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Two Kinds of fMRI Repetition Suppression? Evidence for Dissociable Neural Mechanisms

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Epstein RA, Parker WE, Feiler AM. Two kinds of fMRI repetition suppression? Evidence for dissociable neural mechanisms. *J Neurophysiol* 99: 2877–2886, 2008. First published April 9, 2008; doi:10.1152/jn.90376.2008. Repetition suppression (RS) is a reduction of neural response that is often observed when stimuli are presented more than once. Many functional magnetic resonance imaging (fMRI) studies have exploited RS to probe the sensitivity of cortical regions to variations in different stimulus dimensions; however, the neural mechanisms underlying fMRI-RS are not fully understood. Here we test the hypothesis that long-interval (between-trial) and short-interval (within-trial) RS effects are caused by distinct and independent neural mechanisms. Subjects were scanned while viewing visual scenes that were repeated over both long and short intervals. Within the parahippocampal place area (PPA) and other brain regions, suppression effects relating to both long- and short-interval repetition were observed. Critically, two sources of evidence indicated that these effects were engendered by different underlying mechanisms. First, long- and short-interval RS effects were entirely noninteractive even although they were measured within the same set of trials during which subjects performed a constant behavioral task, thus fulfilling the formal requirements for a process dissociation. Second, long- and short-interval RS were differentially sensitive to viewpoint: short-interval RS was only significant when scenes were repeated from the same viewpoint while long-interval RS less viewpoint-dependent. Taken together, these results indicate that long- and short-interval fMRI-RS are mediated by different neural mechanisms that independently modulate the overall fMRI signal. These findings have important implications for understanding the results of studies that use fMRI-RS to explore representational spaces.

INTRODUCTION

Sensory stimuli tend to elicit a larger functional magnetic resonance imaging (fMRI) response when they are initially encountered than when they are later repeated (Buckner et al. 1998; Grill-Spector et al. 1999; Henson et al. 2000; Kourtzi and Kanwisher 2001; Naccache and Dehaene 2001; van Turennout et al. 2000; Wiggs and Martin 1998). This phenomenon, known as fMRI adaptation (fMRI-A) or fMRI repetition suppression (fMRI-RS), has been adopted as a central tool in cognitive neuroscience because it can be used to probe representational spaces at the subvoxel level (Grill-Spector and Malach 2001). Specifically, the amount of RS on presentation of a stimulus is thought to depend on the processing overlap between that item and previously viewed items. By providing a measure of the extent to which a cortical region considers different stimuli to be "the same" or "different," fMRI-RS permits the coding distinctions made by that region to be identified. Over the past few years, many studies have exploited fMRI-RS to study representational spaces in this man-

ner (see Grill-Spector et al. 2006; Henson 2003; Schacter and Buckner 1998 for review).

Despite its widespread use, however, many basic features of fMRI-RS are not understood. For example, it is unclear whether fMRI-RS is a single phenomenon at the neural level or whether different attenuation mechanisms might be elicited by different repetition regimes (Krekelberg et al. 2006). A critical parameter that has varied between studies is the time interval between the adapting and adapted (i.e., repeated) items. While some studies have induced RS by repeating items within an experimental trial (Kourtzi and Kanwisher 2001), others have induced RS by repeating items over longer intervals that extend across experimental trials (Henson et al. 2000; James et al. 2002; Vuilleumier et al. 2002). Although it is implicitly assumed the RS effect induced by these short- and long-interval repetition paradigms are mediated by the same neural mechanism, this assumption has not been tested. Previous studies (Henson et al. 2004; Sayres and Grill-Spector 2006) have found evidence for quantitative effects of repetition interval (i.e., less RS with longer lags), but the possibility of qualitatively distinct mechanisms has not been addressed.

Relevant to this discussion are results from a series of studies examining the viewpoint-specificity of RS effects in the parahippocampal place area (PPA) (Epstein and Kanwisher 1998), a region of ventral temporal cortex that responds preferentially to complex visual scenes. These studies demonstrated that short-interval RS effects were entirely viewpoint specific, whereas long-interval RS effects showed some degree of viewpoint invariance (Epstein et al. 2003, 2005, 2007a). It is possible that these results can be explained simply by the fact that short- and long-interval RS were measured in different experimental runs during which subjects performed different behavioral tasks (cf. Dobbins et al. 2004). However, an intriguing alternative explanation is that short- and long-interval repetition may activate different RS mechanisms that have different operating characteristics.

The current experiment was designed to resolve this issue by measuring both long- and short-interval RS effects in the same set of trials while subjects performed a single behavioral task. We predicted that if there were separate, dissociable mechanisms underlying each kind of RS, then these two effects would be additive (i.e., noninteractive) (Pinel et al. 2001; Sternberg 2001, 2004) and that we would replicate our previous findings that long-interval repetition effects are more view invariant than short-interval repetition effects. We also examined whether long- and short-interval fMRI-RS impact the same or different cortical regions. To anticipate, our results indicate that long- and short-interval fMRI-RS are engendered

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by distinct mechanisms that coexist within a largely overlapping set of brain regions.

METHODS

Subjects

Sixteen healthy, right-handed volunteers with normal or corrected-to-normal vision were recruited from the local community and gave written informed consent according to procedures approved by the University of Pennsylvania institutional review board. All participants had completed at least two full years of undergraduate education at the University of Pennsylvania to ensure that they were able to accurately perform the various behavioral tasks, which involved identification of campus locations.

MRI acquisition

Scanning was performed at the Center for Functional Neuroimaging at the University of Pennsylvania on a 3T Siemens Trio equipped with an eight-channel multiple-array Nova Medical head coil. T2*-weighted images sensitive to blood-oxygenation-level-dependent (BOLD) contrasts were acquired using a gradient-echo echo-planar pulse sequence (TR = 3,000 ms, TE = 30 ms, voxel size = 3 × 3 × 3, matrix size = 64 × 64 × 45). Structural T1-weighted images for anatomical localization were acquired using a three-dimensional (3D) MPRAGE pulse sequence (TR = 1,620 ms, TE = 3 ms, TI = 950 ms, voxel size = 0.9766 × 0.9766 × 1 mm, matrix size = 192 × 256 × 160). Visual stimuli were rear projected onto a Mylar screen at the head of the scanner with an Epson 8100 3-LCD projector equipped with a Buhl long-throw lens and viewed through a mirror mounted to the head coil. Responses were recorded using a four-button fiber-optic response pad system.

Stimuli

A digital camera was used to obtain images of 48 distinct locations on the University of Pennsylvania campus. For each location, four images were taken, each depicting the same focal point from different viewing angles which were roughly equally spaced (See Fig. 1). These stimuli were used to examine fMRI-RS effects. In previous experiments, we found that fMRI-RS effects in the PPA were unaffected by campus familiarity (Epstein et al. 2007a), so we felt confident that results obtained using these images would generalize to images of unfamiliar locations. In addition to the Penn stimuli, 144 images of the Temple University campus (3 views each of 48 different locations) were used as foil stimuli.

Procedure

The experimental session was divided into three parts (Fig. 1). Part 1 was a study phase performed outside the scanner, part 2 was a test phase performed within the scanner, and part 3 was a functional localizer phase performed within the scanner. Long-interval fMRI-RS was induced by repeating items between the study and test phase, whereas short-interval fMRI-RS was induced by repeating items within trials during the test phase.

During the study phase (outside the scanner), subjects performed a location judgment task in which they used a computer keyboard to report whether each image depicted a location east or west of 36th Street (which runs through the center of campus). This task required subjects to register both the appearance of each image and its identity as a place. Trials were 6.5 s long and consisted of a 500-ms blank warning screen, followed by the presentation of a campus image for 3,300 ms and then a 2,700-ms poststimulus interval during which a fixation cross was visible. Subjects were instructed to respond while either the stimulus or the fixation cross was on the screen. No feedback was given. Two runs of 48 trials were presented with the second run containing the same images as the first run but in a different order.

Half of the images of half of the Penn locations (i.e., 2 views each of 24 locations) were shown during the study phase. The selection of locations was counterbalanced across subjects, while the selection of views for each location was randomized with the constraint that either views 1 and 3 or views 2 and 4 were shown. These images were shown again in the test phase (old views), along with the previously-unseen complementary views of the same locations (new views), and two views each of the 24 remaining locations not shown in the study phase (new places). The test phase followed the study phase by ~20 min.

During the test phase (in the scanner), subjects made Penn/NotPenn judgments on campus photographs. Two images were sequentially presented during each trial, and subject pressed one button if both images were of the Penn campus (67% of trials) and the other button if only one of the images was from Penn (33% of trials). Note that this task required subjects to process both stimuli but did not require them to make judgments about the perceptual similarities and differences between them; thus repetition condition was not confounded with response. Six runs of this task were performed. Each run was 8 min 24 s long and was divided into 72 6-s experimental trials during which image pairs were shown, 12 3-s null trials in which a fixation cross was presented on the screen (thus jittering the interval between experimental trials), and 18-s fixation periods at the beginning and end of the scan. Experimental trials began with a 500-ms blank screen, followed by a 700-ms gray screen with a black outline which alerted subjects to the start of a new trial pairing, followed by another 500-ms blank screen, followed by the sequential presentation of two color images for 700 ms each with a 500-ms interstimulus interval (see Epstein et al. 2007a for details). A fixation cross was then presented for 2400 ms to complete the trial. Subjects were instructed to make speeded responses during the interval between the appearance of the second image and the end of the trial.

As noted in the preceding text, short-interval fMRI-RS was induced by repeating items within trials during the test phase. Specifically, within each trial, the two photographs could either be identical Penn images (no-change trials; 24 per run), images of different views of the same Penn location (viewpoint-change trials; 12 per run), images of different Penn locations (place-change trials; 12 per run), or one image from Penn and one image from Temple (foil trials; 24 per run). These short-interval repetition conditions were crossed with the long-interval repetition conditions so that (for example) there were eight no-change trials constructed out of old view images in each run, eight constructed out of new view images, and eight constructed out of new place images, etc. Across the entire test phase, each of the 144 utilized Penn images (48 old views, 48 new views, 48 new places) was shown five times (twice in a no-change trial, once in a viewpoint-change trial, once in a place-change trial, and once in a foil trial), whereas each of the 144 Temple images was shown only once.

The third phase of the experiment consisted of two functional localizer scans during which subjects made 1-back repetition judgments on images of scenes, non-scene objects, and other stimuli as described previously (Epstein et al. 2005). The stimuli shown during this phase had not been viewed previously in the experiment.

Data analysis

Functional images were corrected for differences in slice timing by resampling slices in time to match the first slice of each volume, realigned with respect to the first image of the scan, spatially normalized to the Montreal Neurological Institute (MNI) template, and spatially smoothed with an 6-mm FWHM Gaussian filter. Data were analyzed using the general linear model as implemented in VoxBo (www.voxbo.org) including an empirically derived 1/f noise model,

Part 1 (Outside of Scanner)

"West or East of 36th Street?" (1 image per trial)

p1, v1	p1, v3	p2, v1	p2, v3
(place 1, view 1)			

Part 2 (In scanner)

"Both Penn, or one Penn one Not Penn?" (2 images per trial)

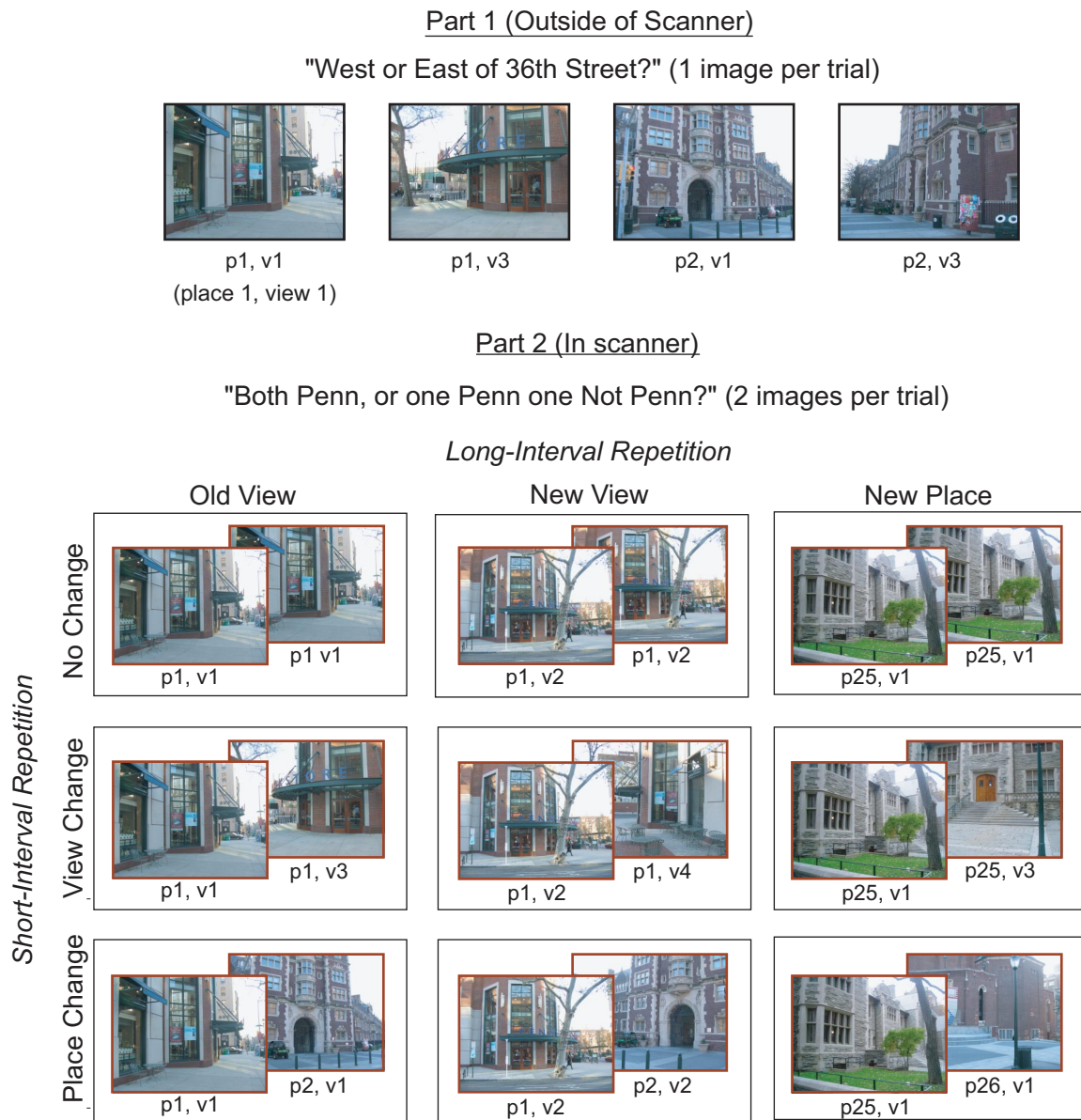*Long-Interval Repetition*

FIG. 1. Experimental design. In part 1 (*top*), subjects made location judgments on images of the University of Pennsylvania campus. This task was performed outside of the scanner and served to prime a subset of the stimuli. Images of half of the campus locations (24 of 48) were presented in part 1; for each of these, 2 of the 4 possible views were shown. In part 2 (*bottom*), subjects were scanned while performing Penn/NotPenn judgments on sequentially presented pairs of scene images. The images could be identical to those shown in part 1 (old views), previously unseen views of the locations shown in part 1 (new views), or images of campus locations that were not previously shown in the experiment (new places). These images were paired within each trial in 3 different ways: the 2 images in each trial could be identical (no change trials), different views of the same place (viewpoint-change trials), or different places (place-change trials). Thus functional magentic resonance imaging (fMRI) response differences among old view, new view, and new place trials reflected long-interval repetition effects (i.e., the effect of repeating a previously seen item later in the experimental session), while fMRI response differences among no-change, viewpoint-change, and place-change trials reflected short-interval repetition effects (i.e., the effect of repeating an item within an experimental trial). Foil trials, in which 1 image was from Penn and the other image was from Temple University, were also included in part 2 but are not illustrated in the figure.

filters that removed high and low temporal frequencies, regressors to account for global signal variations, and nuisance regressors to account for between-scan differences. Both region of interest (ROI) and whole-brain analyses were performed.

ROI ANALYSES.   Functional ROIs were defined for each subject using data from the functional localizer scans by identifying sets of contiguous voxels that responded more strongly to scenes than to common objects in the posterior parahippocampal/collateral sulcus region (PPA), retrosplenial/parietal-occipital sulcus region (RSC), and transverse occipital sulcus (TOS). The significance threshold defining these regions was set on a subject-by-subject basis so that ROIs were

consistent with those identified in previous studies (Epstein and Kanwisher 1998; Epstein et al. 1999, 2007a,b); thresholds ranged from $t > 2.0$ to $t > 4.5$. The time course of MR response during the test phase was then extracted from each ROI (averaging over all voxels) and entered into a general linear model in which the nine trial types (new place/no change, new place/view change, new place/place change, new view/no change, new view/view change, new view/place change, old view/no change, old view/view change, old view/place change), along with the foil trials, were represented as impulse response functions convolved with a canonical hemodynamic response function. This gave parameter estimates (beta values) for the nine trial

types of interest, which were used as the dependent variables in a second-level random-effects ANOVA. We saw little evidence that the pattern of response differed between the left and right hemispheres so data were averaged across corresponding ROIs in both hemispheres before second-level analysis.

WHOLE-BRAIN ANALYSES. Subject-specific beta maps were calculated for contrasts of interest and then smoothed to 10-mm FWHM to facilitate between-subject averaging before entry into a random effects analysis. Clusters of more than 2 voxels the significance of which exceeded $P < 0.001$, uncorrected, are reported.

RESULTS

Behavioral data

During the prescanning study phase, subjects made judgments about whether campus scenes depicted locations on the east or west side of the Penn campus (Epstein et al. 2007b). Mean accuracy on this task was $86.8 \pm 1.7\%$ (mean $\pm$ SE) and mean reaction time was $1,775 \pm 101$ (SE) ms. Although location familiarity was not critical to our hypotheses, the strong performance on this task indicates that subjects processed both the appearances and locations of the scenes.

During the test phase (in the scanner), subjects performed a place discrimination task in which they reported whether or not the two images presented on each trial depicted locations on the Penn campus or not. On foil trials, one of the images was from the Temple University campus; data from these trials were not of theoretical interest and were discarded. ANOVA was performed on the response times (RTs) for the remaining trials. The nine conditions of interest were modeled as two crossed factors each with three levels: long-term repetition condition (new place, new view, old view) and short-term repetition condition (place change, viewpoint change, no change). This analysis revealed highly significant priming effects for both long- and short-interval repetitions [long interval: $F(2,30) = 5.7$, $P < 0.01$; short interval: $F(2,30) = 25.6$, $P < 0.001$, see Table 1]. In other words, RTs were speeded when items from part 1 were repeated in part 2 and also when items were repeated within each trial of part 2. There was no evidence for an interaction between long- and short-interval repetition priming effects ($F < 1$, NS).

Although accuracy was high in all conditions, it was also modulated by repetition condition for both long and short repetition intervals [long interval: $F(2,30) = 4.7$, $P < 0.02$; short interval: $F(2,30) = 5.9$, $P < 0.01$, interaction: $F(4,60) = 2.1$, $P = 0.10$, NS]. The pattern for accuracy (old view > new view > new place, no change > viewpoint change > place change) mirrored the pattern for RT (new place > new view $\simeq$ old view, place change > viewpoint change > no change), indicating that the RT effects could not be explained by a speed-accuracy tradeoff.

In further analyses, we separately examined viewpoint-invariant and -specific RT priming effects for long- and short-interval repetitions. For long-interval repetitions, viewpoint-invariant priming was indexed by faster RTs to new views than to new places, while viewpoint-specific priming was indexed by faster RTs to old views than to new views. For short-interval repetitions, viewpoint-invariant priming was indexed by faster RTs to viewpoint-change trials than to place-change trials, while viewpoint-specific priming was indexed by faster RTs to no-change trials than to viewpoint-change trials (Epstein et al. 2005). In both cases, viewpoint-invariant priming reflects the extent to which recognition of a view of a place is facilitated by previous experience with a different view of the same place, while viewpoint-specific priming reflects the extent to which recognition of a view of a place is additionally facilitated by previous experience with that particular view. Note that under these definitions, viewpoint-invariant and -specific effects can coexist because repetition effects can be partially viewpoint-invariant without being completely viewpoint invariant.

For long-interval repetitions, significant viewpoint-invariant RT priming was observed [new place > new view: $t(15) = 3.8$, $P < 0.01$], but there was no additional priming when places were repeated from the same view [new view > old view: $t(15) = -0.9$, NS]. In contrast, for short-interval priming, both viewpoint-invariant [place change > viewpoint change: $t(15) = 2.4$, $P < 0.05$] and viewpoint-specific effects [viewpoint change > no change: $t(15) = 6.6$, $P < 0.00001$] were observed. Indeed, the viewpoint-specific priming effect was larger than the viewpoint-invariant priming effect for short intervals.

Taken as a whole, these data indicate that previous experience affects behavioral performance over both long and short intervals. Furthermore, long- and short-interval priming effects were noninteractive and were more viewpoint-specific for short-interval repetitions than for long-interval repetitions. Although these results on their own suggest that long- and short-interval RS are mediated by independent mechanisms, prior work indicates that the link between behavioral priming effects and fMRI-RS can be quite tenuous (Xu et al. 2007). Hence our next step was to determine whether similar results were observed in the fMRI response.

Functional ROIs

Previous studies have identified three functionally defined regions of interest that respond strongly to scenes: the PPA, RSC, and TOS. Here we focus primarily on the PPA as repetition effects in this region are the most well-studied and are likely to be closely related to RS effects in neighboring occipitotemporal visual regions such as the lateral occipital complex and fusiform gyrus. Data from the RSC and TOS were similar to those reported below for the PPA. All ROIs were defined using the independent set of functional localizer data acquired during part 3 of the experiment.

The mean size of the PPA was 2.9 ± 1.0 cm^3 in the left hemisphere (range: $1.0–4.3$ cm^3), and 3.6 ± 1.5 cm^3 in the

TABLE 1. *Behavioral data*

	New Place	New View	Old View	Mean
Accuracy				
Place change	0.93	0.95	0.97	0.95
View change	0.95	0.98	0.97	0.97
No change	0.98	0.97	0.98	0.98
Mean	0.95	0.97	0.97	
Reaction times (correct trials only)				
Place change	813	785	797	798
View change	777	737	745	753
No change	698	684	690	690
Mean	763	736	744	

right hemisphere (range: 0.6–5.6 cm^3). These values were consistent with those reported in previous studies (Epstein et al. 2007a,b). A typical PPA ROI of approximately median size (left: 3.1 cm^3, right: 3.3 cm^3) is illustrated in Fig. 2A.

The response in the PPA is plotted in Fig. 2B. ANOVA revealed strong main effects of both long- and short-interval repetition [long-interval: $F(2,30) = 52.0$, $P < 0.000000001$; short-interval: $F(2,30) = 57.3$, $P < 0.0000000001$], consistent with previous studies. Despite the strength of these effects, however, there was no hint of an interaction between them ($F < 1$, $P > 0.5$, NS). Although these analyses were performed on data averaged between the left and right hemisphere, we observed the same results when each hemisphere was analyzed separately. In particular, strong main effects of both long- and short-interval repetition were observed in both hemispheres [long-interval left: $F(2,30) = 45.0$, $P < 0.000000001$, right: $F(2,30) = 49.1$, $P < 0.000000001$; short-interval left $F(2,30) = 57.5$, $P < 0.0000000001$, right $F(2,30) = 51.5$, $P < 0.000000001$], while no interaction was observed in either hemisphere (both $Fs < 1$, $Ps > 0.3$).

The finding of noninteractivity is critical because under additive factors logic (Ganel et al. 2006; Sternberg 2001), it suggests that long- and short-interval RS effects are mediated by dissociable neural mechanisms. Specifically, additive factors logic provides a method for establishing the independence of two underlying processes when one can only observe a composite measure that incorporates outputs from both processes. In the current experiment, the composite measure is the fMRI response in the PPA, and the two underlying processes are hypothesized neural mechanisms that are differentially affected by long- and short-interval repetition. The absence of an interaction between these two factors suggests that each of them affects only one of the underlying processes while leaving the other unchanged. In other words, the independence of the long- and short-interval repetition effects suggests that the processes underlying these effects are *separately modifiable*. [Note that for the preceding logic to hold, we must assume that the contributions of the two underlying processes to the composite measure combine by simple summation (see Sternberg 2001).]

In contrast, if long- and short-interval RS were engendered by the same underlying mechanism, then one would expect the magnitude of one effect to depend on the magnitude of the other, which is not what we observe. For example, suppose that both effects were engendered by a process of neural "sharpening," whereby the set of neurons that respond to an item gets smaller with each presentation (Wiggs and Martin 1998). In this case, one would expect that within-trial RS effects would be smaller for old scenes (i.e., old views) than for new scenes (i.e., new places) because the neural set responding to old scenes should already be reduced, thus leaving less room for further sharpening. The same reasoning applies if one assumes that long- and short-interval RS are both engendered by neural fatigue or some other common mechanism.

One nuance of the additive factors logic is that the conclusion of dissociability is drawn from a failure to find an interaction rather from the observation of a statistically significant effect. This potentially limits our conclusions because the absence of a statistically significant interaction may simply reflect a lack of statistical power rather than true independence in the underlying processes. To clarify our degree of confidence in our results, we calculated a 2×2 interaction term that should be nonzero if the additive model does not hold. This interaction term reflects the degree of interaction between the overall long-interval effect (new place $>$ old view) and the overall short-interval effect (place change $>$ no change). This term was 0.013 ± 0.049 (mean percent signal change). In comparison, the main effects of repetition were 0.180 ± 0.018 (new place $>$ old view) and 0.203 ± 0.019 (place change $>$ no change). In other words, the interaction term was at least an order of the magnitude smaller than the main effects. Although it is never possible to say conclusively that an effect is nonzero, this provides fairly strong evidence that the interaction term is of minimal size.

Additional evidence for independent processes came from examination of the viewpoint-specific and -invariant components of the overall fMRI-RS effects. These components were defined using the same contrasts that were used to define viewpoint-specific and -invariant behavioral priming. Based on previous fMRI results, we expected short-interval repetition effects in the PPA to be largely viewpoint-specific, while we expected long-interval repetition effects to be more viewpoint-invariant. This prediction was borne out by the data (Fig. 3). For short-interval repetition, very strong viewpoint-specific fMRI-RS was observed [viewpoint change $>$ no change: $t(15) = 10.8$, $P < 0.0000001$], while viewpoint-invariant
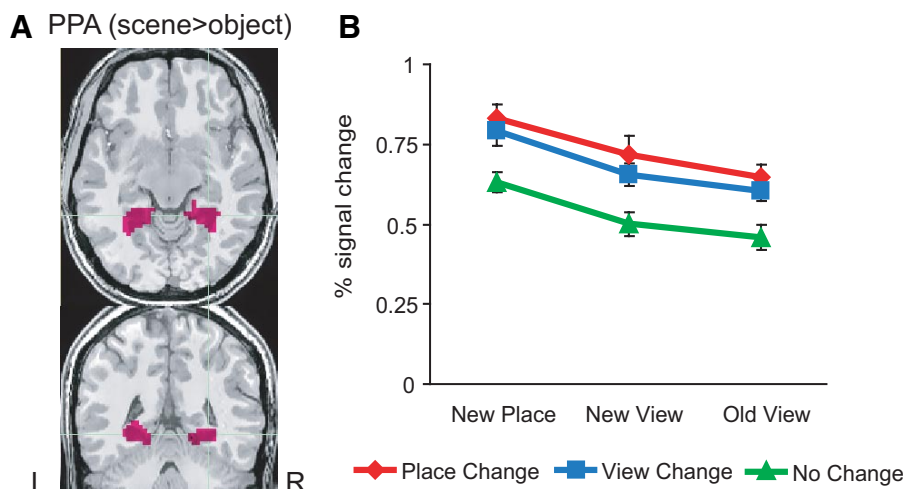
A PPA (scene>object) **B**

FIG. 2. Region of interest analysis. A: parahippocampal place area (PPA) as defined for a typical subject. Colored voxels responded significantly more strongly ($t > 3.0$) to scenes that to objects during the functional localizer scans. B: fMRI response in the PPA for all 9 repetition conditions. Data are averaged over all subjects. Long interval repetition conditions are on the y axis; short-interval repetition conditions are plotted as different lines. Although strong repetition suppression (RS) was observed after both long-interval repetition (new place $>$ new view $>$ old view) and also after short-interval repetition (place change $\geq$ viewpoint change $>$ no change), these 2 effects did not interact with each other, indicating the existence of independent RS processes. Error bars are ± 1 SE.
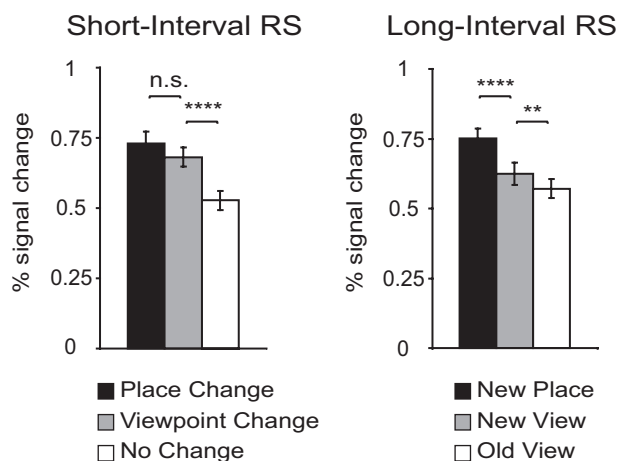
Short-Interval RS   Long-Interval RS

FIG. 3. Same data as Fig. 2 with short- and long-interval fMRI-RS plotted separately by collapsing over the levels of the other repetition condition. Short-interval RS was viewpoint-specific (i.e., the only significant effect was viewpoint change > no change), whereas long-interval RS showed a strong degree of viewpoint invariance (i.e., the new place > new view difference was highly significant). Symbols indicate significance levels for the indicated paired contrasts (**, $P < 0.01$; ****, $P < 0.0001$). Error bars are ±1 SE.

fMRI-RS fell short of significance [place change > viewpoint change: $t(15) = 2.0$, $P = 0.07$]. For long-interval repetition, both viewpoint-invariant and -specific fMRI-RS were observed [new place > new view: $t(15) = 7.1$, $P < 00001$; new view > old view: $t(15) = 3.0$, $P < 0.01$].

To quantify this difference in the degree of viewpoint invariance for long- and short-interval RS, we calculated the fractional viewpoint-invariance for both kinds of repetition by taking the ratio of the viewpoint-invariant RS effect to the total RS effect. For example, for long-term RS this ratio is (NP − NV)/(NP − OV), where NP, NV, OV indicate (respectively) response in the new place, new view, and old view conditions. This ratio is zero when the RS effect is completely viewpoint-specific and 1 when it is completely viewpoint-invariant. The results of this analysis confirmed that long-interval fMRI-RS was significantly more view-invariant than short-interval fMRI-RS in the PPA [long-interval ratio = 0.75, short-interval ratio = 0.05, difference $t(15) = 2.8$, $P < 0.02$]. These data suggest that short- and long-interval fMRI-RS are mediated by mechanisms with different operating characteristics. Furthermore, they potentially provide insight into the neural bases of these mechanisms insofar as they suggest that short-interval fMRI-RS may reflect reactivation of representations that are "earlier" in the visual processing stream, and hence more stimulus-specific, than the representations reactivated in long-interval fMRI-RS. We take up this issue further in the DISCUSSION.

Viewpoint-invariance ratios did not differ significantly between hemispheres [long-interval left = 0.65, right = 0.80, $t < 1$, NS; short-interval left = 0.06, right = 0.04, $t < 1$, NS]. This result contrasts with previously-reported findings of greater viewpoint-invariance in the left hemisphere using long-interval fMRI-RS (Koutstaal et al. 2001; Vuilleumier et al. 2002). This difference likely reflects the fact that the earlier studies used non-scene object stimuli and focused on the fusiform gyrus, whereas the present study uses scene stimuli and focuses on parahippocampal cortex. The contrast between these two results suggests that there is a laterality effect for object processing that is not observed for scene processing.

Whole-brain analysis

A whole-brain analysis was performed to identify regions outside of the scene-selective ROIs that displayed long- and short-interval RS effects. There are two questions of interest here. First, do long- and short-interval RS effects impact the same set of brain regions or different brain regions? The answer to this question is important for understanding whether long- and short-interval RS effects are mediated by different cortical networks or different neural mechanisms within the same cortical network. Second, are there regions of the brain outside of the PPA where long- and short-interval RS effects interact? If so, the argument for dissociable mechanisms would be weakened.

Results of the whole brain analyses are shown in Figs. 4 and 5. We focus on regions exhibiting viewpoint-invariant long-interval RS effects (new place > new view) and viewpoint-specific short-interval RS effects (viewpoint change > no change), as whole-brain analyses of viewpoint-specific long-interval (new view > old view) and viewpoint-invariant short-interval (place change > viewpoint change) RS effects revealed few voxels that exceeded the $P < 0.001$ statistical criterion. Long- and short-interval RS effects impacted many of the same brain regions, including the parahippocampal/fusiform gyri, retrosplenial cortex/parietal-occipital sulcus, transverse occipital sulcus, and superior parietal lobe. Exceptions to this pattern of overlap were observed in the left hippocampus (Fig. 5) and the inferior frontal gyrus in which long-interval RS effects were more evident than short-interval RS effects and the posterior visual cortices in which short-interval RS effects were more evident than long-interval RS effects. Thus long- and short-interval RS effects appear to engage cortical networks that are largely but not completely overlapping. Analysis of the overall RS effects (new place > old view, place change > no change) gave results that were substantially the same.

To probe these data further, we performed ANOVAs on the fMRI response within the regions defined by the above whole-brain analysis (see Table 2). Two aspects of the results are notable. First, in almost every region, both short- and long-interval RS effects were significant irrespective of which effect was used to define the region in the whole-brain analysis. The only exceptions to this rule were the left hippocampus (in which only long-interval RS was significant) and the right posterior visual cortex (in which only short-interval RS was significant). Second, few regions showed evidence of an interaction between long- and short-interval RS. Again there were some exceptions (notable the left superior parietal lobe and transverse occipital regions as defined by the new place > new view contrast). However, even in these regions, the interaction term was relatively small compared with the size of the main effects. Critically, the interaction term was almost zero ($F < 1.2$, $P > 0.2$) in the parahippocampal/fusiform region, left hippocampus, inferior frontal gyri, and right TOS.

Finally we analyzed the interaction between long- and short-interval fMRI-RS across the entire brain. We found no regions in which interactions between these effects were significant. This was the case irrespective of whether the two effects were defined by (new place > new view, view change > no change) or (new place > old view, place change > no change).

In sum, the results of the whole-brain analysis support the idea that long- and short-interval RS effects are mediated by
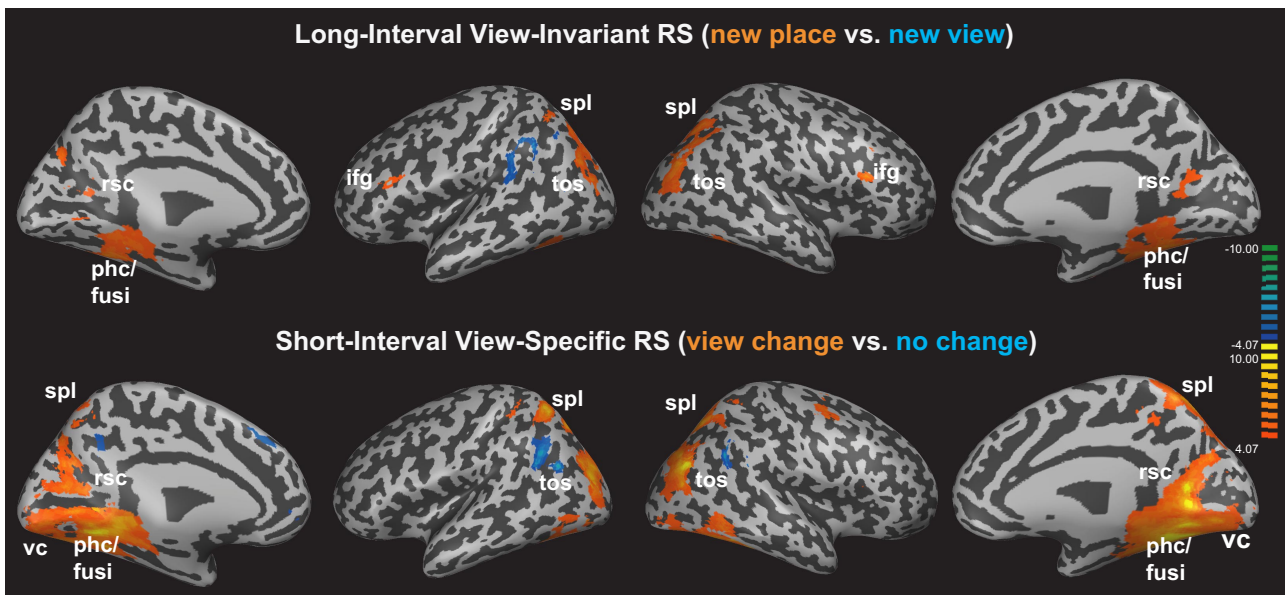
FIG. 4. Whole-brain analysis of long-interval view-invariant RS (*top*) and short-interval view-specific RS (*bottom*). Voxels responding more strongly ($P <$ 0.001, uncorrected) to new places than to new views (*top*) or more strongly to viewpoint change trials than to no change trials (*bottom*) are plotted in orange on an inflated version of the cortex. Blue voxels exhibited the opposite patterns (new views > new places or no change > viewpoint change). From left to right, the 4 views depict the left hemisphere (medial surface), left hemisphere (lateral surface), right hemisphere (lateral surface), and right hemisphere (medial surface). Gyri are light gray on the inflated surface, whereas sulci are dark gray. Both long- and short-interval RS impacted many of the same cortical regions, including the parahippocampal cortex/fusiform gyrus (phc/fusi), retrosplenial cortex (rsc), transverse occipital sulcus (tos), and superior parietal lobule (spl). Long-interval RS was more evident in the inferior frontal gyrus (ifg), whereas short-interval RS was more evident in the visual cortices (vc).

independent mechanisms that operate within a largely overlapping sets of cortical regions.

DISCUSSION

We examined long-interval (i.e., between-trial) and short-interval (i.e., within-trial) fMRI-RS effects using a design in which both effects could be measured in the same set of trials while subjects performed a single behavioral task. Our analyses focused on the PPA, which responds strongly to the scene stimuli used in the current experiment; however, we expect our conclusions to generalize to other stimulus classes and other regions of cortex. We report three main findings. First, although both long- and short-interval fMRI-RS were observed, we found no evidence for an interaction between these effects. Second, consistent with earlier studies, short-interval fMRI-RS was primarily viewpoint specific, whereas long-interval fMRI-RS was more viewpoint invariant. Third, when we extended our analyses to the entire brain, we found that long- and short-

interval fMRI-RS impacted a largely overlapping set of brain regions. Taken as a whole, these results suggest that long- and short-interval fMRI-RS are mediated by distinct neural mechanisms that have different operating characteristics but are spatially coterminous.

The conclusion that long- and short-interval fMRI-RS engage dissociable neural processes is based in part on the consonance of the results with the additive factors logic of Sternberg (2001, 2004). According to this logic, which is analogous to the double dissociation logic often used in neuropsychology, mental or neural processes are considered dissociable if they can be separably modified, that is if varying the strength of one process does not affect the strength of the other. In the current experiment, the two underlying processes are hypothesized neural mechanisms that are differentially affected by long- and short-interval repetition, and separate modifiability was demonstrated by the complete absence of an interaction between long- and short-interval RS effects. In other words, short- and long-interval fMRI-RS are additive factors—their contributions to the fMRI response add linearly without any additional interaction term. This finding provides the first line of evidence for independent processes mediating these two effects.

Our results are consistent with those of an earlier study by Ganel and colleagues (2006), who examined long- and short-interval fMRI-RS effects in object-responsive regions and found no significant interaction. In contrast to the current study, however, this earlier study used a design in which pairs of stimuli shown in the first part of the session were repeated later without re-pairing the items or changing the task (although response modality was varied). Thus the effect of repeating individual items over short intervals was not compared directly to the effect of repeating individual items over
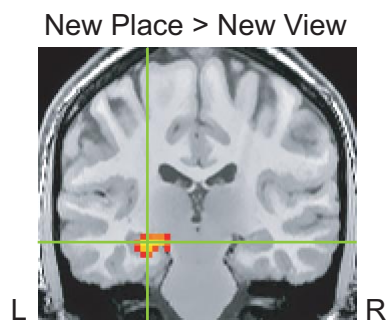
New Place > New View

FIG. 5. Long-interval RS in the left hippocampus. Orange voxels responded more strongly to new places than to new views ($P < 0.001$ uncorrected). Short-interval RS was not observed in this region (Table 2).

TABLE 2. *Analysis of variance within regions that displayed significant long or short-interval RS in the whole-brain analysis*

Region	Long-Interval RS		Short-Interval RS		Interaction	
	F	P	F	P	F	P
Regions defined by long-interval RS (new place > new new view)						
L parahippocampal/fusiform	52.9	<0.000000001	31.8	<0.0000001	1.0	0.43
R parahippocampal/fusiform	48.3	<0.000000001	41.2	<0.00000001	0.1	0.98
L retrosplenial cortex	23.1	<0.000001	18.2	<0.00001	2.3	0.07
R retrosplenial cortex	29.9	<0.0000001	22.4	<0.00001	2.3	0.07
L transverse occipital sulcus	55.7	<0.000000001	16.2	<0.0001	2.8	<0.05
R transverse occipital sulcus	36.9	<0.00000001	36.1	<0.0000001	0.9	0.49
L superior parietal lobe	25.4	<0.000001	15.5	<0.001	3.5	<0.05
R superior parietal lobe	43.8	<0.00000001	13.8	<0.0001	2.5	0.06
L hippocampus	6.4	<0.01	1.9	0.17	0.6	0.64
L inferior frontal gyrus	12.8	<0.0001	6.0	<0.01	0.8	0.56
R inferior frontal gyrus	17.0	<0.0001	5.9	<0.01	0.6	0.67
Regions defined by short-interval RS (view change > no change)						
L parahippocampal/fusiform	26.5	<0.000001	42.1	<0.00000001	0.3	0.87
R parahippocampal/fusiform	25.5	<0.000001	37.5	<0.00000001	0.1	0.99
L retrosplenial cortex	7.2	<0.01	35.6	<0.0000001	0.7	0.57
R retrosplenial cortex	8.0	<0.01	49.0	<0.000000001	0.6	0.67
L transverse occipital sulcus	19.5	<0.00001	29.3	<0.0000001	1.4	0.26
R transverse occipital sulcus	20.6	<0.00001	35.5	<0.0000001	0.7	0.61
L superior parietal lobe	17.2	<0.0001	32.0	<0.0000001	1.4	0.23
R superior parietal lobe	8.3	<0.01	32.3	<0.0000001	1.4	0.26
L visual cortex	3.8	<0.05	22.7	<0.000001	0.2	0.91
R visual cortex	2.2	0.13	27.9	<0.000001	0.3	0.85

RS, repetition suppression; R, right; L, left.

long intervals but rather to the effect of repeating item *pairs*, along with the required response to those pairs, over long intervals. The current design, on the other hand, directly compares the effects of repeating individual items over short versus long intervals without confounding influences of task repetition, which can strongly affect fMRI response (Dobbins et al. 2004).

The second line of evidence for the existence of distinct RS mechanisms comes from the finding that long- and short-interval RS were differentially sensitive to changes in viewpoint. Short-interval RS effects were primarily viewpoint specific in that significant RS was only observed when the two images within a trial depicted the same view of a location. In contrast, long-interval RS showed a greater degree of viewpoint independence, in that strong RS was observed when previously seen locations were presented again from previously unseen views. As noted in the INTRODUCTION, we observed a similar pattern of results (i.e., greater viewpoint independence for long-interval RS) in earlier experiments (Epstein et al. 2005, 2007a). However, these early experiments measured long- and short-interval RS in different runs during which subjects performed different tasks, so it was possible that the results could be explained by task differences rather than differences in repetition interval. The current results, on the other hand, cannot be explained in this manner, because both long- and short-interval RS were measured in the same trials during which subjects were performing a constant task. Rather they strongly suggest that repetition interval per se is critical for determining the viewpoint invariance of RS effects in high-level visual regions.

What accounts for the greater viewpoint independence with longer repetition intervals? One appealing notion is that scene representations may be encoded in a viewpoint-

specific manner, but these representations become less viewpoint specific as the details of the initial encoding event recede into the past (Epstein et al. 2005; Potter et al. 2004). However, this account cannot explain the current data because long- and short-interval RS were sampled at the same points in time. If long- and short-interval RS effects were drawing on the same representation the invariance of which changed over time, then the viewpoint-invariance of the short-interval RS effect would depend on the long-term history, which it does not. The alternative account, which we favor, is that long- and short-interval RS show different degrees of viewpoint specificity because they are mediated by different neural mechanisms.

If different RS mechanisms do exist, this fact may help to clarify apparent discrepancies in the results of earlier studies that have reported both viewpoint specific (Grill-Spector et al. 1999) or viewpoint invariant (James et al. 2002; Vuilleumier et al. 2002) RS in the fusiform/lateral occipital regions responsive to visual objects. This inconsistency is not trivial as the question of whether object representations are viewpoint specific or invariant has been a central one in cognitive psychology (Biederman and Gerhardstein 1993; Bulthoff et al. 1995; Tarr and Pinker 1989). In general, previous experiments reporting viewpoint-invariant RS examined long-interval (across-trial or across-block) RS, while experiments reporting viewpoint-specific RS examined short-interval (within-trial, or within-block) RS. Thus these earlier studies may have arrived at different conclusions because they used repetition paradigms that indexed different kinds of RS.

Our third finding, that long- and short-interval RS effects are largely coterminous, raises the following question: what are the neurophysiological and neuroanatomical bases of the distinct mechanisms that mediate long- and short-interval fMRI-RS?

There are at least two possibilities: the signals that mediate long- and short-interval RS might originate in different regions of the brain, or they might originate locally within each cortical region. We will now consider each of these possibilities in turn.

One plausible version of the different regions hypothesis is that short-interval RS is engendered by bottom-up inputs from regions that are early in the visual processing stream, whereas long-interval RS is engendered by top-down modulation from anterior regions (Friston 2005; James and Gauthier 2006). In this account, the greater viewpoint-invariance of the long-interval RS reflects the fact that earlier-processing regions encode stimuli in a more viewpoint-invariant manner than late-processing regions. Support for this account comes from recent studies that implicate top-down signals from the frontal lobes in object recognition (Bar et al. 2006) and also from neurophysiological studies showing that short-interval RS effects are observable in the initial response to an object (Noguchi et al. 2004; Sawamura et al. 2006) while cross-trial RS effects are found primarily in the later components (Li et al. 1993; McMahon and Olson 2007). However, the results of the whole-brain analysis provide only mixed support for a top-down versus bottom-up account. Although short-interval RS effects were more prominent than long-interval RS effects in early visual regions, as one would expect, we did not find unambiguous evidence for an upstream source for long-interval RS. Rather almost all regions that showed strong long-interval RS also showed strong short-interval RS. An exception was the left hippocampus, which given its role in episodic memory might well be the source of the long-interval RS effect (Schnyer et al. 2006). Future studies might test this hypothesis by examining the functional connectivity between the hippocampus and posterior visual regions during long-interval RS.

The second possibility is that long- and short-interval RS are caused by adaptation mechanisms that originate locally within a region. More specifically, short-interval RS might reflect attenuation at the synaptic inputs to a cortical region, whereas long-interval RS might reflect changes in within-region processing, perhaps caused by within-region changes in synaptic weights. In this account, the greater viewpoint specificity of the short-interval RS would be explained by the fact that the inputs to a region encode information in a more stimulus-specific manner than the outputs. Supporting this account are results from a recent single-cell-recording study by Sawamura and colleagues (2006) that indicated that short-interval RS effects are more stimulus-specific than neural response insofar as these effects are sensitive to differences between stimuli to which the neuron responds with equal firing rates. These authors concluded that short-interval RS effects reflect adaptation at the synaptic inputs, which would be more stimulus specific than the outputs. A possible mechanism for this synaptic adaptation is synaptic depression (Abbott et al. 1997), which is believed to operate on a relatively short time scale of <2 s (Muller et al. 1999). Although it requires further support, this second account is particularly exciting because it holds out the possibility of turning fMRI-RS into a more refined tool for probing neural processing than it has been hitherto. In particular, it suggests that short- and long-interval fMRI-RS could be used to separately and simultaneously probe the inputs and the outputs to a cortical region.

In any case, the current results advance our understanding of fMRI-RS by clearly establish that long- and short-interval repetition effects are dissociable and mediated by distinct mechanisms. Rather than being a direct proxy for neural firing, fMRI-RS may reflect more subtle aspects of cortical response with different aspects of neural processing indexed by suppression effects obtained under different repetition regimes.

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