Neuroimaging Evidence for Dissociable Forms of Repetition Priming

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with the Tyramide Signal Amplification-Direct (Tyramide Red) system (1:100; NEN Life Sciences, Boston, MA). Sections were then incubated overnight with a monoclonal antibody (mAb) to TH (1:10; Roche Molecular Biochemicals), followed by incubation with a fluorescein isothiocyanate (FITC)– conjugated secondary antibody to mouse immunoglobulin G (IgG) (1:75; Vector Laboratories). The specificity of the primary antibodies was confirmed in control experiments in which sections were incubated with preimmune serum instead of primary antibody, or with primary antibody preabsorbed for 48 hours with a 20-fold excess of the peptide to which the antibody was raised, or in the absence of primary antibody. Other sections were double-immunolabeled with antibody to human α-synuclein (as above) and rabbit polyclonal antibody to ubiquitin (1:50 or 0.2 mg/ml; DAKO Corporation, Carpinteria, CA) detected with an FITC-conjugated secondary antibody to rabbit IgG (1:75; Vector Laboratories). To evaluate the integrity of presynaptic terminals and dopaminergic neurons, we double-immunolabeled sections with a mAb to synaptophysin (1:2500; Roche) (Tyramide Red detection system) and a mAb to TH (see above). Brain sections from mice to be compared in any given experiment were processed and immunolabeled in parallel. Three sections were analyzed per mouse, and four serial 2-μm-thick optical sections were obtained per section. For each experiment, the linear range of the intensity of immunoreactive structures in control sections was determined with a MRC1024 (Bio-Rad) confocal microscope. This setting was then used for the collection of all images to be analyzed in the same experiment. Digitized images were transferred to a Power-PC Macintosh computer, and NIH Image 1.4 software was used to calculate the percent image area covered by immunoreactive terminals. The number of TH-positive neurons in the pars compacta of the substantia nigra was estimated essentially as described [A. Hsia *et al.*, *Proc. Natl. Acad. Sci. U.S.A.* **96**, 3228 (1999)].

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23. For Western blot analysis of TH levels, brains were homogenized and separated into cytosolic and particulate fractions as described (*4*). Twelve micrograms of cytosolic fraction per mouse were loaded onto 10% SDS–polyacrylamide gel electrophoresis gels followed by transfer of proteins onto Immobilon membranes and detection of TH with a mAb to TH (1:1000; Roche). Blots were incubated with horseradish peroxidase–coupled secondary antibody and developed with the chemiluminescence reagent (NEN). After exposure of blots to film, the density of bands was quantitated with the ImageQuant system (Molecular Dynamics, Sunnyvale, CA).
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REPORTS

Neuroimaging Evidence for Dissociable Forms of Repetition Priming

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Repetition priming has been characterized neurophysiologically as a decreased response following stimulus repetition. The present study used event-related functional magnetic resonance imaging to investigate whether this repetition-related response is sensitive to stimulus familiarity. A right fusiform region exhibited an attenuated response to the repetition of familiar stimuli, both faces and symbols, but exhibited an enhanced response to the repetition of unfamiliar stimuli. Moreover, both repetition effects were modulated by lag between successive presentations. Further experiments replicated the interactions between repetition, familiarity, and lag and demonstrated the persistence of these effects over multiple repetitions. Priming-related responses are therefore not unitary but depend on the presence or absence of preexisting stimulus representations.

Repetition priming is one of the basic forms of memory in higher nervous systems. It has been studied extensively by cognitive psychologists, often indexed behaviorally as faster reaction times or improved identification accuracy following repetition (*1*). A well-established neurophysiological index of repetition priming is a relative decrease in neural firing with repeated stimulus presentations, referred to as "repetition suppression" (*2*), as found, for example, in inferotemporal regions of the monkey cortex (*3*). Analogous decreases in the hemodynamic response following stimulus repetition have been reported within the human extrastriate cortex in functional imaging studies (*4*). These imaging studies have typically used familiar stimuli, such as common words or pictures of identifiable objects. In the present imaging study, we examined whether repetition priming effects are modulated by stimulus familiarity. By familiarity, we refer to whether or not a representation of the stimulus existed before scanning.

In four experiments conforming to the same basic paradigm, we used functional magnetic resonance imaging (fMRI) (*5*) to measure the event-related hemodynamic response to brief visual stimuli (Fig. 1). Participants (*6*) viewed a baseline image that was replaced by either a face (experiments 1 and 3) or a symbol (experiments 2 and 4). Each stimulus was either familiar (a famous face or a meaningful symbol) or unfamiliar (a nonfamous face or a meaningless symbol) and was presented twice (experiments 1 and 2) or five times (experiments 3 and 4) in a randomly intermixed design. Participants were required to press a key only if the stimulus was a prespecified target, so that the events of interest, the nontarget stimuli, were uncontaminated by motor response requirements. This use of an indirect task removes any explicit requirement for differential attention to stimulus familiarity or repetition. After scanning, participants were shown the stimuli again and judged which could be identified (i.e., faces identified as famous or symbols identified as meaningful). Although the judgments were in good agreement, the differences allowed analyses to be individually tailored to participants' prior experience.

Experiments 1 and 2 employed a two-by-two factorial design in which the events of interest were first and second presentation of familiar (F1 and F2) and unfamiliar (U1 and U2) stimuli. We created statistical parametric maps of voxels exhibiting increased responses to stimulus presentation versus baseline (*7*). These voxels (which comprised mainly bilateral fusiform, right lateral occipital, and inferior frontal regions) were then used as a mask within which to identify brain regions sensitive to two planned, orthogonal comparisons: (i) regions showing greater responses to familiar than to unfamiliar stimuli, (F1 + F2) – (U1 + U2), and (ii) regions showing an interaction between familiarity and repetition, (F1 – F2) – (U1 – U2).

The only regions exhibiting a greater response to familiar than to unfamiliar faces were in the bilateral fusiform cortex (Fig. 2A), close to what has been referred to as the "face area" (*8*). The present results suggest that this region is sensitive to whether or not a face is recognized, perhaps reflecting activation of "face recognition units" (FRUs) (*9*). Similar bilateral fusiform regions, however [given the spatial smoothing of the data (*5*)], exhibited a greater

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response to familiar than to unfamiliar symbols (Fig. 2B), suggesting that the fusiform cortex plays a more general role in the discrimination of similar visual objects (*10*).

A right fusiform region showed an interaction between familiarity and repetition for both faces and symbols (Fig. 2, C and D). This interaction reflected a decreased response to the repetition of familiar stimuli, as observed in most previous imaging studies of repetition priming. In contrast, an increased response to the repetition of unfamiliar stimuli, a "repetition enhancement" effect, was seen. One interpretation of these data is that repetition suppression reflects more efficient processing of repeated familiar stimuli, whereas repetition enhancement reflects a qualitative change in the perception of repeated unfamiliar stimuli. If a single presentation of an unfamiliar face were sufficient to form a new perceptual representation (*11*) (an FRU for example), then the second presentation of that face should result in the same perceptual recognition process and response increase that was seen in our comparison of famous versus nonfamous faces.

In further analysis, we examined whether these repetition effects were modulated by lag between the first and second presentations of stimuli, which ranged from 1 to 147 intervening stimuli (median = 45) or from 8 s to 20 min. With an exponentially decreasing function of lag, a slightly more posterior right fusiform region showed a significant interaction between familiarity and lag for both faces and symbols (*12*). Specifically, the response to the second presentation of familiar stimuli increased with lag, whereas the response to unfamiliar stimuli decreased with lag (Fig. 3). This suggests that both repetition suppression and repetition enhancement had a transient component (and any modification or formation of representations is temporary). Repetition-related lag effects have also been shown neurophysiologically (*13*) and electrophysiologically (*14*). Although priming effects can sometimes be long-lasting (*15*), they are likely to reflect several different processes; our repetition effects appear to reflect one such process that decays over minutes.

A behavioral experiment, predicated on the imaging results, was performed to test the above familiarity-by-repetition interaction and lag effects. Using the same stimuli, we indexed repetition priming by reaction times in a familiarity judgment task (*16*). The priming effect (difference in median correct reaction times for first versus second presentations) was significantly greater for familiar (150 ms) than for unfamiliar (75 ms) faces [$t(12) = 2.13$, $P < 0.05$] and was greater for familiar (124 ms) than for unfamiliar (67 ms) symbols [$t(12) = 2.37$, $P < 0.05$]. Linear regressions of this priming effect against the same exponential function of lag used for the imaging data revealed linear coefficients with magnitudes significantly greater than zero in all cases [$t(12) > 2.98$, $P < 0.05$]. These data confirm that a behavioral index of repetition priming is sensitive to stimulus familiarity and repetition lag over a time scale similar to that in the imaging experiments.

Our findings indicate qualitative differences in the repetition-related responses within the right fusiform cortex for stimuli with and without preexisting representations. We next asked whether this interaction persists over multiple exposures to these stimuli. This question was addressed in two further experiments in which each face or symbol was presented five times throughout the scanning session. Fusiform regions again exhibited greater responses to familiar than to unfamiliar stimuli, on the left for faces and bilaterally for symbols (Fig. 4, A and B). The right fusiform region again exhibited an interaction between familiarity and repetition: For faces

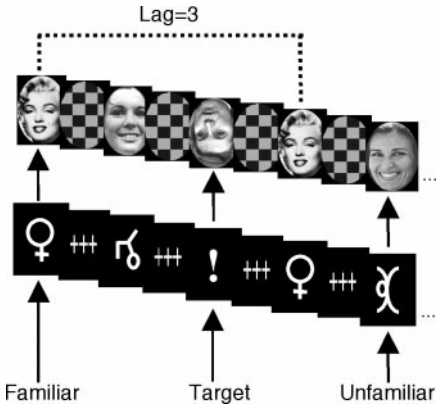

Fig. 1. Experimental paradigm. Gray-scale photographs of famous and nonfamous faces or white-on-black symbols that were meaningful or meaningless were presented against baseline checkerboards or fixation crosses, respectively. Participants made a right-index-finger key press only to the prespecified target (an inverted face or exclamation mark). Stimuli were projected onto a screen 30 cm above the participant, subtending a visual angle of ~10° and 4° for faces and symbols, respectively. Two (experiments 1 and 2) or five (experiments 3 and 4) presentations of 32 familiar and 32 unfamiliar stimuli (together with 22 targets) were randomly ordered for each participant, producing a range of lags between presentations of the same stimulus. Stimuli in experiments 1 and 2 were displayed for 1 s, with a random SOA between 6 and 10 s. Stimuli in experiments 3 and 4 were displayed for 0.5 s, with a two-thirds probability of occurring every minimum SOA of 2 s (*29*). Target detection was near perfect, and more than 95% of famous faces and 75% of meaningful symbols were identified during debriefing.

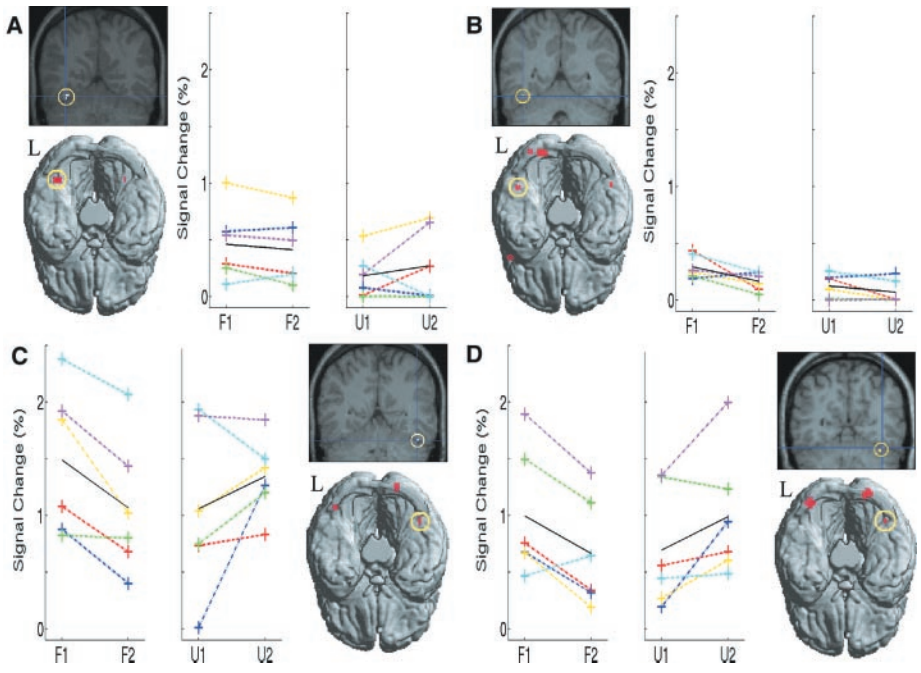

Fig. 2. Regions showing familiarity effects and familiarity-by-repetition interactions in experiments 1 and 2. (**A**) Regions showing greater responses to familiar than to unfamiliar faces. The rendered image is a canonical brain viewed from underneath, with the cerebellum artificially removed; the coronal section is through a normalized T1 structural image from one participant. Colored plots show maxima of the best fitting canonical event-related response for each participant in each condition, from the maximum ($x = -36$, $y = -60$, $z = -15$; BA 37; Z score = 3.81) of a left fusiform region (the solid black line shows the mean across participants). (**B**) Regions showing greater responses to familiar than to unfamiliar symbols. The plots derive from the maximum ($x = -42$, $y = -51$, $z = -15$; BA 37; Z score = 3.15) of a left fusiform region. (**C**) Regions showing a familiarity-by-repetition interaction for faces. The plots derive from the maximum ($x = 45$, $y = -57$, $z = -24$; BA 37; Z score = 3.18) of a right fusiform region. (**D**) Regions showing a familiarity-by-repetition interaction for symbols. The plots derive from the maximum ($x = 42$, $y = -60$, $z = -24$; BA 37; Z score = 3.17) of a right fusiform region. Activated voxels are red, and plots are from regions circled in yellow. L, left.

and symbols, the response to familiar stimuli decreased over the five presentations, whereas the response to unfamiliar stimuli increased (Fig. 4, C and D). Further tests confirmed that this linear interaction continued across all five presentations (*17*). The right fusiform region also showed an effect of repetition lag for faces and symbols, such that repetition suppression and repetition enhancement diminished with lag. Moreover, for symbols, this lag effect was itself modulated by the number of presentations, such that the differential lag sensitivity of repetition effects decreased with the number of repetitions (*18*).

The results of experiments 3 and 4 replicate and extend those of experiments 1 and 2. The overall statistical reliability was confirmed by a final analysis over all four experiments (*19*), conforming to a random effects model across the 24 participants, which revealed a common left fusiform region showing the familiarity effect ($x = -36$, $y = -60$, $z = -18$; Z score = 4.60) and a common right fusiform region showing the familiarity-by-repetition interaction ($x = 48$, $y = -51$, $z = -24$; Z score = 3.58). Furthermore, the consistency in spatial location of these regions was demonstrated at the individual participant level (*20*), again suggesting that these fusiform responses reflect processes that operate over faces and symbols. The continued response decrease with multiple presentations of familiar stimuli is consistent with behavioral priming effects (*21*). The continued increase for unfamiliar stimuli suggests that the familiarization proposed from experiments 1 and 2 is a prolonged process, perhaps reflecting gradual refinement of new perceptual representations (*22*). The lag sensitivity of the repetition effects suggests that such changes are temporary unless consolidated by further repetitions (as confirmed by the sensitivity of lag effects to the number of repetitions in experiment 4).

Our results help resolve an apparent contradiction in the neuroimaging literature as to whether priming is associated with attenuated (*4*) or enhanced (*23, 24*) hemodynamic responses. It has been argued that attenuated responses occur when the same processes are performed on repeated exposures, only faster or more efficiently (*4*), perhaps reflecting lowered thresholds for activating existing representations. We propose that enhanced responses occur whenever additional psychological processes are engaged by repeated exposures, such as those allowed by the formation of new representations (*25*). For example, the first presentation of drawings that represent possible three-dimensional (3D) objects (*23*) would create new structural representations of the corresponding 3D object. Subsequent presentations of the same drawings would produce recognition of those 3D objects, an additional process that was absent from their first presentation, resulting in repetition enhancement. No such processes could occur for the repetition of drawings that do not represent possible 3D objects. Similarly, prior presentation of intact images of famous faces (*24*) would allow subsequent recognition of degraded versions that are otherwise ambiguous, resulting in repetition enhancement. In the absence of a disambiguating stimulus, no additional recognition process is likely, resulting in repetition suppression (*26*). Repetition enhancement would only be

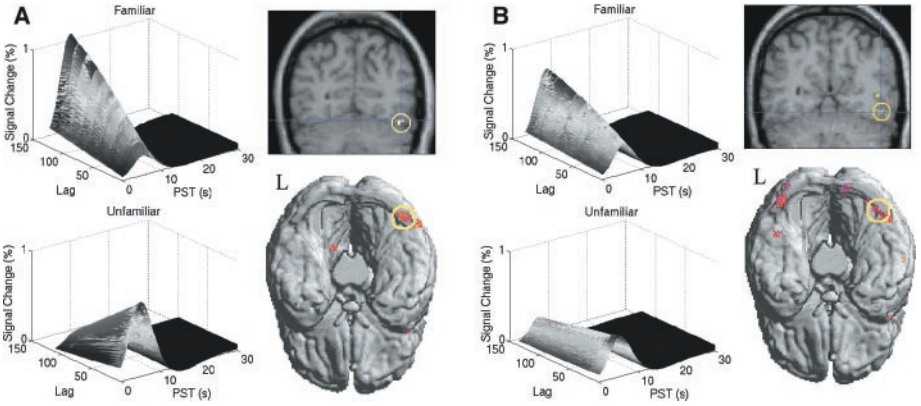

Fig. 3. Regions showing differential lag effects as a function of familiarity in experiments 1 and 2. (**A**) Regions showing a differential lag effect for familiar and unfamiliar faces. Plots show the mean best fitting canonical event-related response across participants to the second presentation of faces, as a function of peristimulus time (PST) and modulation by the exponential function of lag, at the maximum ($x = 48$, $y = -69$, $z = -18$; BA 37; Z score = 3.51) of a right fusiform region. (**B**) Regions showing a differential lag effect for familiar and unfamiliar symbols. The plot derives from the maximum ($x = 51$, $y = -60$, $z = -15$; BA 37; Z score = 2.60) of a right fusiform region. See Fig. 2 for further details.

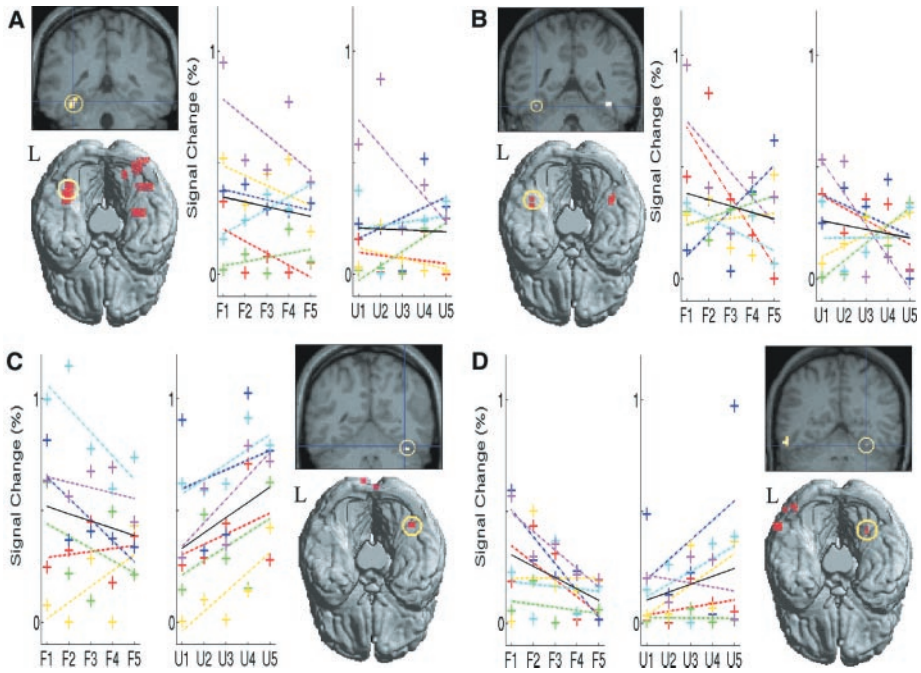

Fig. 4. Regions showing familiarity effects and familiarity-by-repetition interactions in experiments 3 and 4. (**A**) Regions showing greater responses to familiar than to unfamiliar faces. Colored data points show the maximum of the best fitting canonical event-related response for each participant at the maximum ($x = -33$, $y = -48$, $z = -18$; BA 37; Z score = 3.66) of a left fusiform region (colored lines show the linear best fit across presentations 1 through 5; the black solid line shows the mean fit across participants). (**B**) Regions showing greater responses to familiar than to unfamiliar symbols. The plots derive from the maximum ($x = -36$, $y = -48$, $z = -21$; BA 37; Z score = 2.72) of a left fusiform region. (**C**) Regions showing an interaction between familiarity and repetition of faces. The plots derive from the maximum ($x = 39$, $y = -57$, $z = -24$; BA 37; Z score = 2.86) of a right fusiform region. (**D**) Regions showing an interaction between familiarity and repetition of symbols. The plots derive from the maximum ($x = 30$, $y = -54$, $z = -21$; BA 37; Z score = 2.82) of a right fusiform region. See Fig. 2 for further details.

expected in higher visual areas, such as the fusiform cortex, where the additional processes such as recognition occur. Early visual areas that subserve processes common to familiar and unfamiliar, or intact and degraded, stimuli (such as edge analyses, for example) would be expected to show repetition suppression for both stimulus types.

Our findings raise important questions relating to repetition effects observed in single-cell recordings. Few electrophysiological studies have observed significant proportions of neurons with increased firing to stimulus repetition (*27*). However, the relation between firing rates measured from single neurons and hemodynamic responses measured from large populations of neurons remains to be established. It has been suggested that stimulus repetitions produce decreased responses from those neurons coding features that are unnecessary for stimulus identification (*28*). This results in a more selective stimulus representation in which a smaller proportion of neurons remains responsive and, hence, a decrease in the mean firing of a population of neurons. At face value, our observation of increased responses to repetitions of unfamiliar stimuli, which are more likely to entail the formation of new representations than repetitions of familiar stimuli are, is problematic for this theory. Whatever the precise relation between cellular firing rates and regional hemodynamic responses, our data suggest that priming-related neural responses in the human fusiform gyrus are not unitary. Rather, they appear to reflect a complex interplay between the presence or absence of preexisting stimulus representations, the state of formation of new representations, and the lag interval between repetitions.

References and Notes

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5. A 2T VISION system (Siemens, Erlangen, Germany) provided T1 anatomical volume images (1 mm by 1 mm by 1.5 mm voxels) and T2*-weighted echoplanar images (EPIs) (64 by 64 3 mm by 3 mm pixels, TE = 40 ms) with blood oxygenation level–dependent contrast. EPIs comprised 2-mm-thick axial slices that were acquired sequentially every 3 mm and continuously during a single 20-min session. A total of 305 volumes of 46 slices covering the whole brain were acquired in experiments 1 and 2, with a repetition time (TR) of 4.2 s/volume; 667 volumes of 16 slices, angled along the temporal lobe, were acquired in experiments 3 and 4, with a TR of 1.4 s/volume. The first five volumes were discarded to allow for T1 equilibration. Volumes were realigned, resliced using sinc interpolation, and normalized to an EPI template based on the Montreal Neurological Institute reference brain [C. A. Cocosco *et al.*, *Neuroimage* **5**, 425 (1997)] of 3 mm by 3 mm by 3 mm voxels in Talairach space using nonlinear basis functions. T1 structural volumes were coregistered with the mean realigned EPI volumes and normalized with the same deformation parameters. The EPI volumes were smoothed with an 8-mm full width at half maximum (FWHM) isotropic Gaussian kernel and globally scaled to 100. The time series for each voxel were high-pass filtered to 1/240 Hz (experiments 1 and 2) or 1/120 Hz (experiments 3 and 4) and low-pass smoothed by a 4-s FWHM Gaussian kernel.
6. Twenty-four right-handed healthy volunteers (nine males), aged 22 to 38 years (mean age of 27 years), gave informed consent to participate in the study. They were randomly allocated to four groups of six for each experiment.
7. Data were analyzed with the Statistical Parametric Mapping software [SPM99, Wellcome Department of Cognitive Neurology, London; K. J. Friston, *et al.*, *Hum. Brain Mapp.* **2**, 189 (1995)]. The responses to stimulus onsets for each event type, synchronized with the acquisition of the middle slice, were modeled by a canonical hemodynamic response function (HRF) and its temporal derivative. Five event types were modeled in experiments 1 and 2, and eleven were modeled in experiments 3 and 4 (one for each presentation of familiar and unfamiliar stimuli, plus one for target stimuli). These functions, together with a constant term, were used as participant-specific covariates in a fixed effects, general linear model. Linear contrasts on parameter estimates for the canonical HRF generated statistical parametric maps of the t statistic, which were subsequently transformed to Z values. For experiments 1 and 2, the statistical parametric maps were thresholded at $P < 0.001$, uncorrected, and masked with the main effect of stimuli versus baseline, thresholded at $P < 0.01$, uncorrected. Given the prior hypotheses generated from experiments 1 and 2, the statistical parametric maps in experiments 3 and 4 were similarly masked but thresholded at $P < 0.005$.
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12. This model included an additional covariate representing the modulation of second presentations of familiar and unfamiliar stimuli by the function exp(–lag/150), where 150 was the maximum possible lag. Contrasts on this lag effect were masked as before and thresholded at $P < 0.005$ uncorrected. Immediate repetitions (lag = 1), which may represent a special case [S. Bentin and M. Moscovitch, *J. Exp. Psychol. Gen.* **117**, 148 (1988)], were rare, and their removal from analyses had a negligible effect.
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16. A separate group of 12 volunteers (11 males), aged 22 to 30 years (mean age of 26 years), made speeded familiarity judgments to the same stimuli. The stimulus onset asynchrony (SOA) varied randomly between 2 and 4 s, and the order of face and symbol conditions was counterbalanced across participants.
17. The same right fusiform region was revealed when the linear interaction contrast across all five presentations was orthogonalized with respect to the pairwise interaction across the first two presentations, for both faces and symbols. Further tests of quadratic trends did not reveal any right fusiform regions, contrary to an expectation that repetition enhancement for unfamiliar stimuli might asymptote, or switch to repetition suppression, after five presentations (as expected if a number of presentations were sufficient to make unfamiliar stimuli functionally equivalent to familiar stimuli).
18. Parametric effects of presentation number (1 through 5), exponentiated lag (*12*), and the interaction between presentation and lag were modeled separately for familiar and unfamiliar stimuli. Differential lag effects for familiar and unfamiliar stimuli were found in right fusiform regions for faces ($x = 48, y = -57, z = -18$; BA 37; Z score = 2.79) and symbols ($x = 45, y = -42, z = -21$; BA 37; Z score = 3.78). A right fusiform region also showed an interaction between familiarity, presentation number, and lag for symbols ($x = 36, y = -60, z = -31$; BA 37; Z score = 3.32).
19. Images of parameter estimates for the familiarity and familiarity-by-repetition contrasts for each participant were entered into a second-level, one-tailed t test. Some more posterior occipitotemporal regions also showed effects of familiarity, repetition, or lag (compare Figs. 2 through 4), but these regions were less consistent across the four separate analyses, and we concentrate on the middle fusiform cortex because of its prior association with visual object (particularly face) recognition (*8, 10*).
20. The spatial variability of these regions was further quantified by testing each participant separately (thresholded at $P < 0.01$, uncorrected). Taking the maxima from each participant that was closest to the group maxima, we found that the mean and standard deviation of Talairach coordinates (x, y, z) were (–36.5 ± 13.3, –51.5 ± 13.1, –15.0 ± 4.7), (–41.5 ± 3.5, –50.5 ± 4.8, –7.5 ± 10.7), (–38.5 ± 16.7, –49.5 ± 7.8, –17.0 ± 9.8), and (–49.5 ± 8.8, –44.5 ± 15.5, –12.0 ± 10.6) for the familiarity effect and (42 ± 6.8, –55.5 ± 7.3, –20.5 ± 7.7), (40.5 ± 7.7, –55.5 ± 9.4, –26 ± 9.3), (34.5 ± 11.5, –48 ± 12.4, –24.5 ± 6.9), and (36.5 ± 12.5, –44.5 ± 21.7, –19.0 ± 7.9) for the familiarity-by-repetition interaction, across experiments 1 through 4, respectively. Although a trend is evident for a more medial location of the familiarity effect for faces relative to symbols, no reliable differences were detected in the x, y, or z coordinates for either the familiarity effect or the familiarity-by-repetition interaction in comparison of experiments 1 and 3 versus experiments 2 and 4 [t (12) < 1.69, $P > 0.05$].
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25. Our experimental design cannot distinguish the relative influence of explicit versus implicit memory [D. L. Schacter, *J. Exp. Psychol.* **13**, 501 (1987)], and the repetition-related increases may reflect explicit recognition processes [P. J. Reber, C. E. Stark, L. R. Squire, *Learn Mem.* **5**, 420 (1998)].
26. Prior presentation of intact images of unfamiliar faces may [R. J. Dolan *et al.*, *Nature* **389**, 596 (1997)] or may not (*24*) be sufficient for subsequent recognition of degraded versions. In situations where recognition is not achieved, repetition suppression would be expected (*24*).
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