaxic coordinates from experiment 1 of Badgaiyan *et al.* are $x = 40$, $y = -80$, $z = 4$; $x = -44$, $y = -82$, $z = 4$), both studies indicate that regions in or near the ventral visual processing stream show reductions during auditory priming and repetition, thereby raising important questions about the nature and function of those decreases. However, whereas we found that the inferior temporal region that showed repetition-related decreases was activated during baseline task performance compared with fixation, the extrastriate regions that showed priming-related decreases in the study of Badgaiyan and colleagues showed neither increases nor decreases compared with a fixation control. The contrasting patterns may be attributable to differences in behavioural paradigms, imaging procedures or the nature of the regions identified in the two studies.

The inferior temporal region localized in the present study to $x = -43$, $y = -52$, $z = -12$ may be activated independently of visual sensory input and may play a role in the formation, maintenance and/or interlinking of the conceptual lexical/semantic representations involved during task performance (see also e.g. Price *et al.*, 1996; Binder *et al.*, 1997). Notably, in a PET study that also employed auditory presentation but used the verb-generation task, Warburton and colleagues found activation in a slightly superior region, both comparing verb generation against a resting state (peak at $x = -48$,

$y = –50$, $z = –7$) and when comparing verb generation with a verb-noun comparison task (judge whether a presented verb and noun are appropriately matched, peak at $x = –50$, $y = –50$, $z = –12$) (Warburton *et al.*, 1996). These authors pointed to several convergent findings from investigations of semantic dementia (e.g. Hodges *et al.*, 1992) and presurgical explorations of epileptic patients (e.g. Luders *et al.*, 1991), as well as lesion and other studies, suggesting that this region is involved in language processing and, particularly, 'may have a key role linking meaning with words' (Warburton *et al.*, 1996, p. 173). Bookheimer and colleagues also note that this region has strong connections with Wernicke's area and explicitly suggest that it appears to be important 'for naming or verbally 'tagging' recognizable stimuli but is not modality specific' (Bookheimer *et al.*, 1995).

Evidence from the present investigations suggests that, as item repetition decreases the demand for manipulating or interconnecting these (possibly intermediate) lexical or semantic representations, the activity within inferior temporal regions may decrease. This places the effect more in line with ideas of conceptual rather than perceptual (data-driven) priming. However, at present we can state with certainty only that the processes engaged are amodal in nature. The relationship of these amodal processes to traditional notions of conceptual processes is nonetheless intriguing. Thus, the situation within the brain may be more complex than was initially expected (e.g. Schacter and Buckner, 1998), and the link between perceptual/conceptual processes and between anterior and posterior brain regions is only now beginning to be understood. Regions contiguous with regions within the ventral visual processing stream, such as the inferior temporal region highlighted by the present series of studies, may play a role in conceptual repetition priming.

A neural model of conceptual priming suggested by the present data is that amodal lexical/semantic processes, which may be triggered initially by modality-specific cues, will proceed via an interaction between the frontal cortex and posterior regions, including regions within the inferior temporal cortex. The interaction between frontal and posterior regions probably involves a top-down influence. During lexical/semantic processing tasks, the interaction between frontal and posterior brain regions decreases in response to direct item repetition. This reduction is manifested as a decrease in the blood oxygenation level-dependent-contrast fMRI signal and faster response times (priming). Thus, the human brain takes advantage of prior stimulus–response exposures by reducing the amount of time-consuming frontally mediated processes required to complete the task. Such processes may be those that allow a flexible response-selection mode in novel situations that are less relevant when an item can directly specify a response via prior experience (Raichle *et al.*, 1994).

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References

Backman L, Almkvist O, Andersson J, Nordberg A, Winbald B, Reineck R, et al. Brain activation in young and older adults during implicit and explicit retrieval. J Cogn Neurosci 1997; 9: 378–91.

Badgaiyan RD, Schacter DL, Alpert NM. Auditory priming within and across modalities: evidence from positron emission tomography. J Cogn Neurosci 1999; 11: 337–48.

Baker JR, Hoppel BE, Stern CE, Kwong KK, Weisskoff RM, Rosen BR. Dynamic functional imaging of the complete human cortex using gradient-echo and asymmetric spin-echo echo-planar magnetic resonance imaging. Proceedings of the Society of Magnetic Resonance First Scientific Meeting and Exhibition; 1993. p. 1400.

Bassili JN, Smith MC, MacLeod CM. Auditory and visual word-stem completion: separating data-driven and conceptually driven processes. Q J Exp Psychol 1989; 41A: 439–53.

Binder JR, Rao SM Human brain mapping with functional magnetic resonance imaging. [Review]. In: Kertesz A, editor. Localization and neuroimaging in neuropsychology. San Diego: Academic Press; 1994. p. 185–212.

Binder JR, Frost JA, Hammeke TA, Cox RW, Rao SM, Prieto T. Human brain language areas identified by functional magnetic resonance imaging. J Neurosci 1997; 17: 353–62.

Blaxton TA. Investigating dissociations among memory measures: support for a transfer-appropriate processing framework. J Exp Psychol: Learn Mem Cogn 1989; 15: 657–68.

Blaxton TA, Bookheimer SY, Zeffiro TA, Figlozzi CM, Gaillard WD, Theodore WH. Functional mapping of human memory using PET: comparisons of conceptual and perceptual tasks. Can J Exp Psychol 1996; 50: 42–56.

Bookheimer SY, Zeffiro TA, Blaxton T, Gaillard W, Theodore W. Regional cerebral blood flow during object naming and word reading. Hum Brain Mapp 1995; 3: 93–106.

Buchel C, Price C, Friston K. A multimodal language region in the ventral visual pathway. Nature 1998; 394: 274–7.

Buckner RL, Tulving E. Neuroimaging studies of memory: theory and recent PET results. [Review]. In: Boller F, Grafman J, editors. Handbook of neuropsychology, Volume 10. Amsterdam: Elsevier; 1995. p. 439–66.

Buckner RL, Petersen SE, Ojemann JG, Miezin FM, Squire LR, Raichle ME. Functional anatomical studies of explicit and implicit memory retrieval tasks. J Neurosci 1995a; 15: 12–29.

Buckner RL, Raichle ME, Petersen SE. Dissociation of human prefrontal cortical areas across different speech production tasks and gender groups. J Neurophysiol 1995b; 74: 2163–73.

Buckner RL, Bandettini PA, O'Craven KM, Savoy RL, Petersen SE, Raichle ME, et al. Detection of cortical activation during averaged single trials of a cognitive task using functional magnetic resonance imaging. Proc Natl Acad Sci USA 1996a; 93: 14878–83.

Buckner RL, Raichle ME, Miezin FM, Petersen SE. Functional anatomic studies of memory retrieval for auditory words and visual pictures. J Neurosci 1996b; 16: 6219–35.

Buckner RL, Goodman J, Burock M, Rotte M, Koutstaal W, Schacter D, et al. Functional-anatomic correlates of object priming in humans revealed by rapid presentation event-related fMRI. Neuron 1998a; 20: 285–96.

Buckner RL, Koutstaal W, Schacter DL, Dale AM, Rotte M, Rosen BR. Functional-anatomic study of episodic retrieval. II. Selective averaging of event-related fMRI trials to test the retrieval success hypothesis. Neuroimage 1998b; 7: 163–75.

Cabeza R, Nyberg L. Imaging cognition: an empirical review of PET studies with normal subjects. J Cogn Neurosci 1997; 9: 1–26.

Chee MW, O'Craven KM, Bergida R, Rosen BR, Savoy RL. Auditory and visual word processing studied with fMRI. Hum Brain Mapp 1999; 7: 15–28.

Demb JB, Desmond JE, Wagner AD, Vaidya CJ, Glover GH, Gabrieli JD. Semantic encoding and retrieval in the left inferior prefrontal cortex: a functional MRI study of task difficulty and process specificity. J Neurosci 1995; 15: 5870–8.

Gabrieli JDE, Desmond JE, Demb JB, Wagner AD, Stone MV, Vaidya CJ, et al. Functional magnetic resonance imaging of semantic memory processes in the frontal lobes. Psychol Sci 1996; 7: 278–83.

Haxby JV, Horwitz B, Ungerleider LG, Maisog JM, Pietrini P, Grady CL. The functional organization of human extrastriate cortex: a PET-rCBF study of selective attention to faces and locations. J Neurosci 1994; 14: 6336–53.

Hodges JR, Patterson K, Oxbury S, Funnell E. Semantic dementia: progressive fluent aphasia with temporal lobe atrophy. Brain 1992; 115: 1783–806.

Kawashima R, O'Sullivan BT, Roland PE. Positron-emission tomography studies of cross-modality inhibition in selective attention tasks: closing the 'mind's eye'. Proc Natl Acad Sci USA 1995; 92: 5969–72.

Kirsner K, Dunn JC, Standen P. Domain-specific resources in word recognition. [Review]. In: Lewandowsky S, Dunn JC, Kirsner K, editors. Implicit memory: theoretical issues. Hillsdale (NJ): Lawrence Erlbaum; 1989. p. 99–122.

Kwong KK, Belliveau JW, Chesler DA, Goldberg IE, Weisskoff RM, Poncelet BP, et al. Dynamic magnetic resonance imaging of human brain activity during primary sensory stimulation. Proc Natl Acad Sci USA 1992; 89: 5675–9.

Lezak MD. Neuropsychological assessment. 3rd ed. New York: Oxford University Press; 1995.

Luders H, Lesser RP, Hahn J, Dinner DS, Morris HH, Wyllie E, et al. Basal temporal language area. Brain 1991; 114: 743–54.

Ogawa S, Tank DW, Menon R, Ellermann JM, Kim SG, Merkle H, et al. Intrinsic signal changes accompanying sensory stimulation:

functional brain mapping with magnetic resonance imaging. Proc Natl Acad Sci USA 1992; 89: 5951–5.

Ojemann JG, Buckner RL, Akbudak E, Snyder AZ, Ollinger JM, McKinstry RC, et al. Functional MRI studies of word-stem completion: reliability across laboratories and comparison to blood flow imaging with PET. Hum Brain Mapp 1998; 6: 203–15.

Petersen SE, Fiez JA. The processing of single words studied with positron emission tomography. [Review]. Annu Rev Neurosci 1993; 16: 509–30.

Petersen SE, Fox PT, Posner MI, Mintun M, Raichle ME. Positron emission tomographic studies of the cortical anatomy of single-word processing. Nature 1988; 331: 585–9.

Press WH, Teukolsky SA, Vetterling WT, Flannery BP. Numerical recipes in C: the art of scientific computing. 2nd ed. New York: Cambridge University Press; 1992.

Price CJ, Wise RJ, Warburton EA, Moore CJ, Howard D, Patterson K, et al. Hearing and saying: the functional neuro-anatomy of auditory word processing. Brain 1996; 119: 919–31.

Raichle ME, Fiez JA, Videen TO, MacLeod AK, Pardo JV, Fox PT, et al. Practice-related changes in human brain functional anatomy during nonmotor learning. Cereb Cortex 1994; 4: 8–26.

Rajaram S, Roediger HL 3rd. Direct comparison of four implicit memory tests. J Exp Psychol: Learn Mem Cogn 1993; 19: 765–76.

Reese TG, Davis TL, Weisskoff RM. Automated shimming at 1.5 T using echo-planar image frequency maps. J Magn Reson Imaging 1995; 5: 739–45.

Roediger HL III, McDermott KB. Implicit memory in normal human subjects. [Review]. In: Boller F, Grafman J. Handbook of neuropsychology, Vol. 8. Amsterdam: Elsevier; 1993. p. 63–131.

Roediger HL III, Buckner RL, McDermott KB. Components of processing. [Review]. In: Foster JK, Jelicic M. Unitary versus multiple systems accounts of memory. New York: Oxford University Press; 1999. p. 31–65.

Schacter DL, Buckner RL. Priming and the brain. [Review]. Neuron 1998; 20: 185–95.

Schacter DL, Church BA. Auditory priming: implicit and explicit memory for words and voices. J Exp Psychol: Learn Mem Cogn 1992; 18: 915–30.

Schacter DL, Tulving E. Memory systems 1994. Cambridge (MA): MIT Press; 1994.

Schacter DL, Chiu C-Y, Ochsner KN. Implicit memory: a selective review. [Review]. Annu Rev Neurosci 1993; 16: 159–82.

Schacter DL, Alpert NM, Savage CR, Rauch SL, Albert MS. Conscious recollection and the human hippocampal formation: evidence from positron emission tomography. Proc Natl Acad Sci USA 1996; 93: 321–5.

Shulman GL, Fiez JA, Corbetta M, Buckner RL, Miezin FM, Raichle ME, et al. Common blood flow changes across visual tasks: II. Decreases in cerebral cortex. J Cogn Neurosci 1997; 9: 648–63.

Squire LR, Ojemann JG, Miezin FM, Petersen SE, Videen TO, Raichle ME. Activation of the hippocampus in normal humans: a

functional anatomical study of memory. Proc Natl Acad Sci USA 1992; 89: 1837–41.

Talairach J, Tournoux P. Co-planar stereotaxic atlas of the human brain. Stuttgart: Thieme; 1988.

Thompson-Schill SL, D'Esposito M, Aguirre GK, Farah MJ. Role of left inferior prefrontal cortex in retrieval of semantic knowledge: a reevaluation. Proc Natl Acad Sci USA 1997; 94: 14792–7.

Ungerleider LG. Functional brain imaging studies of cortical mechanisms for memory. [Review]. Science 1995; 270: 769–75.

Vandenberghe R, Price C, Wise R, Josephs O, Frackowiak RS. Functional anatomy of a common semantic system for words and pictures. Nature 1996; 383: 254–6.

Wagner AD, Schacter DL, Rotte M, Koutstaal W, Maril A, Dale AM, et al. Building memories: Remembering and forgetting of verbal experiences as predicted by brain activity. Science 1998; 281: 1188–91.

Warburton E, Wise RJS, Price CJ, Weiller C, Hadar U, Ramsay S, et al. Noun and verb retrieval by normal subjects: studies with PET. [Review]. Brain 1996; 119: 159–79.

Wiggs CL, Martin A. Properties and mechanisms of visual priming. [Review]. Curr Opin Neurobiol 1998; 8: 227–33.

Wise R, Chollet F, Hadar U, Friston K, Hoffner E, Frackowiak RS. Distribution of cortical neural networks involved in word comprehension and word retrieval. Brain 1991; 114: 1803–17.

Zarahn E, Aguirre GK, D'Esposito M. Empirical analyses of blood oxygenation level-dependent fMRI statistics. I. Spatially unsmoothed data collected under null-hypothesis conditions. Neuroimage 1997; 5: 179–97.