

Rapid Functional Reorganization in Human Cortex Following Neural Perturbation

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Despite the human brain's ability to rapidly reorganize neuronal activity patterns in response to interactions with the environment (e.g., learning), it remains unclear whether compensatory mechanisms occur, on a similar time scale, in response to exogenous cortical perturbations. To investigate this, we disrupted normal neural function via repetitive transcranial magnetic stimulation and assessed, using fMRI, activity changes associated with performance on a working memory task. Although transcranial magnetic stimulation disrupted neural activity in task-related brain regions, performance was not affected. Critically, another brain region not previously engaged by the task was recruited to uphold memory performance. Thus, functional reorganization of cortical activity can occur within minutes of neural disruption to maintain cognitive abilities.

Introduction

The adult human brain is now appreciated to be highly plastic, with rapid cortical functional reorganization serving as a hallmark of learning (Dehaene et al., 2011). Functional reorganization of neural activity patterns occurs in real-world scenarios in response to aging (Cabeza et al., 2002), disease (Hillary et al., 2003), stroke (Voytek et al., 2010), and traumatic brain injury (Castellanos et al., 2011) to counteract the detrimental effects of neuronal loss or dysfunction. This reorganization often occurs chronically, over a period ranging from days to years. To assess acute plasticity, studies inducing transient neural disruption via repetitive transcranial magnetic stimulation (rTMS) have demonstrated that contralateral cortical homologs compensate for dysfunctional neural activity within minutes of stimulation (Sack et al., 2005; Lee and D'Esposito, 2012). Yet, it is unknown whether fast reorganization, in which unaffected regions take on a compensatory role to uphold learning, may occur in areas distantly removed from the site of neural insult that are unrelated to the affected network but used to retain performance abilities.

To address this, we implemented rTMS to perturb function in neural networks involved in top-down modulation during a delayed-recognition working memory paradigm (Rutman et al., 2010; Chadick and Gazzaley, 2011). Top-down modulation serves selective attention by enhancing or suppressing neural activity in sensory cortical regions based on whether the stimulus is

attended or ignored, respectively (Duncan et al., 1997). Because the brain operates via functional, distributed neural networks, perturbation of activity in a network node reverberates through interconnected areas (Ruff et al., 2009). rTMS has previously been demonstrated to disrupt top-down modulation in visual cortical regions via perturbation of the prefrontal cortex (PFC), which in turn resulted in memory performance decrements (Zanto et al., 2011). However, those results showed that performance in some participants was less affected by rTMS than in others, or not impacted at all, possibly as a result of neural compensatory mechanisms. Unfortunately, the low spatial resolution of EEG available in that study made it difficult to assess whether compensatory activity in other regions was recruited. Furthermore, if compensatory neural areas were engaged, it is important to identify whether it arises from (1) a contralateral cortical homolog, (2) other task-related areas, or (3) the recruitment of additional brain regions that are not involved in the task. Therefore, the current study used fMRI to examine this potential neuroplasticity. It was hypothesized that, in response to rTMS to the same PFC region perturbed in our previous study (inferior frontal junction [IFJ]), either diminished top-down modulation of activity in visual cortex would be observed concomitant with memory performance deficits, or compensatory neural mechanisms would be engaged to uphold performance.

Materials and Methods

Participants. Twenty-two healthy individuals (mean age 24.2 years, 12 females) participated in the experiment. All participants gave informed consent to engage in the study according to procedures approved by the Committee for Human Research at the University of California. Three participants did not complete both sessions and were excluded from analyses.

Experimental task. The experiment consisted of two fMRI sessions performed on separate days using the same delayed recognition task. The first session served to identify a participant-specific rTMS target at the right IFJ. The second session implemented the same experimental task; however, each task was preceded by active rTMS or sham rTMS (where

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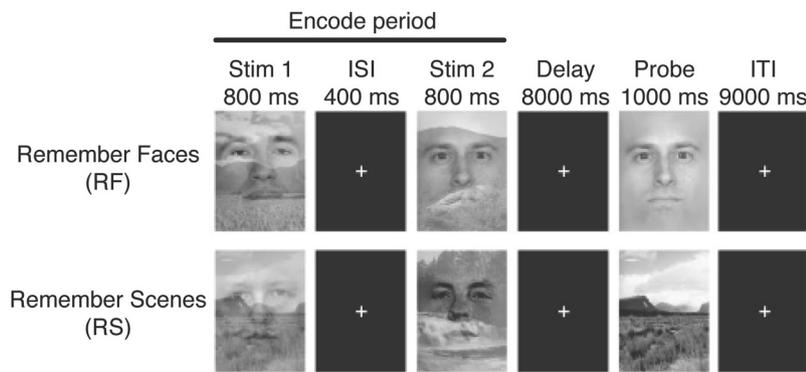


Figure 1. Experimental tasks.

the coil was angled 90° away from the head) to the right IFJ. The experiment consisted of two selective-attention, delayed-recognition tasks (Fig. 1): Remember Faces (RF) and Remember Scenes (RS), similar to previous work (Rutman et al., 2010; Chadick and Gazzaley, 2011).

Stimuli consisted of partially transparent grayscale images of faces overlapped with natural scenes so that each image was visible and served to hold bottom-up sensory information constant. Thus, neural differences between tasks were due solely to top-down goals. Participants were instructed to either remember the two faces (and ignore scenes; RF) or remember the two scenes (and ignore faces; RS) and then respond with a button press as quickly as possible (without sacrificing accuracy) whether the probe image matched either of the items held in memory. Stimuli were presented foveally, and a central fixation cross was presented between stimuli and trials. Each task was randomized across the experiment and participants and consisted of 30 trials per task. On visit 1, tasks were separated into two blocks each (15 trials per block), whereas visit 2 used one block per task (30 trials) and each block was preceded by either rTMS or sham rTMS. Thus, participants were presented 4 task blocks for each visit. Paired *t* tests were conducted to assess performance across tasks ($p < 0.05$).

fMRI. All fMRI data were collected on a Siemens 3T MAGNETOM Trio. Echo planar imaging data were acquired (flip angle = 90°, echo time = 25 ms, repetition time = 2 s) from 33 interleaved axial slices (0.5 mm gap) with a 1.8 × 1.8 × 3 mm voxel size (field of view = 23 cm, 128 × 128 matrix). Raw BOLD data were corrected offline for slice-timing acquisition and motion artifacts. A 5 mm isotropic Gaussian smoothing kernel was applied before modeling the data. To aid in anatomical localizations of BOLD activity, we acquired high-resolution T1-MPRAGE images (1 × 1 × 1 mm voxel size, field of view = 160 × 240 × 256 mm, repetition time = 2300 ms, echo time = 3 ms, flip angle = 9°).

Data analysis. Before beginning the experimental tasks for each visit, participants were presented a 1-back memory task for faces and scenes that served as a localizer for face (fusiform face area [FFA]) (Wojciulik et al., 1998) and scene (parahippocampal place area [PPA]) (Epstein and Kanwisher, 1998) ROIs. BOLD data from the face and scene localizers were analyzed using a GLM and contrasted against each other. ROIs were selected in native space as the most significant cluster of activation in the fusiform gyrus (for faces) or parahippocampal gyrus (for scenes) in the right hemisphere. For each experimental task, the encoding, maintenance, and retrieval stages were modeled with their own separate regressor in the GLM.

To identify rTMS targets for visit 2, functional connectivity network maps (Gazzaley et al., 2004; Rissman et al., 2004) were created for each participant based on fMRI data from visit 1. To calculate functional connectivity maps, every trial was modeled with a separate regressor in the GLM and a mean β value was extracted for each ROI (per trial). The ROI β values from the encoding period were correlated across trials with every voxel in the brain to find regions with covariant activity. We applied a Fisher's *r*-to-*z* transformation, and *z* values were subsequently normalized to the Montreal Neurological Institute (MNI; 2 × 2 × 2 mm voxel size) template and Gaussian smoothed (5 mm full width at half maximum) for group level analysis. All contrasts were assessed via

planned *t* tests, and cluster thresholding based on Monte Carlo simulations was used to correct for multiple comparisons, resulting in a corrected significance of $p < 0.01$.

Transcranial magnetic stimulation. A Magstim Standard Rapid TMS Unit (Jali Medical) was used to generate pulses with a 70 mm figure-eight induction coil. TheBrainsight frameless stereotaxic software (Rogue Research) was used to coregister the participant's head, coil, and T1-weighted MRI images. The IFJ target for rTMS was identified by each individual participant's functional connectivity data from visit 1 between the PPA and RS task, which was subsequently overlaid onto their T1-weighted MRI image. During the second visit, repetitive 1 Hz TMS was applied to the right IFJ for 10 min, with the TMS handle oriented approxi-

mately parallel to the Sylvian fissure, while participants remain seated upright in a room adjacent to the fMRI and watched the diagram Futurama. rTMS pulse intensity was held at 65% of the maximum stimulator output for each participant. This intensity was chosen on the basis of pilot data that found it to be, on average, 120% of the active motor threshold. After rTMS application, participants were placed into the fMRI and began the task within 1 min and 40 s (on average) from rTMS offset. During the second visit, participants were presented each task twice: once with rTMS before task and once with sham rTMS, with the order of sham and actual rTMS stimulation counterbalanced across participants. Sham rTMS consisted of holding the coil over the IFJ but angled 90° away from the head. The duration of each task during the second visit was 10 min. Participants wore earplugs for the entire duration of the experiment to protect against noise from the fMRI and rTMS.

Results

Task-based BOLD activity from the first fMRI session confirmed top-down modulation of activity in the visual cortical ROIs during the encoding stage of the task, replicating previous fMRI findings using this task (Chadick and Gazzaley, 2011). Specifically, attended stimuli resulted in enhanced BOLD activity in the FFA/PPA relative to activity for ignored stimuli (FFA (RF > RS): $t_{(18)} = 3.34$, $p < 0.01$; PPA (RS > RF): $t_{(18)} = 8.46$, $p < 0.01$). Furthermore, functional connectivity analysis using these ROIs as seeds revealed that PFC areas were associated with these visual cortical regions during the encoding period. Notably, the right IFJ displayed strong functional connectivity with the right PPA during RS encoding (RS > RF) and was selected as the target for rTMS (Fig. 2) because of its between-subject consistency, its documented identification as a network node in this task (Chadick and Gazzaley, 2011), and its previously revealed causal role in top-down modulation (Zanto et al., 2011). The right FFA did not exhibit similar functional connectivity with the right IFJ. Therefore, IFJ rTMS effects were expected to selectively affect PPA top-down activity modulation.

Behavioral measures indicated that accuracy and response times were not altered because of rTMS for either task (RF accuracy: rTMS mean 81%, SEM 2%, sham mean 80%, SEM 2%, $t_{(18)} = 0.19$, $p = 0.85$; RF response time: rTMS mean 1085 ms, SEM 88 ms, sham mean 1087 ms, SEM 82 ms, $t_{(18)} = 0.06$, $p = 0.96$; RS accuracy: rTMS mean 82%, SEM 2%, sham mean 85%, SEM 1%, $t_{(18)} = 1.41$, $p = 0.18$; RS response time: rTMS mean 1095 ms, SEM 95 ms, sham mean 1095 ms, SEM 88 ms, $t_{(18)} = 0.01$, $p = 0.99$).

Univariate ROI data from the second session were submitted to a repeated-measures ANOVA with rTMS (Stim, Sham) and task (RF, RS) as factors. For the PPA, main effects for task (RS > RF; $F_{(1,18)} = 39.42$, $p < 0.01$) and rTMS (Stim > Sham; $F_{(1,18)} =$

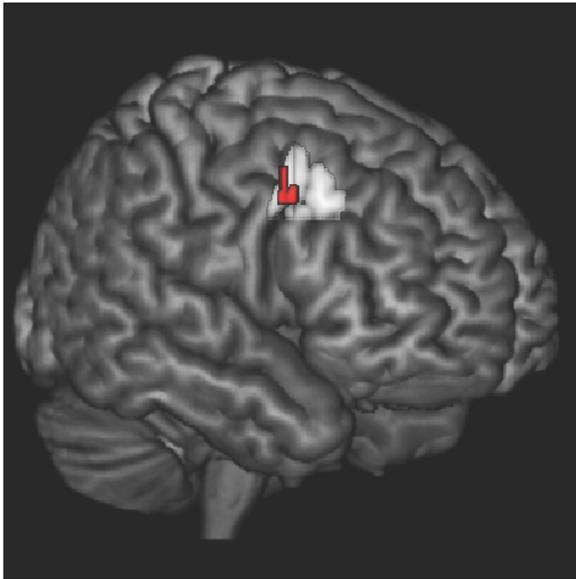


Figure 2. Example of a participant's IFJ region targeted for rTMS (red area within cutout). Data are presented in normalized space but were targeted for rTMS in native space.

5.00, $p < 0.05$) were observed. Additionally, a task \times rTMS interaction was observed ($F_{(1,18)} = 6.07$, $p < 0.05$). *Post hoc t* tests indicated that rTMS (relative to sham rTMS) to right IFJ targets (applied over each participant's functionally defined ROI within 2 min before fMRI recording) selectively perturbed suppression of activity in the PPA for irrelevant scenes (i.e., RF Stim $>$ RF Sham), while preserving enhancement of activity in this region for relevant scenes (i.e., RS Stim = RS Sham; Fig. 3A; PPA RF: $t_{(18)} = 3.81$, $p < 0.01$; PPA RS: $t_{(18)} = 0.23$, $p = 0.82$). Moreover, the overall magnitude of top-down modulation (RS-RF) in the PPA declined because of rTMS (Fig. 3B; $t_{(18)} = 2.46$, $p < 0.05$). Activity in the FFA, which was not functionally connected to the IFJ, exhibited a main effect of task (RF $>$ RS; $F_{(1,18)} = 18.52$, $p < 0.01$) but no rTMS main effect or interaction. Thus, top-down modulation was observed in the FFA but was not affected by IFJ rTMS (Fig. 3; $p > 0.19$, each comparison). This was the predicted finding because the right IFJ was selected using the PPA as a seed in the connectivity analysis.

Because suppression of PPA activity for irrelevant scenes (during RF) was perturbed by IFJ rTMS, but memory performance did not decline, we hypothesized that compensatory changes in the brain occurred to account for retained performance during the RF task. In contrast, in the RS task neither performance nor PPA/FFA modulation was affected by rTMS, and so no compensatory neural changes were expected for this task. To address these hypotheses, whole-brain BOLD univariate activity contrasts were compared between rTMS and sham for each task (i.e., RF and RS). For the RF task, in which the PPA exhibited rTMS-induced decline in suppression of irrelevant stimuli, several regions became more active after rTMS (relative to sham): the left lateral occipital complex (LOC), supplementary motor cortex, right superior parietal lobule, and bilateral post-central gyrus (Fig. 4A; Table 1). Interestingly, no regions exhibited a decline in activity resulting from rTMS. These findings are consistent with recent reports of activity increases after rTMS (Ward et al., 2010; Andoh and Paus, 2011) and corroborate reports indicating that BOLD activity changes resulting from TMS may occur in distant cortical regions but not necessarily under

the site of stimulation (for review, see Bestmann et al., 2008). Furthermore, as hypothesized, no activity differences were observed for the RS task.

To identify whether the regions that displayed increased activity in the RF task after active rTMS served as compensatory mechanisms, the associated behavioral performance was compared between two participant groups segregated by the median rTMS-induced BOLD activity change during the RF task (i.e., rTMS – sham rTMS) for each region. This analysis showed that those participants who recruited the LOC more (i.e., rTMS \gg sham rTMS) exhibited faster response times after rTMS (compared with sham) (Fig. 4B, gray bar; $t_{(8)} = 2.65$, $p < 0.05$), whereas participants who used LOC less exhibited slower performance after rTMS (compared with sham) (Fig. 4B, black bar; $t_{(8)} = 2.32$, $p < 0.05$). And so, although the total population (averaging over these two groups) exhibits no performance change resulting from rTMS (as described above), it is clear that the effects of rTMS on working memory response time (stim – sham) is contingent on the magnitude of LOC recruitment (Fig. 4B; low LOC $>$ high LOC group; $t_{(16)} = 3.52$, $p < 0.01$). Thus, the increased activity in the LOC may be considered compensatory during the RF task.

To ensure that the median split effects were not the result of differences in the order of rTMS stimulation, the effect of rTMS on working memory response time (stim – sham) was assessed between participants who received rTMS first and those who received sham rTMS first. Results indicate no rTMS effects on performance based on the order of rTMS stimulation ($t_{(16)} = 1.35$, $p = 0.20$). Importantly, no other neural region exhibited such a relationship between BOLD activity during working memory encoding and subsequent behavior (i.e., response time or accuracy; Table 1). Moreover, the LOC did not exhibit significant functional connectivity with the PPA or IFJ, after sham or active rTMS. Although this does not preclude the possibility of “background connectivity” between the LOC and PPA or IFJ (Al-Aidroos et al., 2012), the lack of functional connectivity as well as the absence of significant BOLD univariate activity during the first fMRI session or after sham rTMS during the second fMRI session underscore the independence of the LOC from the previously identified task network. Despite the lack of functional connectivity between the LOC and PPA, an across-participant correlation was conducted between the LOC and PPA activity after rTMS stimulation to further assess the compensatory role of the LOC. Results showed that participants who used LOC more after rTMS were the same participants who exhibited the greatest declines in PPA suppression ($r = 0.54$, $p < 0.05$). Together, these results suggest that a task-unrelated cortical region may be used within minutes of neural perturbation to retain working memory performance.

Analysis of whole-brain activity did not uncover any compensatory activity in the PPA or IFJ contralateral homologs (i.e., in the left hemisphere). However, to fully address any potential compensatory role, an ROI analysis was conducted. PPA and IFJ ROIs were identified for each participant in the left hemisphere in the same manner as they were identified in the right hemisphere. Analogous to the previous analysis, RT performance was compared between two participant groups segregated by the median rTMS-induced BOLD activity change during the RF task (i.e., rTMS – sham rTMS) for each region. Results showed no performance differences between the groups based on activity changes in the left PPA or left IFJ (each comparison, $p > 0.37$). Thus, contralateral homologs most likely did not play a role in retaining working memory performance after rTMS.

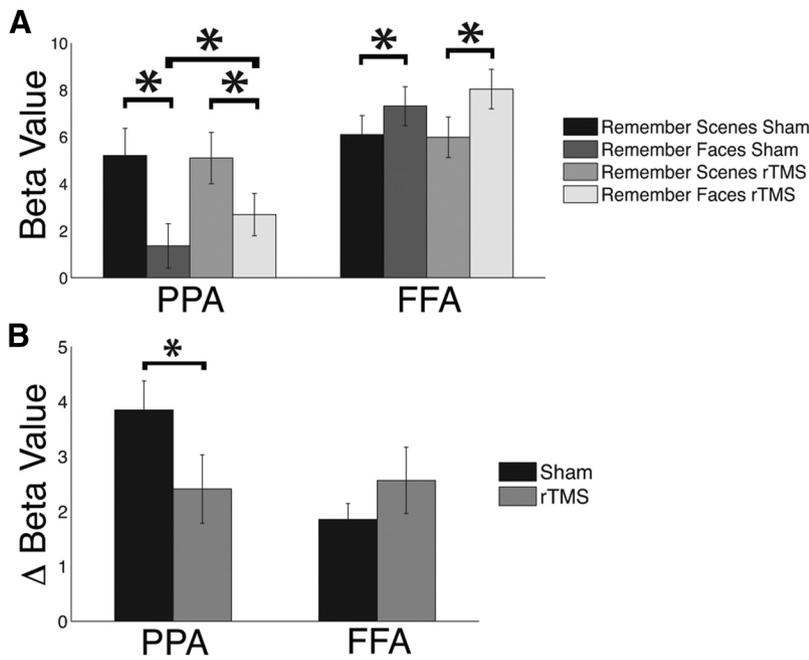


Figure 3. Visual cortical region of interest effects induced by perturbing IFJ via rTMS. **A**, Both PPA and FFA exhibit top-down activity modulation (i.e., attend > ignore). However, only PPA activity displays selective decline in suppressing irrelevant information during the RF task. **B**, The magnitude of activity modulation (attend – ignore) declines in the PPA after rTMS (relative to sham). Δ = attend – ignore (PPA: RS – RF; FFA: RF – RS). * $p < 0.05$. Error bars reflect standard error.

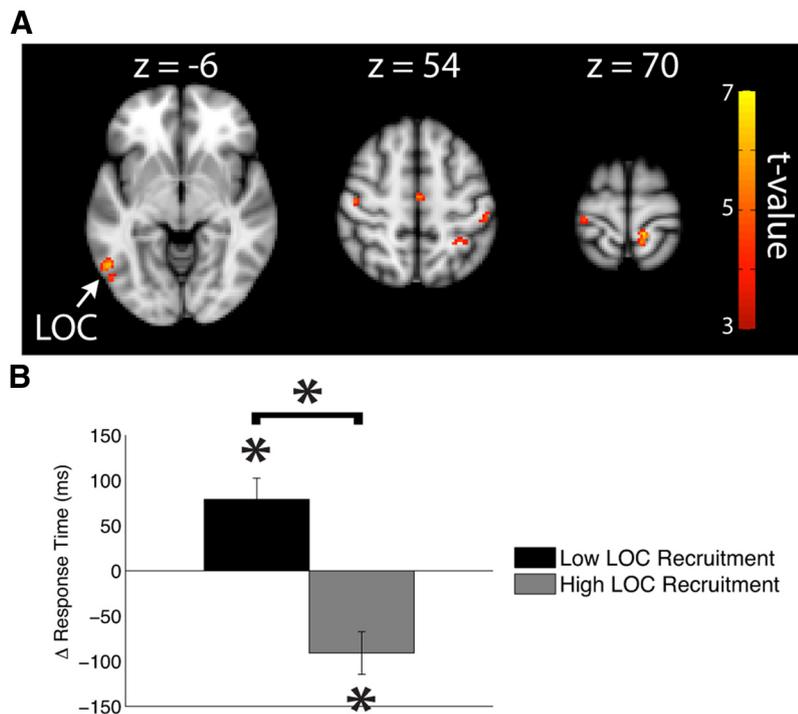


Figure 4. Whole-brain contrasts between actual rTMS and sham rTMS during the RF encoding period. **A**, Left LOC (left), left supplementary motor (middle), right superior parietal lobule (middle), and bilateral postcentral gyrus (middle and right) became more active during face encoding after rTMS. **B**, Participants who recruited LOC more after rTMS yielded enhanced response time performance (gray bar), whereas those who used LOC less exhibited rTMS-related declines in performance (black bar). Δ = rTMS – sham rTMS. * $p < 0.05$. Error bars reflect standard error.

Discussion

The results of this study provide evidence for a causal role of the IFJ in influencing top-down modulation of activity in scene-selective sensory cortex (i.e., PPA), a comparable find-

ing to our recent study showing an impact of IFJ rTMS on color processing using a similar version of this task (Zanto et al., 2011). However, despite this decline in neural modulation, working memory performance was maintained. Further analysis revealed that response time was differentially impacted by rTMS mediated by the recruitment of another visual cortical region, which was not previously used by the task (i.e., the LOC). Thus, LOC activity seems to compensate for neural perturbations only minutes after rTMS to the IFJ to retain behavioral performance.

The LOC is commonly considered to be selectively involved in object shape processing (Kourtzi and Kanwisher, 2001) and not face processing (Kanwisher and Yovel, 2006). Furthermore, this specific LOC subregion was not identified as a face selective region by our face region localization procedure, nor was it active in an assessment of task-based activity in fMRI session 1. Therefore, functional reorganization in response to neural disturbances not only occurs rapidly, on the order of minutes, but recruits task-unrelated cortical areas to preserve working memory performance.

Although it could be argued that compensation may not be necessary, as neither FFA activity nor performance was affected during the RF task, it is important to note that the negative impact of distraction on working memory performance has been well documented (for review, see Hasher et al., 2007), and it is marked by an increase in sensory cortical activity to irrelevant stimuli (Vogel et al., 2005; Zanto and Gazzaley, 2009). For example, when instructed to remember faces and ignore scenes, older adults (compared with younger adults) as well as sleep-deprived younger adults (compared with when they are well rested) exhibit increased neural activity to irrelevant scenes (i.e., in the PPA), whereas activity to relevant faces (i.e., in the FFA) remained unchanged (Gazzaley et al., 2005; Kong et al., 2012). Importantly, the increased activity to the irrelevant scenes was accompanied by decreased working memory performance during the task as well as increased incidental long-term memory performance for scenes. Thus, failure to suppress neural activity to irrelevant

stimuli may decrease working memory performance by overloading working memory stores with irrelevant information (Vogel et al., 2005; Zanto and Gazzaley, 2009). Here, we showed that PPA activity to irrelevant scenes increased after

Table 1. BOLD activity increases during the RF task after actual rTMS compared with sham

Region	Center of mass (MNI)			Volume (mm ³)	RT: low versus high activity	
	x	y	z		t value	p value ^a
Superior parietal lobule (L)	−38	−38	60	1526	1.23	0.24
Lateral occipital complex (L)	−52	−62	−4	1166	3.52	0.003
Supplementary motor (L)	−2	−14	50	836	0.63	0.53
Postcentral gyrus (L)	−46	−28	50	671	0.41	0.69
Postcentral gyrus (R)	10	−42	70	515	1.77	0.10
Precentral gyrus (L)	−42	−16	62	486	0.70	0.50
Postcentral gyrus (R)	44	−20	52	408	−0.31	0.76

^ap values for the comparison of RT data between a median split of subjects who exhibited low activity increases (RF > RS) and high activity increases (RF >> RS).

rTMS to the right IFJ, which would predict reduced working memory performance based on previous research. Yet, performance at the group level did not change. However, an increase in LOC activity after rTMS predicted retained working memory performance, such that those participants who did not use the LOC displayed decreased performance measures. Together, these results suggest that compensation was used to retain performance after perturbed neural activity.

These findings support recent rTMS research that provides causal evidence for the prefrontal and parietal cortex as a source of top-down activity modulation in visual cortex (Taylor et al., 2007; Miller et al., 2011), which in turn directly affects subsequent memory performance (Zanto et al., 2011). In the current study, the rTMS effect was selective in influencing activity associated with processing irrelevant, and not relevant, scenes (i.e., PPA activity during RF task), suggesting a dissociation between networks that enhance activity to relevant information and those that suppress activity to irrelevant information. Although it is not entirely clear why the ability to enhance PPA activity to relevant scenes was unaffected by rTMS, declines in PFC function have consistently led to a selective decreased ability to suppress irrelevant information (Knight et al., 1999; Aron et al., 2004; Gazzaley et al., 2005; Geerligs et al., 2012; Kong et al., 2012). The data suggest that, to compensate for this disruption in scene suppression, LOC activity increased, most likely reflecting a change in how the stimuli (overlapped faces and scenes) were processed. Given the role of the LOC in object selectivity (Kourtzi and Kanwisher, 2001), it is possible that the faces were encoded differently than would be under normal circumstances. Face stimuli may have been processed more as objects, when the irrelevant, overlapped scene was less suppressed. Thus, after rTMS, the increased LOC activity during face encoding may have served to overcome the negative impact of the increased activity to the irrelevant scenes by changing the encoding strategy. In support of this, activity in the left, not right, LOC is known to increase when naming objects (Large et al., 2007; Chouinard and Goodale, 2010). This suggests that participants may have incorporated a verbal strategy to retain performance after rTMS.

We have previously observed functional connectivity between the FFA and IFJ in anticipation of face stimuli (Bollinger et al., 2010, 2011) as well as during working memory encoding of face stimuli (Chadick and Gazzaley, 2011). Although it is unclear why PPA-IFJ functional connectivity was more prominent than FFA-IFJ functional connectivity, this does not preclude the possibility that IFJ may play a role in FFA modulation. Rather, these data suggest that, during work-

ing memory encoding of overlapped faces and scenes, the IFJ exhibits a preference for functional connectivity with scene-selective regions. It is therefore tempting to hypothesize that this preference may underlie strategies used to distinguish an overlapped face and scene. As scene information encompassed a greater visual area than face information (i.e., scenes were not obstructed in the corners), this could benefit scene encoding through pattern completion processes. Along the same lines, encoding faces into working memory may also benefit from scene pattern completion, so that once formed, they can be suppressed to properly extract facial features. Although speculative, this hypothesis supports the interpretation that TMS-induced disruption of the IFJ resulted in a strategy difference that incorporates the LOC.

The notion that IFJ rTMS selectively affects activity modulation for ignoring scenes stands at odds with our previous observation that rTMS to the IFJ impacts activity modulation to both relevant and irrelevant color (Zanto et al., 2011). This discrepancy may result from the stimuli used in each experiment. We have previously shown that older adults exhibit a suppression deficit for ignoring scenes (Gazzaley et al., 2005) and ignoring faces (Gazzaley et al., 2008), but not for color or motion stimuli (Zanto et al., 2010). Therefore, complex stimuli, such as faces and scenes, may use more multifaceted neural networks to modulate activity in higher-level stimulus selective regions.

It should be noted that the suppression deficit in older adults is thought to stem from functional alterations between visual cortex and PFC regions (Gazzaley and D'Esposito, 2007). Thus, a parallel may be drawn with the current data that shows an rTMS-induced suppression deficit in younger adults after the perturbation of a PFC control region. However, it has been shown that older adults often use compensatory PFC regions to retain performance (Cabeza et al., 2002), whereas younger adults in the current study recruited another visual cortical region, the LOC. Although this difference may reflect age-based differences in compensatory mechanisms, it may also be a reflection of the very different time course of perturbation. Age-related neural decline occurs over the course of years, whereas rTMS may perturb neural function within minutes. Another possibility why younger adults recruited the LOC as opposed to a PFC region (as in aging) may involve available resources. The effects of rTMS are localized to a specific cortical region and its interconnected functional network (Ruff et al., 2009), whereas older adults exhibit widespread cortical atrophy and white matter degradation (Rabbitt et al., 2007) that may result in a shift from posterior to anterior processing (Davis et al., 2008). The availability of resources may also explain why a contralateral homolog (e.g., left PPA) was not used for compensation. Although rTMS to the right IFJ affected the right PPA's ability to suppress activity for irrelevant scenes, a similar decline in suppression was observed in the left PPA. Thus, the left PPA was not available for compensation.

The cognitive reserve hypothesis has been proposed to account for the repeated observation that the amount of neural pathology or damage does not necessarily relate to the clinical manifestation of the damage (Stern, 2002). Here we provide supporting evidence such that memory performance variability stems from individual differences in the brain's ability to compensate for neural disruption by rapidly reorganizing cortical activity, notably the capacity to recruit neural areas for tasks in which they are not otherwise used. Additional re-

search will be required to illuminate why some individuals are more adept at this functional reorganization than others.

The observed functional recruitment of the LOC occurred within minutes of the application of rTMS. Compensation for widespread cortical atrophy in normal aging occurs gradually over the course of decades (Rabbitt et al., 2007; Davis et al., 2008), whereas stroke patients who undergo more localized neural disturbances in a much shorter period of time exhibit compensatory reorganization within weeks of acute neural trauma (Cramer and Riley, 2008). Here we observed compensation within minutes of rTMS, with effects on a similar time scale to a stroke, but with a more focal spatial distribution than most cortical lesions. Thus, the rate of neuroplastic changes in response to neural functional compromise may depend on the magnitude or extent of disruption as well as its speed of progression. Interestingly, the rate of reorganization after rTMS is akin to the time course reported for neural activity changes that underlie learning (Messinger et al., 2001; Berry et al., 2009). One intriguing possibility to explore is whether the rate at which functional reorganization occurs in response to a neural insult is related to an individual's rate of learning.

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