nature neuroscience

Reductions in neural activity underlie behavioral components of repetition priming

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Repetition priming is a nonconscious form of memory that is accompanied by reductions in neural activity when an experience is repeated. To date, however, there is no direct evidence that these neural reductions underlie the behavioral advantage afforded to repeated material. Here we demonstrate a causal linkage between neural and behavioral priming in humans. fMRI (functional magnetic resonance imaging) was used in combination with transcranial magnetic stimulation (TMS) to target and disrupt activity in the left frontal cortex during repeated classification of objects. Left-frontal TMS disrupted both the neural and behavioral markers of priming. Neural priming in early sensory regions was unaffected by left-frontal TMS—a finding that provides evidence for separable conceptual and perceptual components of priming.

Recent experience with an item leads to quicker recognition and classification of that item upon subsequent encounters. This implicit form of memory is commonly referred to as "behavioral priming" and occurs even in the absence of conscious remembering[1,2]. Neuroscientific investigations consistently reveal reductions in neural activity that accompany this repetition-based learning facilitation. These activity reductions are seen both at the level of single cells in nonhuman primates[3–5] and across a host of brain areas extending from posterior sensory to frontal cortices in humans[6–10]. Although this neural phenomenon generalizes across a range of behavioral priming situations, the loci of such "neural priming" effects vary and are restricted to a subset of the brain regions engaged during task performance with novel material. Repeated semantic classification of visually presented objects, for example, consistently yields reduced activity in extrastriate visual regions and in the left inferior frontal gyrus (LIFG)[11,12].

One speculation is that neural priming reflects fine-tuning of the neuronal response, or a suppression of neurons within the neuronal population, perhaps because those neurons that are no longer needed drop out of the responsive pool[3,13,14]. Such effects could occur either early in the processing stream at the level of object recognition in sensory cortices (perceptual priming) or at later stages during semantic classification in frontal and temporal cortices (conceptual priming)[15]. The precise neurophysiological mechanism that reduces neural activity is unclear, and the relationship between neural priming and behavioral priming remains indirect—evidenced only by the co-occurrence of these two phenomena. A fundamental question remains: does neural priming in a given brain region contribute to the behavioral facilitation afforded to repeated items, or is it epiphenomenal to behavior?

One possibility is that neural priming in brain regions thought to be involved in conceptual priming (*e.g.*, LIFG) is necessary for behavioral priming. Alternatively, neural priming in sensory cortices may subserve behavioral priming and the neural reductions observed in frontal regions may simply reflect a feed-forward propagation of the changes in neural activity arising earlier in perceptual regions. To test these possibilities, we combined fMRI and TMS to target and transiently disrupt left-frontal activity during an object classification task (**Fig. 1**).

In an initial fMRI session, subjects performed a semantic classification task (living/nonliving) for a series of objects that were either repeated or novel. In a second session, subjects received TMS while performing the classification task on a new set of objects. The use of TMS allowed for noninvasive and transient disruption of cortical activity in a circumscribed region of cortex. We used activation maps from the initial fMRI session, which compared trials with novel objects to those with repeated objects, to identify subject-specific neural priming foci within the LIFG. These single-subject activation maps were then superimposed on the subject's anatomical brain image and used to guide the positioning of the TMS coil on the subject's head. This approach permitted real-time, continuous monitoring of the coil position with respect to the site of interest.

For each presented object, TMS was delivered to either the LIFG region identified during fMRI scanning (left-frontal TMS) or the hand region of left motor cortex (control-site TMS). The motor region was included as a control site to ensure that TMS effects were specific to left-frontal stimulation and not a property of global cortical disruption. During the TMS session, each object was presented twice and was accompanied by a 10-Hz train of stimulation lasting 500 ms. Onset of the TMS was tailored to each subject's individual response profile from the initial fMRI session (**Fig. 2**; see Methods).

To assess both the behavioral and neurophysiological consequences of TMS, we performed a second fMRI scan on each subject immediately after the TMS session. Critically, this post-TMS scanning session allowed behavioral responses to be recorded in the absence of potentially

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Published online 31 July 2005; doi:10.1038/nn1515

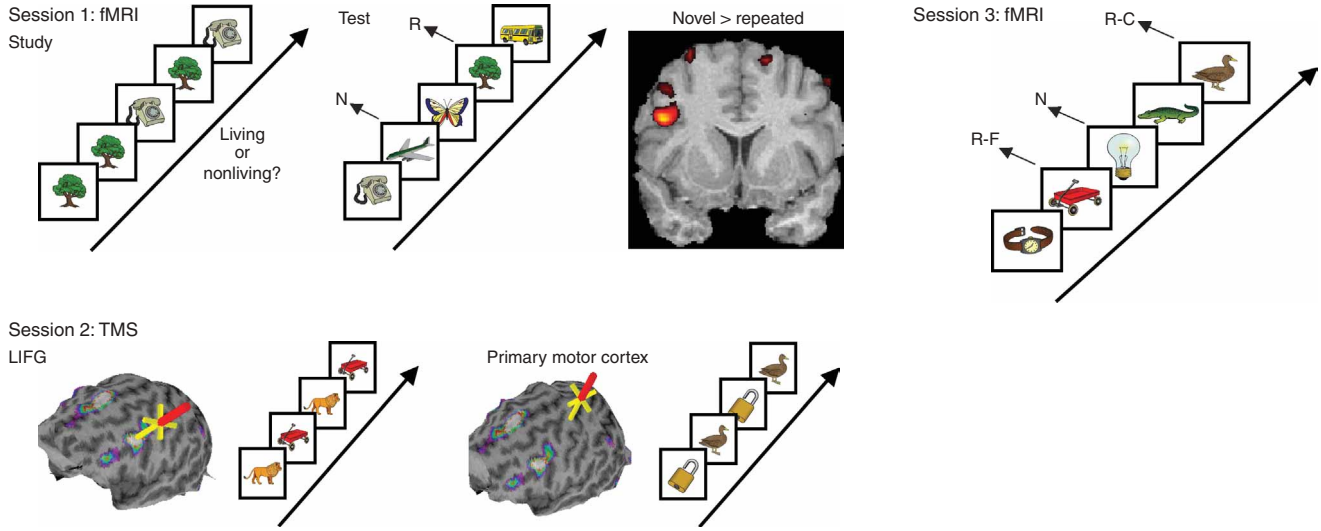

Figure 1 Experimental design. In Session 1, subjects made living/nonliving judgments for a series of colored objects. Each object was repeated six times prior to fMRI scanning. During fMRI, subjects judged repeated objects and novel objects that were presented for the first time. Single-subject activation maps comparing novel (N) to repeated (R) objects were used to identify neural priming effects in the LIFG. In Session 2, subjects received TMS to either the LIFG or a control site (left motor cortex) while performing the same task on a new set of objects. Each object was presented twice and was accompanied by TMS for each presentation. In Session 3, subjects were again imaged with fMRI while judging repeated objects that were previously paired with left-frontal TMS (R-F), repeated objects that were previously paired with control-site TMS (R-C) and novel objects (N).

confounding TMS effects (such as peripheral nerve stimulation) and also permitted simultaneous recording of the neural correlates of the behavior. During this final session, subjects performed the living/nonliving classification task for three types of objects: novel objects, repeated objects that were previously presented with left-frontal TMS during the first two presentations, and repeated objects that were previously presented with control-site TMS during the first two presentations. Of interest were the neural activity and response latencies that accompanied this third presentation of each repeated object.

RESULTS

Session 1: fMRI

Behaviorally, repeated objects were classified more quickly (560 ± 27 ms (mean ± s.e.m. throughout)) than novel objects (621 ± 35 ms) in the first fMRI session ($t_{10} = 5.99$, $P < 0.001$). Consistent with prior neuroimaging work, this behavioral facilitation for repeated objects was accompanied by reduced neural activity in a network of brain regions (**Fig. 3**).

Session 2: TMS

Accuracy during the semantic classification task while undergoing TMS was near perfect and was unaffected by TMS site (left-frontal mean, 99.5% correct; control-site mean, 98.9% correct; $P > 0.55$). Similarly, response latencies during TMS administration (left-frontal TMS: first presentation, 549 ± 40 ms; second presentation, 539 ± 35 ms; control-site TMS: first presentation, 601 ± 56 ms; second presentation, 546 ± 38 ms) did not differ as a function of TMS site or repetition (main effect of TMS site, $F < 1$; main effect of repetition, $F_{1,10} = 2.41$, $P = 0.15$; interaction, $F < 1$).

Response latencies acquired during TMS administration were not considered to be a pure measure of behavioral priming, as these measures were contaminated by peripheral effects resulting from TMS. Specifically, TMS at the intensity and frequency used here produced discomfort due to contraction of facial muscles. Also, as expected, left-motor (control) TMS produced right-hand movement while subjects responded. Instead, the behavioral and neural consequences of functionally targeted TMS were examined simultaneously in a subsequent fMRI session.

Session 3: fMRI

Subjects viewed three classes of objects during the final fMRI session: repeated objects that had been paired with left-frontal TMS (repeated-frontal), repeated objects that had been paired with left-motor TMS (repeated-control) and novel objects (novel). To assess the effects of TMS on neural priming, we conducted hypothesis-driven region-of-interest (ROI) analyses on six brain regions: left posterior-inferior frontal cortex (Brodmann's area 44 (LIFG; BA 44); *x y z* peak location: –42 9 24), left anterior-inferior frontal cortex (BA 45/47; −54 30 0), left posterior temporal cortex (BA 21/37; −57 −66 −6), left fusiform gyrus (BA 37; −33 −75 −21), left middle occipital gyrus (left MOG; BA 19; −36 −84 9) and the left inferior occipital gyrus (left IOG; BA 18; −39, −83, −1). The six brain regions were identified in an unbiased manner

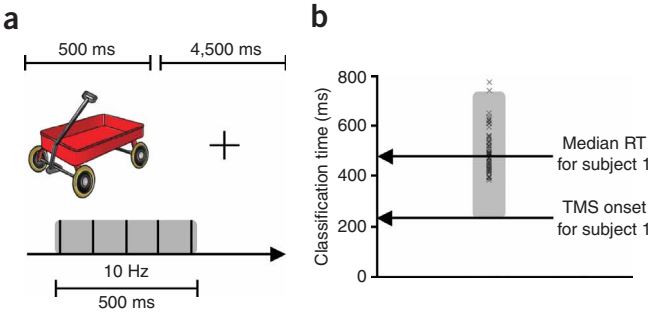

Figure 2 TMS timing parameters. (**a**) Objects were presented for 500 ms, with a 4,500-ms inter-trial interval. Each stimulation consisted of a 10-Hz train lasting for 500 ms. (**b**) TMS onset was catered to each subject's individual response times, with TMS stimulation time-locked to occur 250–310 ms before each subject's median response time based on their response latencies from the first MRI session.

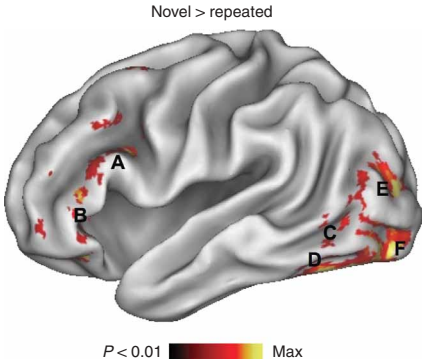

Figure 3 Neural priming before TMS. Whole-brain group statistical activation map comparing novel to repeated items ($P < 0.01$) overlaid on an inflated cortical rendering of the left hemisphere. Regions that survived a more stringent statistical threshold ($P < 0.001$) were investigated further using an ROI analysis in the post-TMS fMRI scan (Session 3). At this threshold, repetition-related reductions were observed in the posterior (A) and anterior (B) portions of the inferior frontal gyrus, middle temporal gyrus (C), fusiform gyrus (D), middle-occipital gyrus extending into the superior occipital gyrus (E) and the IOG (F). Weaker activations ($P < 0.01$) were noted along the middle frontal gyrus in BA 9 and BA 10, and in the inferior temporal gyrus in BA 21/37.

based on the group statistical map comparing novel to repeated objects in Session 1.

Results revealed a functional dissociation in neural priming between sensory and frontal cortices. An analysis of variance (ANOVA) examining two factors, object type (repeated-frontal, repeated-control and novel) and brain region (LIFG [BA45/47] and MOG [BA 18/19]), showed a significant main effect of object type ($F_{2,20} = 15.44$, $P < 0.001$), no significant main effect of region ($F_{1,10} = 3.93$, $P = 0.10$) and a significant interaction between object type and region ($F_{2,20} = 9.80$, $P < 0.005$). Planned comparisons showed that left-frontal TMS had no impact on the subsequent neural priming effects observed in the left MOG (novel > repeated, $t_{10} = 2.21$, $P < 0.05$; **Fig. 4a**). By contrast, left-frontal TMS disrupted the ensuing neural priming reductions in the LIFG that normally accompany repeated semantic classification of objects (novel = repeated, $P > 0.56$; **Fig. 4a**). Importantly, control-site TMS did not disrupt neural priming in either region (MOG: novel > repeated, $t_{10} = 2.37$, $P < 0.05$; LIFG: novel > repeated, $t_{10} = 2.05$, $P < 0.05$; **Fig. 4b**). Additionally, when signal change for the two classes of repeated objects were compared directly, a significant difference was noted in the LIFG (repeated-frontal > repeated control; $t_{10} = 2.25$, $P < 0.05$) but not in the MOG ($P > 0.5$).

A region of the left posterior temporal cortex (middle temporal gyrus; BA 21/37) showed a qualitatively similar pattern to the left inferior frontal region. Left-frontal TMS also diminished the neural reductions in the left posterior temporal cortex that are typically associated with repeated semantic classifications (novel versus repeated, $P > 0.55$), whereas objects previously presented during control-site TMS showed a trend toward neural priming when compared to novel objects (novel > repeated, $t_{10} = 1.47$, $P = 0.086$; **Supplementary Fig. 1** online). When compared directly, the difference in neural activity between repeated-frontal objects and repeated-control objects was significant (repeated-frontal > repeated-control, $t_{10} = 1.84$, $P < 0.05$).

Three of the neural priming regions identified in Session 1 (left BA 44, left fusiform gyrus and left IOG) did not show significant neural priming effects (novel > repeated) in Session 3 after left-frontal TMS and control-site TMS. This is not surprising, given that Session 3 was necessarily less sensitive to neural priming effects than Session 1 because of TMS constraints. In Session 1, repeated objects were presented for the seventh, eight and ninth times. In Session 3, repeated objects were presented for only the third time.

The ROI analysis was based on activations observed in Session 1. To determine whether neural priming effects were present in any additional brain regions during Session 3, we used a conjunction analysis. The conjunction analysis identified brain regions that were jointly active when classification of novel objects was contrasted with both types of repeated objects (that is, novel > repeated-frontal AND novel > repeated-control; $P < 0.025$). Results of this analysis revealed significant neural priming effects in the same region of the left MOG (as identified in Session 1) and a region of the left IOG (BA 18; −41 −87 −4) that overlapped with the IOG region identified in Session 1. Further analysis of the IOG region defined in this way revealed intact neural priming for both frontal-stimulated and control-site-stimulated objects (novel > repeated-frontal, $t_{10} = 2.52$, $P < 0.05$; novel > repeated-control, $t_{10} = 3.86$, $P < 0.005$). Neural activity did not differ between classification of repeated-frontal and repeated-control objects ($P = 0.47$).

Importantly, the behavioral effects mirrored the neural effects observed in the LIFG (**Fig. 5**). An ANOVA examining object type (repeated-frontal, repeated-control and novel) revealed a significant main effect ($F_{2,20} = 4.62$, $P < 0.05$). Left-frontal TMS significantly reduced the subsequent behavioral facilitation that normally accompanies repeated classification of objects. Specifically, responses to repeated objects that had been presented twice during left-frontal TMS (repeated-frontal) were no faster during their third repetition than responses to novel objects (novel [602 ms] = repeated-frontal [594 ms], $t_{10} = 1.07$, $P = 0.15$). Put simply, subjects responded to these repeated objects as if they were doing so for the first time. Moreover, the

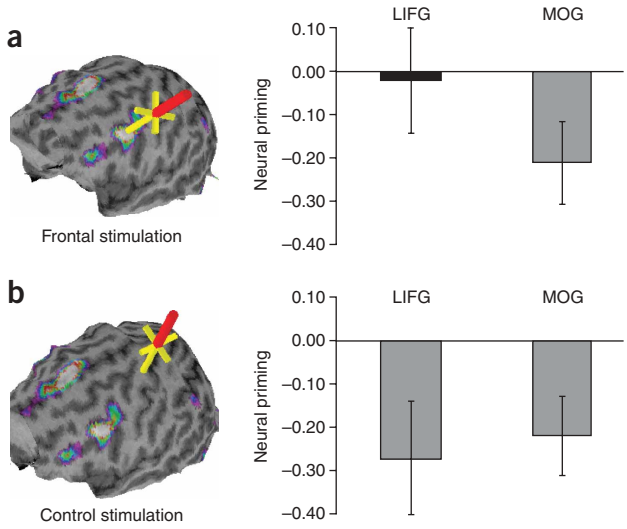

Figure 4 Neural priming after TMS. Graphs depict hemodynamic reductions in activity in the LIFG and MOG following left-frontal TMS (**a**) and control-site TMS (**b**). Signal change is reported as the difference in activity between semantic classification of repeated objects and that of novel objects. Gray bars denote a significant neural priming effect. Error bars indicate s.e.m. Left-frontal TMS eliminated neural priming in the LIFG but did not disrupt neural priming in the MOG. Control-site TMS had no effect on neural priming in either region.

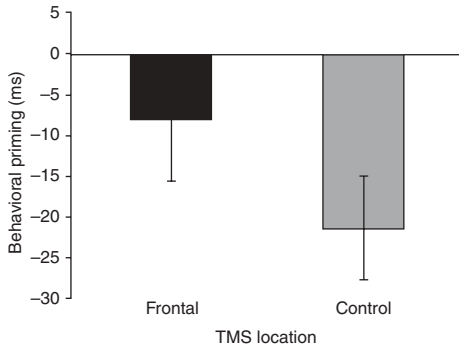

Figure 5 Behavioral priming after left-frontal and control-site TMS. Graph depicts the behavioral facilitation for repeated objects (measured as the difference in response latencies between repeated and novel objects). Gray bar denotes a significant behavioral priming effect. Error bars indicate s.e.m. Left-frontal TMS significantly reduced the behavioral facilitation afforded to repeated objects.

disruption of behavioral priming after TMS was not a result of global cortical disruption. Normal behavioral priming was observed for repeated objects that had been presented during control-site TMS (repeated-control); these repeated objects were classified faster than novel objects (novel [602 ms] > repeated-control [581 ms], $t_{10} = 3.34$, $P < 0.005$). When compared directly, the difference in response latency between repeated-frontal objects and repeated-control objects was also significant ($t_{10} = 1.82$, $P = 0.05$).

DISCUSSION

These findings provide direct evidence that neural priming in the left-frontal cortex is the basis for conceptual priming. Numerous studies report instances of neuronal[3,4] and hemodynamic[6–9,16–19] reductions associated with implicit memory and repetition-accompanied learning, but the correlative nature of these investigations has, until now, precluded a direct linkage between these two phenomena (for review, see ref. 11).

Decreases in neural activity can accompany other forms of learning as well. For example, practice-related hemodynamic decreases are commonly observed as tasks become automated[9,20–25], and similar decreases are reported in patients during the recovery of motor function following stroke[26]. Such practice-related reductions often occur in conjunction with increases in other cortical regions[9,21–25,27–29], a finding that has prompted debate over whether the neural reductions reflect circuit efficiency (analogous to priming) or whether the neural reductions are simply a byproduct of the fact that the task is being performed in a different way (via recruitment of different brain regions). The present findings suggest that the neurophysiological reductions that accompany procedural learning in these other domains may well serve a causal purpose.

Neural priming may reflect a mechanism of pruning irrelevant connections between or within regions and tuning the representations of those neurons that still remain in the responsive pool[3,5,13]. When considered within the framework of a semantic classification task, these changes may serve to facilitate more fluent access to pertinent object information. Such an account is consistent with recently demonstrated correlations between the magnitude of neural priming and reductions in response latencies during semantic classification of objects[10,30].

Here we show that when initial experience with an object is accompanied by cortical disruption of LIFG activity, neural regions involved in the retrieval, selection or representation of object knowledge must be re-engaged at full capacity the next time that object is encountered, and the behavioral advantage normally associated with repetition is not realized. In line with this idea, the pattern of activity in a region of left posterior temporal cortex following TMS was similar to that of the LIFG. Activity in these two regions is often similar in conceptual priming tasks, regardless of the sensory modality used[9,31–33]. One speculation is that posterior temporal cortex activity is mediated via top-down modulation from the frontal cortex, and behavioral priming is supported via the interaction of these two regions during semantic search and retrieval.

Although we have reported clear differences in neural and behavioral priming following left-frontal but not control-site TMS, it should be noted that TMS to left-inferior frontal regions can produce greater levels of discomfort than does TMS to motor cortex. This leaves open the possibility that differences in discomfort between the two stimulation sites influenced the reported effects and highlights one of the many challenges researchers face when selecting appropriate control conditions in TMS studies. Several factors influenced our selection of motor cortex as the control condition. An ideal control site should (i) show comparable levels of activation for both trial types of interest (in this case novel and repeated objects), (ii) be homologous to the TMS site of interest (*e.g.*, right inferior frontal gyrus, RIFG) and (iii) be accessible to TMS (on the midline or lateral surface of the cortex).

The RIFG would normally fulfill these criteria; presumably, the use of a right-frontal control site would also control for the effects of discomfort and distraction. Several brain imaging studies of priming, however, have shown repetition-related reductions in the right-hemisphere homolog of the LIFG[10,34–37]. Indeed, repetition-related reductions were observed at a more lenient threshold ($P < 0.01$) in RIFG in the present study during Session 1. For this reason, in designing our study, we explicitly avoided the RIFG as a control site. Instead, we selected the left motor cortex as the control site because this region is active (and hence easy to identify by fMRI) during object classifications that require a button press, but it does not show repetition-related reductions in imaging studies of priming. Although the use of a motor cortex control site does not necessarily control for TMS-induced discomfort levels associated with the LIFG site, we believe that the behavioral data acquired during TMS administration (Session 2) minimize this concern considerably, as response latencies during left-frontal and control-site TMS did not differ.

The observation of spared neural priming effects in the middle and inferior occipital gyri following left-frontal TMS indicates that conceptual and perceptual components of priming can operate independently. Indeed, patient studies reveal dissociable impairments in conceptual and perceptual priming following damage to frontal-temporal[38] and occipital[39] cortices, respectively. Our results provide a context in which to consider these findings in the intact brain by showing that neural priming effects in the visual cortex are not linked to upstream effects in the frontal cortex. Although neural priming in sensory regions was unaffected by left-frontal or control-site stimulation, behavioral priming in the intact brain may be realized through the aggregate contributions of neural priming in frontal and sensory cortices. That is, neural priming in sensory regions may contribute to behavioral priming during semantic classification tasks, but it is not sufficient to produce behavioral priming in the absence of neural priming in frontal cortex.

METHODS

Subjects. Twelve right-handed subjects between the ages of 22 and 30 were recruited from the Dartmouth community. All subjects were native speakers of English, were strongly right-handed as measured by the Edinburgh handedness

inventory[40] and gave informed consent in accordance with the guidelines set by the Committee for the Protection of Human Subjects at Dartmouth College. Of the 12 subjects, one subject failed to show a behavioral measure of priming in the initial fMRI session and therefore did not participate in the TMS session. Results reported here reflect data analyzed from the remaining 11 participants (5 male; mean age 26).

Study procedure. The study was carried out in three sessions. In Session 1, subjects were scanned using event-related fMRI while they made semantic classifications (living/nonliving) of novel and repeated line-drawn colored objects (**Supplementary Methods**). Functional data were acquired in two runs. Repeated objects (presented for the seventh, eighth and ninth times) and novel objects were presented individually in the center of the screen for 500 ms, at a rate of one every 2,000 ms, and subjects were instructed to make their decisions as quickly as possible (by button press), without sacrificing accuracy. Functional data from this fMRI session were analyzed to identify regions showing neural priming effects by contrasting classifications of novel objects to classifications of repeated objects.

In Session 2, subjects underwent TMS while performing the object classification task on a new item set. Regions of the left-inferior frontal gyrus and left motor cortex were identified for TMS on a subject-by-subject basis. Each subject's high-resolution anatomical image, overlaid by his or her functional data from Session 1, was displayed as a three-dimensional representation. The focus of frontal TMS was defined functionally by locating subject-specific regions that demonstrated repetition-related reductions (novel > repeated) within the pars triangularis or pars opercularis of the left hemisphere (Brodmann's areas 44/45/47). The hand area of the primary motor cortex was used as a TMS control site to ensure that the effects of TMS were not due to global cortical disruption. The control site (left motor cortex) was identified from functional activation maps in Session 1 by comparing all object classification judgments to the baseline control task (visually fixating a cross-hair). The TMS coil position was then adjusted within the motor activation area until a visible motor-evoked potential (MEP) was elicited in the right hand muscles. TMS intensity was set at 110% MEP.

For each TMS site, a set of 30 objects was presented. Objects were presented for 500 ms, with a 4,500-ms intertrial interval. Each object was presented twice, and TMS was administered to the same site for each presentation of the object. Each stimulation consisted of a 10-Hz train lasting for 500 ms. TMS onset was catered to each subject's individual response times. Median response times were calculated from each subject's performance during fMRI (median response times ranged from 506 to 810 ms). To isolate the conceptual components of priming, TMS stimulation was time-locked to occur 250–310 ms before a subject's median response time. The mean stimulation onset across the group was 334 ms after stimulus onset (range 254–500 ms).

Subjects underwent two runs of TMS, one in which objects were accompanied by left-frontal TMS and one in which objects were accompanied by control-site TMS. Stimulation and timing protocols were identical for both left-frontal and control-site TMS.

Session 3 immediately followed TMS. Subjects were rescanned using event-related fMRI. The average time between TMS and this final fMRI scan was 15 min. Functional data were acquired in three runs. Once again, subjects made living/nonliving judgments about colored, line-drawn objects. Subjects were presented with novel objects, repeated objects that were previously presented with left-frontal TMS, and repeated objects that were previously presented with control-site TMS. Trial types were pseudorandomly intermixed with trials of fixation, such that each trial type followed every other trial type equally often.

fMRI data analysis. Functional data were analyzed using the general linear model for event-related designs in SPM99 (Wellcome Department of Cognitive Neurology; **Supplementary Methods**). Data from Session 3 were analyzed using hypothesis-driven ROI analyses. Frontal and visual ROIs were identified in an unbiased manner based on the group statistical map comparing novel to repeated objects in Session 1 (threshold, $P = 0.001$, uncorrected). To calculate signal intensities for each of these regions, spherical ROIs of 8-mm radius were created. For each subject, signal intensities from each ROI were calculated separately for each condition in Session 3, and then examined statistically. This ROI method was done in normalized MNI atlas space to permit a random effects analysis that would generalize across the human population.

Note: Supplementary information is available on the Nature Neuroscience website.

ACKNOWLEDGMENTS

We thank R. Henson and A. Martin for their helpful comments on an earlier version of this manuscript, and R. Magge and T. Laroche for their technical assistance. This work was supported by a US National Institutes of Health grant (MH64667) to W.M.K. and the Dartmouth Brain Imaging Center. G.S.W. is a graduate fellow of the Natural Sciences and Engineering Research Council of Canada.

COMPETING INTERESTS STATEMENT

The authors declare that they have no competing financial interests.

Received 5 April; accepted 8 July 2005
Published online at http://www.nature.com/natureneuroscience/

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