

Modulation of Neural Activity during Object Naming: Effects of Time and Practice

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Repeated exposure to objects improves our ability to identify and name them, even after a long delay. Previous brain imaging studies have demonstrated that this experience-related facilitation of object naming is associated with neural changes in distinct brain regions. We used event-related functional magnetic resonance imaging (fMRI) to examine the modulation of neural activity in the object naming system as a function of experience and time. Pictures of common objects were presented repeatedly for naming at different time intervals (1 h, 6 h and 3 days) before scanning, or at 30 s intervals during scanning. The results revealed that as objects became more familiar with experience, activity in occipitotemporal and left inferior frontal regions decreased while activity in the left insula and basal ganglia increased. In posterior regions, reductions in activity as a result of multiple repetitions did not interact with time, whereas in left inferior frontal cortex larger decreases were observed when repetitions were spaced out over time. This differential modulation of activity in distinct brain regions provides support for the idea that long-lasting object priming is mediated by two neural mechanisms. The first mechanism may involve changes in object-specific representations in occipitotemporal cortices, the second may be a form of procedural learning involving a reorganization in brain circuitry that leads to more efficient name retrieval.

Introduction

Recognizing an object and producing its name is a cognitive skill that humans perform without apparent effort. Irrespective of its automaticity, however, object naming is improved by experience. Behavioral studies have shown that repeated exposure to an object speeds up naming that same object again. This phenomenon, usually referred to as 'repetition priming', develops quickly and is long lasting: speeded naming responses can be observed 48 weeks after a single exposure to an object (Cave, 1997). Long-lasting facilitation of object naming occurs regardless of whether someone remembers having seen the object before, and is preserved in amnesic patients (Cave and Squire, 1992). This suggests that this form of learning is independent of the medial temporal lobe memory system. The occurrence of long-lasting object priming implies that naming an object may lead to a permanent change in the efficiency with which that object is processed in the future. In the present study we investigate the neural mechanisms mediating long-lasting facilitation of object naming, and we aim to dissociate between changes at perceptual and higher-order levels of the object-naming system.

The major processing components in object naming include perceptual, semantic, syntactic, phonological and articulatory processing stages. Lesion and brain imaging studies have demonstrated that these components are subserved by an interconnected network of widely distributed cortical areas, including bilateral occipital, temporal, left inferior frontal, left precentral, and left insula cortices (Price *et al.*, 1999; Indefrey

and Levelt, 2000). In principal, experience-related changes could occur at each of these levels of representation.

A commonly reported neural change associated with object repetition is a decrease in activity in occipitotemporal brain regions known to be involved in object identification (Schacter and Buckner, 1998; Wiggs and Martin, 1998). One of the neural mechanisms that has been proposed to underlie this decrease in cortical activity is 'repetition suppression'. Single cell recordings from monkey cortex have demonstrated that stimulus repetition leads to a gradual decrease in firing rates of a subset of activated neurons in inferotemporal cortex (Miller and Desimone, 1994; Ringo, 1996). These effects are highly stimulus specific (Li *et al.*, 1993) and long lasting (Brown *et al.*, 1987). As was suggested by Desimone (Desimone, 1996), this selective reduction in firing rates with object repetition could reflect the creation of sparse, yet more object-form specific representations which, in turn, leads to enhanced object identification.

Consistent with this view, functional brain imaging investigations of humans have demonstrated decreased activity in occipitotemporal cortices associated with object repetition (Buckner *et al.*, 1998; Reber *et al.*, 1998; Dehaene *et al.*, 2001; Donaldson *et al.*, 2001; Koutstaal *et al.*, 2001). Repetition-related activation decreases in the ventral object processing stream have been shown to be stimulus specific (Grill-Spector *et al.*, 1999; Koutstaal *et al.*, 2001) and to also occur for objects without a prior representation in memory (van Turennout *et al.*, 2000; Henson *et al.*, 2002). However, repetition-related decreases have also been shown to partly depend on experimental task. For example, Henson *et al.* (Henson *et al.*, 2002) showed that the response in the right fusiform gyrus was reduced for repeated faces using a fame-judgement task, but not when using a recognition memory task. It remains unclear which part of the repetition-related decreases in occipitotemporal cortices is task specific and which is occurring automatically across tasks.

Object repetition-related changes are not limited to reduced activity in occipitotemporal cortices. In addition, brain imaging studies have associated object repetition with decreased activity in left inferior frontal cortex (Buckner *et al.*, 1998; van Turennout *et al.*, 2000; Dhond *et al.*, 2001), increased activity in a right fusiform region (Henson *et al.*, 2000, 2002), and increased activity in the left insula (van Turennout *et al.*, 2000). These findings strongly suggest that object priming cannot be explained by a single mechanism such as sparse encoding of object form, but also includes changes at higher levels of the object naming system.

Recently, we have obtained evidence on long-lasting cortical changes following object naming in healthy humans (van Turennout *et al.*, 2000). In an event-related functional magnetic resonance imaging (fMRI) study, subjects named a series of briefly presented (200 ms) pictures of objects intermixed with nonsense objects. Three days later, subjects saw these pictures

again, together with new pictures and a repetition of the new pictures after 30 s, while fMRI images were obtained. The results showed an immediate (30 s) and long-lasting (3 day) decrease in neural activity in bilateral occipitotemporal cortex following both nameable and nonsense object repetition. In addition, decreases in left inferior frontal activity were observed concurrent with increases in left insula activity only for nameable objects. Importantly, while in posterior regions changes in activity were found to be greatest for items repeated after a short delay, changes in anterior regions were mainly observed when 3 days intervened between the first and second object presentations. These differences in time course and direction of the effects suggest that changes in posterior and anterior regions may reflect two distinct learning mechanisms: the rapid formation of sparser, yet more object-form specific, representations in occipitotemporal cortices, coupled with more slowly developing experience-induced reorganization of the brain circuitry underlying lexical retrieval in anterior regions (i.e. left inferior frontal and insular cortices).

In the present study we pursued this idea of two distinct mechanisms underlying long-lasting object priming by further investigating the effects of time on repetition-related neural changes. Using event-related fMRI, we measured the hemodynamic responses to objects that had been named once before at different time intervals before the scanning session (1 h, 6 h and 3 days). This allowed us to track the effects of time on experience-related changes in more detail than we were able to do in our previous study. In addition, we measured event-related responses to objects that had been named three times in a period of 3 days before the scanning session, and to a set of objects that had been named three times in a period of 90 s during the scanning session. Thus, the study design allowed us to directly test for an interaction between the effect of multiple exposures and time. If decreased activity in occipitotemporal regions is associated with a change in the encoding of object form, then multiple exposures to the same object should result in decreasing responses, irrespective of delay. In contrast, for anterior regions we predict differential effects as a function of time. If, as suggested by our previous findings, changes in anterior regions are indeed time dependent, then multiple exposures should not eliminate this effect of time: irrespective of the number of exposures, changes in anterior regions will develop along a slower time course than changes in posterior regions.

The design of the study is summarized in Figure 1. Importantly, all different event types were presented randomly intermixed in one and the same scanning session. The use of this experimental design eliminates possible confounds such as differences in signal intensity between sessions, anticipation, habituation and strategic adaptation to a specific event type that may develop when the same stimulus types are presented sequentially within a block (D'Esposito *et al.*, 1999). By using a rapid, randomly intermixed event-related design, differential fMRI responses can be directly attributed to differences in experience with the specific objects.

Materials and Methods

Subjects

Ten subjects (two female; age range, 22–28 years) participated in the fMRI study, and 15 participated in the behavioral study. All subjects were right handed and native speakers of English. All subjects gave written informed consent and were compensated for participation. The experimental protocol was approved by the institutional review board of the National Institute of Mental Health.

Stimuli and Design

Stimuli included 300 black on white line drawings of common objects. All of the line drawings had been pretested in a pilot study to ensure that they elicited consistent naming responses. Each subject in the fMRI study participated in four sessions: one scanning session preceded by three behavioral sessions at different time intervals before scanning: 3 days, 6 h and 1 h. The subjects' task was to name the objects aloud in the pre-scanning sessions and silently in the fMRI session. Three days before the fMRI session subjects were presented with 120 line drawings. Half of these line drawings were presented again 6 h before scanning and again 1 h before scanning, each time intermixed with a novel set of 60 line drawings. During the fMRI session subjects saw all the stimuli they had seen in the pre-scanning sessions, intermixed with a novel set of line drawings and three repetitions of these novel stimuli at ~30 s intervals. Thus, during scanning we measured the hemodynamic responses to objects that were named previously only once prior to scanning (with lags of 1 h, 6 h and 3 days), to objects that were named multiple times over the time course of 3 days (the same objects seen 1 h, 6 h and 3 days prior to scanning) and to objects seen repeatedly at 30 s intervals during the scanning session. The design of the study is illustrated in Figure 1. In addition to the objects, 60 visual-noise stimuli were included to create a low-level, visual baseline condition (see Fig. 1). The visual-noise stimuli were presented randomly intermixed with the objects. Visual-noise stimuli were of the same size as the objects and all stimuli were presented in an identical way. Subjects were instructed to look at the noise patterns without producing a verbal response. The assignment of objects to the different event-types was counterbalanced across subjects. In this way, all objects contributed equally to each condition so that differences in results could not be explained by differences in stimulus characteristics.

Procedure

Stimulus presentation was controlled by a Macintosh computer, using Superlab (Cedrus Corp., San Pedro, CA). Stimuli were presented in a pseudorandom order. Each stimulus was presented for 200 ms, with a mean stimulus onset asynchrony of 2.5 s (randomly jittered between 1.5 and 3.5 s). During the inter-stimulus interval the screen was blank. In the pre-scanning and behavioral sessions subjects were seated in a soundproof booth and the stimuli were projected onto a computer screen positioned in front of the subject. Naming latencies were measured by a voice key, time locked to picture onset. In the fMRI session, stimuli were projected onto a translucent screen located at the subject's feet using a magnetically shielded projector. Subjects viewed the images by a mirror mounted above their head.

The behavioral learning effect was established in a separate study. Procedure, stimuli and design were the same as described for the fMRI study, except that subjects were instructed to name the objects aloud in all four sessions.

Scanning Parameters

For each subject, four time-series of 96 whole-brain images were obtained using a gradient-echo, echo-planar scanning sequence (32 sagittal slices, 4.4 mm thick, repetition time (T_R) = 2 s, echo time (T_E) = 40 ms, 64×64 matrix, 3.75×3.75 mm² voxels) on a 3.0 T General Electric Signa MRI scanner. During the same session, a high-resolution-anatomical scan was obtained using a three-dimensional fast spoiled gradient echo sequence (124 sagittal slices, 1.2 mm thick, T_R = 15 ms, T_E = 7 ms, FOV = 24 cm, 256 256 matrix).

Imaging Analysis

Images were corrected for slice timing using the middle slice as a reference, and realigned to correct for interscan movement using AFNI (Cox, 1996). Resulting images were analysed using Statistical Parametric Mapping (SPM99, Wellcome Department of Cognitive Neurology, London, UK). Volumes were spatially normalized to a standard EPI template in Talairach space (Talairach and Tournoux, 1988) and transformed into $2 \times 2 \times 2$ mm³ voxels. Normalized data were spatially smoothed with a Gaussian kernel (full-width at half maximum = 6 mm). Image time-series were high-pass filtered to remove low-frequency components and were ratio normalized to a whole brain mean signal of 100.

Statistical analyses were performed in the context of the general linear

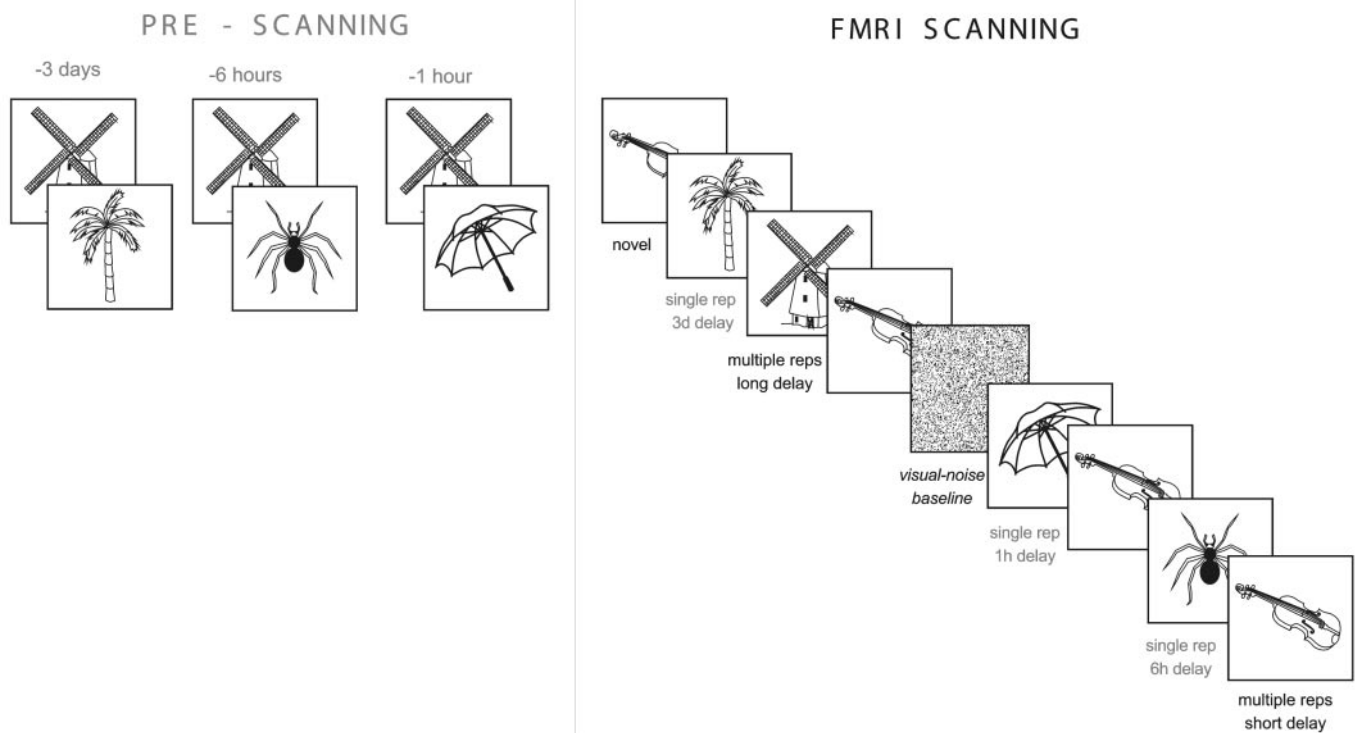


Figure 1. Summary of the experimental design. Pictures of objects were presented at three intervals before scanning: 3 days, 6 h, or 1 h. One set of pictures was presented at each of the three intervals and once again during scanning (multiple repetitions, long delay), while different sets of pictures were presented only once before scanning at one of the three long-term intervals and once again during scanning (3 day delay, 6 h delay, 1 h delay). In addition, during scanning, a novel set of pictures was presented (novel) and this set was repeated three times during the scanning session at intervals of 30 s (multiple repetitions, short delay). In all sessions, pictures were presented randomly intermixed, for 200 ms, at a rate of, on average, 2.5 s.

model as employed in SPM99. The statistical model included nine effects of interest: novel items, single repetitions at four delays (30 s, 1 h, 6 h and 3 days), multiple repetitions at three delays (60 s, 90 s and 3 days) and visual noise. A constant was included for each subject as effect of no interest. The evoked hemodynamic responses for each of the nine event-types were modelled as delta functions and convolved with a synthetic hemodynamic response function and its temporal derivative (Friston *et al.*, 1998). Parameter estimates for each of the event types, i.e. the relative contribution of each event to the mean voxel time series, were obtained with least-squares and specific effects were tested by applying linear contrasts to the parameter estimates for each event. In analysing the data, we first performed a fixed effect analysis identifying all voxels that showed a significant increase in activity for all objects relative to a visual noise baseline ($P < 0.005$, uncorrected for multiple comparisons). Repetition-specific effects were tested at those voxels showing a main effect of object naming by applying linear contrasts to the parameter estimates of the novel and repeated events. Regions of interest were defined on the basis of this initial, fixed effect analysis, for pre-scan and within-scan repetitions separately, by selecting all voxels showing both a significant overall effect of object naming ($P < 0.005$, uncorrected for multiple comparisons) and a significant overall effect of object repetition ($P < 0.05$, uncorrected for multiple comparisons). In a second stage, random effects analyses were performed, testing for effects of time and multiple exposures on repetition-related changes in the regions of interest.

Averaged regional hemodynamic responses were computed for all voxels surviving these thresholds in distinct brain regions. To test for main effects and interactions of time and practice within those regions, a repeated-measurement analysis of variance (ANOVA) was performed on the subject averaged regression coefficients obtained in each of the regions. Then, to test for differences in repetition effects as a function of delay and practice, *t*-tests were performed on the averaged regression coefficients obtained for the specific events.

Results

Behavioral Results

Naming latencies obtained in the behavioral study are presented in Figure 2. Figure 2A shows that significantly faster naming latencies were observed for repeated as compared to novel objects at all delays (paired *t*-tests, $P < 0.001$). As can be seen in Figure 2B, additional exposures to the same picture led to further decreases in naming latencies. A repeated-measurement ANOVA revealed main effects of delay [$F(1,14) = 40.96$, $P < 0.001$] and number of exposures [$F(3,14) = 89.32$, $P < 0.001$], and an interaction between those two factors [$F(3,14) = 7.24$, $P < 0.001$]. For objects that were repeated three times within 90 s, naming latencies decreased 117 ms ($P < 0.001$) for the first repetition, 150 ms ($P < 0.001$) for the second repetition and then stabilized at this level (see Fig. 2B). For objects repeated over the time course of 3 days, naming latencies were sped up to a larger extent after three as compared to one repetition ($P < 0.001$, priming effects were 97 and 40 ms for three repetitions and one repetition respectively). As can be seen in Figure 2B, larger priming effects ($P < 0.001$) were obtained for objects repeated three times within a short (90 s, 150 ms priming) as compared to a long (3 day, 97 ms priming) interval.

Imaging Results

Relative to a visual-noise baseline, naming novel and repeated objects activated a large network of cortical regions including posterior bilateral ventral occipitotemporal, left inferior temporal, left insula, left basal ganglia, left premotor and anterior cingulate cortices. Within these regions, we tested for decreases

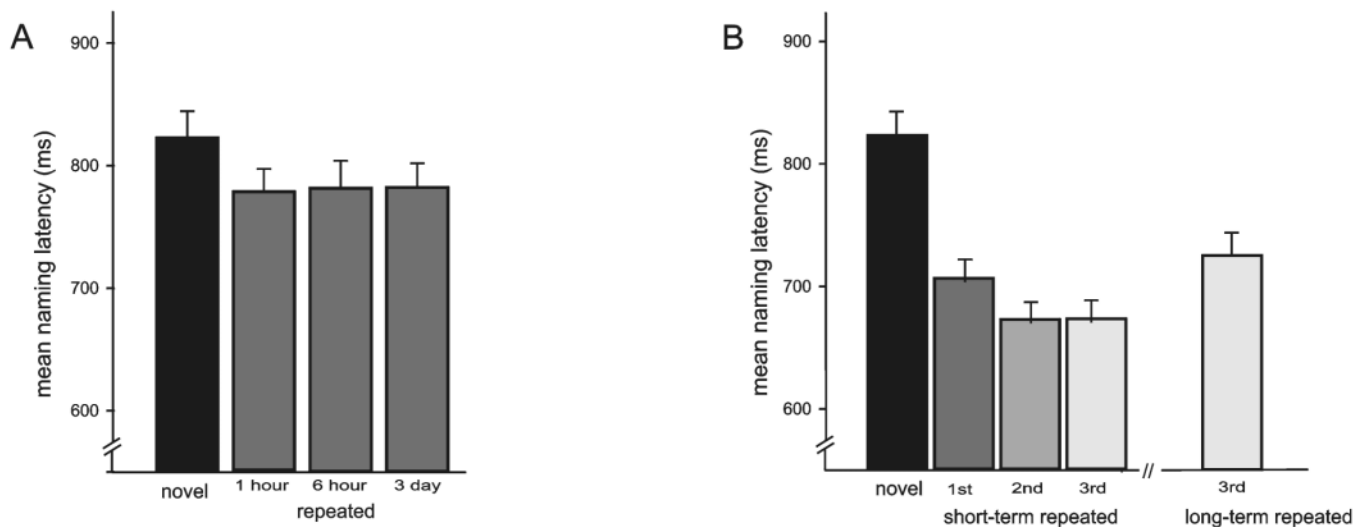


Figure 2. Long-lasting repetition priming observed in the behavioral study. (A) Mean naming latencies and standard errors for novel objects, and objects repeated once after 1 h, 6 h and 3 days. (B) Mean naming latencies and standard errors for novel objects, for objects repeated for the first, second and third times at 30 s intervals and objects repeated for the third time after 3 days.

and increases in activity as a function of experience. Table 1 displays the maxima of all brain regions showing differential responses to novel as compared to repeated objects.

Long-lasting Changes Following a Single Exposure to an Object

Brain regions showing long-lasting changes in activity as a function of a single object repetition are shown in Figure 3A. Repetition-related decreases in activity were observed in bilateral occipitotemporal and left inferior frontal cortices (shown in yellow). Repetition-related increases in activity were observed in the left anterior insula and left basal ganglia (shown in red). The group-averaged regression coefficients obtained at each of the different repetition delays for the distinct brain regions are shown in Figure 3B. These values reflect the relative contribution of novel objects and objects repeated at different delays, to the grand-averaged regional fMRI time series. Paired samples *t*-tests showed that compared to novel, responses were significantly reduced at all delays in bilateral occipitotemporal cortices [1 h: L $t(9) = 5.69$, $P < 0.001$; R $t(9) = 7.80$, $P < 0.001$; 6 h: L $t(9) = 7.73$, $P < 0.001$, R $t(9) = 5.34$, $P < 0.001$; 3 days: L $t(9) = 3.85$, $P < 0.005$; R $t(9) = 7.03$, $P < 0.001$] and in the left inferior frontal cortex [1 h: $t(9) = 2.52$, $P < 0.03$; 6 h: $t(9) = 1.80$, $P = 0.05$; 3 days: $t(9) = 3.10$, $P < 0.01$]. In addition, compared to novel objects, repeated objects led to increased activity in the left insula and the left basal ganglia at all delays [1 h: insula $t(9) = -2.68$, $P < 0.03$; BG $t(9) = -1.72$, $P = 0.06$; 6 h: insula $t(9) = -2.27$, $P < 0.03$; BG $t(9) = -2.00$, $P < 0.05$; 3 days: insula $t(9) = -2.0$, $P < 0.05$; BG $t(9) = -2.15$, $P < 0.05$]. However, pairwise comparisons of the regression coefficients for repeated objects did not show significant differences between the delays in any of these brain regions ($P > 0.05$).

Time-dependent Changes Following Multiple Exposures to the Same Object

Repetition-related changes following multiple exposures to the same object are shown in Figure 4. Figure 4A,B displays changes in activity that were observed after four exposures to the same object over the time course of 90 s (short-term repetitions) and Figure 4C,D display changes for objects that were shown four

times over the time course of 3 days (long-term repetitions). Similar to changes observed after a single repetition, multiple repetitions of the same object led to decreased activity in bilateral occipitotemporal and left inferior frontal cortices and, in addition, to increased activity in the left insula and the left basal ganglia.

To examine whether multiple repetitions led to larger changes than single repetitions, pairwise comparisons were performed on the mean regression coefficients obtained for the first and third repetitions of an object. Since for the long-term repetitions no scanning was performed during the first three presentations of an object, regression coefficients obtained for the objects repeated once after 3 days were used for the comparison. As there were no differences between the responses to objects repeated at different long-term delays (see Fig. 3), the same results were obtained when comparing regression coefficients obtained for objects repeated three times over the time course of 3 days with regression coefficients obtained for objects repeated once after 1 h, 6 h or 3 days. In bilateral occipitotemporal regions we found that responses were smaller after the third repetition of an object as compared to the first repetition of that object. This additional decrease in activity was observed for short-term repetitions [L $t(9) = 2.05$, $P < 0.05$; R $t(9) = 2.10$, $P < 0.05$] as well as for long-term repetitions [L $t(9) = 2.91$, $P < 0.01$; R $t(9) = 1.90$, $P = 0.05$]. Responses to the second repetition were measured for short-term repetitions only, and are not displayed in the figure. Pairwise comparisons showed no significant differences between the second and third repetition of an object ($P > 0.1$). In left inferior frontal cortex we observed an additional decrease for multiple as compared to single repetitions. In contrast to posterior regions, however, this additional decrease was observed only for long-term repetitions [$t(9) = 2.15$, $P < 0.05$]. In the left insula and basal ganglia no significant differences were observed between the first and multiple repetitions for either the short- or long-term repetitions (see Fig. 4).

To further investigate the difference in the time course of familiarization effects in posterior and anterior regions, we selected all voxels in occipitotemporal and left inferior frontal cortex that showed an overall effect of object repetition in the

Table 1

Brain regions showing experience-related changes in activity

Region	Overall effects of naming novel and repeated objects				Main effects of naming novel objects											
	x	y	z	vol (mm ³)	x	y	z	vol(mm ³)								
L occipitotemporal	-42	-86	-6	20 792	-42	-88	-4	17 384								
	-48	-68	-14		-48	-66	-16									
R occipitotemporal	34	-92	-12	11 872	44	-68	-18	10 000								
	44	-68	-18		32	-46	-22									
	32	-46	-22													
L inferior frontal	-52	10	4	2606	-54	12	4	7896								
	-44	14	20		-42	14	24									
	-54	30	10	912	-54	28	12									
L insula	-24	0	4	1168	no significant voxels ($P > 0.005$)											
L basal ganglia	-16	-2	16													
	-16	12	4													
Changes following a single repetition																
	30 s delay				1 h delay				6 h delay				3 day delay			
	x	y	z	vol (mm ³)	x	y	z	vol (mm ³)	x	y	z	vol (mm ³)	x	y	z	vol (mm ³)
Decreased activity																
L occipitotemporal	-46	-86	-2	13 176	-46	-64	-16	6384	-44	-86	-4	504	-52	-64	-18	1424
	-50	-64	-18						-44	-70	-16	928	-40	-56	-30	1016
									-34	-60	-28	560				
R occipitotemporal	44	-66	-20	7576	40	-74	-6	936	36	-88	4	352	32	-68	-30	440
	30	-42	-24		46	-56	-22	2976					36	-46	-28	704
L inferior frontal	-56	16	8	736	-52	8	36	272					-54	10	36	144
	-50	28	14	896	-56	16	8	1256	-56	16	10	288	-52	14	2	1448
					-54	26	16	536	-54	26	14	384	-56	26	14	440
Increased activity																
L insula	-34	8	0	240	-32	6	-2	928	-34	4	-2	1160	-32	8	-2	280
					-22	6	-16									
L basal ganglia	-24	10	16	272	-22	6	14	168	-22	8	16	392	-22	8	16	280
Changes following multiple repetitions																
	Short delay				Long delay											
Decreased activity																
L occipitotemporal	-46	-68	-16	14 976	-50	-62	-16	15 112								
R occipitotemporal	34	-50	-24	8832	30	-42	-22	9000								
L inferior frontal	-52	12	6	920	-52	10	34	304								
	-44	14	24	232	-44	14	24	2240								
	-52	28	14	848	-50	28	14	912								
Increased activity																
L insula	-32	6	-2	344	-30	6	-2	336								
L basal ganglia	-24	10	16	332	-24	10	4	96								

Talairach and Tournoux coordinates of the maxima from bilateral occipitotemporal, left inferior frontal and left insular cortices, and left basal ganglia showing increased activity for naming objects as compared to baseline and maxima from those regions showing an effect of object repetition. Z-scores are >3.12 ; $P < 0.001$, for all maxima.

group analyses. Figure 5 shows the grand-averaged regional time courses and regression coefficients obtained from those voxels for the novel objects and the objects that were familiarized over the time course of 90 s and 3 days. As illustrated in this figure, while responses were reduced to a similar extent in bilateral occipitotemporal regions for short and long delays, prolonging the repetition delay led to an additional reduction of responses in the left inferior frontal cortex. Pairwise comparisons of the mean regression coefficients showed that while no significant differences were obtained between long and short delays in occipitotemporal regions, in the left inferior frontal cortex responses were significantly more reduced after long as compared to short delays between repetitive exposures [$t(9) = 2.43$, $P < 0.05$]. In contrast, repetition-related increased activity in the left insula and basal ganglia regions was equivalent at short and long delay intervals.

Discussion

The present study provides new insights into the dynamics of cortical activity within the object naming system. The fMRI data show that naming pictures of common objects leads to long-lasting changes in cortical activity that can be measured when those pictures are named again, even after a long delay. The magnitude of these changes is modulated as a function of time and experience. Importantly, different patterns of change were observed in posterior and anterior brain regions, suggesting that distinct neural mechanisms mediate the long-lasting facilitation of object naming.

Repetition Suppression in Occipitotemporal Cortex

The present data are consistent with the hypothesis that repetition suppression is one of the neural mechanisms

mediating long-lasting facilitation of object naming. Replicating our previous findings, we found that activity in occipitotemporal regions decreased as object naming became more efficient with repetition, and that this decrease in activity can still be measured after a 3 day delay (van Turennout *et al.*, 2000). The magnitude of repetition-related decreases was the same across the various

repetition delays (1 h, 6 h and 3 days) for single repetitions, indicating that in occipitotemporal regions repetition effects remained stable over the time course of 3 days. This pattern of results matched the behavioral priming effects: naming latencies were facilitated to the same extent at each of the long-term repetition delays.

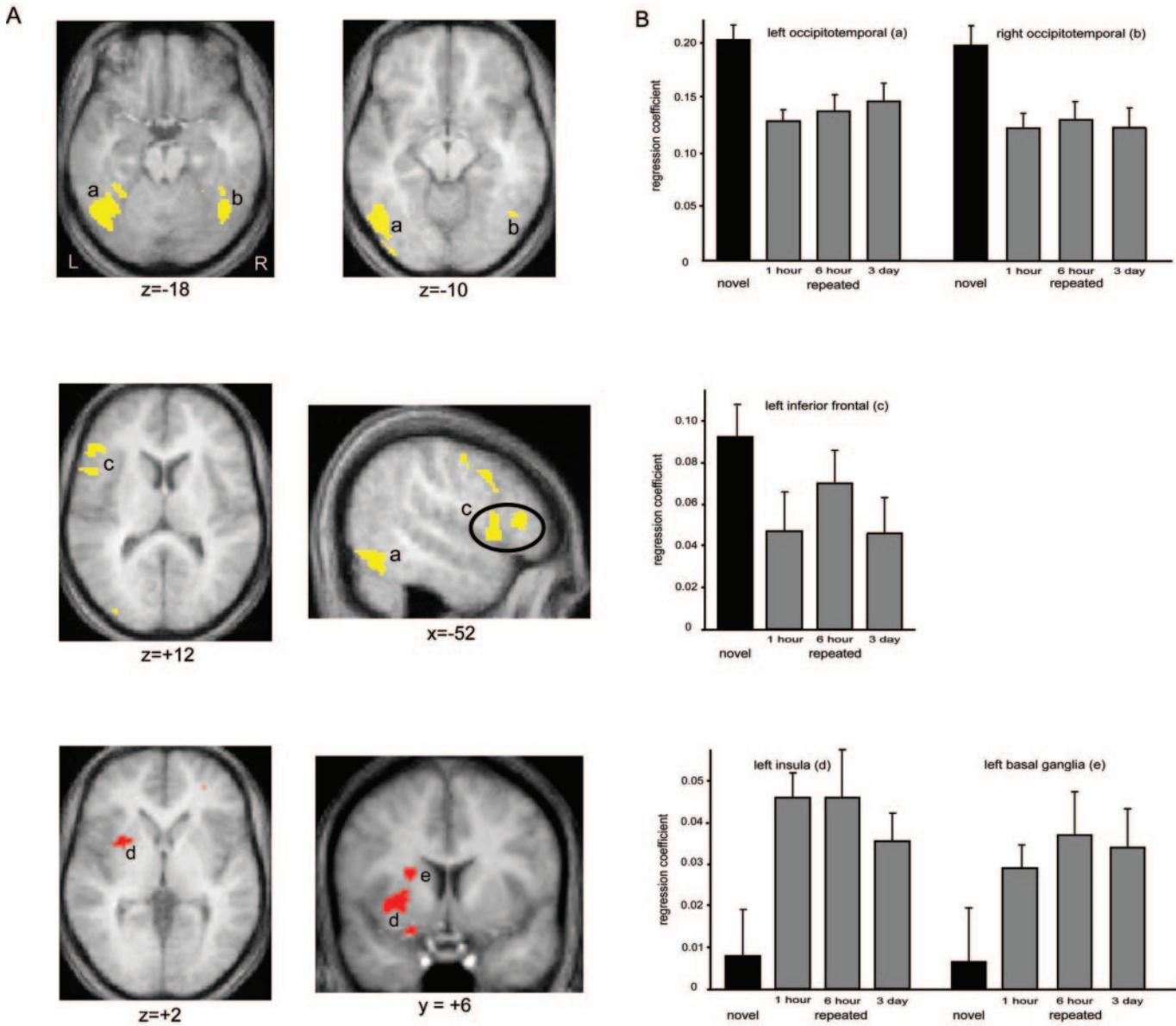
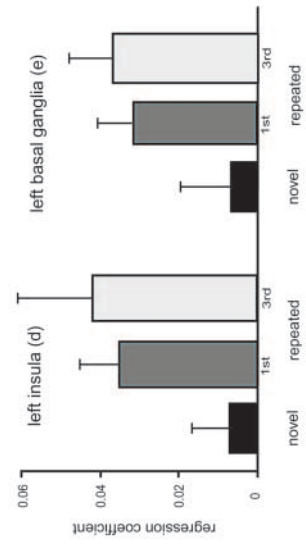
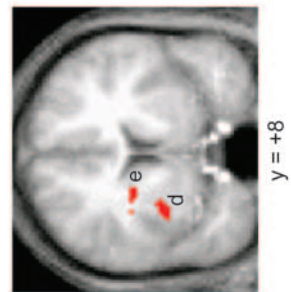
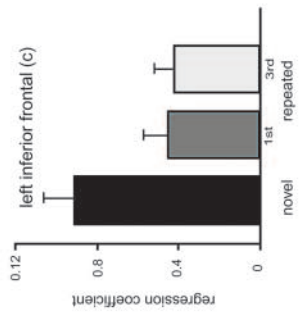
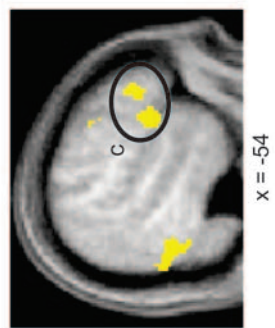
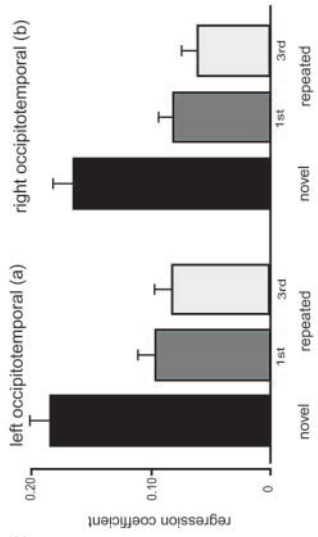
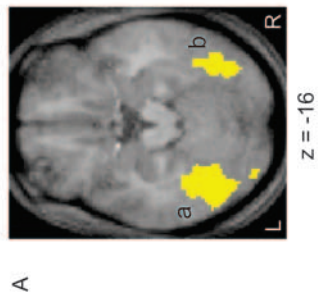


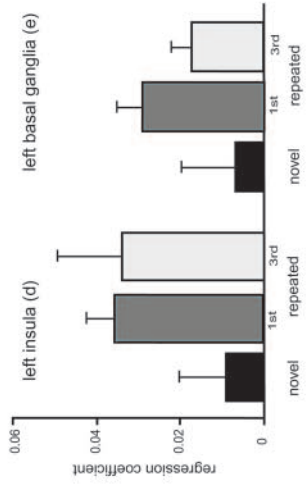
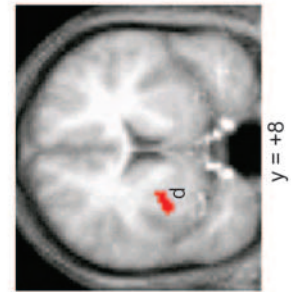
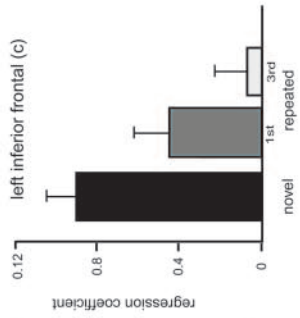
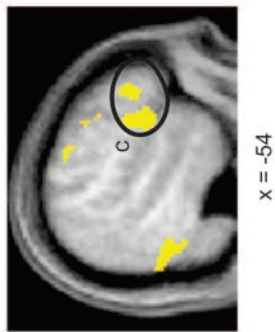
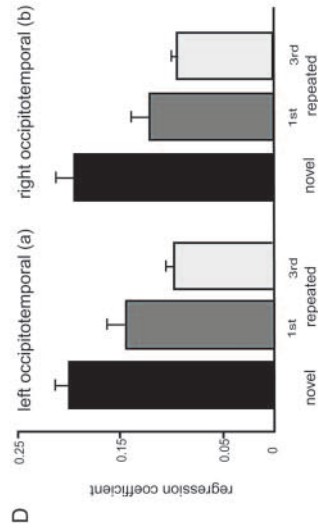
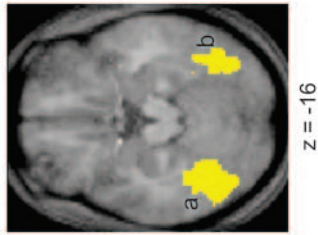
Figure 3. Group averaged fMRI results showing long-lasting changes in activity after a single exposure to an object. (A) Axial, lateral and coronal slices through occipitotemporal (a, b), inferior frontal (c), insular (d) and basal ganglia (e) regions showing decreased responses (displayed in yellow) and increased responses (displayed in red) for repeated as compared to novel objects. Results are overlaid on the group-averaged normalized anatomical image. (B) Group-averaged regional responses computed from all voxels active during object naming and showing an effect of long-term object repetition. Shown are the mean regression coefficients obtained for novel objects, and repeated objects at 1 h, 6 h and 3 days delay, for each of the regions displayed in (A). Error bars reflect the standard error across subjects.

Figure 4. Group averaged results showing changes in activity after multiple repetitions of an object. (A) Axial, lateral and coronal slices through regions showing decreased responses (displayed in yellow) and increased responses (displayed in red) for objects that were repeated three times in a period of 90 s. (B) Group-averaged regional responses computed from all voxels active during object naming and showing an effect of multiple, short-term object repetition. Shown are the mean regression coefficients obtained for novel objects and for objects that were repeated for first and the third time, for each of the regions showing an effect in (A). (C) As in (A), but for objects repeated multiple times in a period of 3 days. (D) As in (B), but for voxels showing an effect of multiple, long-term object repetition. Error bars reflect the standard error across subjects.

Multiple repetitions: Short delay



Multiple repetitions: Long delay



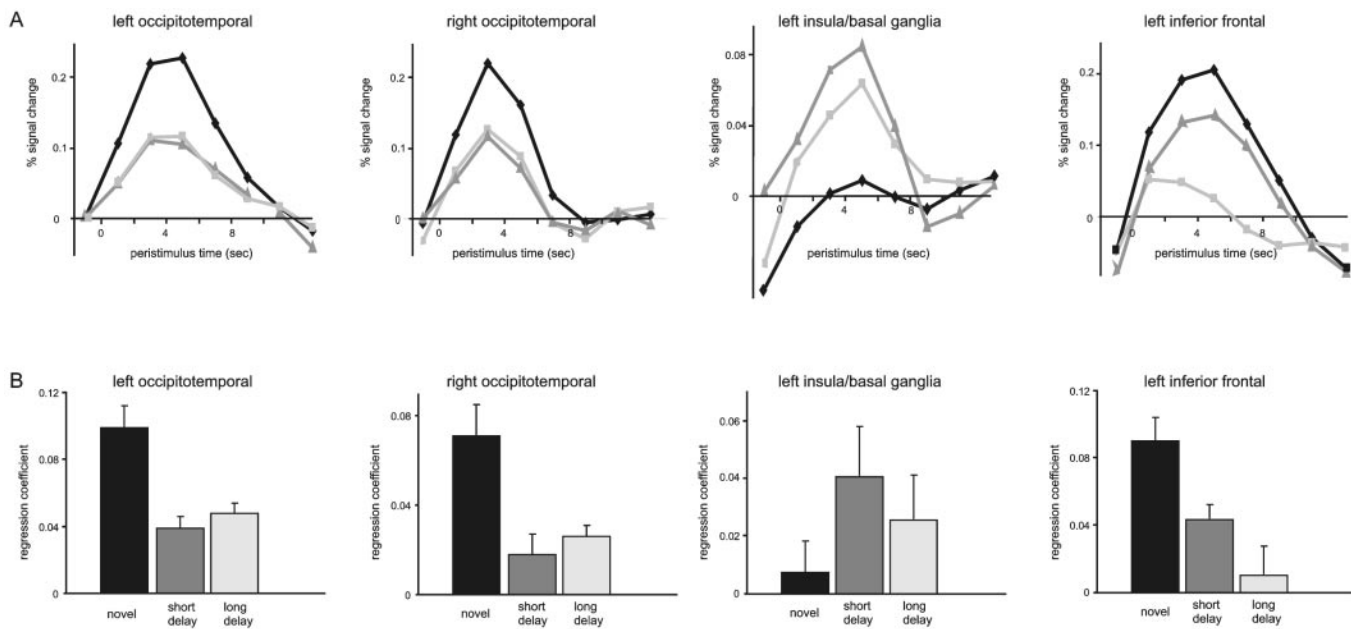


Figure 5. Group-averaged results showing the effect of time on experience-related changes in activity. (A) Average event-related hemodynamic responses in bilateral occipitotemporal, left insula/basal ganglia and the left inferior frontal cortices, computed from all voxels active during object naming and showing an overall effect of object repetition. Shown are group-averaged regional responses for novel objects (black lines), objects repeated multiple times over the time course of 90 s (dark grey lines) and objects repeated multiple times over the time course of 3 days (light grey lines). Responses are plotted as a function of event-onset, binned every 2 s. (B) Group-averaged regional regression coefficients for objects and voxels as described in (A). Error bars reflect the standard error across subjects.

Moreover, we found that hemodynamic responses in the ventral pathway declined as naming latencies became faster through multiple exposures to the same object. This larger reduction in activity with increased object familiarity is again consistent with the hypothesis put forward by Desimone (Desimone, 1996) that as object-form specific features are learned through multiple exposures to the same object, less and less cells are necessary to encode and identify that specific object.

Nevertheless, several alternative explanations could be offered, including a repetition-related decrease in the threshold for activating a pre-existing object representation, or a reduction in attentional demands. For example, repetition-related decreases in neural response may be a consequence of reduced attentional resources needed to identify an object as it becomes more familiar with repeated exposure. While it is difficult to fully rule out these possibilities based solely on neuroimaging data, an attention-based explanation is unlikely to provide an adequate account of the findings. First, it is unclear how this attention mechanism would operate in the context of an event-related design in which the different event types were randomly intermixed, thus preventing the development of strategies or anticipatory responses. Secondly, reduced attention as a function of familiarity cannot account for the different patterns of decreased response in posterior cortex and inferior frontal cortex as a function of delay, nor for the repetition-related increases in neural activity observed in the left insula and basal ganglia. In fact, these region-specific patterns of change rule out any explanation that appeals to a single mechanism, regardless of whether it is a change in processing demands or a change in the structure of the object representation itself.

Procedural Learning in Anterior Regions

Consistent with our previous findings, in addition to the experience-induced decrease in occipitotemporal regions,

object repetition was associated with a long-lasting decrease in activity in the left inferior frontal cortex. Activity in the left inferior frontal cortex during object naming has mainly been associated with post-lexical phonological code retrieval (Poldrack *et al.*, 1999; Indefrey and Levelt, 2000). Repetition-related reductions in activity in this region have been reported to occur in a variety of semantic and phonological tasks (Raichle *et al.*, 1994; Demb *et al.*, 1995; Wagner *et al.*, 1997, 2000b; Buckner *et al.*, 1998, 2000; Schacter and Buckner, 1998; Thompson-Schill *et al.*, 1999). Decreased activity in the more anterior part of left inferior frontal cortex has mainly been related to task-specific reductions in semantic processing demands (Thompson-Schill *et al.*, 1999; Wagner *et al.*, 2000b). In contrast, decreased activity in posterior left inferior frontal cortex occurs across different semantic tasks, and has been related to increased efficiency in phonological code retrieval (Wagner *et al.*, 2000b).

In the present study we observed repetition-related decreases in both anterior and posterior parts of the left inferior frontal cortex. Since object naming was used as an experimental task, these decreases could be related to increased accessibility of semantic as well as phonological features of the object's name. The data showed that decreased activity can be observed 1 h after initial presentation of the object, and does not change with delays of up to 3 days. Critically, the data also showed that the decrease observed in left inferior frontal cortex is qualitatively different from the decrease obtained in occipitotemporal regions. Whereas in posterior regions repetition-related decreases were not affected by the length of the delay, responses in the left inferior cortex were more strongly reduced when more time intervened between successive exposures to the same object. Specifically, in left inferior frontal cortex we observed that multiple exposures to the same object led to a larger change in activity than a single exposure only if exposures were spaced out over time. These results are consistent with our

previous findings that experience-related changes in the left inferior frontal cortex are time dependent.

These time-dependent changes in left inferior frontal cortex support the idea that changes in anterior brain regions reflect a type of learning that is distinct from the repetition suppression effect observed in the ventral visual pathway. What type of mechanism could this be? Previously we proposed that decreased activity in left inferior frontal cortex could reflect a form of procedural learning, related to increased automaticity in object naming (van Turennout *et al.*, 2000; Martin and van Turennout, 2002). As the linkage between an object and its name becomes more automatic as a result of experience, naming becomes less dependent on the left inferior frontal cortex, and more dependent on the left insula. The engagement of the insula in the automation of verbal tasks was first proposed by Raichle and colleagues, who showed that as task performance became more automatic with practice in a verb generation task, activity increased in insular cortex bilaterally and decreased in left inferior frontal cortex, among other changes (Raichle *et al.*, 1994; Petersen *et al.*, 1998). In line with this idea we observed that activity in the left insula increased for repeated as compared to novel objects. In the present study we also observed increased activity in the left basal ganglia. Studies of patients with basal ganglia disorders (i.e. patients with Parkinson's disease and Huntington's disease) have firmly established that the basal ganglia are necessary for the acquisition of skills (Willingham, 1999). It has also been established that this skill learning is not limited to motor tasks. For example, these patients show impairments on a variety of implicit associative learning tasks, e.g. stimulus classification learning (Knowlton *et al.*, 1996), suggesting that the basal ganglia play a crucial role in the formation of implicit stimulus-response associations (Knowlton, 2002). Evidence from brain imaging studies has supported basal ganglia involvement in skill and association learning (Grafton *et al.*, 1995; Poldrack and Gabrieli, 2001). Recently, Poldrack *et al.* (Poldrack *et al.*, 2001) showed differential engagement of the medial temporal lobe and the basal ganglia in a stimulus classification task. Initially, task performance depended heavily on the medial temporal lobe, with no activity in the basal ganglia, while over the course of learning activity in the medial temporal lobe diminished and the basal ganglia became activated. Based on this dynamic change in the involvement of the two structures the authors suggested different roles in learning: the medial temporal system is engaged in development of new stimulus representations, and the basal ganglia mediate the creation of fast and automatic stimulus-response associations.

Our findings suggest the possibility of a similar dynamic, learning-related change involving inferior frontal cortex and the insula and basal ganglia. Anatomical studies have demonstrated that the basal ganglia are connected to almost all regions of the frontal cortex through five distinct circuits (Alexander *et al.*, 1986) and that the insula is connected to many structures including inferior frontal, temporal cortices and the basal ganglia (Augustine, 1996). Moreover, studies of patients with focal lesions of the left anterior insular cortex (Dronkers, 1996) indicate that this region plays an important role in speech articulation. Thus the behavioral impairments associated with damage to the basal ganglia or the insula, and the neural connections between these regions and inferior frontal cortex, provide support for the idea of a learning-related reorganization of neural circuitry whereby the link between a pre-existing phonetic representation of the object's name, and a novel picture of that object, becomes automatic with practice and

time. When pictures of objects were named for the first time, there was little activity in the basal ganglia, or in the insula. However, after an object was named once, activity in both the left basal ganglia and the left insula increased during subsequent naming of that same object. At the same time, whereas initially object naming was strongly dependent on the left inferior frontal cortex, involvement of this region was reduced after the object had been named again, and was barely detectable for objects that had been named multiple times over the time course of 3 days (Fig. 5). Based on these and previous data, we propose that long-lasting facilitation of object naming results, in part, from the creation of an automatic link between an object's features and its associated phonetic representation. Specifically, we propose that, whereas phonetic retrieval is initially subserved by the left inferior frontal cortex, it is at least partially taken over by the left anterior insula and the basal ganglia as naming a specific object becomes more automatic.

Conclusions

The present study demonstrates that neural activity in distinct regions of the object naming system is differentially modulated by time and experience. The data provide support for the existence of two neural mechanisms mediating long-lasting object priming. The first mechanism may involve changes in object-specific representations in occipitotemporal cortices, leading to improved object recognition. The second mechanism may be a form of procedural learning involving a reorganization in brain circuitry that leads to more efficient name retrieval in response to a specific object.

Finally, we need to consider two possible confounds. The first one concerns the fact that we have interpreted our results solely in terms of implicit memory effects. However, in addition to being able to name objects faster, subjects are usually also capable of recognizing the objects they have previously seen. Brain imaging studies have shown that explicit memory affects repetition-related changes in both posterior and anterior brain regions (Henson *et al.*, 2002; Wagner *et al.*, 2000a). It has long been known that recognition memory improves when repetitions are spaced out over long, relative to short intervals of time-spaced versus massed practice (Ebbinghaus, 1885/1964). This behavioral spacing effect could, in principle, be related to the time-dependent decreases we observed in the left inferior frontal cortex. However, contrary to this view, Wagner *et al.* (Wagner *et al.*, 2000a) recently reported a negative correlation between long-lagged priming effects in left inferior frontal cortex, and explicit memory. Explicit memory for words got significantly worse as behavioral priming effects increased and activity in left inferior frontal cortex decreased. This suggests that the larger decreases in activity that we observed in the left inferior frontal cortex for long as opposed to short repetition delays is not likely to be explained by explicit memory effects. However, the exact relationship between the observed patterns of change and implicit and explicit memory processes remains a topic of investigation.

A second issue that needs to be addressed concerns our interpretation of decreased activity in occipitotemporal regions as repetition suppression. The assumption underlying this claim is that a decrease in the hemodynamic responses measured from a specific brain region reflects a decrease in the mean firing rate of the population of neurons in that region. There have been reports, however, suggesting that a decrease in the peak magnitude of the fMRI response can be (partly) explained by a shorter peak latency of the response (James *et al.*, 2000).

Intracranial recordings in inferior temporal cortex from humans have shown that both the latency and the amplitude of neural responses is affected by item repetition (Fernández *et al.*, 2001). Importantly, Fernández and colleagues showed a dissociation between explicit and implicit memory: Whereas peak response latencies were modulated as a function of recognition, with shorter latencies for recognized items, peak amplitudes were reduced for repeated items regardless of the accuracy of the recognition judgement. Decreased hemodynamic responses likely reflect a number of underlying neural processes (Henson and Rugg, 2003). The nature of these processes and their effect on the hemodynamic response measured by fMRI remain to be determined.

Notes

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