

Neural Basis of Repetition Priming during Mathematical Cognition: Repetition Suppression or Repetition Enhancement?

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Abstract

■ We investigated the neural basis of repetition priming (RP) during mathematical cognition. Previous studies of RP have focused on repetition suppression as the basis of behavioral facilitation, primarily using word and object identification and classification tasks. More recently, researchers have suggested associative stimulus-response learning as an alternate model for behavioral facilitation. We examined the neural basis of RP during mathematical problem solving in the context of these two models of learning. Brain imaging and behavioral data were acquired from 39 adults during novel and repeated presentation of three-operand mathematical equations. Despite widespread decreases in activation during repeat, compared with novel trials, there was no direct relation between the behavioral facilitation and the degree of repetition suppression in

any brain region. Rather, RT improvements were directly correlated with repetition enhancement in the hippocampus and the posteromedial cortex [posterior cingulate cortex, precuneus, and retrosplenial cortex; Brodmann's areas (BAs) 23, 7, and 30, respectively], regions known to support memory formation and retrieval, and in the SMA (BA 6) and the dorsal midcingulate ("motor cingulate") cortex (BA 24d), regions known to be important for motor learning. Furthermore, improvements in RT were also correlated with increased functional connectivity of the hippocampus with both the SMA and the dorsal midcingulate cortex. Our findings provide novel support for the hypothesis that repetition enhancement and associated stimulus-response learning may facilitate behavioral performance during mathematical problem solving. ■

INTRODUCTION

Repetition priming (RP) refers to facilitation in behavioral performance upon subsequent exposure to a stimulus (Henson, 2003; Henson, Shallice, & Dolan, 2000; Scarborough, Cortese, & Scarborough, 1977). RP has been widely used to investigate the neural and the behavioral mechanisms that underlie rapid learning. In conjunction with improvements in RT, stimulus repetition is often accompanied by attenuation of neural responses (repetition suppression; RS), which can be recorded either at the level of single cells (Rainer & Miller, 2000; Desimone, 1996; Miller, Li, & Desimone, 1991) or across multiple brain regions ranging from unimodal sensory to heteromodal association cortices (Maccotta & Buckner, 2004; Henson, 2003; Buckner & Koutstaal, 1998; Buckner et al., 1995; Domb et al., 1995; Raichle et al., 1994).

The precise location and extent of attenuation in neural activity depends on the level of information processing required by the task, and researchers frequently distinguish between perceptual and conceptual priming in this context. Perceptual priming is mainly related to

the physical attributes of the stimulus, whereas conceptual priming is mainly related to semantic processing and decision making independent of the physical attributes. At the perceptual level, priming effects emerge in modality-specific cortical regions that are involved in extracting physical features of stimuli (Gilaie-Dotan, Nir, & Malach, 2008; Bergerbest, Ghahremani, & Gabrieli, 2004; Doniger et al., 2001; Grill-Spector et al., 1999). With greater cognitive demand, RS is also observed in "higher order" cortical regions, including temporal lobe areas specific to, for example, recognition of objects (Koutstaal et al., 2001), scenes (Bunzeck, Schutze, & Duzel, 2006; Blondin & Lepage, 2005), faces (Bunzeck et al., 2006; Eger, Schweinberger, Dolan, & Henson, 2005), or words (Orfanidou, Marslen-Wilson, & Davis, 2006). Most previous studies of RP have focused on perceptual and conceptual priming of objects and words (Roediger, 2003). With visually presented objects, participants are typically asked to decide whether images depict living or non-living objects (Wig, Grafton, Demos, & Kelley, 2005), natural or manufactured objects (Zago, Fenske, Aminoff, & Bar, 2005), indoor or outdoor scenes (Bunzeck et al., 2006; Turk-Browne, Yi, & Chun, 2006), and possible or impossible objects (Habeck, Hilton, Zarah, Brown, & Stern, 2006). With visually presented words, participants

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are typically asked to distinguish between living or non-living items (Lustig & Buckner, 2004; Maccotta & Buckner, 2004), and with words presented aurally, participants are asked to decide whether words were real or pseudowords (Gagnepain et al., 2008; Orfanidou et al., 2006) and whether environmental sounds were made by an animal (Bergerbest et al., 2004). Tasks that involve semantic processing (e.g., retrieving conceptual information about words or objects) typically show RS effects in the pFC, primarily within the left inferior frontal cortex (IFC; Lustig & Buckner, 2004; Maccotta & Buckner, 2004; Wagner, Gabrieli, & Verfaellie, 1997; Buckner et al., 1995; Demb et al., 1995). Here, we examine the generalizability of findings from previous RP studies with a novel task involving mathematical problem solving and a control task involving number identification.

We investigate the neural basis of behavioral improvements upon repeated processing of mathematical information in the context of two current models. The more prominent of these models of RP, the “tuning” model (Wiggs & Martin, 1998; Desimone, 1996; Li, 1993), posits that performance improvements result from concurrent reductions in neural responses (Desimone, 1996; Morton, 1969). Neuronal populations that are not essential for processing the stimuli drop out of the initial cell assembly, yielding more efficient processing (Wiggs & Martin, 1998; Gupta & Cohen, 1990). Evidence for fine tuning of neuronal representations comes from the finding that brain areas that demonstrate RS are typically a subset of those that were originally involved in performing the task (Henson, 2003) and that RS increases with repeated stimulus presentations (Sayres & Grill-Spector, 2006; Grill-Spector & Malach, 2001; Henson et al., 2000).

Despite considerable evidence that repeated task performance results in both behavioral facilitation and RS, evidence supporting a link between the two has been generally weak (McMahon & Olson, 2007). In the first place, only a relatively small number of brain imaging studies of RP have reported examining the relation between behavioral changes and RS. Of these, the most consistent findings to date have been an association between behavioral facilitation and RS in the IFC (Gagnepain et al., 2008; Bunzeck et al., 2006; Orfanidou et al., 2006; Wig et al., 2005; Zago et al., 2005; Bergerbest et al., 2004; Lustig & Buckner, 2004; Maccotta & Buckner, 2004). Wig et al. (2005) found that disrupting activity by applying transcranial magnetic stimulation to the pars triangularis region of the left IFC [Brodmann’s area (BA) 45] during initial stimulus presentation interfered with RP. However, it is not clear what role, if any, the IFC plays in facilitating performance during repeated stimulus processing. Importantly, these same studies did not find a direct relationship between improvements in behavioral performance and other brain areas that had displayed RS, including the occipital cortex (Bunzeck et al., 2006; Wig et al., 2005), the cerebellum (Bunzeck et al., 2006; Orfanidou et al., 2006), the fusiform cortex (Orfanidou et al., 2006; Maccotta & Buckner, 2004), the

parahippocampal gyrus (Turk-Browne et al., 2006), and the caudate nucleus (Bunzeck et al., 2006). Thus, the link between RS and behavioral facilitation has only been consistently demonstrated in the IFC. However, other studies have reported improvements in behavioral performance without any decreases in activity in the IFC (Eger, Henson, Driver, & Dolan, 2004; Henson, Shallice, Gorno-Tempini, & Dolan, 2002), and individuals with lesions in the IFC (Broca’s aphasia) nonetheless demonstrate intact lexical-semantic priming (Hagoort, 1997). A further challenge to the tuning model is the finding that RS is not always accompanied by behavioral improvements (Henson & Mouchlianitis, 2007; Lin & Ryan, 2007; Ryan & Schnyer, 2007).

An alternative, but not necessarily mutually exclusive, model has recently been proposed, which posits that performance enhancements during repeated stimulus presentation may arise from rapid stimulus-response learning (Schnyer, Dobbins, Nicholls, Schacter, & Verfaellie, 2006; Dobbins, Schnyer, Verfaellie, & Schacter, 2004; Logan, 1990). Under this model, an association is formed between a stimulus and a particular response during initial stimulus presentation; during repeated presentation of the stimulus, the appropriate response is cued, bypassing more elaborate semantic processing that accompanied initial stimulus presentation (Horner & Henson, 2008). In support of this model, Dobbins et al. (2004) found that despite using the same stimuli upon repeated presentation, changing the task rules diminished behavioral facilitation. This study demonstrated that it was not the repeated processing of the stimuli that was resulting in behavioral facilitation but rather the formation of an association between the stimulus and its correct response. Behavioral facilitation may therefore be more directly related to brain systems that support associative learning rather than RS. It would then be expected that associative learning would involve repetition enhancement as stimulus-response mappings are formed. Although increases in neural activity have been reported in conjunction with RP (Bunzeck et al., 2006; Orfanidou et al., 2006; Fiebach, Gruber, & Supp, 2005; Zago et al., 2005; Henson et al., 2000), surprisingly few studies have found a direct relation between behavioral facilitation and increased neural activity. A notable exception is the recent study by Horner and Henson (2008), which found that repetition enhancement within the posterior pFC (BA 44/6) reflected performance improvements, whereas RS within posterior perceptual regions reflected facilitation of perceptual processing independent of performance improvements.

The main goal of our study is to investigate the neural basis of RP during mathematical problem solving. We used fMRI to examine the neural basis of RP during a task involving three-operand addition and subtraction. There have been no previous brain imaging studies of RP using such tasks to our knowledge, although one behavioral study had demonstrated robust RP effects using both visual word and symbolic representations of simple addition problems (Sciama, Semenza, & Butterworth, 1999). The

neural basis of these performance improvements is unknown. To address this question, we compared RP during two conditions, one involving mathematical calculation (MC condition) and a second involving number identification (NI condition). We aimed to compare the magnitude of RP in the two conditions and to identify brain regions that mediate RP in these two conditions. Accordingly, we examined both neural RS and repetition enhancement and their relation to performance improvements.

We predicted that the MC condition, which involves semantic fact retrieval and problem solving, would show a greater magnitude of behavioral improvements compared with the NI condition, which involves basic number recognition. We also predicted that changes in brain responses during the MC condition would be more widespread and involve the PPC, notably in the intraparietal sulcus (IPS), the pars triangularis region of the IFC, and the ventral premotor cortex—regions consistently implicated in many prior studies of mathematical cognition (Delazer, Benke, Trieb, Schocke, & Ischebeck, 2006; Delazer, Karner, Zamarian, Donnemiller, & Benke, 2006; Houde & Tzourio-Mazoyer, 2003; Menon, Mackenzie, Rivera, & Reiss, 2002; Rivera, Menon, White, Glaser, & Reiss, 2002; Gruber, Indefrey, Steinmetz, & Kleinschmidt, 2001; Menon, Rivera, White, Eliez, et al., 2000; Menon, Rivera, White, Glover, & Reiss, 2000; Rickard et al., 2000; Dehaene, Spelke, Pinel, Stanescu, & Tsivkin, 1999). We further hypothesized that under the tuning model of RP, the magnitude of behavioral priming would be positively correlated with RS in the prefrontal and the parietal cortex. If, on the other hand, RP arises from stimulus-response association, we would expect that performance improvements would be related to increased activity in brain regions implicated in associative memory formation, notably the hippocampus and other medial-temporal lobe (MTL) regions (Schnyer et al., 2006). Finally, within the context of these two models, we test the hypothesis that changes in functional connectivity may also contribute to improvements in performance. First, we examine whether regions that exhibit RS also demonstrate performance-related increases in functional connectivity. This would suggest that the formation of stronger interactions allows these regions to process information more efficiently, thus partially explaining the link between performance improvement and decreased activation. Secondly, we examine whether regions involved in mnemonic and motoric processes demonstrate performance-related increases in functional connectivity. This would suggest that stimulus-response association arises in part from increased crosstalk between such regions.

METHODS

Participants

Forty-one healthy adults (20 males and 21 females) between the ages of 18 and 35 years ($M = 22.6$ years, $SD =$

4.172 years) participated in the study. Two subjects had large movement artifacts in their fMRI data, and they were subsequently excluded from the study. Participants were recruited from the Stanford University community after giving written informed consent. All protocols were approved by the Human Subjects Committee at Stanford University School of Medicine, and participants were treated in accordance with the American Psychological Association “Code of Conduct.”

fMRI Task

The experiment consisted of four conditions, involving novel and repeated presentation of MC trials [MC novel (MC-N) and MC repeat (MC-R)] and NI trials [NI novel (NI-N) and NI repeat (NI-R)] tasks. The MC-N and the NI-N epochs consisted entirely of novel (previously unseen) stimuli, whereas the MC-R and the NI-R epochs consisted entirely of stimuli contained in the previous MC-N or NI-N epoch, respectively. Participants were presented with 16 alternating MC and NI epochs, each lasting 28 sec. Two counterbalanced versions were used, such that half of the participants began with MC and the other half began with NI. The repeated version of each novel MC (NI) epoch was presented in the subsequent MC (NI) epoch; for example, a subject who began with the MC epoch would see the sequence—MC-N, NI-N, MC-R, NI-R—repeated four times with different sets of novel stimuli each time. Repeated trials in the MC condition used the same problems and the same outcomes as in the novel trials. To ensure that responses were not dependent on simple two-operand fact retrieval (e.g., $2 + 4 = 6$), we used three-operand trials to facilitate MC and subsequent response learning.

Each MC epoch consisted of seven 3-operand equations of the form $a + b - c = d$ (e.g., $5 + 4 - 2 = 7$), using only single-digit numerals and addition and subtraction operators. Participants pressed one of two keys to indicate whether the equation was correct or incorrect. Fifty percent of equations were correct, and equations were randomly presented. Incorrect equations had answers that were adjusted randomly by ± 1 and ± 2 . Each NI epoch consisted of seven 7-symbol strings (e.g., $4 @ 3 \& 2 \circ 5$). Participants pressed one of two keys to indicate whether the string contained the numeral 5. Half the strings contained the numeral 5 and half did not, and the strings were randomly generated. Each equation or string was presented for 3.5 sec followed by a blank screen for 0.5 sec.

fMRI Data Acquisition

Images were acquired on a 3-T GE Signa scanner using a standard GE whole head coil (software Lx 8.3). Head movement was minimized during scanning by a comfortable custom-built restraint. A total of 28 axial slices (4.5-mm thickness) parallel to the AC–PC line and covering the whole brain were imaged using a T2*-weighted gradient-echo spiral pulse sequence (repetition time =

2000 msec, echo time = 30 msec, flip angle = 70°, 1 interleave). The field of view was 20 cm, and the matrix size was 64 × 64, providing an in-plane spatial resolution of 3.125 mm. To reduce blurring and signal loss arising from field inhomogeneities, we used an automated high-order shimming method based on spiral acquisitions before acquiring functional MRI scans (Speelman, Simpson, & Kirsner, 2002). To aid in localization of functional data, we used a high-resolution T1-weighted spoiled gradient recalled inversion recovery three-dimensional MRI sequence with the following parameters: inversion time = 300 msec, repetition time = 8 msec; echo time = 3.6 msec; flip angle = 15°; 22 cm field of view; 124 slices in coronal plane; 256 × 192 matrix; 2 NEX, acquired resolution = 1.5 × 0.9 × 1.1 mm. The images were reconstructed as a 124 × 256 × 256 matrix with a 1.5 × 0.9 × 0.9-mm spatial resolution. Structural and functional images were acquired in the same scan session.

fMRI Data Analysis

Preprocessing

The first five volumes were not analyzed to allow for signal equilibration effects. A linear shim correction was applied separately for each slice during reconstruction using a magnetic field map acquired automatically by the pulse sequence at the beginning of the scan. Functional MRI data were then analyzed using SPM5 analysis software (<http://www.fil.ion.ucl.ac.uk/spm>). Images were realigned to correct for motion, corrected for errors in slice timing, spatially transformed to standard stereotaxic space [based on the Montreal Neurological Institute (MNI) coordinate system], resampled every 2 mm using sinc interpolation, and smoothed with a 4-mm FWHM Gaussian kernel to decrease spatial noise prior to statistical analysis. Translational movement in millimeters (x , y , z) and rotational motion in degrees (pitch, roll, yaw) were calculated based on the SPM5 parameters for motion correction of the functional images in each subject. None of the participants had movement greater than 3 mm of translation or 3° of rotation.

Individual Subject Analyses

Task-related brain activation was identified using a general linear model. Individual subject analyses were first performed by modeling task-related conditions. For the mathematical cognition task, brain activity related to the four task conditions (MC-N, MC-R, NI-N, and NI-R) was modeled using boxcar functions with the SPM canonical hemodynamic response function and a temporal derivative to account for voxelwise latency differences in hemodynamic response. The boxcar function for a given task condition was equal to “1” throughout each of the four 28-sec epochs of the condition and “0” otherwise. Low-frequency drifts at each voxel were removed using a high-

pass filter (0.5 cycles/min), and serial correlations were accounted for by modeling the fMRI time series as a first degree autoregressive process (Friston et al., 1997). The following comparisons were performed: (1) MC minus NI; (2) MC-N minus MC-R; and (3) NI-N minus NI-R. Voxelwise t statistics maps for each comparison were generated for each participant using ANOVA on the respective contrast images.

Group Analyses

A group-level analysis for each comparison was performed by entering the individual-subject contrast maps into a random-effects analysis. The resulting voxelwise t statistic maps were used to determine group-level activation for each comparison. Significant clusters of activation were determined using a voxelwise statistical height threshold of ($p < .01$), with corrections for multiple spatial comparisons at the cluster level ($p < .01$). In addition, two group-level covariate analyses were performed between brain activation and behavioral measures: (1) MC-N minus MC-R versus RT improvements in the MC condition, and (2) NI-N minus NI-R versus RT improvements in the NI condition. The “RT improvement” in the MC (NI) condition for each subject was defined as the difference between the subject’s average RT across novel MC (NI) trials and average RT across repeated MC (NI) trials.

Activation foci were superimposed on high-resolution T1-weighted images, and their locations were interpreted using known neuroanatomical landmarks (Duvernoy, Bourgouin, Cabanis, & Cattin, 1999). MNI coordinates were transformed to Talairach coordinates using a non-linear transformation (Brett, 2000).

ROI Analysis

ROIs were defined based on a subset of significant ($p < .01$) activation clusters identified in the analysis described above (see also Tables 1 and 2). The percentage of signal change was extracted from the mean time series of each ROI and within each task condition, using the MarsBaR toolbox (Brett, 2000). An average percent signal change value for a given condition was computed by finding the average signal amplitude within a 12- to 30-sec time window of each epoch corresponding to that condition and normalizing that value to a percentage of the baseline (defined as the mean signal in the ROI across the entire scan). Details of the percent signal change calculation are provided in the MarsBaR documentation (<http://marsbar.sourceforge.net/>). A Wilcoxon sign-rank test was used to test for significant differences in percentage signal change across task conditions. Linear regression of percent signal change against RT within the MC-R minus MC-N and the NI-R minus NI-N conditions was performed to test whether RS or repetition-induced increases in neural activation were significantly correlated with behavioral improvements.

Table 1. Brain Regions That Showed RS during the Calculation and Identification Conditions

<i>Regions</i>	<i>Brodmann's area</i>	<i>p Value (Corrected)</i>	<i>No. of Voxels</i>	<i>Peak Z Score</i>	<i>Peak MNI Coordinates (mm)</i>
<i>(A) Mathematical Calculation: Novel Minus Repeat</i>					
L IFC, OFC, insula	47, 45, 48	<.01	363	3.78	-40, 24, 4
R IFC, insula, putamen, caudate, globus pallidum	47, 11, 48	<.01	326	4.17	18, 16, 6
L putamen, caudate, ventral striatum		<.01	358	4.08	-14, 12, -12
R SMA, midcingulate cortex, SFG	6, 32	<.01	403	3.70	24, 8, 62
R rolandic operculum, precentral gyrus, postcentral gyrus	6, 4	<.01	819	4.15	54, -8, 14
L/R thalamus		<.01	285	4.40	4, -16, 4
L supramarginal, postcentral gyrus	40, 2, 4	<.01	233	4.09	-58, -28, 34
L calcarine sulcus, middle occipital gyrus	17, 19, 37	<.01	242	4.26	-18, -72, -10
R lingual gyrus, fusiform gyrus	17, 18, 19	<.01	283	3.60	18, -72, -10
R middle and inferior occipital gyrus, lateral fusiform gyrus	19, 37	<.01	240	4.00	38, -82, -2
<i>(B) Number Identification: Novel Minus Repeat</i>					
R fusiform gyrus, inferior temporal gyrus	19, 37	<.01	227	4.37	36, -66, -16
R superior parietal lobule	7, 17	<.01	157	3.81	22, -74, 50

SFG = superior frontal gyrus.

Table 2. Brain Regions Where Reaction Time Improvements Were Correlated with Repetition Enhancement

<i>Regions</i>	<i>Brodmann's areas</i>	<i>p Value (Corrected)</i>	<i>No. of Voxels</i>	<i>Peak Z Score</i>	<i>Peak MNI Coordinates (mm)</i>
<i>(A) Mathematical Calculation: Novel Minus Repeat</i>					
Positive correlation					
R hippocampus	34	<.01	155	4.24	20, -16, -14
L/R dorsal midcingulate cortex, SMA	24d, 6	<.01	351	4.07	2, -22, 48
L/R posteromedial cortex (PCC, precuneus retrosplenial cortex) and lingual gyrus	23, 30, 7	<.01	481	4.21	-18, -54, 8
Negative correlation					
<i>ns</i>					
<i>(B) Number Identification: Novel Minus Repeat</i>					
Positive correlation					
<i>ns</i>					
Negative correlation					
<i>ns</i>					

PCC = posterior cingulate cortex.

Functional Connectivity Analysis

Functional connectivity between pairs of ROIs was assessed by finding the correlation between the two ROI time series for each participant. To examine the functional connectivity for each separate task condition, we extracted and used temporal segments from the relevant condition (accounting for hemodynamic delay) in the correlation. Significance was assessed by applying the Fisher transformation to the correlation coefficients and performing a sign-rank test on the resulting z -values. In addition, we tested for performance-related changes in functional connectivity between MC-N and MC-R conditions by regressing the change in z -values against the change in RT. Detailed procedures are described in a previous publication (Menon & Levitin, 2005).

RESULTS

Behavioral

Participants were required to verify the accuracy of three-operand equations (e.g., $4 + 5 - 7 = 2$) during the MC condition and indicate whether the number “5” was present in a string of symbols during the NI condition. The mean RT for the MC condition was 2121 msec ($\sigma = 359$ msec) during novel presentation of stimuli and 2021 msec ($\sigma = 357$ msec) during repeated presentation of stimuli. For the NI condition, the mean RT for novel presentation was 959 msec ($\sigma = 243$ msec) and the mean RT for repeated presentation was 926 msec ($\sigma = 232$ msec). A two-way repeated measures ANOVA with the factors stimulus type (MC vs. NI) and presentation type (novel

vs. repeat) revealed a significant interaction, $F(1,41) = 7.44, p < .05$, partial $\eta^2 = .16$. Post hoc simple effect contrasts showed that mean RTs for the MC conditions were significantly higher than mean RTs for the NI conditions, $F(1,38) = 590.375, p < .001$, partial $\eta^2 = .94$, and mean RTs for the novel conditions were significantly higher than mean RTs for the repeated conditions, $F(1,38) = 23.46, p < .001$, partial $\eta^2 = .38$. Differences between RTs for novel and repeated trials were significant in both the MC, $F(1,38) = 23.468$, partial $\eta^2 = .38, p < .001$, and the NI conditions, $F(1,41) = 7.447$, partial $\eta^2 = .16, p < .05$, as shown in Figure 1A. Changes in RT between novel and repeated trials, for both MC and NI conditions, are plotted for each subject in Supplementary Figure 1.

Similar repeated measures ANOVA conducted using accuracy as the dependent variable did not reveal any significant interactions or main effects, as shown in Figure 1B.

Brain Activation in the MC Compared with the NI Condition

We demarcated brain regions that showed significant activation during MC beyond basic number processing and motor response. Compared with NI, the MC condition revealed greater activation bilaterally in the superior and inferior parietal cortex (BAs 7, 40, 39), the precuneus, the IFC (BA 47/12) and adjoining insula, the calcarine (BA 17), the lingual gyrus (BA 18), the right middle occipital (BA 19), the left superior occipital gyrus, the SMA (BA 6), the anterior/midcingulate cortex (BA 32/24), and the BG and thalamus, as shown in Figure 2A and Supplementary Table 1.

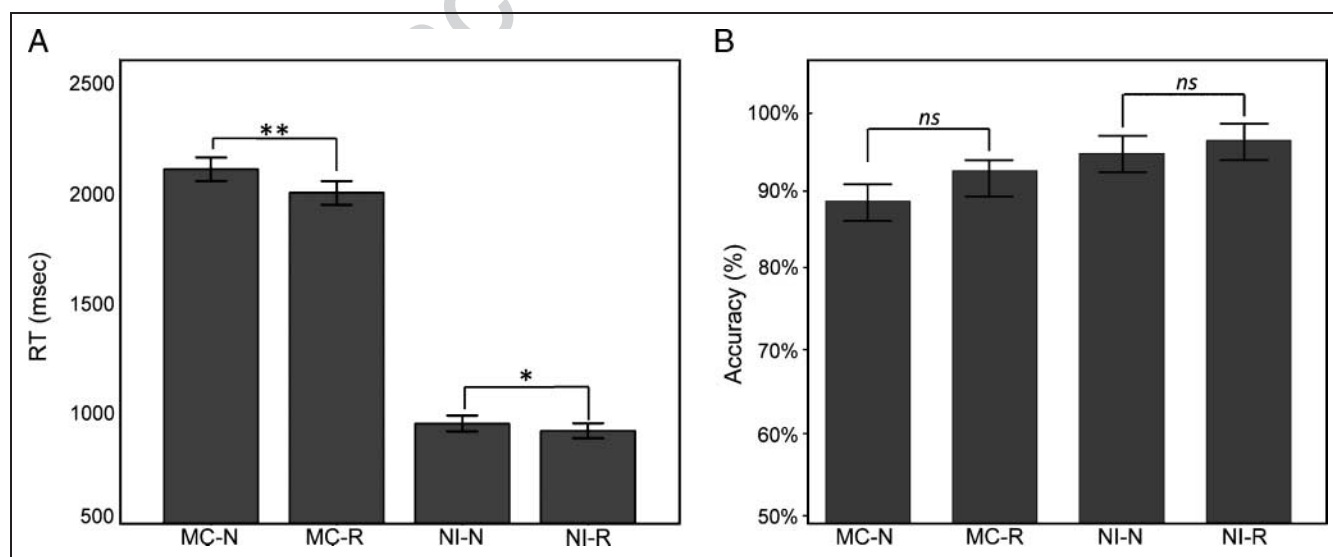


Figure 1. Behavioral changes underlying RP during MC and NI. (A) RT during both the MC and the NI conditions were significantly lower in the repeat compared with the novel trials. RP effects are larger for the MC compared with the NI conditions. (B) Accuracy differences between novel and repeated trials were not significant in both the MC and NI conditions. MC-N = mathematical calculation, novel; MC-R = mathematical calculation, repeat; NI-N = number identification, novel; NI-R = number identification, repeat.

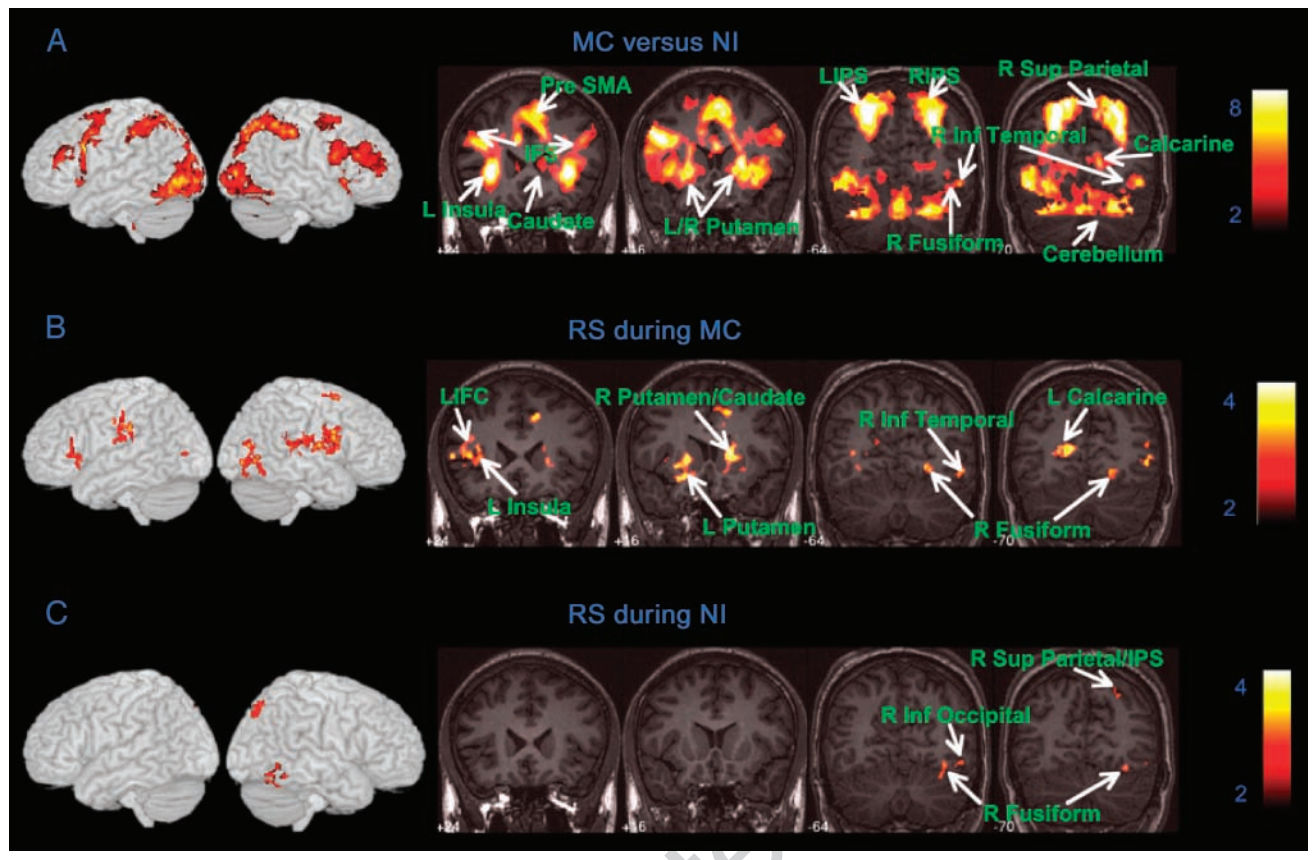


Figure 2. Brain regions that showed task-related activation and RS. (A) Overall task-related activation during the MC compared with the NI condition. (B) In the MC condition, RS was detected bilaterally in the IFC, the middle and inferior occipital cortex, the inferior temporal cortex, the BG, and the thalamus. (C) In the NI condition, RS was detected only in the posterior regions of the right hemisphere, within the inferior temporal cortex and the superior parietal cortex.

Brain Regions Showing RS

MC Condition

Repeated trials elicited reduced activation bilaterally in cortical regions in the middle and inferior occipital (BA 19), the inferior frontal gyrus (BA 47), the right superior frontal gyrus (BA 6), the middle and inferior temporal gyrus (BA 37), the precentral and postcentral gyri (BAs 4, 6), the left supramarginal (BA 40), the bilateral calcarine (BA 17), the dorsal midcingulate cortex (dmCC, BA 24d), the lingual (BA 18) and fusiform gyri (BA 37), and the thalamus and BG (Figure 2A, Table 1A). Analysis of regional signal change in clusters that showed significant RS (Table 1A) confirmed significant RS effects, as illustrated for responses in the left and right IFC, the left calcarine, and the right fusiform gyrus (Figure 3A–D). In contrast, when we examined the left and the right IPS clusters activated during the MC compared with the NI condition, no significant RS effects were found in either the left and the right IPS (Figure 3E–F).

NI Condition

Repeated presentation of the number strings elicited reduced activation only in the posterior regions of the

right hemisphere. RS was detected in the fusiform gyrus (BA 37), the superior occipital gyrus (BA 19), the superior parietal lobule (BA 7), and the cuneus (Figure 2C, Table 1B). No brain regions showed significantly greater activation during the repeat compared with the novel stimulus presentation.

Neural Correlates of Behavioral Facilitation

MC Condition

Regression analysis was used to assess the relationship between RT improvement and changes in neural response between novel and repeated MC trials. The magnitude of RS was not correlated with improvement in RT. The magnitude of increases in activation with repeated presentation was, however, correlated with improvement in RT in three distinct regions: (1) the right hippocampus, (2) the left and right SMA and the dmCC, and (3) the retrosplenial cortex, posterior cingulate cortex, precuneus, and anterior lingual gyrus (Figure 4, Table 2). Because RTs are variable across subjects, we performed additional analysis to examine changes in brain activation correlated with normalized changes in RT. Critically, we found that both

hippocampus and midcingulate cortex responses were correlated with percent changes in RT (specifically, the percent decrease in RT from MC-N to MC-R). Supplementary Figure 2 shows results from this new analysis. In addition, we examined whether brain activation in the MC-N condition was predictive of RT improvement; no significant clusters were found.

NI Condition

No regions showed significant correlations between RT changes and either increases or decreases in brain activation from the novel to the repeated trials in the NI condition.

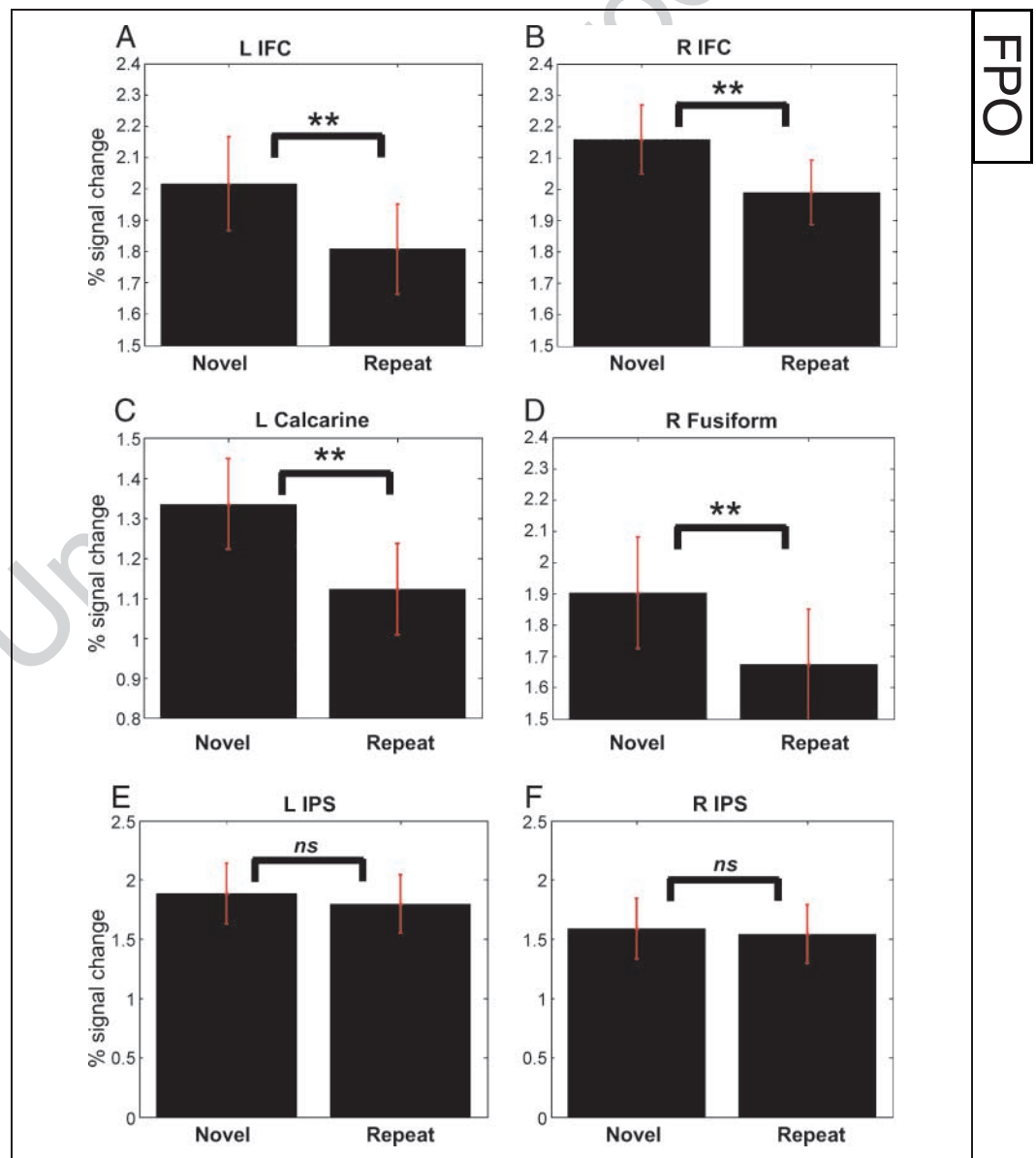
ROI analyses were used to further clarify the relationship between RT improvement and the observed RS effects. ROIs were created based on individual clusters

demonstrating RS in the MC and the NI conditions and were separately analyzed for the presence of significant correlations between RT improvement and RS. There were no significant relations between RT improvement and RS within any of the individual clusters. Improved accuracy was not correlated with either increases or decreases in activation anywhere in the brain during either the MC or the NI conditions.

Changes in Functional Connectivity Associated with Repetition Enhancement

Within brain regions that showed repetition enhancement between the novel and the repeat MC conditions, we examined whether changes in interregional functional connectivity were predictive of RT improvement. Significant correlations between increases in functional connec-

Figure 3. RS during mathematical problem solving. Significant reductions in brain activation during the repeated compared with the novel MC condition were found in the (A) left IFC, (B) right IFC, (C) left calcarine, and (D) right fusiform gyrus. No significant reductions were found in (E) the left or (F) the right IPS.



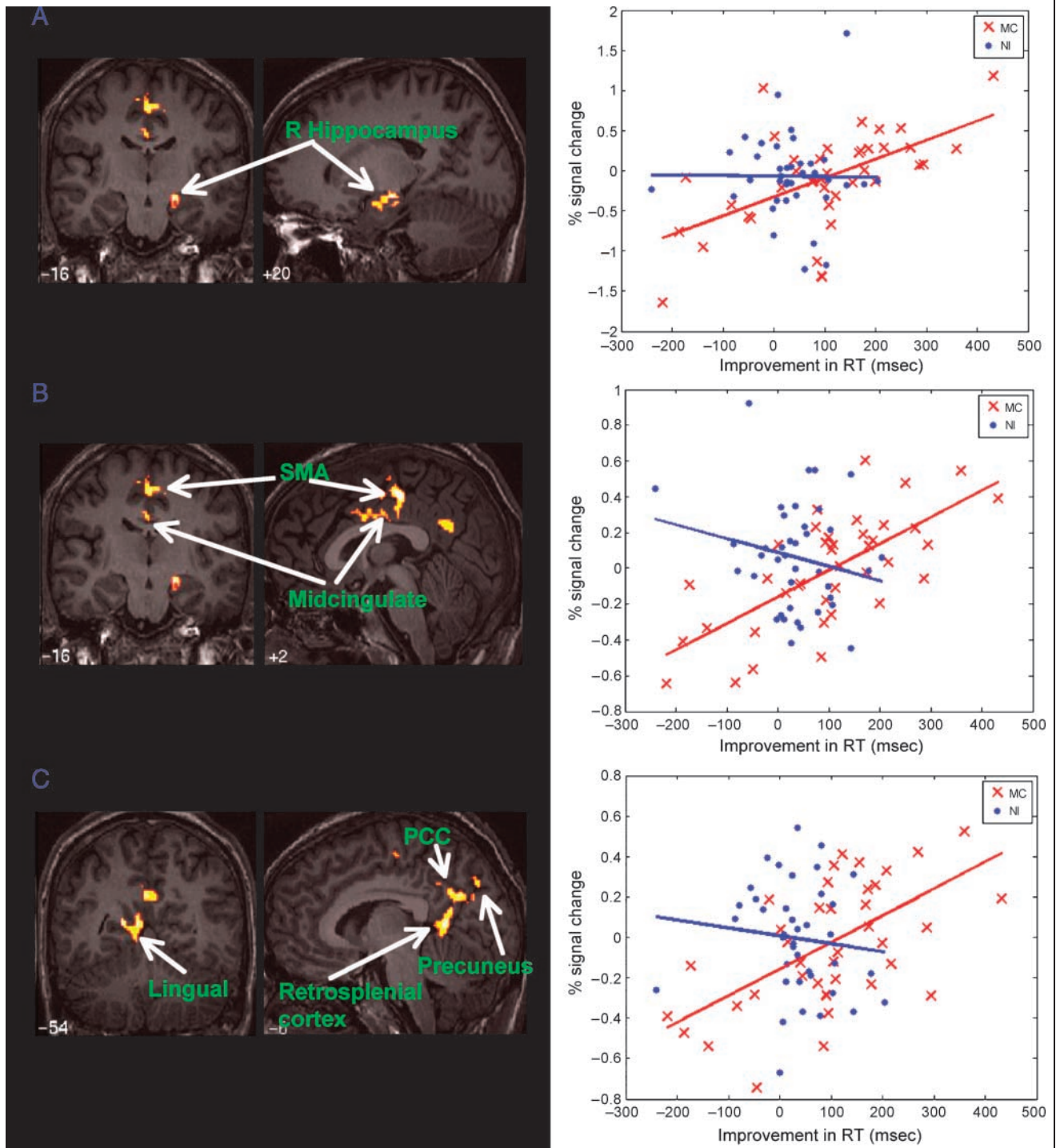


Figure 4. Brain areas where RT improvements were correlated with repetition enhancement during mathematical problem solving. Brain areas in which activation during the novel compared with the repeat trials was associated with RT improvements. Left column: Coronal and sagittal views of the (A) hippocampus, (B) dmCC and SMA, and (C) posterior medial cortex, including the retrosplenial cortex, posterior cingulate cortex. Right column: For all three cortical clusters, improvements in RT were significantly correlated with the percentage signal change between the novel and the repeat trials for the MC but not the NI condition.

tivity and improvement in RT were found between the right hippocampus ROI and the dmCC/SMA ROI ($p < .05$ FDR corrected for multiple comparisons), as shown in Figure 5. We further clarified that the functional connectivity between these ROIs was significant during both

the MC-N ($\bar{r} = .21, Z = .24; p < .001$) and the MC-R ($\bar{r} = .26, Z = .29; p < .001$) conditions. We then partitioned the combined dmCC/SMA cluster into separate dmCC and SMA ROIs and found that the right hippocampus was significantly correlated with both ($p < .01$ and $p <$

.002, respectively). Finally, we examined whether functional connectivity in the MC-N condition was predictive of RT improvement; no significant relationships were obtained.

Changes in Functional Connectivity Associated with RS

Within brain regions that showed RS between the novel and the repeat MC conditions, we examined whether changes in interregional functional connectivity might be predictive of RT improvement. We focused on the functional connectivity of the left IFC and the nine other brain regions that showed significant RS effects (as shown in Table 1). Functional connectivity between these regions showed no increases between the novel and the repeat conditions ($p > .05$). Furthermore, RT improvement was not significantly correlated with changes in functional connectivity between these regions ($p > .05$). Similar results were found for all other regions taken pairwise.

DISCUSSION

The primary goals of our study were to investigate the neural mechanisms underlying RP of mathematical information and to examine behavioral and neural changes in the context of two models of RP. At the behavioral level, we observed robust RP effects in both the MC and the NI conditions. RTs were significantly faster during the repeated compared with the novel trials during both conditions, with mean RT decrements of 100 msec in the MC condition and 33 msec in the NI condition. There were no significant changes in accuracy, perhaps because performance levels were uniformly high and close to ceiling

during the initial presentation. With repeated stimulus presentation, widespread decreases in brain response within the frontal, the temporal, and the occipital lobes were observed in the MC condition. However, performance improvements were not correlated with the degree of RS. Instead, we found that improvements in RT were associated with increased activation in three brain areas—(1) the hippocampus, (2) the SMA and the dMCC cortex, and (3) the posterior cingulate cortex, precuneus, and adjoining retrosplenial cortex. Our findings provide new information about the neural basis of RP during mathematical problem solving.

RS during Number Identification and Mathematical Problem Solving

RS was observed in both the NI and the MC conditions, with significantly stronger effects in the MC condition. In the NI condition, RS was restricted to the right posterior cortex, encompassing the fusiform gyrus and superior parietal lobule within dorsal and the ventral stream regions implicated in priming perceptual and abstract representations of numbers (Ansari, 2008; Hubbard, Piazza, Pinel, & Dehaene, 2005; Naccache & Dehaene, 2001). These findings are consistent with previous studies demonstrating RS in the same regions during word and object recognition (Henson, 2003), and they suggest that RS in these areas is related primarily to stimulus identification.

During the NI condition, RS was not observed in the IFC or any other region of pFC. In contrast, widespread and robust bilateral RS of the IFC, the extrastriate cortex and middle occipital gyrus, the fusiform gyrus, the dorsal striatum, and the thalamus accompanied repeated performance of MC trials. RS in some of these regions, most notably in the IFC, has been reported during semantic

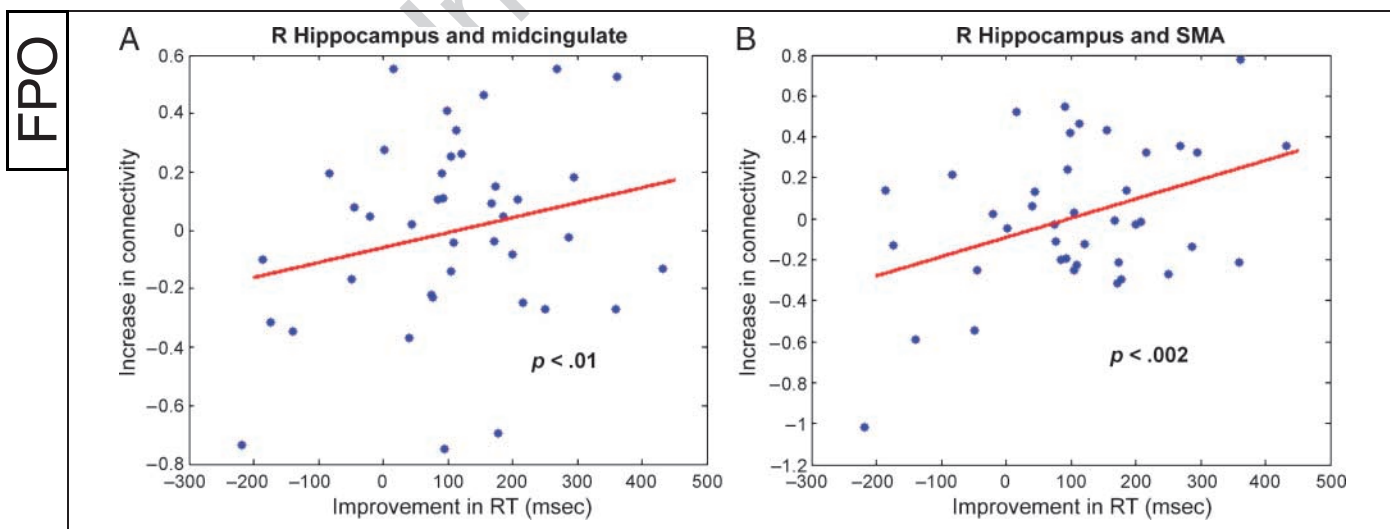


Figure 5. RT improvements were correlated with increased functional connectivity of the hippocampus. Improvements in RT were significantly correlated with increase in function connectivity (A) between the right hippocampus and the dMCC and (B) between the right hippocampus and the SMA.

processing of objects and words (Henson et al., 2000; Buckner, Koutstaal, Schacter, Wagner, & Rosen, 1998; Blaxton et al., 1996; Hamann & Squire, 1996). This suggests that RS effects observed here reflect general cognitive processes, a view consistent with previous findings that the IFC and other nonparietal regions play a supportive role in MC (Menon, Rivera, White, Glover, et al., 2000). Practice-related reductions in the extent and magnitude of activity within a cortical network encompassing bilateral ventral and dorsal pFC, ACC, and fusiform gyrus have been consistently observed during arithmetic learning (Delazer et al., 2003, 2005; Qin et al., 2003) and also across a wide range of nonmathematical tasks (Hill & Schneider, 2006; Chein & Schneider, 2005). Although these changes arise from experimental manipulations where problems are repeated more than once, they overlap with several regions that showed RS in the MC condition. Whether this same constellation of brain regions shows single-trial RS in tasks unrelated to mathematical cognition is at present not clear. Nevertheless, our findings suggest a common role for the left IFC in RP of both mathematical and nonmathematical stimuli (Henson & Rugg, 2003; Sohn, Goode, Stenger, Carter, & Anderson, 2003). The left IFC has been widely implicated in verbal memory retrieval (Martin & Cheng, 2006; Thompson-Schill & Botvinick, 2006; Wagner, Pare-Blagoev, Clark, & Poldrack, 2001), and memory retrieval is critical in solving multistep mathematical problems such as those used in our study (Danker & Anderson, 2007). Collectively, these studies suggest that the IFC contributes to more efficient memory retrieval during repeated mathematical problem solving. However, IFC responses were not directly correlated with RP in our study, leaving unclear its precise role in facilitating the observed behavioral improvements.

Interestingly, RS was not observed in left and right PPC regions that are known to play a crucial role in mathematical cognition. Functional brain imaging studies have shown that the IPS region plays a crucial role in performing arithmetic calculations, independent of other processing demands such as working memory (Delazer et al., 2003; Zago & Tzourio-Mazoyer, 2002; Menon, Rivera, White, Glover, et al., 2000). Patients with damage to the PPC demonstrate significant deficits in performance of mental addition and subtraction tasks (Delazer, Benke, et al., 2006; Barnea-Goraly, Eliez, Menon, Bammer, & Reiss, 2005; Levin et al., 1996; Takayama, Sugishita, Akiguchi, & Kimura, 1994; Benton, 1987), and in normal healthy controls, transcranial magnetic stimulation over the IPS disrupts numerosity processing (Cappelletti, Barth, Fregni, Spelke, & Pascual-Leone, 2007). As expected, PPC regions, notably along the banks of the IPS, showed strong activation during the MC condition compared with the NI condition, and yet there was no evidence for RS in these regions even at a liberal threshold ($p < .05$, uncorrected). Critically, the observed effect sizes for RS in the left and the right IPS were extremely small (Cohen's $d = .05$ and $.03$, respectively). This suggests that the PPC is fully recruited each time

MC is performed, in contrast to the IFC and other frontal lobe regions. The invariant and obligatory nature of activation in these parietal regions further confirms the critical role of the IPS and surrounding cortex in processing mathematical information.

Performance Improvements during Mathematical Problem Solving Are Related to Repetition Enhancement, Not RS

We hypothesized that under the tuning model of RP, the magnitude of behavioral priming would be positively correlated with prefrontal and parietal regions that showed RS in the MC condition. On the other hand, under the stimulus-response learning model of RP, we predicted that performance improvements would be related to increased activity in brain regions associated with associative memory formation, notably the hippocampus and other MTL regions. We found that RT improvements during the MC condition were associated with increases, rather than decreases, in brain response during the processing of repeat compared with novel stimuli. Importantly, we found that responses in the hippocampus were positively correlated with the magnitude of RT improvements. Our findings are consistent with and extend previous findings concerning the role of the MTL in behavioral facilitation. For example, Schnyer et al. (2006) reported that, compared with healthy controls, patients with MTL lesions demonstrate decreased behavioral facilitation and also found that patients with amnesia failed to show a priming advantage for multiple repetitions; indeed, our findings suggest that the MTL can mediate performance enhancements even after a single repetition. Although the location and the extent of MTL lesions and its overlap across the amnesiacs studies were unspecified in the study of Schnyer et al., our study provides new information about the anatomical specificity of anterior hippocampal regions involved in rapid learning. Whereas most previous human neuroimaging studies of the hippocampus have focused on its role in accurate recall of recently encoded information (Henson, Hornberger, & Rugg, 2005), our study shows that the hippocampus can contribute to rapid improvements in RT, independent of accuracy.

Although several previous studies have reported that behavioral improvements were correlated with RS in the IFC (Gagnepain et al., 2008; Bunzeck et al., 2006; Orfanidou et al., 2006; Wig et al., 2005; Zago et al., 2005; Bergerbest et al., 2004; Lustig & Buckner, 2004; Maccotta & Buckner, 2004), we did not observe any such effects here in either the MC or the NI conditions. One explanation for this difference could be that, unlike the word and object classification tasks used in most prior studies, our tasks did not involve complex semantic processing.

The well-known role of the hippocampus in mediating episodic memory formation (Giovanello, Schnyer, & Verfaellie, 2004; Kirwan & Stark, 2004; Ranganath et al., 2004; Davachi, Mitchell, & Wagner, 2003; Cohen, Poldrack,

& Eichenbaum, 1998) suggests the possibility that explicit retrieval may be in effect during mathematical problem solving. At one extreme end of this argument, one might posit that when presented with mathematical equations the second time, participants may be simply recalling their previous responses without recalculation of the problem. However, this is unlikely because mean RTs on repeated MC trials were still about 2 sec, significantly longer than RTs in the NI condition that involved more effortless recognition of number and symbol strings. Furthermore, brain regions such as the PPC, which are crucial for MC, were recruited equally during novel and repeated trials. We believe it is more likely that participants were still performing calculations on repeated trials and that there was facilitation at some stage in the process, perhaps because of faster recall of partial sums or emerging familiarity of the stimuli and the associated response. It is important to note that many tasks involving RP may involve some form of explicit recognition, unless the primes are presented subconsciously (Horner & Henson, 2008). In some cases, explicit recognition of the stimulus may occur after the response has been made (Henson & Rugg, 2003). Our finding that MTL activation was correlated with RT improvements raises the possibility that subjects may have recognized components of the problem solution prior to response, perhaps because of the temporally extended and sequential nature of information processing involved in mathematical problem solving.

Decreases in RT with repetition were also correlated with increased activation in a cluster encompassing the lingual gyrus extending dorsally along the banks of the isthmus of the cingulate gyrus to the posterior medial cortex. The lingual gyrus is part of a hierarchical pathway that provides processed visual input to the hippocampus (Van Essen, Anderson, & Felleman, 1992), suggesting that some aspects of the stimulus-response associations observed in our study may be initiated upstream from the hippocampus. The posterior medial cortex, which includes the posterior cingulate cortex (BA 23), the precuneus (BA 7), and the adjoining retrosplenial cortex (BA 30), is tightly coupled to the hippocampal formation (Parvizi, Van Hoesen, Buckwalter, & Damasio, 2006) and is also thought to be involved in directed recollection of previously seen items (Cavanna & Trimble, 2006; Vincent et al., 2006). It is noteworthy that RP in our study was also associated with neural changes in the SMA and the dMCC. The SMA has been consistently implicated in motor response learning (Lee & Quessy, 2003; Aizawa, Inase, Mushiake, Shima, & Tanji, 1991) and sensorimotor adaptation (Paz, Natan, Boraud, Bergman, & Vaadia, 2005). The dorsal motor cingulate area is tightly linked with the SMA and the primary motor cortex (Hatanaka et al., 2003). Anatomical connectivity analysis also indicates that this region is tightly coupled to the lateral parietal surface, including the inferior parietal cortex and much of IPS (Vogt, Berger, & Derbyshire, 2003), suggesting a mechanism by which the motor system can be primed to respond during MC. To our knowledge, this is the first time that a relationship

has been established between behavioral facilitation during RP and repetition enhancements of the SMA and dMCC. Our findings are consistent with the suggestion that the dMCC plays a pivotal role in reorganizing activity in a host of motor structures to produce appropriate behavioral outputs (Vogt, Hof, & Vogt, 2004). The coactivation of brain regions important for memory and motor learning suggests that learning of stimulus-response associations may contribute to RP.

RT Improvements Are Associated with Increased Hippocampal Functional Connectivity

We further hypothesized that under the stimulus-response learning model of RP, performance improvements would be related to increased connectivity of brain regions associated with associative memory formation, notably the hippocampus. Our analysis focused on the functional connectivity of MTL with other brain regions that showed repetition enhancement. This analysis showed that increases in functional connectivity of the right hippocampus with both the dMCC and the SMA, but not the posteromedial cortex, were significantly correlated with improvements in RT. This finding suggests that connectivity of brain regions important for memory and motor learning plays an important role in mediating RP and further supports the hypothesis that stimulus-response associations may facilitate performance during mathematical problem solving.

We also examined the hypothesis that the magnitude of behavioral priming would be positively correlated with functional connectivity changes among prefrontal and parietal regions that showed RS in the MC condition. We were particularly interested in the IFC, based on its purported causal role in behavioral priming (Wig et al., 2005). However, in our data, there was no evidence for significant changes in functional connectivity in the MC compared with NI conditions between the left IFC and any of these brain regions, although each of these regions showed RS. Further, changes in RT were not related to changes in functional connectivity between the IFC and other brain regions or between any other pairs of brain regions. These findings further rule out the possibility that RS is the primary source of behavioral improvement during mathematical problem solving in our study.

Conclusion

Most previous studies of RP have focused on tasks involving word and object recognition. In these domains, attention has focused on RS as the mechanism underlying behavioral facilitation. Here, we took a different approach and examined the neural basis of RP during mathematical problem solving. We showed that mechanisms other than RS may play an important role in mediating RT improvements, even when RP is accompanied by widespread RS. In particular, we found that repetition enhancement in the hippocampus, the posteromedial cortex, and the SMA

contributed significantly to performance improvements. Our results are consistent with findings in amnesiacs that MTL damage can impair RP (Schnyer et al., 2006) and further suggest that the enhanced recruitment of brain regions responsible for STM formation and their increased functional connectivity with motor learning systems can contribute to behavioral improvements (Suzuki, 2008). Our results provide novel support for the stimulus-response learning hypothesis of RP and help to elucidate the neural mechanisms underlying rapid learning in the context of tasks involving mathematical problem solving. The assumption that RS underlies all behavioral improvements during RP is therefore an oversimplification (Busch, Groh-Bordin, Zimmer, & Herrmann, 2008; Schacter, Wig, & Stevens, 2007; Ganel et al., 2006; Fiebach et al., 2005). It is much more likely that the memory and the brain systems underlying facilitation of behavior during RP depend on both the cognitive processes and the knowledge structures evoked during a specific task (Roediger, 2003).

Acknowledgments

The authors thank Sarah Wu and Shanti Shanker for their assistance with the initial stages of data analysis. This research was supported by an NSF Graduate Fellowship and a Stanford Graduate Fellowship to C. C. and by grants from the NIH (HD047520 and HD059205) and the NSF (BCS/DRL-0750340) to V. M.

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Uncorrected Proof